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Nitrile *N*-oxides and nitrile imines as electrophilic partners for the discovery of novel isocyanide multicomponent reactions: an innovative strategy for the synthesis of molecular scaffolds useful in medicinal chemistry

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Chapter 1

Introduction

1.1 Introduction

Modern drug discovery is facing with the challenge of designing chemical reactions that are capable of providing most of different structural molecules with a minimum number of synthetic steps.[1–5]

Classical chemical reactions correspond to equilibria between one or two reagents and their products.

In theory, the perfect chemical reactions form their products irreversibly, without the competing formation of by-products, affording the desired products in quantitative yield. This ideal situation is anyway very far from the reality. Finally, using the two-component chemistry to form complex products, requires usually sequences of chemical reactions leading to reduced overall yield.[6]

On the contrary, in the multicomponent reactions (MCRs) three or more different starting materials are combined, in one step, to give a product that incorporates substantial portions of all the components, reducing the number of synthetic steps necessary to form the desired molecules.[7,8]

Indeed, over the last decades, multicomponent reactions have demonstrated their ability and efficiency in the generation of chemical diversity, being an extremely powerful synthetic tool for medicinal chemists and pharmaceutical industry.[9–12]

1.2 Multicomponent reactions (MCRs)

Reaction in which more than two starting compounds react to form a product in such a way that the majority of the atoms of the starting materials can be found in the product are called multicomponent reactions.[8]

To note that MCRs do not directly convert their educts into the products, but they are sequences of subreactions that proceed stepwise. Ideally, all reaction equilibria in the MCR mixture are reversible, except one, thus providing the driving force to shift all intermediates and starting materials towards a single final product.

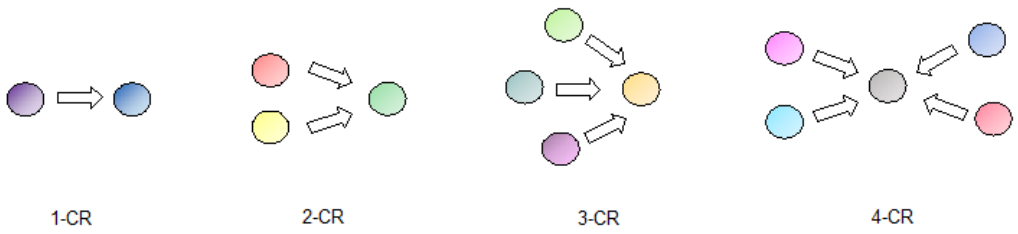


Figure 1. Schematic presentation of a one component reaction, a two component reaction, and a three and four component (adapted from reference 5).

Compared to conventional multistep organic syntheses, MCRs are advantageous due to their greater efficiency and the accessibility to a large number of molecules with broad structural diversity. The experimental simplicity of one-pot procedures is also a major benefit, they are easier to carry out than multistep syntheses and require a single final purification. Finally, the structure of the reaction product can be modified by systematic variation of each input.[5]

A selection of the most important named MCR discovered starting from 1850 are reported herein (Figure 2).

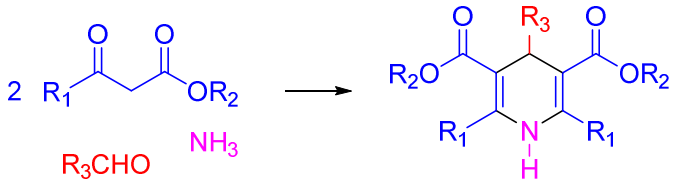
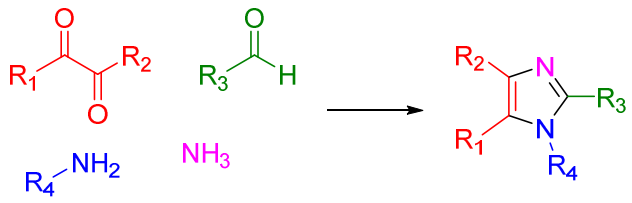
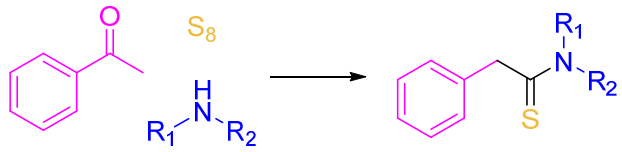
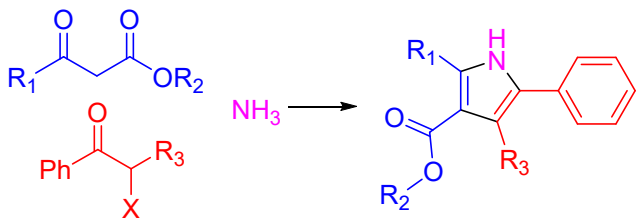
Name of the reaction	Year of discovery	Example
Strecker synthesis[13]	1850	
Hantzsch dihydropyridine synthesis[14]	1882	
Radziszewski imidazole synthesis[15]	1882	
Willgerodt-Kindler reaction[16,17]	1887	
Döebner reaction[18,19]	1887	
Hantzsch pirrole synthesis[20,21]	1890	

Figure 2. Named MCRs.

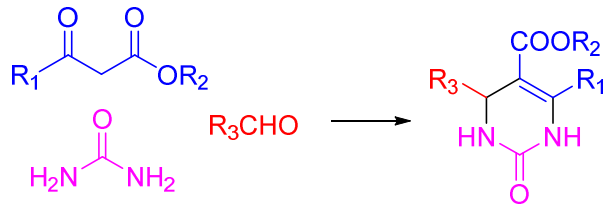
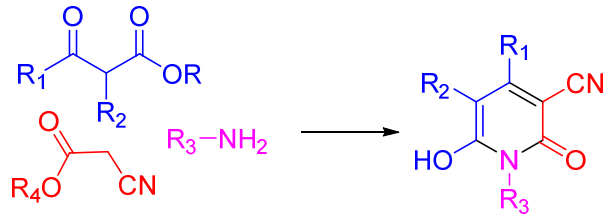
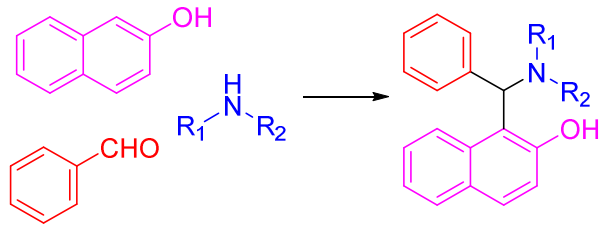
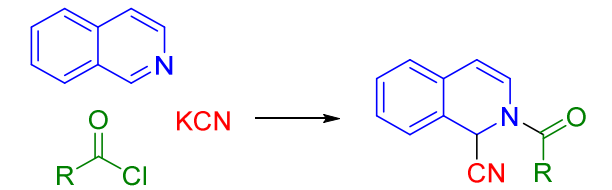
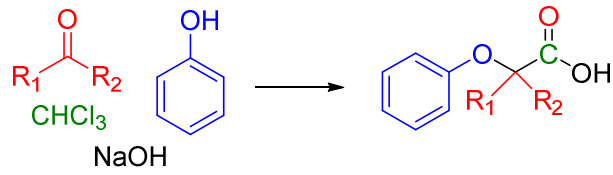
Name of the reaction	Year of discovery	Example
Biginelli reaction[22–25]	1891	
Guareschi reaction[26,27]	1896	
Betti reaction[28,29]	1900	
Reissert reaction[30]	1905	
Bargellini reaction[31]	1906	

Figure 2. Named MCRs (*continued*).

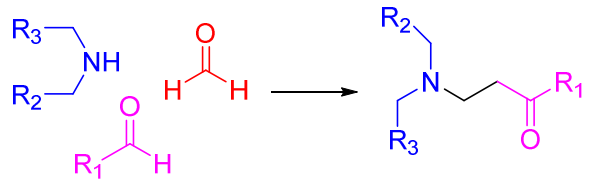
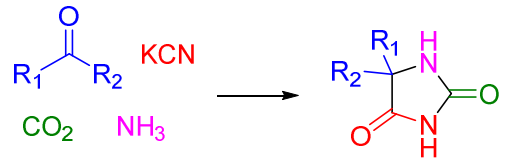
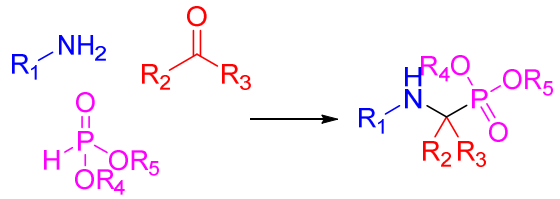
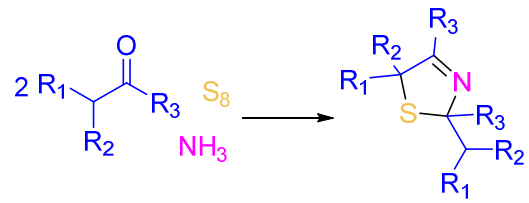
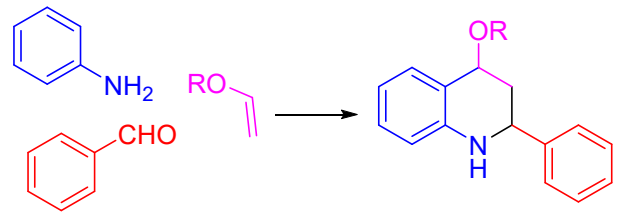
Name of the reaction	Year of discovery	Example
Mannich reaction[32]	1912	
Bucherer-Bergs hydantoin synthesis[33,34]	1929	
Kabachnik-Fields synthesis[35,36]	1952	
Asinger reaction[37]	1956	
Povarov reaction[38]	1963	

Figure 2. Named MCRs (*continued*).

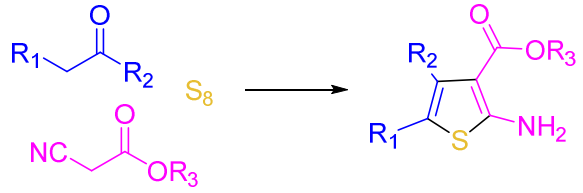
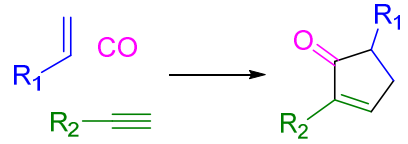
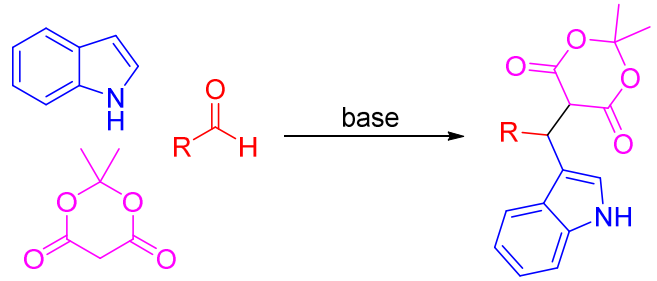
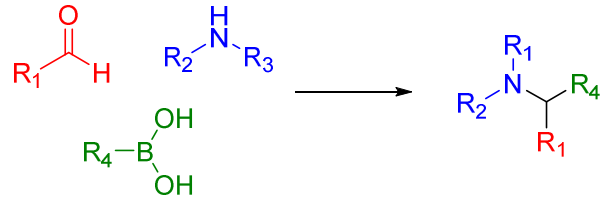
Name of the reaction	Year of discovery	Example
Gewald reaction[39]	1966	
Pauson-Khand reaction[40]	1977	
Yonemitsu synthesis[41]	1978	
Petasis reaction[42]	1993	

Figure 2. Named MCRs (*continued*).

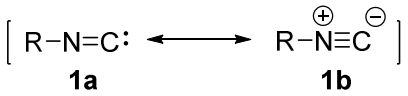
As shows in Figure 2, a vast number of MCRs have been reported in the literature, but special subclasses isocyanide based MCRs (IMCRs) are probably the most documented ones.[1,5,10,43–46]

1.3 Isocyanides

Isocyanides (or isonitriles or carbylamine) represent a class of stable organic compounds with the functional group -N≡C.[47]

Isocyanides are considered as highly "unpleasant" compounds, due to their vile odor. However, higher molecular weight isocyanides are often solid and odorless.

Isocyanides are considered resonance forms between divalent carbon forms **1a** and zwitterions **1b** (Scheme 1). The carbon atom of the isocyano group can exhibit a carbene-like reactivity that is reflected in the resonance structure **1a**, conversely, the linear structure of isocyanides is well represented by the dipolar resonance structure **1b**, which has a nucleophilic character.[48,49]



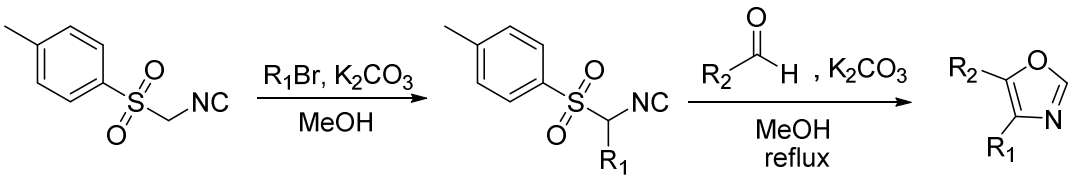
Scheme 1. Resonance structures of isocyanides.

Isocyanides are stable under basic treatment (they are often made under basic conditions), but they are quite sensitive to acids. In the presence of aqueous acidic solutions, isocyanides react to give the corresponding formamides by an acidic hydrolysis and this is a generally convenient method for removing the horrible smell of isocyanides.[50,51]

The chemistry of isocyanide is characterized by three properties: the α-acidity, the easy formation of radicals and the α-addition.

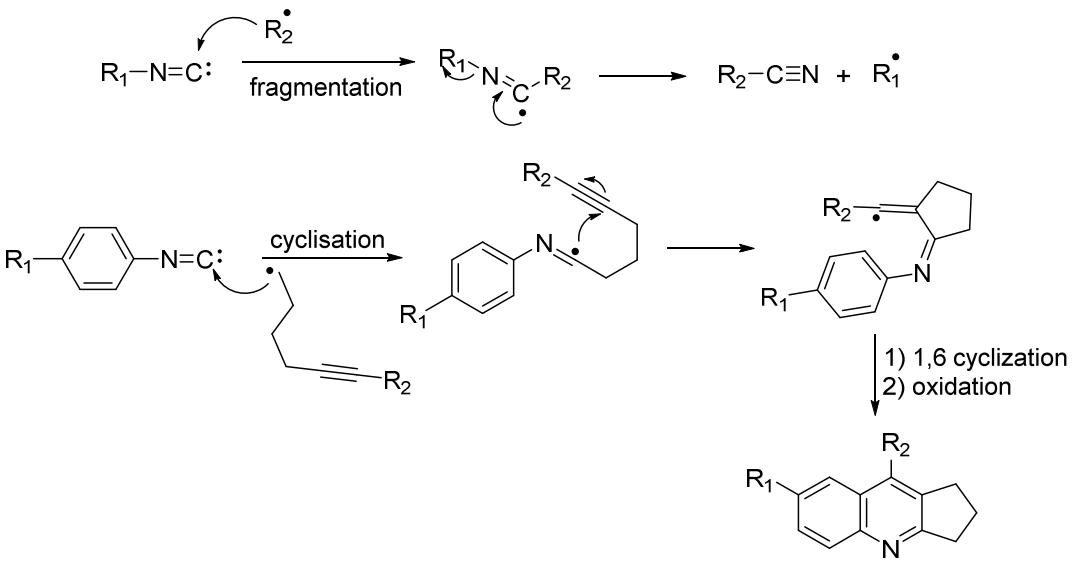
The α-acidity of the isocyanides is further increased by electron-withdrawing substituents in the α-position such as carboxylic ester, nitriles and phosphonic ester

or sulfonyl group. In certain cases, a weak base is sufficient to alkylate the isonitrile. This property has been widely studied for the synthesis of oxazoles [51,52] pyrroles,[53] triazoles. [30] For instant, Van Leusen reported an oxazole synthesis to oxazoles from toluenesulfonylmethyl isocyanide (TosMIC) and an aldehyde (Scheme 2).[53]



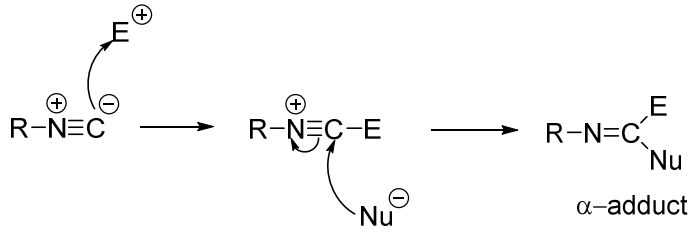
Scheme 2. Synthesis of oxazole starting from TosMIC.

In the radical reaction of isocyanides, radicals are able to add on isonitriles to form an imidoyl radical species, which can then fragment into a nitrile and an alkyl radical[55] or can react intramolecularly with an unsaturated system to give cyclic compounds[56] (Scheme 3).



Scheme 3. Addition of a radical on an isonitrile.

Finally, isocyanides are able to react with nucleophiles and electrophiles at the same isocyanide carbon-atom through an "*α*-addition", to give an "*α*-adducts"[5] (Scheme 4).



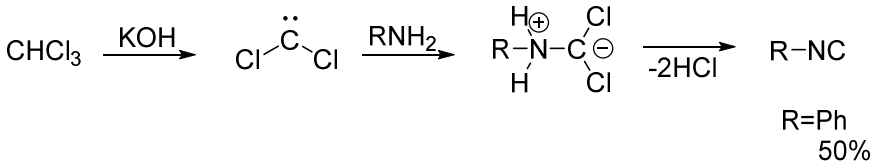
Scheme 4. Formation of *α*-adducts.

This characteristic is unique in organic chemistry, both nucleophile and electrophile attacks will occur on the terminal carbon atom. After the attack of the isocyanide on an electrophile, the divalent carbon becomes electrophilic and can be attacked by a nucleophile, and conversely although rarer it can react first with a nucleophile and then with an electrophile.

Only a few isocyanides are commercially available, but they can be easily prepared in one or two steps.

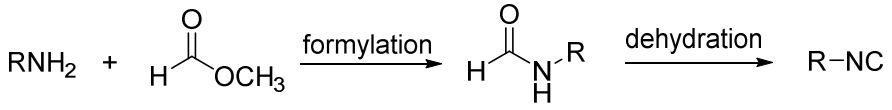
The first isocyanide compound, allyl isocyanide, was obtained by Lieke in 1859, from the reaction of allyl iodide and silver cyanide.[57]

In 1867, Hofman described a new approach via the condensation of a primary amine with a dichlorocarbene, generated in situ by reacting chloroform with potassium hydroxide[58] (Scheme 5). However this method suffers from a lack of reproducibility, low yield and difficulties of separation of isocyanides from amines.[59]



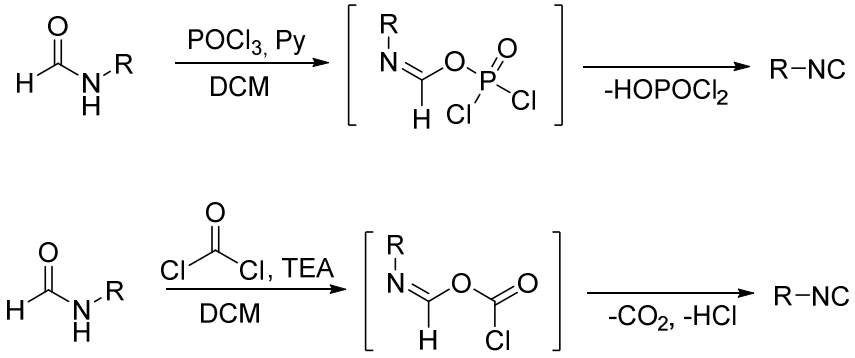
Scheme 5. Hofman synthesis of isocyanide (carbylamine method).

In 1958, Ivar Ugi optimized the formation of isocyanide using the dehydration of *N*-monosubstituted formamide, prepared from condensation of primary amines with methyl or ethyl formate or formic acid (Scheme 6).[60]



Scheme 6. Synthesis of isocyanide by dehydration of formamide.

Various dehydrating agents can be used (for example phosgene, P_2O_5, $POCl_3$, $(CO)_2Cl_2$, $SOCl_2$, PBr_3) in the presence of a base like pyridine, triethylamine, diisopropyl ethylamine. This method is compatible with a larger number of substrates, so it is the most used.

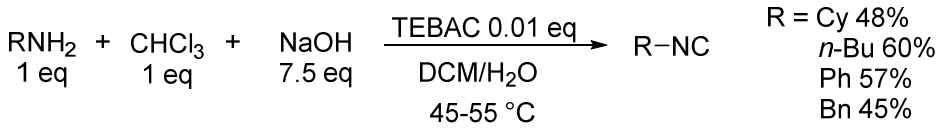


Scheme 7. Synthesis of isocyanide by dehydration of formamide (using $POCl_3$ or phosgene as a dehydrating agent).

In 1972, Weber, Gokel and Ugi improved the Hofman method of carbylamine by carrying it out in a biphasic medium: a mixture of dichloromethane and water in the presence of a phase transfer catalyst (Scheme 8).[61,62]

In this method, the attack of the primary amine on dichlorocarbene is more selective and the method is high yielding (up to 70% after purification) and more reproducible.[63] In this case dichlorocarbene may be generated efficiently from chloroform and aqueous NaOH in a heterogeneous system by use of the phase

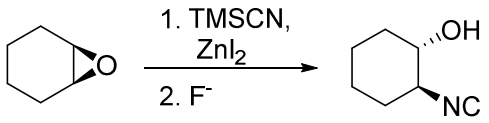
transfer catalyst benzyltriethylammonium chloride. This method improves the selectivity of the addition of the dichlorocarbene to the primary amine, and limits the formation of side products. For this reason, it is utilized still today for the preparation of a great number of isocyanides.



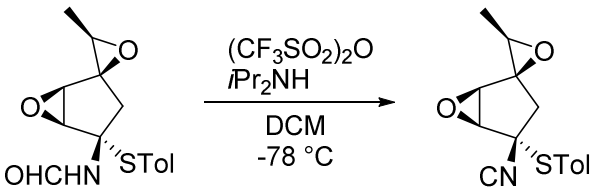
Scheme 8. Synthesis of isocyanides improved by Ugi.

Other synthesis have been reported, but they are less general and more substrate specific (Figure 3).[8]

Gassman *et al*, 1982[64]



Baldwin *et al*, 1990[65]



Kitano *et al*, 1998[66]

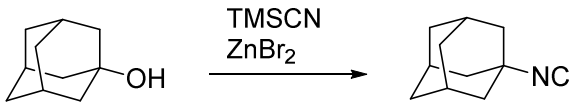


Figure 3. Other synthesis of isocyanides.

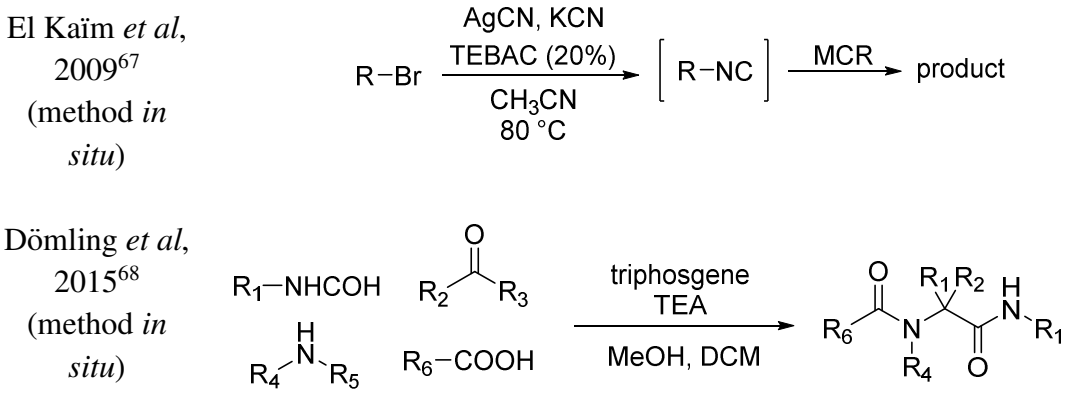
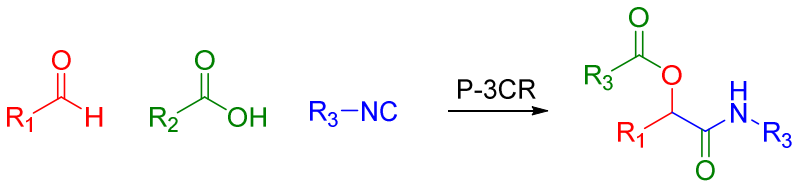


Figure 3. Other synthesis of isocyanides (*Continued*).

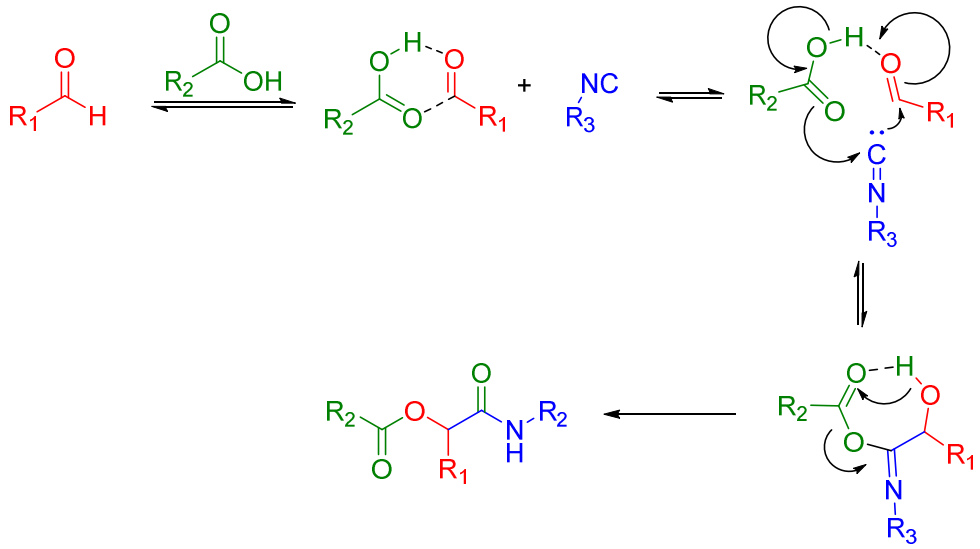
1.4 Isocyanide based multicomponent reactions (IMCRs)

The Passerini reaction was the first reported isocyanide based multi-component reaction. It was discovered by Mario Passerini in 1921. This three-component reaction (which is abbreviated as P-3CR) involves a carboxylic acid as a nucleophile, an oxo component (aldehyde or ketone) and an isocyanide to give an α-hydroxy carboxamide (Schema 9).



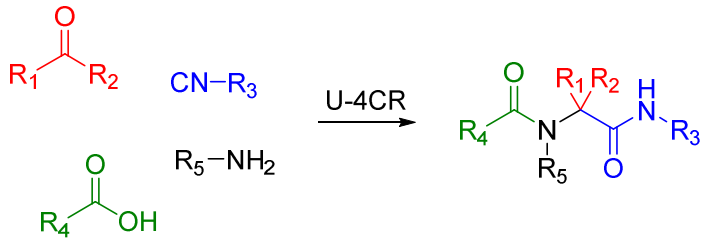
Scheme 9. Passerini reaction P-3CR.

The exact mechanism was subject of some uncertainty. The most accepted mechanism involves the formation of the adduct between the carboxylic acid and the carbonyl compound; the isocyanide then inserts into this intermediate followed by nucleophilic addition of the isocyanide to give the nitrilium ion. The carbonyl carbon acts as electropile and the oxygen of the carboxylic acid as nucleophile, and their addition into the isocyanide carbon atom is simoultaneous. The final, non-reversible step is a Mumm type rearrangement: the intramolecular transfert of the acyl. This is the driving force of the reaction, where an unstable iminoanhydride intermediate converts into a stable adduct (Scheme 10).[49,69,70]



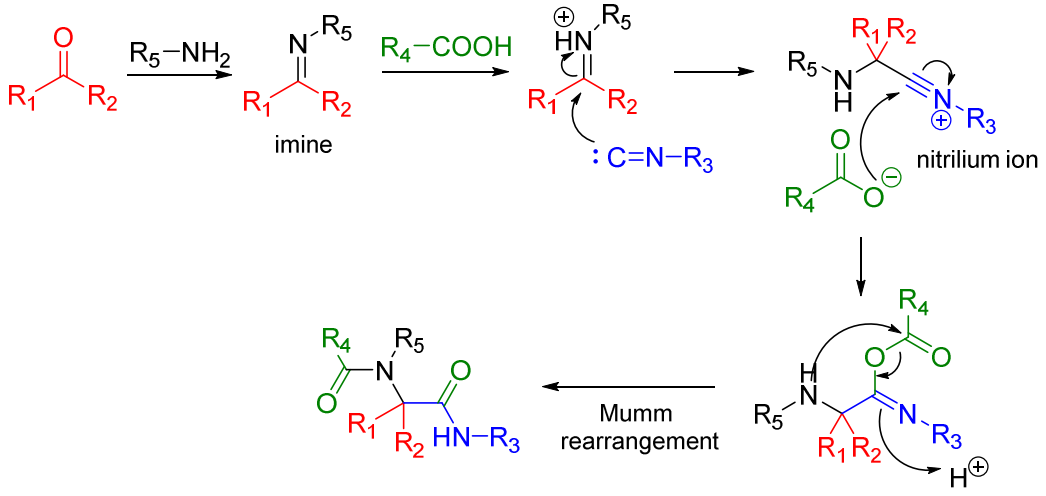
Scheme 10. Mechanism of the Passerini 3-component reaction.

In 1959, Ivar Karl Ugi extended the scope of the Passerini reactions by adding an amine. The Ugi reaction (U-4CR) is defined as the reaction of a carboxylic acid (as a nucleophile), a ketone or aldehyde, an amine, and an isocyanide.[7,71,72] The reaction is typically carried out in methanol or 2,2,2-trifluoroethanol in high reactant concentrations (Scheme 11).



Scheme 11. Ugi reaction U-4CR.

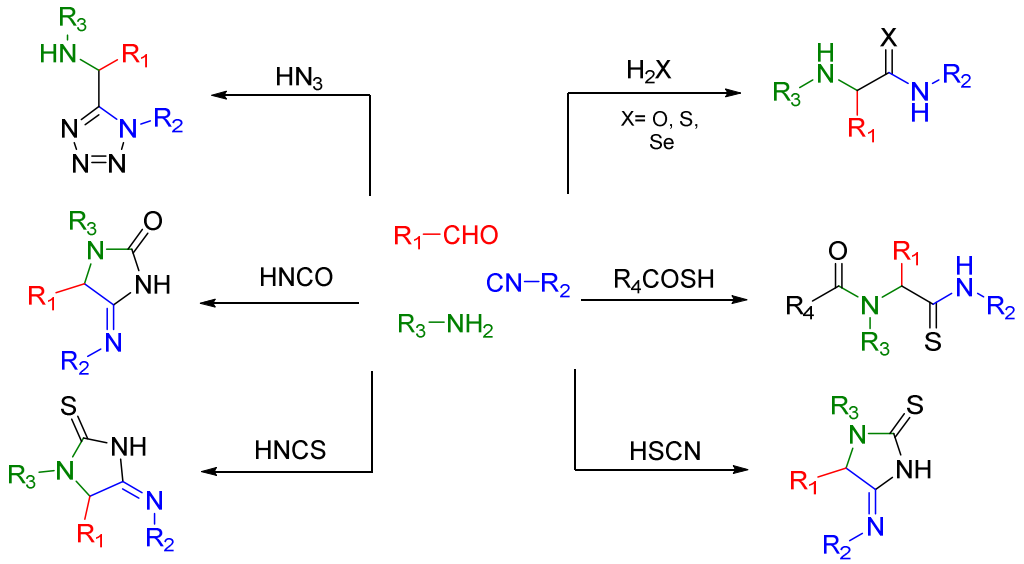
The initial step is the formation of an imine from the amine and the carbonyl compound, followed by protonation with carboxylic acid. Subsequently the nucleophilic attack of the isocyanide to the iminium ion, produces the formation of the highly reactive nitrilium intermediate. The nitrilium is then attacked by the carboxylate ion, and as a result of intramolecular Mumm rearrangement, the reaction yields a bis-amide (Scheme 12).[70]



Scheme 12. Mechanism of the Ugi 4-component reaction.

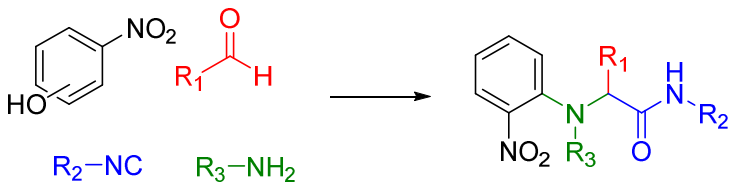
Interestingly, Ugi, compared to Passerini reaction, is much more versatile, not only in terms of library size, but also in terms of scaffolds. This can be attributed to the many different nucleophiles and amine components that have been described to date for the Ugi reaction.[5]

The nature of the components may vary widely; for example, the acid component may be hydrazoic acid, hydrogen thiosulfate, isocyanic and isothiocyanic acids, hydrogen selenide, a thiocarboxylic acid or water (Scheme 13).[73]



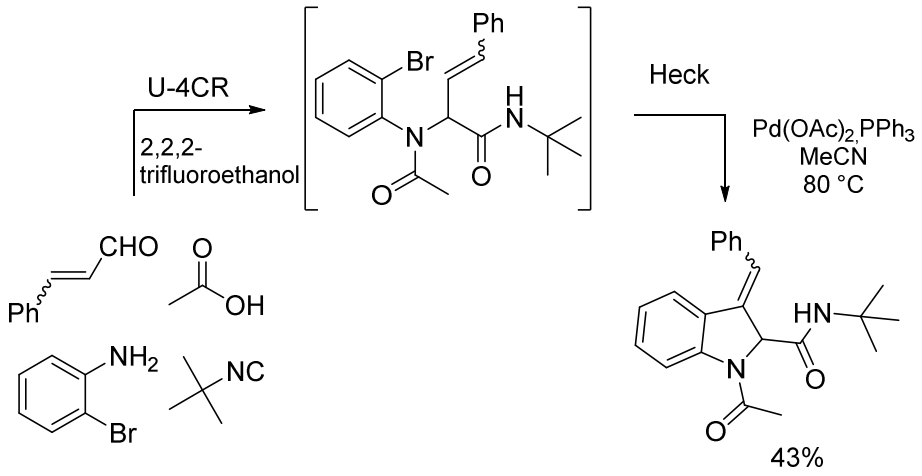
Scheme 13. Selected acid surrogates in Ugi-type couplings.

Pioneering work by El Kaïm and Grimaud led to the discovery of a new Ugi-Smiles reaction. In this case an electron deficient phenol such as 2-nitrophenol replaces the carboxylic acid. The mechanism is believed to involve activation of the aldehyde by the weakly acidic phenol (pKa ~ 4.2) which makes the carbonyl electrophilic vulnerable to attack by the isocyanide. The incipient nitrilium ion formed is attacked by the phenol followed by an S_NAr leading to an α-aryloxy amide. The key step is believed to be the irreversible Smiles rearrangement of the intermediate phenoxyimidate adduct, instead of the classical Mumm acyl transfer rearrangement (Scheme 14).[74,75]

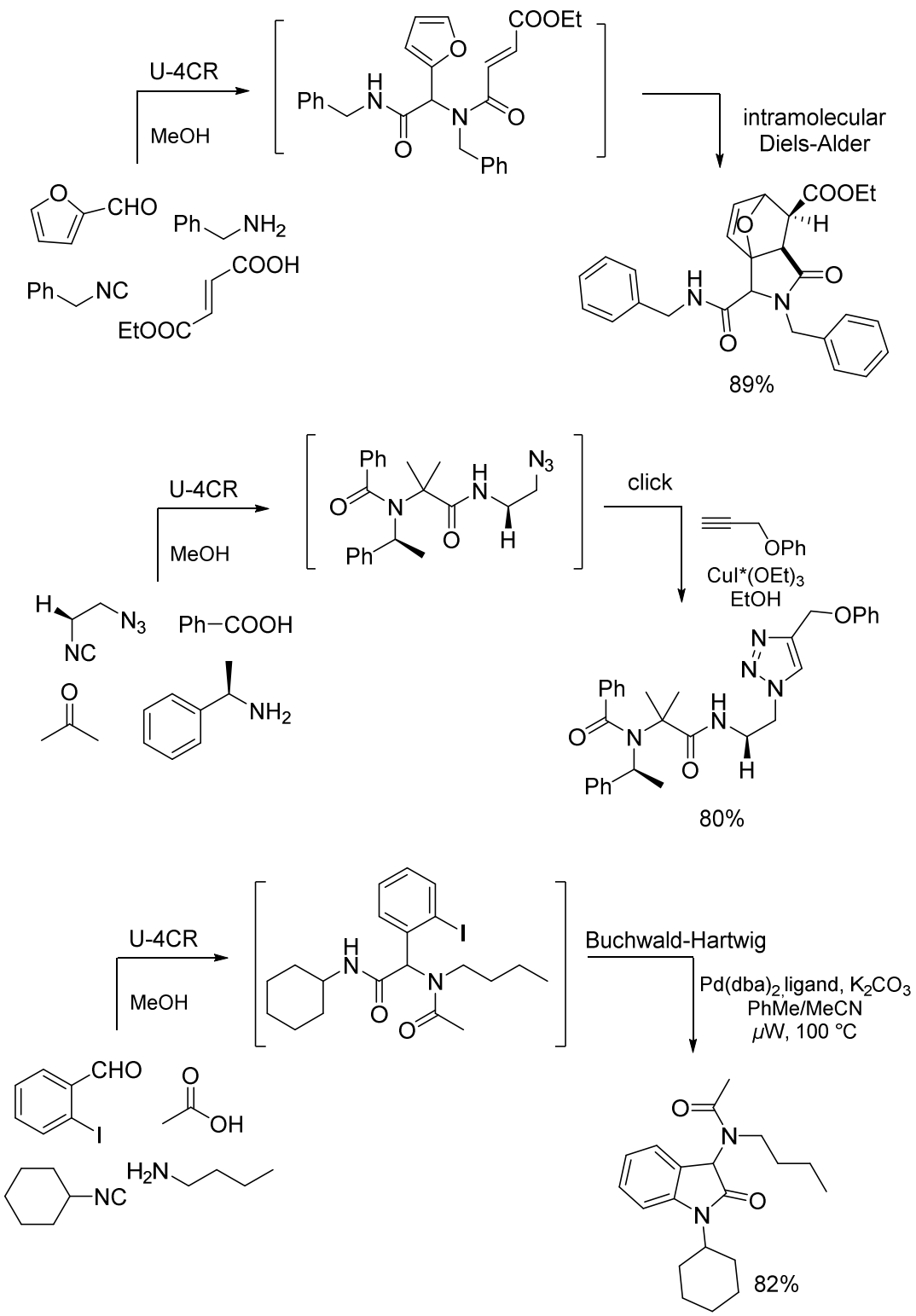


Scheme 14. Ugi-Smiles reaction.

Depending upon the R groups, post Ugi reactions have been reported. For example Ugi-Heck[76], Ugi-Diels-Alder[77], Ugi-click[78,79] and Ugi-Buchwald-Hartwig[80] reactions, whereby the Ugi bis-amide with reactive functional groups undergoes secondary reactions to form a ring (Scheme 15) . Linear bis-amides on the other hand are useful in the synthesis of peptides (linear and cyclic) and peptidomimetics.[81]

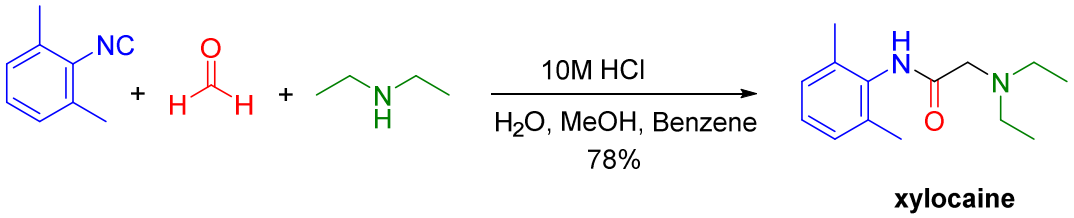


Scheme 15. Examples of Ugi-Heck, Ugi-Diels-Alder, Ugi-click and Ugi-Buchwald-Hartwig reactions.



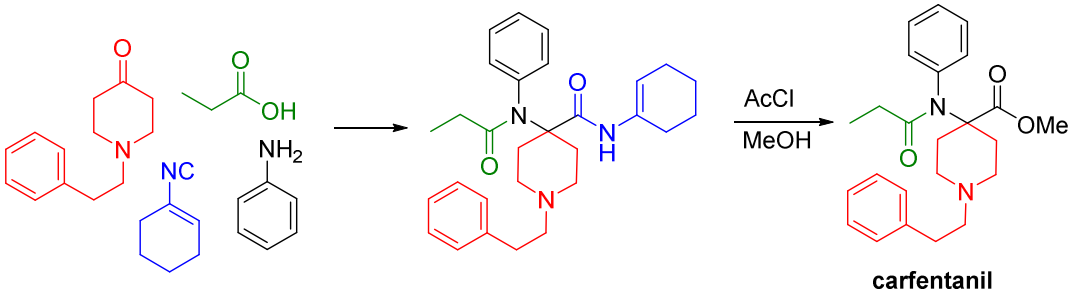
Scheme 15. Examples of Ugi-Heck, Ugi-Diels-Alder, Ugi-click and Ugi-Buchwald-Hartwig reactions (*continued).*

One well known example of utilizing the Ugi reaction in medicianal chemistry is the one-pot synthesis of the local anesthetic xylocaine (Scheme 16).[7]



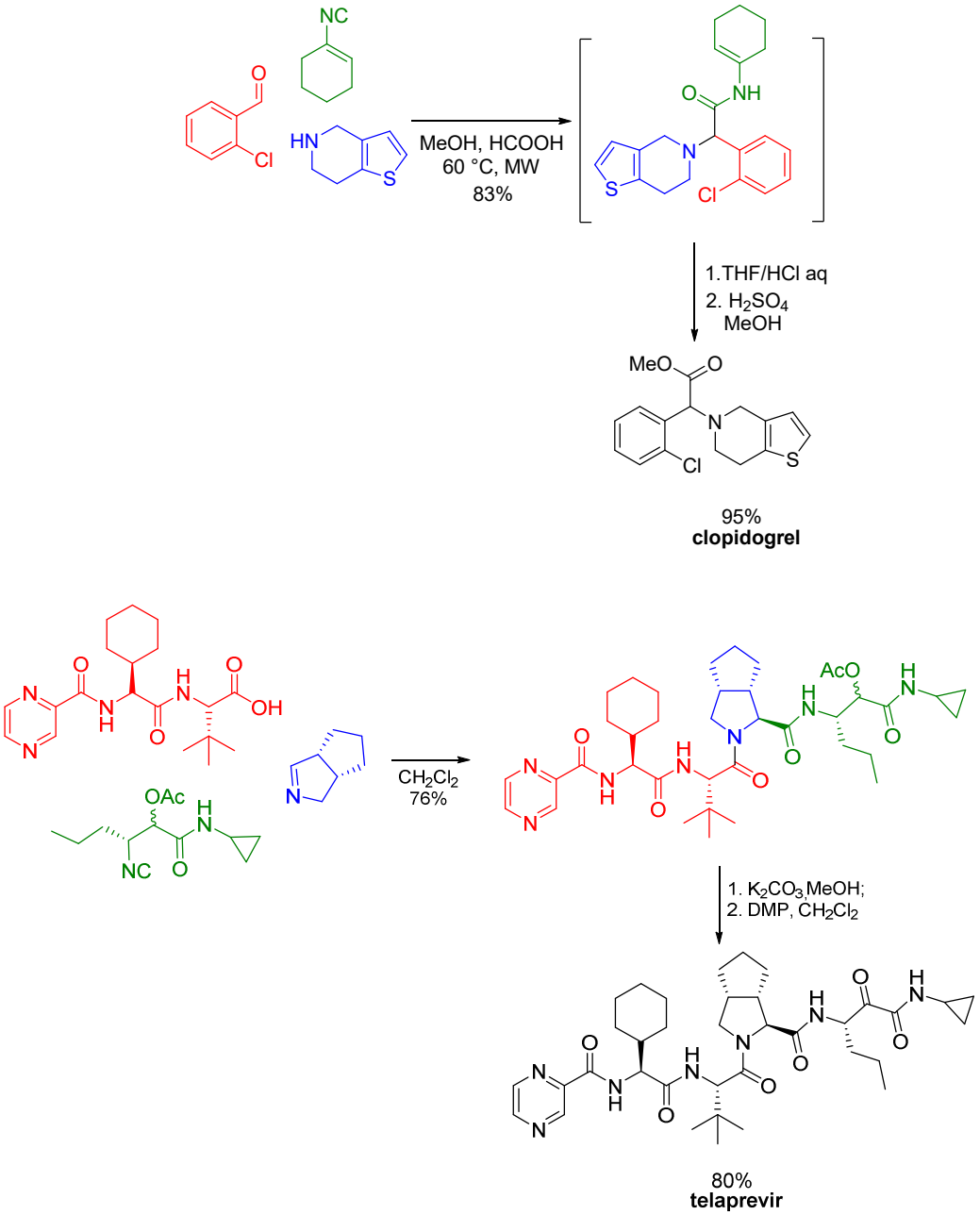
Scheme 16. Ugi's synthesis of xylocaine.

A more recent pharmaceutical application using MCR is the synthesis of fentanyl and carfentanil, two potent analgesics acting primarily on μ opiod receptor (Scheme 17).[82]

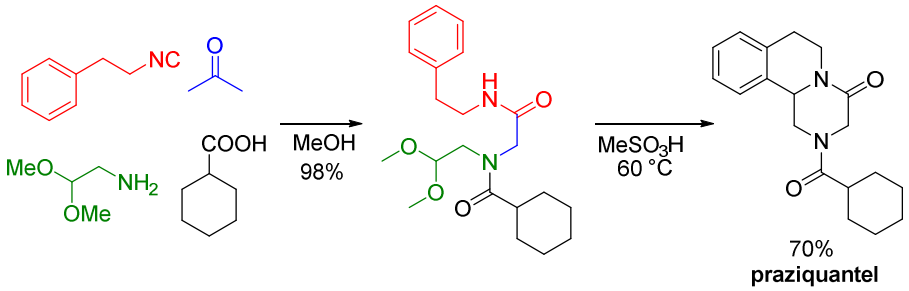


Scheme 17. Synthesis of carfentanil by the U-4CR.

Three more examples of the potential use of MCRs in the field of generic drug production, is the two-step synthesis of clopidogrel (Plavix®), an antiplatelet agent, telaprevir (Incivek®), used in HCV treatment, and praziquantel (Biltricide®), an anthelmintic (Scheme 18).[83–86]



Scheme 18. Examples of application of Ugi reaction.



Scheme18. Examples of application of Ugi reaction (*continued).*

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Chapter 2

Outline of the thesis

2.1 Outline of the thesis

The rapid and easy access to biologically relevant compounds, associated with the scaffold diversity, obtainable via multicomponent reactions, it has been recognized in our laboratory as a preferred method to design and discover biologically active compounds.[1–11]

In this context is inserted the idea of this thesis. The major objective is related to the discovery of new multicomponent reactions, which can rapidly lead to the synthesis of important scaffold in medicinal chemistry either not easily accessible via the classical two-component chemistry or never reported in literature.

Our research was focused on searching for neglected electrophilic groups that could replace the carbonyl component in the Passerini reaction.

We have investigated, in particular, the role of two species: *Z*-chlorooximes and hydrazonoyl chlorides, able to generate 1,3-dipolar species, respectively, nitrile *N*-oxides and nitrile imines which can be attacked by the isocyanide. The ephemeral nitrilium ion created can then be intercepted by a third component.

In Chapters 3 and 9 an overview of the chemical features and the existing literature on *Z*-chlorooximes and hydrazonoyl chlorides, with particular attention to their reactivity with isocyanide, is reported.

In Chapter 4, the discovery of a novel multicomponent reaction between *Z*-chlorooximes, isocyanides and amines to obtain *C*-oximinoamidines is described.

In Chapter 5, the use of an *α*-isocyanoacetamides for the synthesis of aryl-α-ketoamide amides is disclosed. In this reaction the nitrilium ion can be intramolecularly intercepted by an internal nucleophile to produce 1,3-oxazol-2-oxime, which undergoes opening of the oxazole ring and deoximation reaction.

In Chapter 6, a new methodology for synthesis of aryloxyimino amides via Smiles rearrangement of the MCR product among aromatic *Z*-chlorooximes, isocyanides, and electron-deficient phenols is presented.

In Chapter 7, a multicomponent reaction using hydroxylamines as hypernucleophilic traps, to form aminodioximes and 5-amino-1,2,4-oxadiazoles by Mitsunobu−Beckmann rearrangement is reported.

In Chapter 8, the details of general mechanism of the reaction between nitrile *N*-oxides, isocyanide and a third component is treated.

In Chapter 10, the synthesis of aminocarbonyl *N*-acylhydrazones by a three-component reaction among isocyanides, hydrazonoyl chlorides, and carboxylic acids is discussed.

Chapter 11 shows the one-pot three-component synthesis of furo[2,3-*d*]pyridazin-4(5*H*)-ones, while in a Chapter 12 an efficient synthesis of 1-arylindazole-3-carboxamides followed by a chemoselective Buchwald–Hartwig intramolecular cyclization is presented.

Finally, in Chapter 13 all the multicomponent reactions discovered along with the molecular scaffolds obtained, are summarized.

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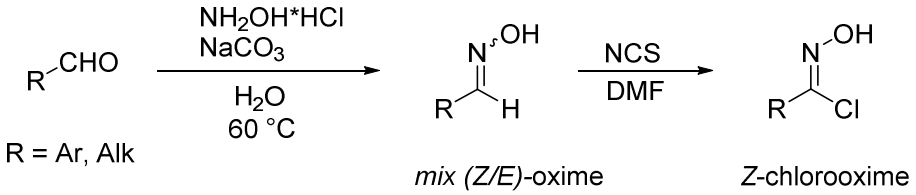
Chapter 3

Prologue (I): Nitrile *N*-oxides as electrophilic partners in IMCRs

3.1 Introduction

Z-chlorooximes (also known as *Z*-hydroximoyl chlorides) are organic compounds that contain the functional group RC(NOH)Cl with a double bond between the nitrogen and the carbon atom.

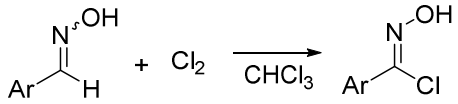
Usually, they can be easily prepared starting from an aldehyde and hydroxylamine hydrochloride, in presence of base, to give a *Z/E* mixture of aldoxime. The aldoximes then react with *N*-chlorosuccinimide in DMF at room temperature to produce *Z*-chlorooximes (Scheme 1).[1,2]



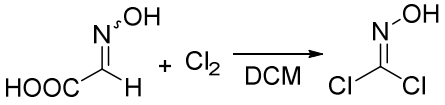
Scheme 1. Synthesis of *Z*-chlorooximes.

The method of chlorination using NCS in DMF is quite general and is applicable both on alkyl and aromatic aldoximes. The only disadvantage is in case of electron rich aromatic aldoximes. For example, when applied to 2-furancarbaldehyde oxime the chlorination of the ring cannot be suppressed.[3]

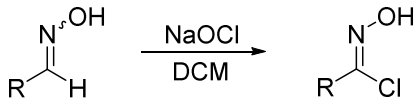
Other methods for the preparations of hydroximoyl chlorides, have been reported in literature and they are listed in Table 1.



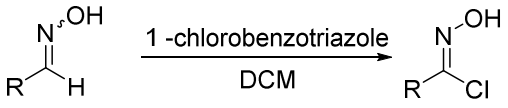
Chiang in 1971[4]



Chiarino *et al* in 1988[5]

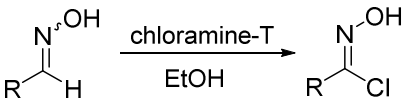


Lee in 1982[6]

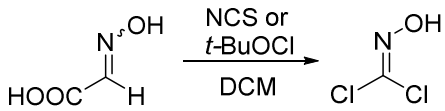


R = Aryl

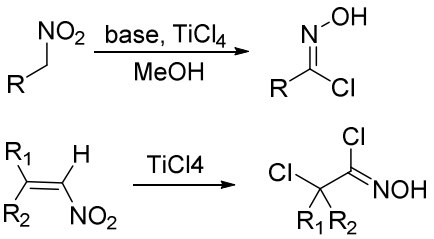
Kim *et al.* in 1990[7]



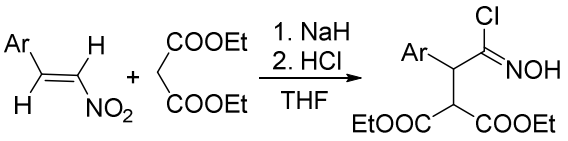
Hassner *et al.* in 1989[8]



Halling *et al* in 1991[9]



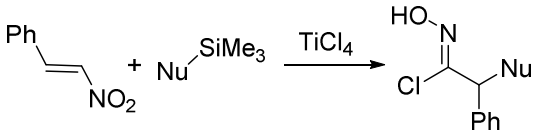
Kumara *et al.* in 1996[10,11]



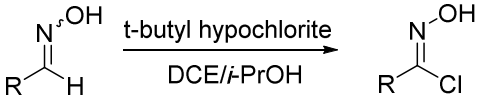
(Reported also the substitution of diethyl malonate by propargyl alcohol, ethanethiol, diethyl phosphite).

Kuo-His Kao *et al.* in 1998[12]

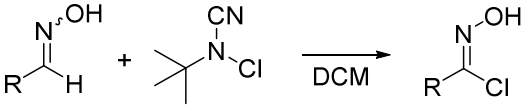
Kanemasa *et al.* in 2000[3]



Yan *et al.* in 2002[13]



Ye *et al.* in 2003[14]



Kumar *et al.* in 2006[15]

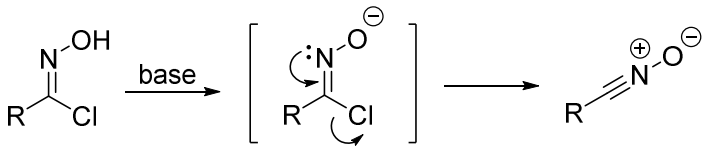
Table 1. Main methods for the synthesis of *Z*-chlorooximes.

Aromatic chlorooximes are sufficiently stable to be purified by column chromatography and they can be stored at 0 °C without decomposing. On the other hand, aliphatic chlorooximes are much more delicate, decomposing during isolation and purification procedures. For this reason it is better to use the crude reaction mixture after their preparation.

Independently from the stereochemistry of the starting oxime, chlorooximes are always obtained in the *Z* formand never as mixture of *Z* and *E* isomers.[16] Although the reason for the observed formation of *Z*-chlorooximes is not completely clear, it is possible to speculate that the formation of an intramolecular Cl···H hydrogen bond preferentially stabilizes this geometrical isomer over the opposite one.[17,18]

E-chlorooxime can only be formed by introduction of an acyl group to the Z form. This allows for the photoequilibration of isomers and subsequently removal of the acyl group.

Z-chlorooximes are able to generate the electrophilic species nitrile *N*-oxides under very mild reaction conditions of base-mediated dehydrochlorination (Scheme 2).[19]



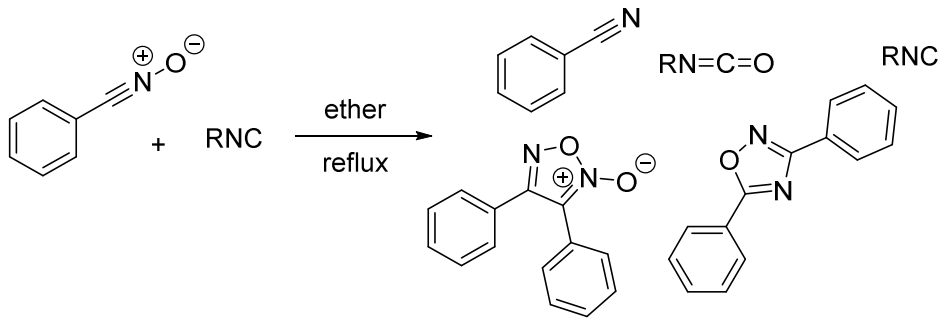
Scheme 2. Formation of nitrile *N*-oxides.

It is interesting to highlight that *E* isomers react 10^7 fold more slowly than the corresponding Z isomers, and this discrepancy can be rationalized by the fact that *Z*-chlorooximes have the lone pair of nitrogen atom antiperiplanar to the chlorine atom, facilitating its expulsion after deprotonation of the hydroxyl group.[18,20]

Before 2011 there were only three papers about the two-component reaction between nitrile *N*-oxides and isocyanides. The first one was reported in 1964 by

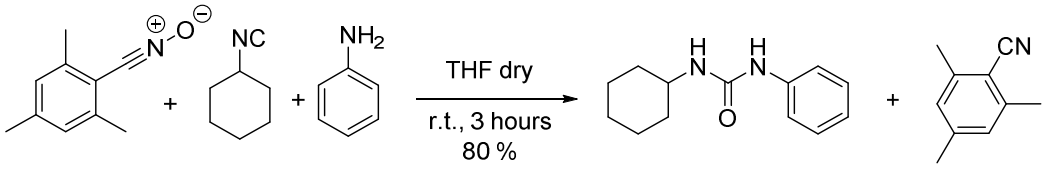
R. Olofson (Harvard University). Studying the decomposition of *N*-alkyl furazanium salts, he envisaged that nitrile *N*-oxides could react with isocyanides to give cyanides and isocyanides via oxygen transfer or 1,3-dipolar cycloaddition.[21]

The second paper was by Paola Vita Finzi (University of Pavia) and dated 1965.[22] She reported that isocyanides reacted with benzonitrile *N*-oxide in diethyl ether under refluxing conditions to form benzonitrile and isocyanates. However, the reaction did not appear to be clean and the authors recovered several byproducts: diphenylfuroxan, the product of benzonitrile oxide dimerization, 3,5-diphenyl-1,2,4-oxadiazole, formed by condensation of benzonitrile oxide with benzonitrile, and unreacted isocyanide (Scheme 3).



Scheme 3. The products in the reaction between nitrile *N*-oxides and isocyanides.

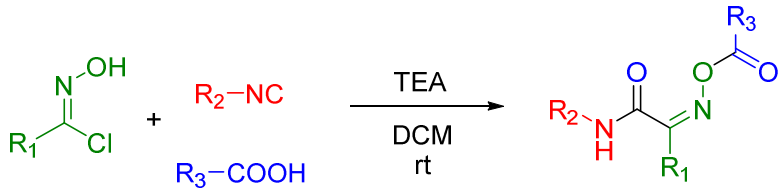
In 1980 a paper by Derek Barton and co-workers (Imperial College, London)[23] reconsidered this reaction with the aim to find a novel methodology to convert an isocyanide into an amine.They chose the sterically hindered and more stable 2,4,6-trimethylbenzonitrile *N*-oxide, in order to prevent self-dimerization to furoxans. When the reaction was attempted between 2,4,5-trimethybenzonitrile *N*-oxide, cyclohexyl isocyanide, and aniline, *N*-cyclohexyl-*N*′-phenylurea was obtained in 80% yield (Scheme 4).[18]



Scheme 4. One-pot synthesis of unsymmetrical urea.

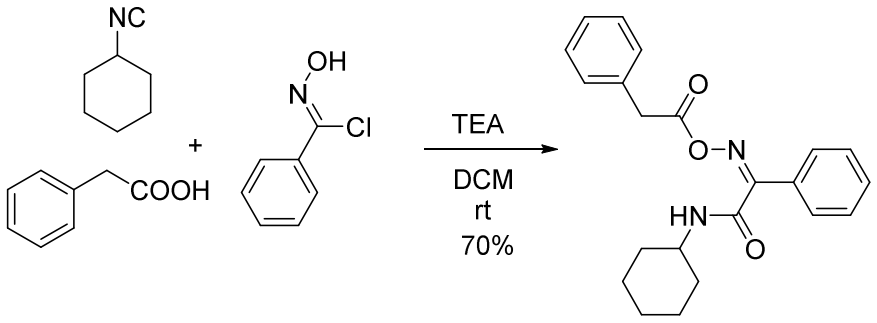
3.2 Reaction between *Z*-chlorooximes, isocyanides and carboxylic acids

In 2011 in the laboratory where I carried out my Ph.D., it was reported a novel multicomponent reaction among *Z*-chlorooximes, isocyanides, and carboxylic acids to afford *syn*-*α*-oximinoamides with a high level of stereospecificity (Scheme 5).[24]



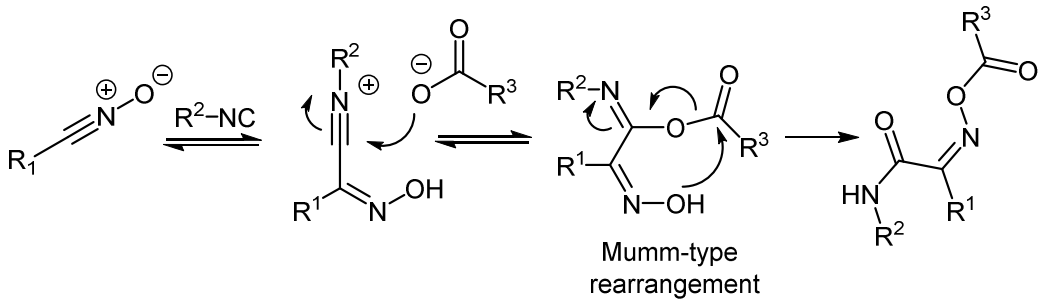
Scheme 5. General reaction with carboxylic acid.

In detail, the reaction between *Z*-phenylchlorooxime, cyclohexyl isocyanide and phenylacetic acid in dichloromethane, in the presence of 1 eq. of triethylamine, at room temperature allows to obtain the desired *syn*-oximinoamide in 70% yield (Scheme 6).



Scheme 6. Three-component reaction between cyclohexylisocyanide, phenylacetic acid and benzylchloroxime.

Mechanistically speaking, the nitrile *N*-oxide, generated from *Z*-chlorooximes, reacts with isocyanide to form the nitrilium intermediate that is then intercepted by the carboxylate ion. The intermediate so obtained undergoes an irreversible Mumm-type rearrangement mediated by the *syn*-oxime driving all the equilibria to the final *syn*-*α*-oximinoamide (Scheme 7).



Scheme 7. General mechanism between *Z*-chlorooximes, isocyanide and carboxylic acid.

The reaction was general in scope as a wide range of both chlorooximes (aliphatic, aromatic, heteroaromatic) and isocyanides (primary, secondary, tertiary isocyanide) proved to react smoothly in the aforementioned reaction conditions. Only aromatic isocyanides did not react. The reaction was tolerant to primary, secondary, and tertiary isocyanides but failed with aromatic isocyanides. Both aliphatic and aromatic carboxylic acids participated well in the reaction. The

presence of electron-withdrawing or electron-releasing groups on the benzoic acid did not affect the course of the reaction (Figure 1).

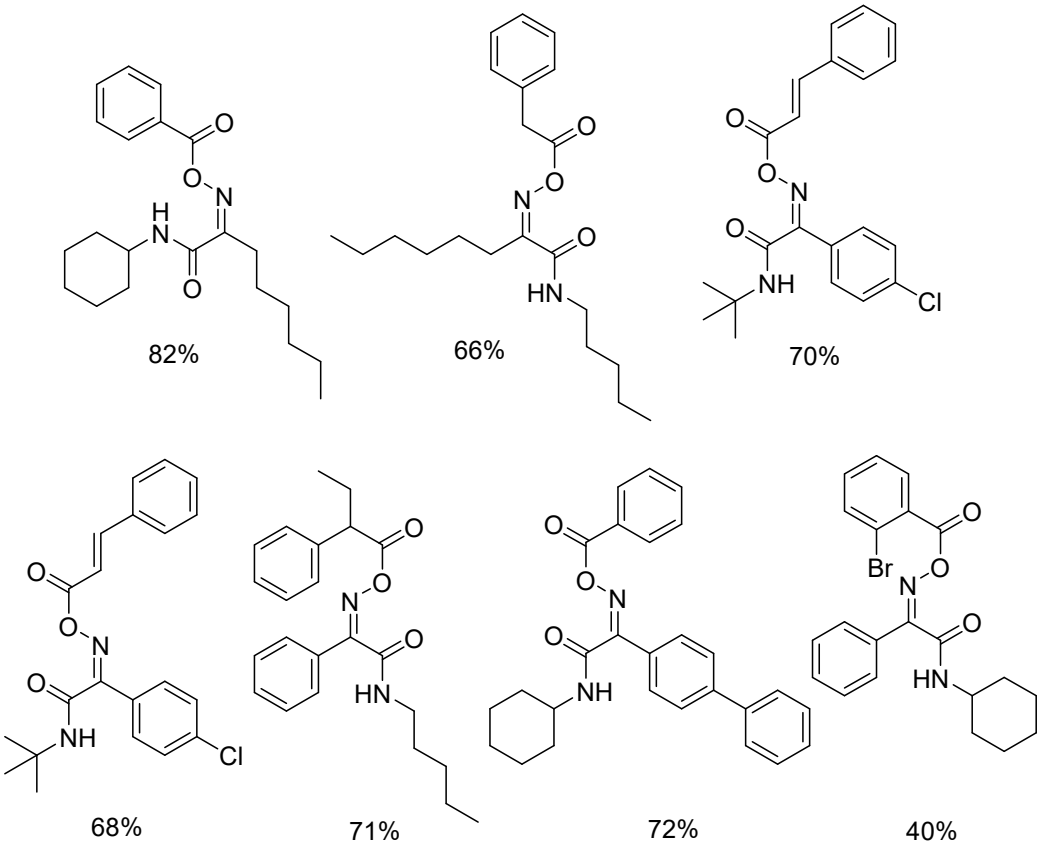


Figure 1. Selected examples of *syn*-oximinoamides synthesized.

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Chapter 4

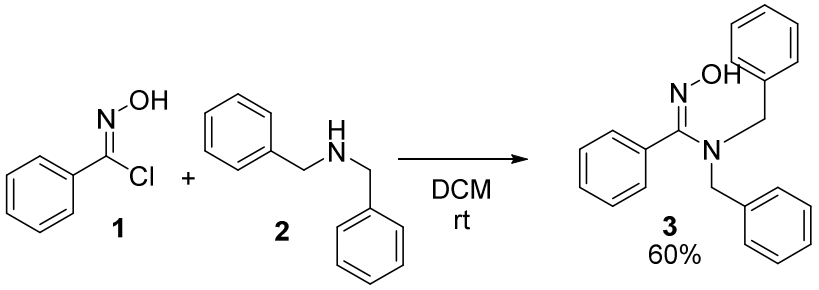
Isocyanide-mediated multicomponent synthesis of *C*-oximinoamidines

4.1 Results and discussion

Starting from the multicomponent reaction with *Z*-chlorooximes, isocyanides, and carboxylic acids discussed in Chapter 3,[1] we hypothesized we could introduce a novel level of complexity by using an amine as a third component.

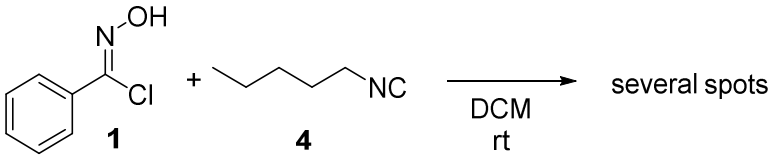
In principle, in this case several scenarios are possible as reactions between chlorooximes and amines, via nitrile *N*-oxide, are well known in literature for giving amidoximes.[2–5]

However, initial experiments, reveled to us that the reaction between one equivalent of *Z*-phenylchlorooxime **1** and two equivalents of *N*,*N*-dibenzylamine **2** was slugghish and not clean requiring at least 10 hours to go to completeness to give **3** in 60% yield (Scheme 1).



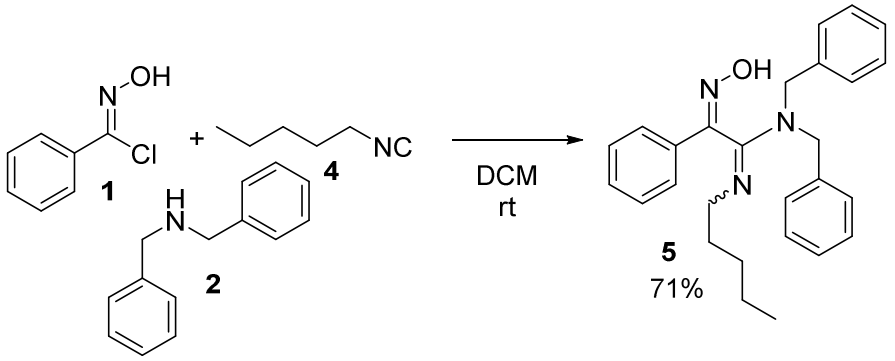
Scheme 1. Synthesis of amidoxime **3**.

On the other hand, when pentylisocyanide **4** was reacted with the *Z*-phenylchlorooxime **1** in dichloromethane at room temperature, after six hours, the TLC analysis revealed a complex mixture and it was not possible to isolate an established product (Scheme 2).



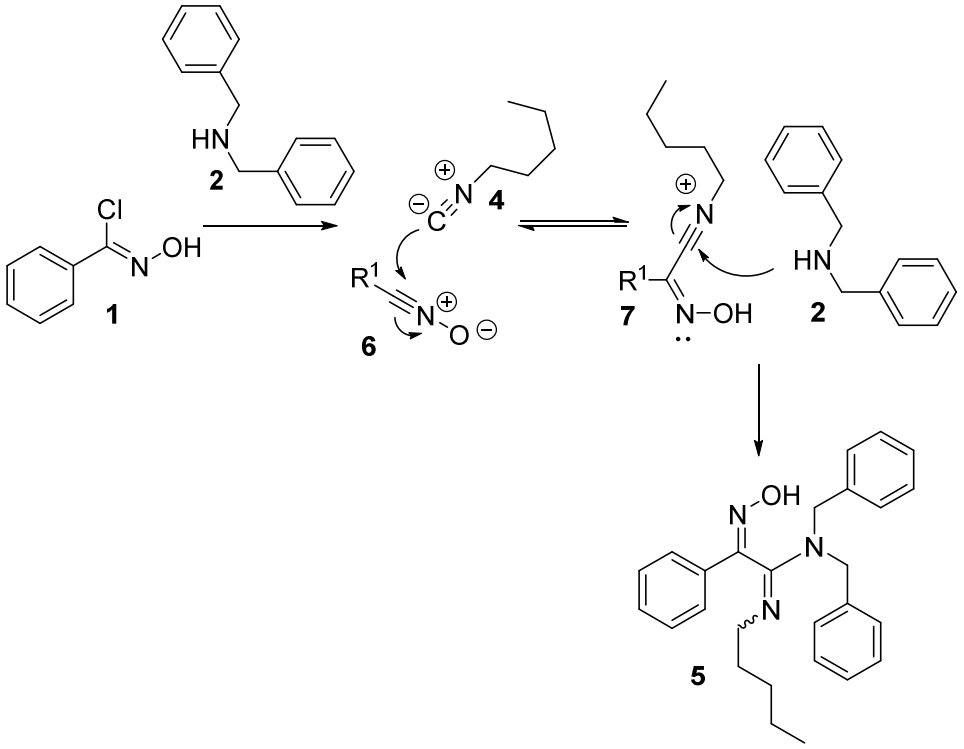
Scheme 2. Reaction between *Z*-phenylchlorooxime and isocyanide.

However, this disappointing scenario dramatically changed when in the third experiment an amine (2 equivalents) was present in the flask. Indeed, we could observe, after three hours, the neat formation of a novel product (**5**) which incorporated all the reactants. Spectroscopic analyses determined the formation of an *α*-oximinoamidine in 71% yield, a novel chemical moiety never reported before to the best of our knowledge (Scheme 3).



Scheme 3. Three component synthesis of *C*-oximinoamidines.

The proposed mechanism for this new multicomponent transformation is depicted in Scheme 4. The *Z*-phenylchlorooxime **1** reacts with a base **2**, forming the corresponding nitrile *N*-oxide **6**, rapidly intercepted by pentylisocyanide **4** to give a nitrilium ion intermediate **7**, eventually stereospecifically trapped by the amine, to afford the final product **5**. Indeed, it was well established by Professor Hegarty that nitriulium species react with nucleophiles is a stereospecific way with the entering nucleophile and the lone pair *trans* from each other.[6]



Scheme 4. Proposed mechanism.

Unlike those of most amidines,[7,8] the ^{1}H and ^{13}C spectra of the final adducts recorded at 80 °C reveal, in most cases, the lack of geometrical isomerism pointing to a fast equilibrium between the two geometrical isomers.

This novel multicomponent reaction was examined using different *Z*-chlorooximes (**1, 8-12**), isocyanides (**4, 13-16**), and amines (**2, 17-23**) (Figure 1). *Z*-Chlorooximes were readily prepared by reacting oximes with *N*-chlorosuccinimide in DMF.[9–13]

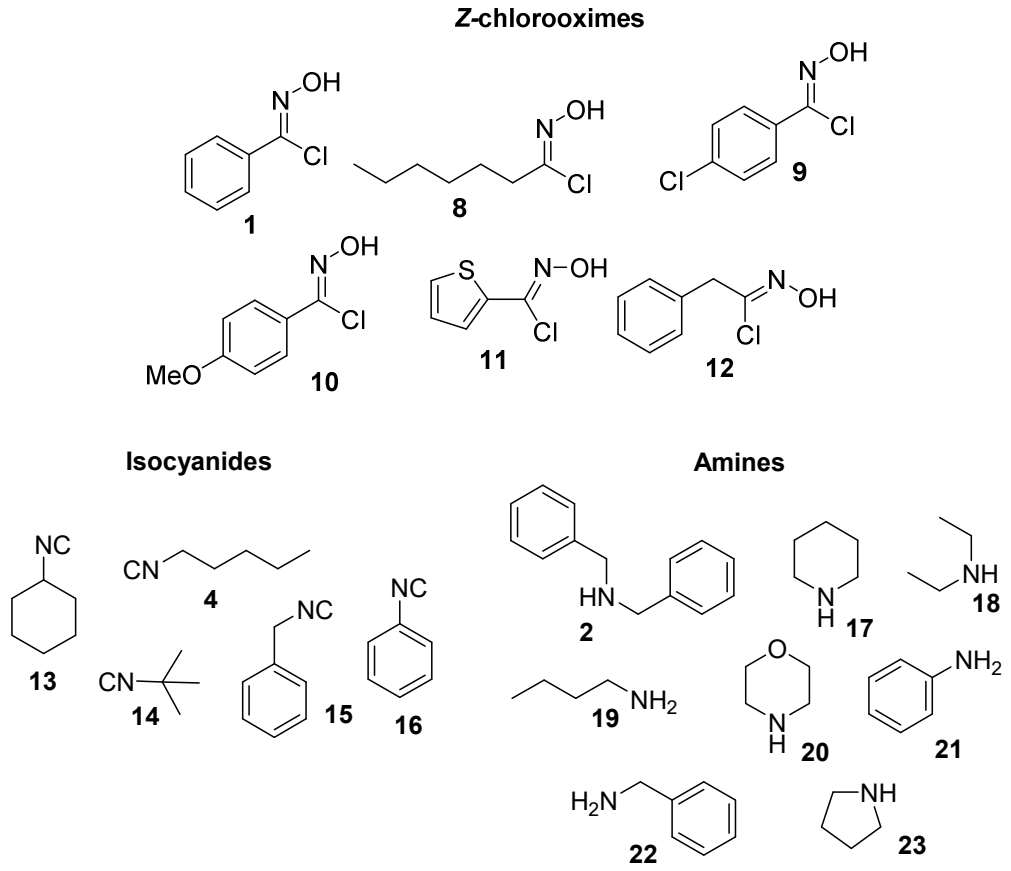


Figure 1. Building blocks.

As shown in Figure 2, the reaction was quite general. Yields varied from 80% to 26%; this result depends on the purification step, since these compounds are extremely polar. The reaction was tolerant to primary, secondary and tertiary isocyanides, but failed with aromatic isocyanides. Indeed, reaction of phenylchlorooxime **1** with phenylisocyanide **16** and morpholine **20** only gave the adduct between the chlorooxime and the morpholine in 61% yield. This result was not surprising in the light of the reduced nucleophilicity of aromatic isocyanides.[14] Both primary and secondary amines were good partners for the reaction, and even aniline reacted, although in low yield. The presence of electron-withdrawing or

electron-donating groups on the phenyl ring of arylchlorooximes does not seem to alter the course of the reaction.

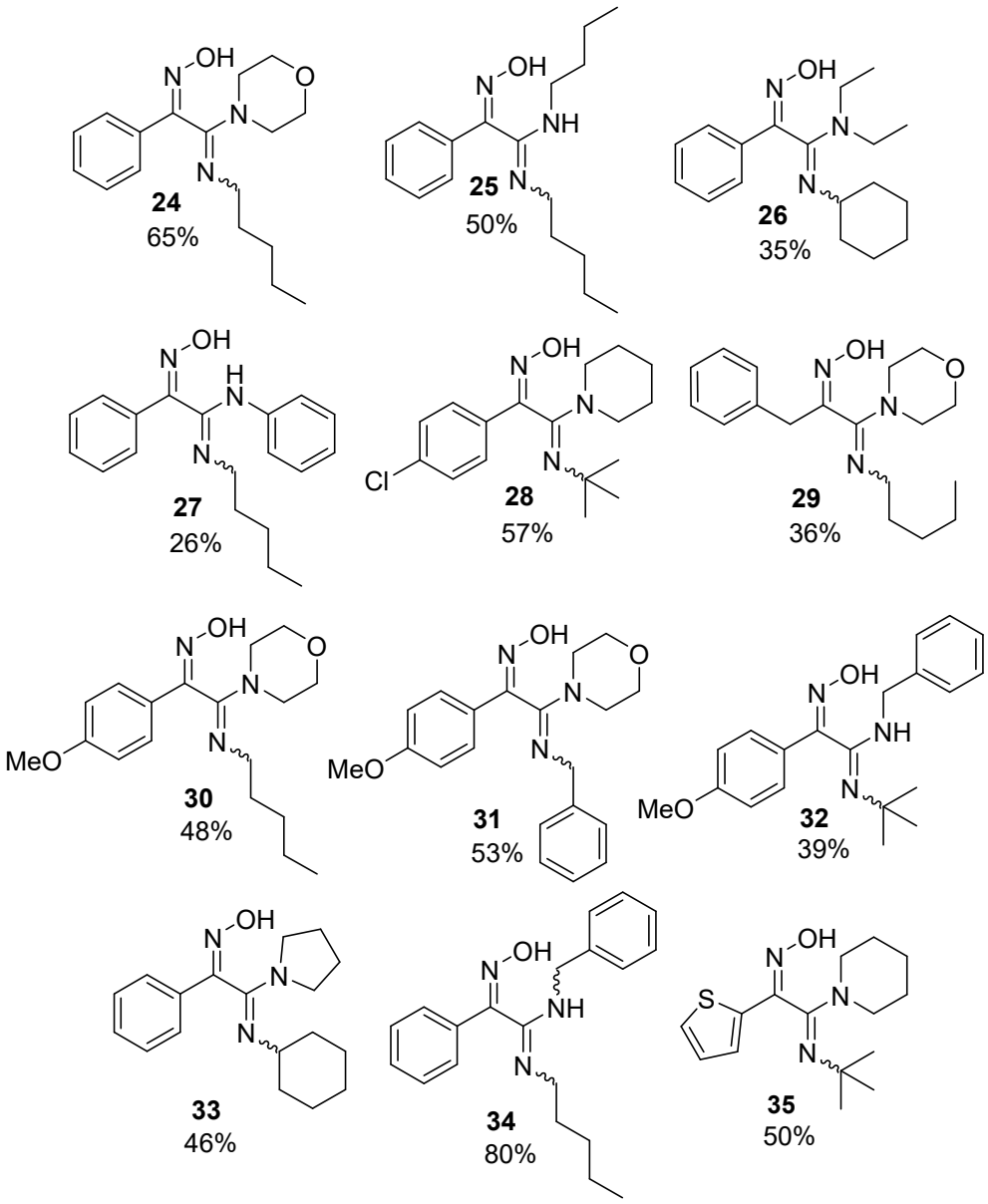


Figure 2. Synthesized *C*-oximinoamidines.

The structure and the stereochemistry of **24** was unambiguously established by a single crystal X-ray diffraction analysis.

Figure 3 shows the molecular structure of **24**, disordered at C14 and C16 of the morpholine moiety. The two alternate conformations of the ring show a site occupancy of 75% and 25% for the labeled atoms, respectively.

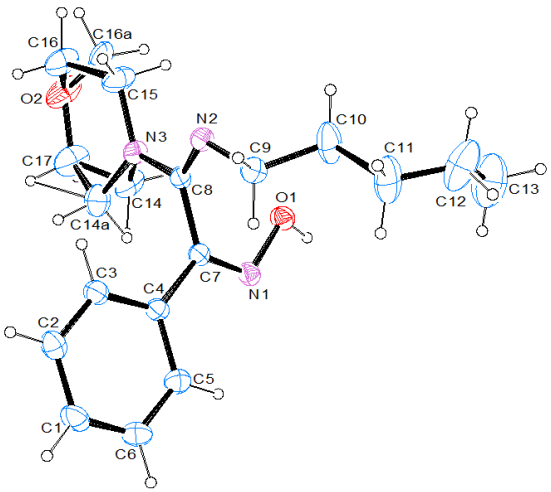


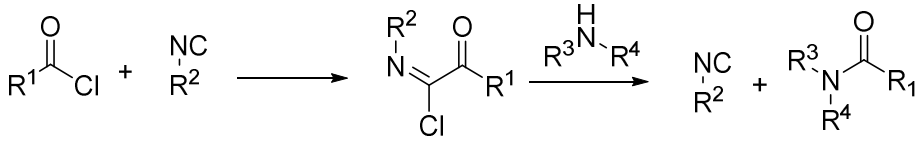
Figure 3: ORTEP[15] view of **24** and the relative arbitrary atom-numbering scheme (thermal ellipsoids at 40% probability).

Both imino groups show a *Z*-conformation in the solid state. The two rings are almost perpendicularly oriented, as shown by the N3-C8-C7-C4 are linked through strong hydrogen bond interactions between O1-H1a···N2, forming chains running in the *a* axis direction.

4.2 Conclusions

In conclusion, we developed a novel multicomponent reaction that generates to *C*-oximinoamidines, a class of previously unreported compounds which could be used as starting materials for further elaborations taking advantage of the presence of the oxime.[16–18]

Remarkably, the use of *Z*-chlorooximes makes it possible to overcome the lack of reactivity of the isocyanide-Nef adduct[19] with amines, owing to a higher reactivity of the carbonyl. Indeed, *C*-acylamidines have never been synthesized starting from *α*-keto imidoyl chlorides and amines.[20,21] The *Z*-chlorooximes can therefore be considered excellent surrogates for acyl chlorides in the reaction with isocyanides (Scheme 5).



Scheme 5. Isocyanide Nef reaction and reaction between imidoyl chlorides and amines.

4.3 Experimental section

Solvents and Reagents. Commercially available solvents and reagents were used without further purification. Dichloromethane was dried by distillation over P_2O_5 and stored over activated molecular sieves (4 Å). When needed, the reactions were performed in ovendried glassware under a positive pressure of dry nitrogen.

Chromatography. Column chromatography was performed on silica gel 60 (Merck Kieselgel 230-400 mesh ASTM) using the indicated eluents. Thin layer chromatography (TLC) was carried out on 5 x 20 cm plates with a layer thickness of 0.25 mm (Merck Silica gel 60 F_{254}). When necessary they were visualized using Dragendorff's reagent.

Spectra. Infrared spectra were recorded on a FT-IR Thermo-Nicolet Avatar spectrometer with absorption maxima (νmax) recorded in wavenumbers (cm^{-1}). NMR spectra were recorded using a JEOL ECP 300 MHz spectrometer. Chemical shifts (δ) are quoted in parts per million referenced to the residual solvent peak. The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; hept, heptet; m, multiplet; br, broad singlet. Coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were recorded on a Thermo Finningan LCQ-deca XP-*plus* mass spectrometer equipped with an ESI source and an ion trap detector. Melting points were determined using a Stuart Scientific SMP3 apparatus and remain uncorrected.

General preparation of chlorooximes (1, 8-12)

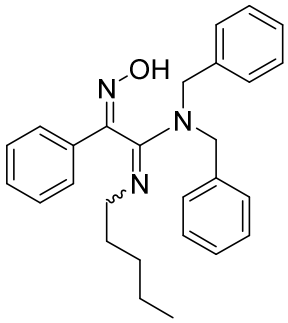
The oxime (1 eq.) was dissolved in DMF and *N*-chlorosuccinimide (1 eq.) was added portionwise. The reaction was stirred at room temperature until all the oxime was consumed as judged by TLC (typically 2 hours). The reaction was poured in water, diethyl ether was added, and the two layers were separated. The ethereal phase was washed with water (x3) and brine (x1), dried over sodium sulfate and concentrated under reduced pressure. The aromatic chlorooximes were purified by column chromatography (PE/EtOAc 9:1) and stored at 4 °C; aliphatic chlorooximes were unstable and they were immediately used in the next step without further purification.

All the chlorooximes used are known compounds and their nature was confirmed by comparision of their melting points or ^{1}H and ^{13}C-NMR spectra.

General preparation of *C*-oximinoamidines (5, 24-35)

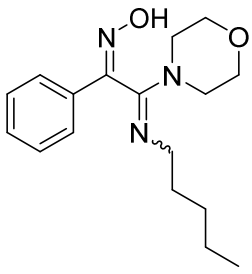
The chlorooxime (1 eq.) was dissolved in dry dichloromethane. Isocyanide (1 eq.), and amine (2 eq.) were added and the reaction was stirred at room temperature under a nitrogen atmosphere until all the chlorooxime was consumed (typically 3 hours as judged by TLC). The reaction mixture was concentrated under reduced pressure and the crude material was purified by column chromatography.

(2*Z*)-*N*,*N*-dibenzyl-2-(hydroxyimino)-*N'*-pentyl-2-phenylacetimidamide (5).



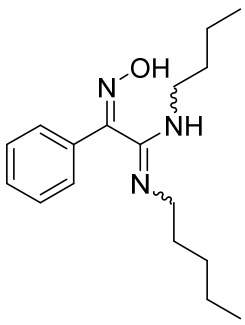
Oxime 400 mg (2.57 mmol), isocyanide 249 mg (2.57 mmol), amine 1.014 g (5.14 mmol), DCM dry 4 mL, reaction time 3 hours. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 5:5, EtOAc, EtOAc/MeOH 9:1) and crystallized in methanol to give the product as white solid (755 mg, yield 71%). ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 11.65 (s, 1H), 7.56 (br s, 2H), 7.38 (br s, 3H), 7.21 (br s, 10H), 4.36 (br s, 4H), 3.04 (m; 2H), 1.45 (br s, 2H), 1.20 (br s, 4H), 0.79 (br t; 3H); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 153.2, 149.9, 137.7, 132.3, 129.2, 128.4, 127.7, 127.6, 126.4, 125.3, 49.5, 48.5, 30.8, 28.8, 21.5, 13.4; IR (KBr) 2923, 2851, 2632, 1593, 1451, 953 ν_{max}/cm^{-1}; M.P. 170-171 °C; Found: C, 78.35; H, 7.40; N, 10.34; $C_{27}H_{31}N_3O$ requires C, 78.42; H, 7.56; N 10.16 %; MS (ESI) m/z 414 $(M+H)^+$.

(1*Z*)-2-morpholino-2-(pentylimino)-1-phenylethanone oxime (24).



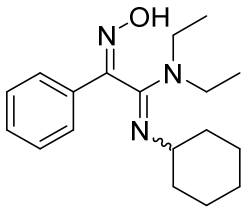
Oxime 400 mg (2.57 mmol), isocyanide 249 mg (2.57 mmol), amine 447 mg (5.14 mmol), DCM dry 4 mL, reaction time 2 hours. The crude material was purified by column chromatography (eluents: PE/EtOAc 8:2, 5:5, EtOAc, EtOAc/MeOH 9:1) and crystallized in methanol to give the product as white solid (503 mg, yield 65%). ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 11.45 (br s, 1H), 7.61 (br s, 2H); 7.42 (br s, 3H), 3.54 (m, 4H), 3.29 (m, 2H), 3.16 (m, 2H), 3.0-2.80 (m, 2H), 1.38 (m, 2H), 1.19 (br s, 1.18), 0.79 (t, J = 7.0 Hz); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 154.8, 150.7, 133.3, 130.5, 129.8, 126.3, 66.9, 50.5, 45.6, 32.0. 30.0, 22.8, 14.8; IR (KBr) 2929, 2647, 1624, 1444, 1263, 1118 ν_{max}/cm^{-1}; M.P. 156-157 °C; Found: C, 67.42; H, 8.35; N, 13.82; $C_{17}H_{25}N_3O_2$ requires C, 67.30; H, 8.31; N 13.85 %; MS (ESI) m/z 304 $(M+H)^+$.

(2*Z*)-*N*-butyl-2-(hydroxyimino)-*N′*-pentyl-2-phenylacetimidamide (25).



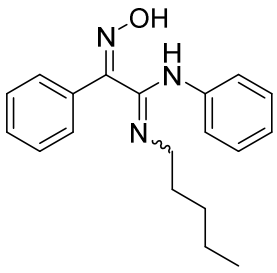
Oxime 200 mg (1.29 mmol), isocyanide 125 mg (1.29 mmol), amine 188 mg (2.58 mmol), DCM dry 2 mL, reaction time 4 hours. The crude material was purified by column chromatography (eluents: PE/EtOAc 8:2, 5:5, EtOAc, EtOAc/MeOH 9:1) to give the product as yellowish oil (186 mg, yield 50%).
^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 8.30 (s, 1H), 7.63 (m, 2H), 7.48 (n, 3H), 3.22 (br s, 4H overlapped with water), 1.52 (br s, 4H), 1.25 (br s, 6H), 0.82 (br t, 6H); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 156.9, 147.4, 131.8, 130.8, 129.6, 126.0, 40.4 (2C, overlapped with DMSO), 31.2, 28.8, 28.7, 22.1, 19.8, 14.1, 13.9; IR (KBr) 2959, 1652, 1557, 1456 ν_{max}/cm^{-1}; Found: C, 70.35; H, 9.24; N, 14.30; $C_{17}H_{27}N_3O$ requires C, 70.55; H, 9.40; N 14.52 %; MS (ESI) m/z 290 $(M+H)^+$.

(2*Z*)-*N′*-cyclohexyl-*N*,*N*-diethyl-2-(hydroxyimino)-2-phenylacetimidamide (26).



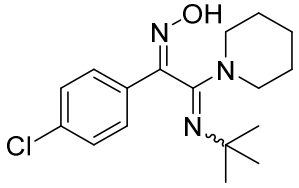
Oxime 200 mg (1.29 mmol), isocyanide 141 mg (1.29 mmol), amine 189 mg (2.58 mmol), DCM dry 2 mL, reaction time 12 hours. The crude material was purified by column chromatography (eluents: PE/EtOAc 8:2, 7:3, 5:5, EtOAc, EtOAc/MeOH 9:1) and crystallized in methanol to give the product as yellowish solid (135 mg, yield 35%).
^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 7.56 (m, 2H), 7.40 (m, 3H), 3.4-3.0 (br s, 4H), 2.78 (m, 1H), 1.8-1.0 (m, 10H), 0.98 (br t, 6H); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 151.1, 150.8, 133.8, 130.0, 120.2, 126.0, 58.6, 35.6, 35.4, 26.1, 24.7, 13.7; IR (KBr) 2930, 2852, 1582, 1436, 1257 ν_{max}/cm^{-1}; M.P. 157-157.5 °C; Found: C, 71.70; H, 9.23; N, 14.05; $C_{18}H_{27}N_3O$ requires C, 71.72; H, 9.03; N 13.94 %; MS (ESI) m/z 302 $(M+H)^+$.

(2*Z*)-2-(hydroxyimino)-*N′*-pentyl-*N*,2-diphenylacetimidamide (27).



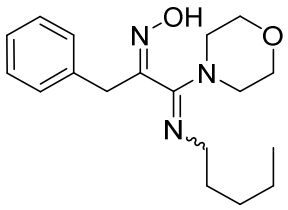
Oxime 200 mg (1.29 mmol), isocyanide 125 mg (1.29 mmol), amine 240 mg (2.58 mmol), DCM dry 2 mL, reaction time 2 hours. The crude material was purified by column chromatography (eluents: PE/EtOAc 7:3) to give the product as yellowish solid (102 mg, yield 26%).
^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 7.46 (br s, 2H), 7.28 (br s, 3H), 6.98 (br t, 2H), 6.76 (br s, 3H), 3.34 (br s, 2H), 1.64 (br s, 2H), 1.30 (br s, 4H), 0,91 (br s, 3H); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 151.8, 151.6, 133.3, 129.5, 129.4, 128.9, 126.2, 121.8 (2C), 120.4; 40.2 (overlapped with DMSO), 29.3, 28.7, 22.3, 14.4; IR (KBr) 3309, 2931, 2664, 1589, 1688, 1406, 1209 ν_{max}/cm^{-1}; M.P. 150-151 °C; Found: C, 73.97; H, 7.56; N, 13.32; $C_{19}H_{23}N_3O$ requires C, 73.76; H, 7.49; N 13.58 %; MS (ESI) m/z 310 $(M+H)^+$.

(1*Z*)-2-(tert-butylimino)-1-(4-chlorophenyl)-2-(piperidin-1-yl)ethanone oxime (28).



Oxime 300 mg (1.57 mmol), isocyanide 131 mg (1.57 mmol), amine 267 mg (3.14 mmol), DCM dry 3 mL, reaction time 2 hours. The crude material was purified by column chromatography (eluents: PE/EtOAc 5:5, EtOAc, EtOAc/MeOH 9:1) and crystallized in methanol to give the product as white solid (286 mg, yield 57%).
^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 11.45 (br s, 1H), 7.54 (d, J = 8.8 Hz, 2 H, AA′XX′), 7.41 (d, J = 8.8 Hz, 2 H, AA′XX′), 3.24 (br s, 2H), 3.10 (br s, 2H), 1.47-1.30 (m. 6H), 0.98 (s, 9H); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 153.2, 147.8, 134.4, 133.9, 129.2, 128.0, 53.1, 45.1, 31.9, 26.1, 25.1; IR (KBr) 2856, 2582, 1568, 1488, 1198, 932 ν_{max}/cm^{-1}; M.P. 216-216.5 °C; Found: C, 63.80; H, 7.68; N, 13.24; $C_{17}H_{24}ClN_3O$ requires C, 63.44; H, 7.52; N 13.06 %; MS (ESI) m/z 322 $(M+H)^+$.

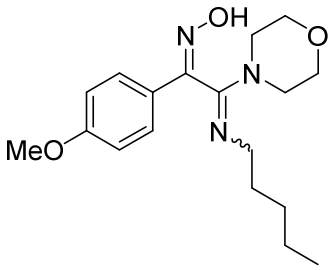
(2*Z*)-1-morpholino-1-(pentylimino)-3-phenylpropan-2-one oxime (29).



Oxime 400 mg (2.36 mmol), isocyanide 230 mg (2.36 mmol), amine 411 mg (4.72 mmol), DCM dry 4 mL, reaction time 2 hours. The crude material was purified by column chromatography (eluents: PE/EtOAc 8:2, 7:3, 5:5, EtOAc) to give the product as amorphous yellowish solid (269 mg, yield 36%).
^{1}H-NMR (300 MHz, DMSO-*d*$_6$) mixture of geometrical isomers, the signals are referred to the main isomer) δ 7.24 (br s, 5H), 3.56 (m,

4H), 3.38 (m, 2H), 3,27 (m, 2H), 3.08 (m, 4H, overlapped with DMSO), 1.42 (m, 2H), 1.25 (m, 4H), 0.87 (m, 3H) ; ^{13}C-NMR (75 MHz, DMSO-*d*$_6$ mixture of geometrical isomers, the signals are referred to the main isomer) δ 161.1, 154.7, 150.0, 127.5, 125.5, 115.0, 66.6, 55.8, 50.1, 45.4, 31.5, 29.6, 22.4, 14.2 ; IR (KBr) 2931, 2858, 1636, 1455, 1113, 700 ν_{max}/cm^{-1}; Found: C, 64.95; H, 8.36; N, 12.34; $C_{18}H_{27}N_3O_3$ requires C, 64.84; H, 8.16; N 12.60 %; MS (ESI) m/z 318 $(M+H)^+$.

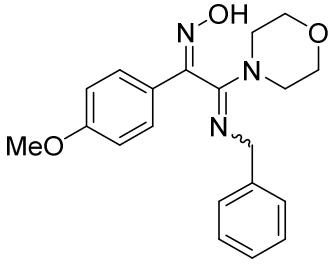
(1*Z*)-1-(4-methoxyphenyl)-2-morpholino-2-(pentylimino)ethanone oxime (30).



Oxime 250 mg (1.35 mmol), isocyanide 131 mg (1.35 mmol), amine 235 mg (2.70 mmol), DCM dry 3 mL, reaction time 12 hours. The crude material was purified by column chromatography (eluents: PE/EtOAc 8:2, 5:5, EtOAc, EtOAc/MeOH 9:1) to give the product as amorphous yellowish solid (216 mg, yield 48%).

^{1}H-NMR (300 MHz, DMSO-*d*$_6$, mixture of geometrical isomers, the signals are referred to the main isomer) δ 7.49 (m, 2H, AA′XX′), 6.98 (m, 2H, AA′XX′), 3.80 (s, 3H), 3,53 (br s, 4H), 3,31 (m, 2H), 3.23-2.90 (m, 4H, overlapped with DMSO), 1.42 (m, 2H), 1.22 (m, 4H), 0.80 (br t, 3H); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$ mixture of geometrical isomers, the signals are referred to the main isomer) δ 161.1, 154.7, 150.0, 127.5, 125.5, 115.0, 66.6, 55.8, 50.1, 45.4, 31.5, 29.6, 22.4, 14.2 ; IR (KBr) 2930, 2855, 2681, 1608, 1511, 1252, 1115, 838 ν_{max}/cm^{-1}; Found: C, 64.95; H, 8.36; N, 12.34; $C_{18}H_{27}N_3O_3$ requires C, 64.84; H, 8.16; N 12.60 %; MS (ESI) m/z 334 $(M+H)^+$.

(1*Z*)-2-(benzylimino)-1-(4-methoxyphenyl)-2-morpholinoethanone oxime (31).

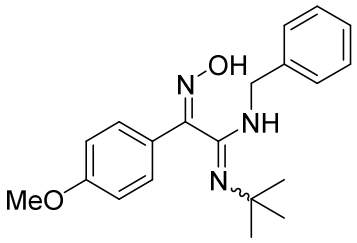


Oxime 250 mg (1.35 mmol), isocyanide 158 mg (1.35 mmol), amine 235 mg (2.70 mmol), DCM dry 3 mL, reaction time 12 hours. The crude material was purified by column chromatography (eluents: PE/EtOAc 8:2, 5:5, EtOAc, EtOAc/MeOH 9:1) and crystallized in methanol to give the product as white solid (250 mg, yield 53%).

^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 11.3 (br s, 1H), 7.53 (d, 2H, J = 8.6 Hz, AA′XX′), 7. 23 (d + m, 5H), 6.99 (d, 2H, J = 8.6 Hz, AA′XX′), 4.16 (d, 1H, J = 15.6 Hz, AB), 4.11 (d, 1H, J = 15.6 Hz, AB), 3.79 (s, 3H), 3.56 (m, 4H), 3.38 (m,

2H), 3.30 (m. 2H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 161.2, 155.4, 150.0, 142.6, 128.3, 127.9, 127.6, 126.4, 125.3, 115,1, 66.8, 55.9, 53.9, 45.4; IR (KBr) 2970, 2847, 2554, 1591, 1511, 1240, 831 ν_{max}/cm^{-1}; M.P. 199-199.5 °C; Found: C, 68.15; H, 6.83; N, 11.74; $C_{20}H_{23}N_3O_3$ requires C, 67.97; H, 6.56; N 11.89 %; MS (ESI) m/z 354 $(M+H)^+$.

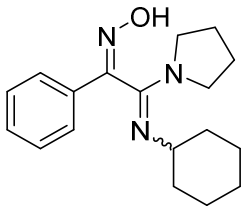
(2*Z*)-*N*-benzyl-*N′*-(tert-butyl)-2-(hydroxyimino)-2-(4-methoxyphenyl) acetimidamide (32).



Oxime 250 mg (1.35 mmol), isocyanide 112 mg (1.35 mmol), amine 289 mg (2.70 mmol), DCM dry 3 mL, reaction time 12 hours. The crude material was purified by column chromatography (eluents: PE/EtOAc 8:2, 5:5, EtOAc, EtOAc/MeOH 9:1) to give the product as yellowish solid (177 mg, yield 39%).

^{1}H-NMR (300 MHz, DMSO-d_6, mixture of geometrical isomers, the signals are referred to the main isomer) δ 7.40 (m, 2H, AA′XX′), 7.2-6.9 (m, 5 H), 6.80 (m, 2H, AA′XX′), 3.9 (br s, 2H), 3.6 (s, 3H), 1.28 (s, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6 mixture of geometrical isomers, the signals are referred to the main isomer) δ 160.7, 152.3, 150.1, 143.2, 128.1, 127.6 (2C), 126.5, 126.0, 114.6, 55.7, 54.0, 51.5, 29.8; IR (KBr) 2971, 2633, 1629, 1518, 1252 ν_{max}/cm^{-1}; M.P. 112-113 °C; Found: C, 70.02; H, 7.65; N, 12.34; $C_{20}H_{25}N_3O_2$ requires C, 70.77; H, 7.42; N 12.38 %; MS (ESI) m/z 340 $(M+H)^+$.

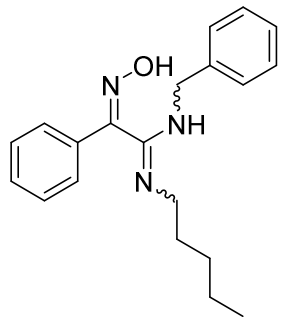
(1*Z*)-2-(cyclohexylimino)-1-phenyl-2-(pyrrolidin-1-yl)ethanone oxime (33).



Oxime 250 mg (1.61 mmol), isocyanide 176 mg (1.61 mmol), amine 229 mg (3.22 mmol), DCM dry 3 mL, reaction time 3 hours. The crude material was purified by column chromatography (eluents: PE/EtOAc, 5:5, EtOAc, EtOAc/MeOH 9:1) and crystallized in methanol to give the product as off-white solid (220 mg, yield 46%).

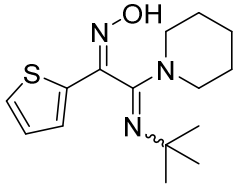
^{1}H-NMR (300 MHz, DMSO-d_6) δ 9.97 (s, 1H), 7.62 (br s, 2H), 7.52 (br s, 3H), 4.0-3.8 (m, 2H), 3.4-3.2 (m, 2H), 3.0 (overlapped to water, 1H), 2.1-0.8 (m, 10 H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 155.4, 146.2, 131.6, 130.1, 129.9, 125.7, 57.4, 50.8, 50.0, 33.2, 32.5, 25.2, 24.9, 24.3; IR (KBr) 3414, 3054, 1652, 1446, 1410, 1053 ν_{max}/cm^{-1}; M.P. 302-304 °C (dec.); Found: C, 72.45; H, 8.64; N, 13.82; $C_{18}H_{25}N_3O$ requires C, 72,21; H, 8.42; N 14.03 %; MS (ESI) m/z 300 $(M+H)^+$.

(2*Z*)-*N*-benzyl-2-(hydroxyimino)-*N'*-pentyl-2-phenylacetimidamide (34).



Oxime 250 mg (1.61 mmol), isocyanide 156 mg (1.61 mmol), amine 345 mg (3.22 mmol), DCM dry 3 mL, reaction time 12 hours. The crude material was purified by column chromatography (eluents: PE/EtOAc 5:5, EtOAc, EtOAc/MeOH 9:1) to give the product as amorphous yellowish solid (418 mg, yield 80%).
^{1}H-NMR (300 MHz, DMSO-*d*$_6$, mixture of geometrical isomers and tautomeric forms, the signals are referred to the main isomer) δ 7.80-7.23 (m, 10 H), 6.59 (br s, NH), 4.03 (br s, 2H), 3.27 (br s, 2H), 1.56 (br s, 2H), 1.24 (br s, 4H), 0.83 (br s, 3H); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$ mixture of geometrical isomers and tautomeric forms, the signals are referred to the main isomer) δ 156.8, 147.8, 135,7, 132.0, 130.5, 129.4, 128.9, 128.6, 128.0, 127.8, 49.1, 43.3, 28.9, 28.8, 22.2, 14.2; IR (KBr) 3010, 2573, 1652, 1455, 1382, 694 ν_{max}/cm^{-1}; Found: C, 74.56; H, 8.13; N, 12.65; $C_{20}H_{25}N_3O$ requires C, 74.27; H, 7.79; N 12.99 %; MS (ESI) m/z 324 $(M+H)^+$.

(1*E*)-2-(tert-butylimino)-2-(piperidin-1-yl)-1-(thiophen-2-yl)ethanone oxime (35).



Oxime 250 mg (1.55 mmol), isocyanide 129 mg (1.55 mmol), amine 264 mg (3.10 mmol), DCM dry 3 mL, reaction time 12 hours. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 5:5, EtOAc, EtOAc/MeOH 9:1) and crystallized in methanol to give the product as white solid (224 mg, yield 50%).
^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 7.48 (dd, J = 4.9/1.2 Hz, 1H), 7.04 (m, 2H), 3.3 (m, 2H), 3.1 (m overlapped with water, 2H), 1.6-1.4 (m, 6H), 1.06 (s, 9H); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 150.3, 147.0, 139.1, 128.4, 127.8 (2C), 53.0, 45.3, 31.8, 26.1, 25.2; IR (KBr) 2932, 2861, 2662, 1563, 1427, 1197 ν_{max}/cm^{-1}; M.P. 196-196.5 °C; Found: C, 61.42; H, 7.90; N, 14.46; $C_{15}H_{23}N_3OS$ requires C, 61.40; H, 7.90; N 14.32 %; MS (ESI) m/z 294 $(M+H)^+$.

Single crystal X-ray diffraction

Prismatic crystals of **24**, obtained from methanol, were used for data collection on an Enraf Nonius CAD-4 diffractometer with graphite monochromated Mo-Kα radiation. The lattice parameters were determined and refined by least squares fit of 25 high angle reflections. The structure was solved by direct methods[22] and refined by full matrix least-squares on F^2.[23] All the non-hydrogen atoms were refined anisotropically. The H-atoms positions, were introduced in calculated positions in their described geometries and allowed to ride on the attached carbon atom with fixed isotropic thermal parameters (1.2 Ueq or 1.5 Ueq of the parent carbon atom). All non-H-atoms were refined anisotropically. For the morpholine ring, two set of positions were defined for C14 and C16 atoms, and their site-occupation factors were refined as 0.75(1) for major orientation.

A summary of the crystal data and structure refinement is presented in Table 1.

CCDC number 963850 for **24** (excluding structure factors) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

formula	$C_{17}H_{25}N_3O_2$
FW (g mol^{-1})	303.4
T (K)	293(2)
λ (Å)	0.71073
Crystal system	monoclinic
Space group	P 2_1/a
a (Å)	11.620(8)
b (Å)	8.989(8)
c (Å)	15.810(8)
β (°)	93.74(1)
V(Å^3)	1640(2)
Z	4
ρ(calc) (Mg m^{-3})	1.229
F(000)	656
Sample Size (mm^3)	0.6×0.13×0.08
θ range (°)	2.59 – 25.04
Limiting indices	-13≤ *h*≤ 13, -1≤ *k* ≤10, -1≤ *l* ≤18
Reflections collected / unique	3670 / 2893
Completeness to θ	99.6%
Data, restrains, parameters	2893, 0, 230
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	0.988
R(*F*), *wR*(F^2) for $I > 2\sigma(I)$ *R*(*F*)	0.078, 0.1916
Largest diff. peak and hole (e Å^{-3})	0.311, -0.326

Table 1. Summary of crystal data and structure refinement for **24**

4.4 References

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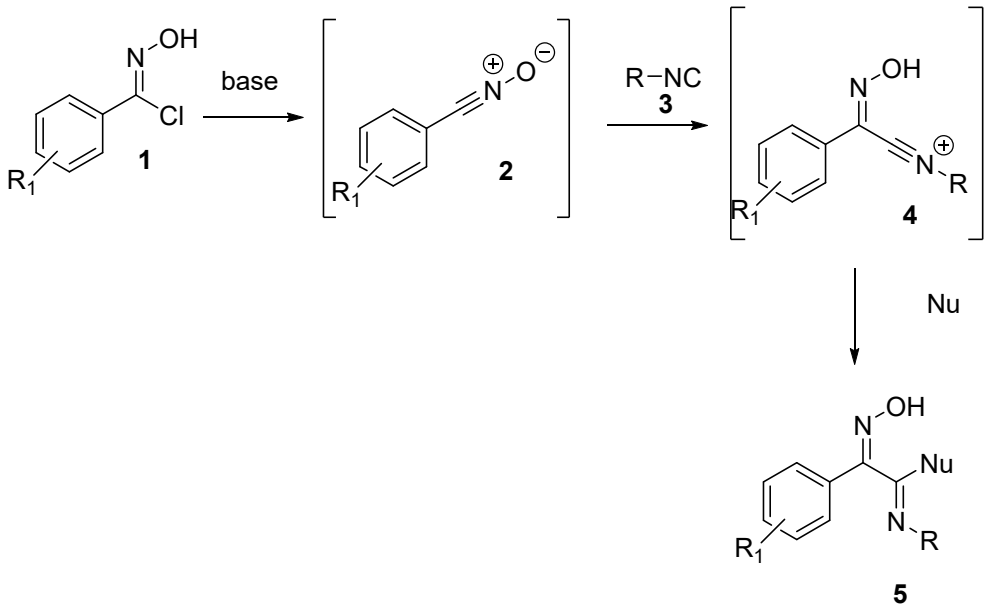
Chapter 5

Reaction between *Z*-arylchlorooximes and *α*-isocyanoacetamides: a procedure for the synthesis of aryl-*α*-ketoamide amides

5.1 Results and discussion

As demonstrated in Chapter 3 and 4, nitrile *N*-oxide species (generated via base dehydrochlorination of *Z*-chlorooximes **1** – Huisgen's *in situ* method)[1] are able to react in a stereospecific way with isocyanides **3** under mild reaction conditions (TEA, room temperature, dichloromethane) to give a nitrilium ion **4**, which can be further intercepted by a third nucleophiles (Scheme 1).[2,3]



Scheme 1. Proposed scheme for the formation of novel MCRs via nitrile-*N*-oxide species.

It was therefore reasonable to think that an isocyanide containing an internal nucleophile could intramolecularly intercept the nitrilium ion species generating a novel molecular framework (Figure 1).

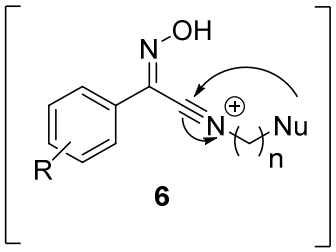
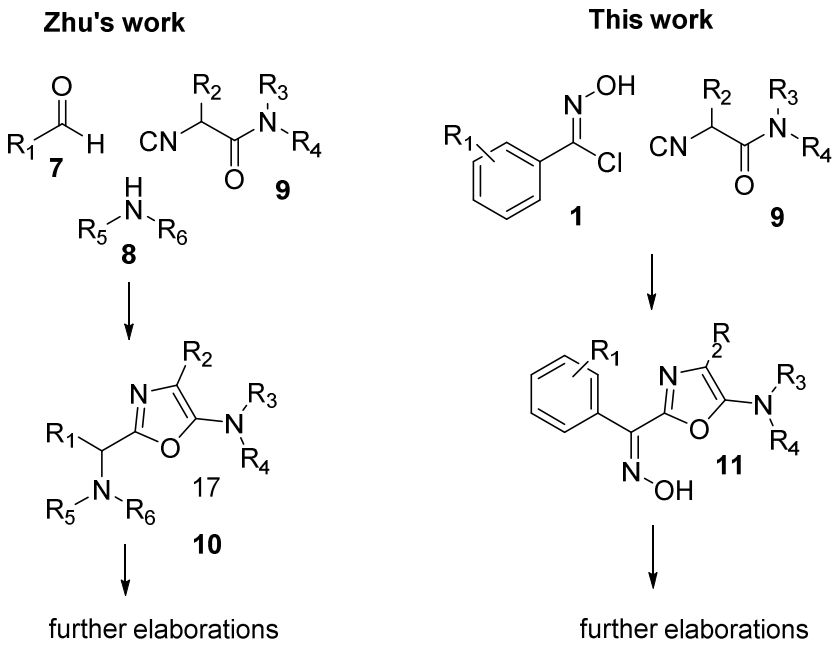


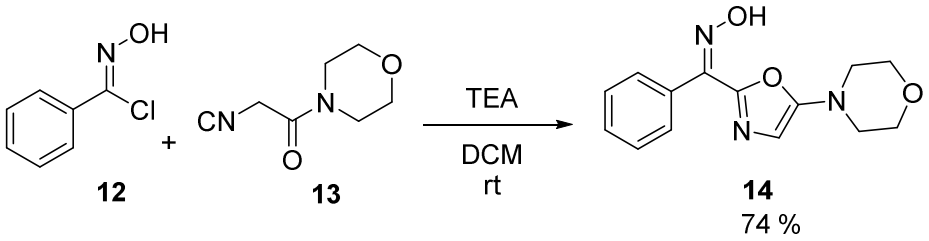
Figure 1. Intramolecularly trapping of the nascent nitrilum ion.

Inspired by pioneering works by Zhu, who demonstrated that *α*-isocyanoacetamides **9**, when involved in a three component reaction, along with aldehydes **7** and primary or secondary amines **8**, are able to afford 5-aminooxazoles **10** through interception of the nitrilium ion by the oxygen atom of the amide,[4] we reasoned that *α*-isocyanoacetamides could in principle react with the nitrile-*N*-oxides and then intermolecularly intercept the nascent nitrilium species (Scheme 2).



Scheme 2. Comparison between Zhu's work and the reaction described in this chapter.

As starting point for our study, we chose the reaction between phenylchlooroxime **12** and the 4-(isocyanoacetyl)morpholine **13**. The reaction was carried out without TEA and with 1 equivalent of TEA in dichloromethane at room temperature. With our delight the reaction with 1 equivalent of TEA was completed after 2 h giving the desired compound **14** in 74% yield after column chromatography (Scheme 3).



Scheme 3. Reaction between *Z*-phenylchlorooxime and 4-(isocyanoacetyl)morpholine.

Not surprisingly, when the reaction was carried out without TEA, we did not notice the formation of the desired product **14** and the *Z*-phenylchlorooxime **12** was recovered after column chromatography.

Using these already optimized reaction conditions (1 eq. of TEA, rt, DCM), the scope and limitations of this novel reaction were explored. *Z*-Phenylchloroxime (**12**) or *Z*-phenylchloroximes bearing electron-withdrawing (**15, 19, 20, 21, 22**) or electron-donating (methyl- or methoxy-, **16** and **17**, respectively) substituents on the para position were chosen, as well as one *Z*-heteroarylchloroxime with a thiophene ring (**18**). *α*-isocyanoacetamides (**13, 23-30**) exhibit two points of diversity: the amide function derived from cyclic secondary amines (as for **13**, **23-25, 29, 30**) or noncyclic secondary amine (as **28**) and the *α*-substitution (methyl- or benzyl, **23** and **24**, **25**, respectively) (Figure 2).

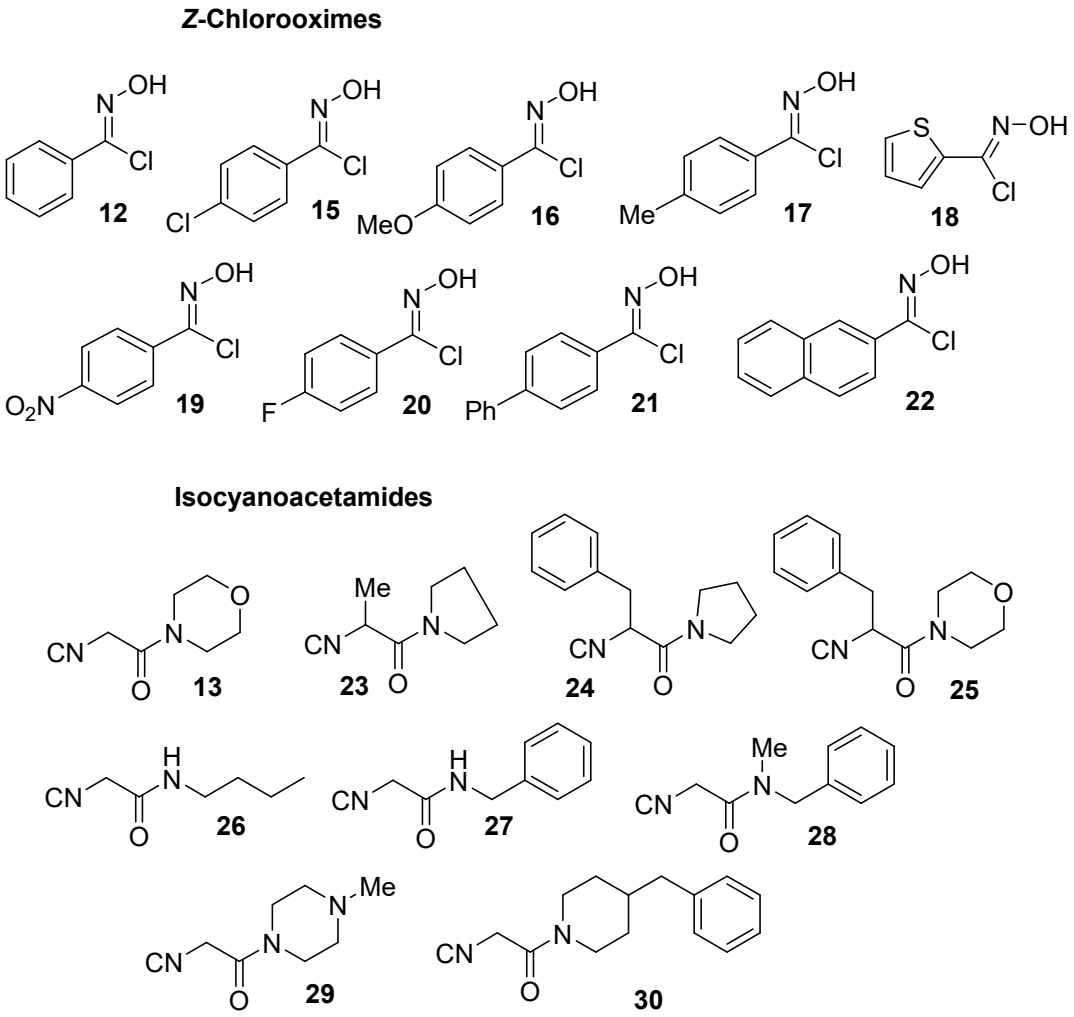


Figure 2. Structure of *Z*-chlorooximes and *α*-isocyanoacetamides used.

Arylchlorooximes were prepared by chlorination of the corresponding oximes with *N*-chlorosuccinimide,[5] while *α*-isocyanoacetamides were easily accessible by amidation of the corresponding *α*-isocyanomethylester using the Dömling procedure,[6] while for the *α*-substituted *α*-isocyanoacetamides the alkylation was carried out in the presence of cesium hydroxide.[7]

The reaction appeared to be quite general, not depending on electronic factors, as *Z*-arylchloroximes bearing both electronwithdrawing and electron-donating substituents reacted smoothly with the different isocyanoacetamides giving the

desired 1,3-oxazol-2-oxime derivatives (**31-47**) in good yields (ranging from 32% to 88%) (Figure 3).

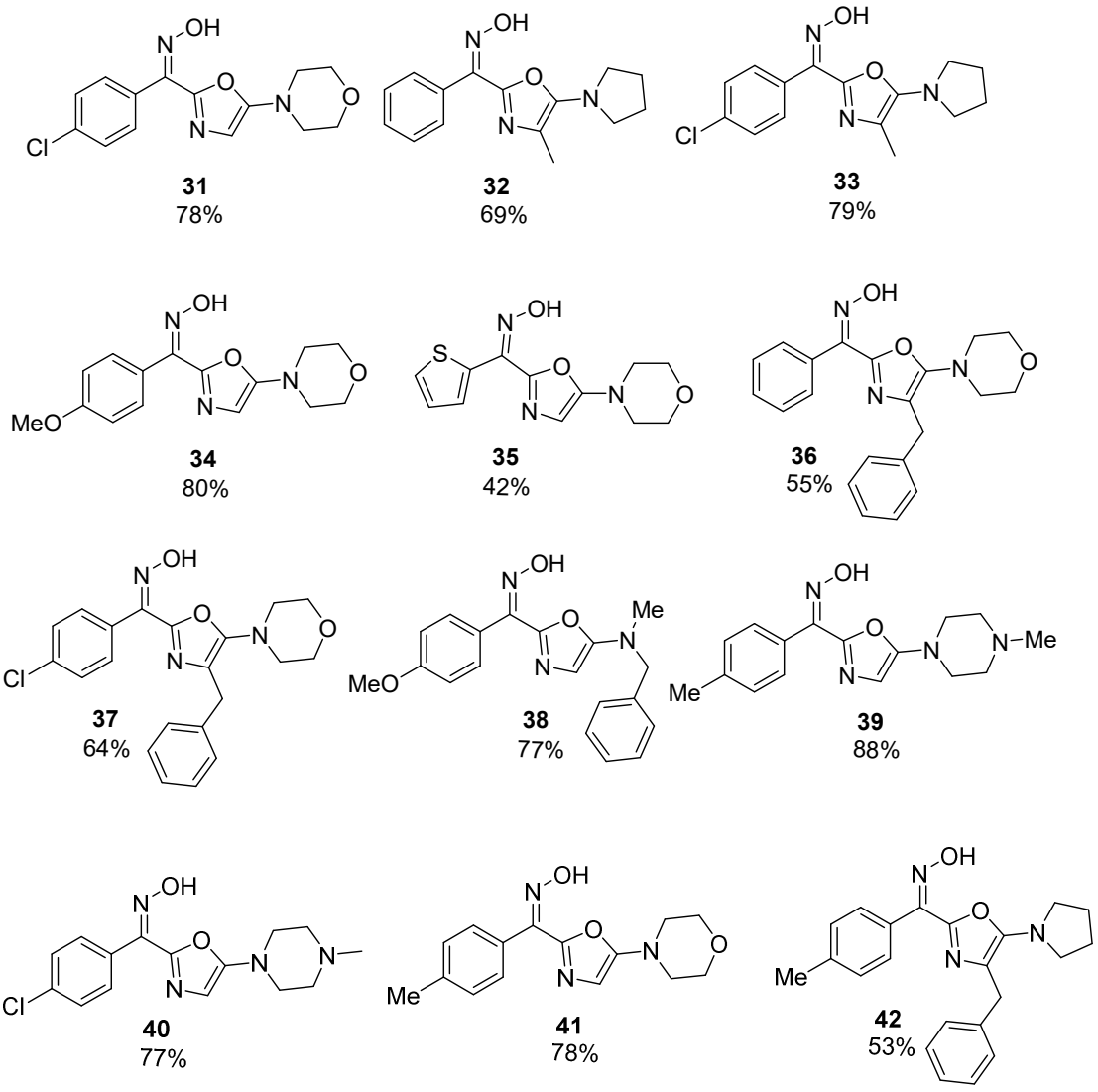


Figure 3. Synthesized 1,3-oxazol-2-oxime derivatives.

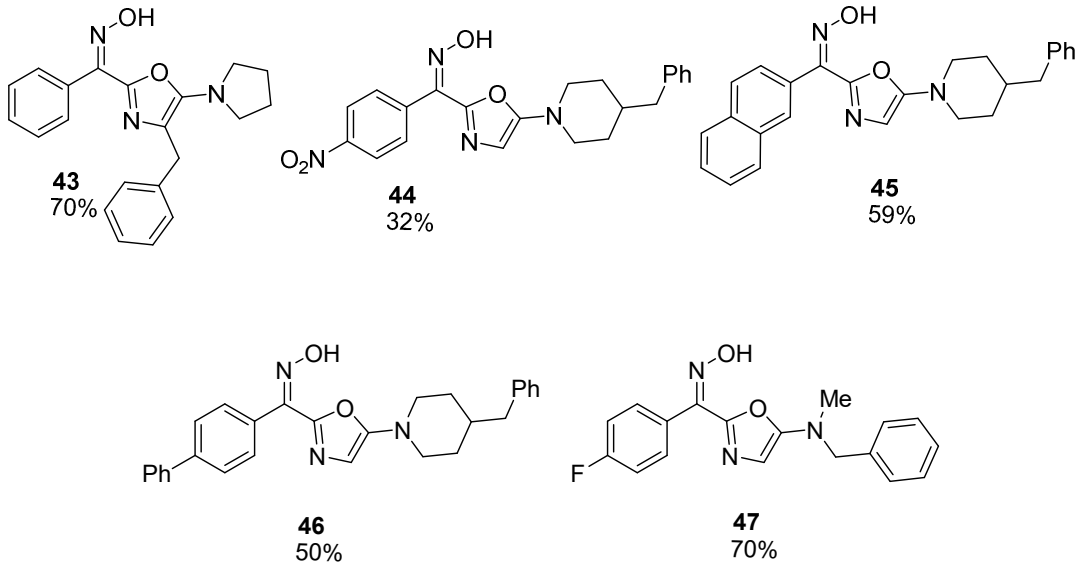


Figure 3. Synthesized 1,3-oxazol-2-oxime derivatives (*Continued).*

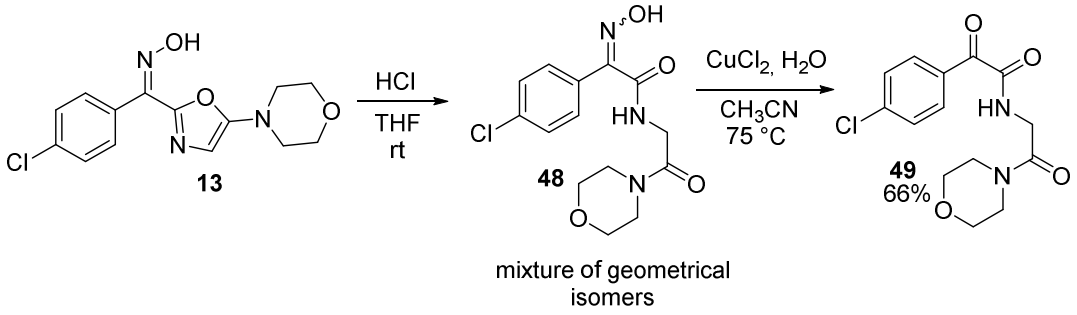
When isocyanoacetamide **29** was used, TEA was not necessary, as the basic nitrogen of piperazine was able to trigger the formation of the nitrile *N*-oxide species. The reaction failed when a secondary amide was present in the isocyanoacetamides (**26** and **27**); anyway this behavior is not surprisingly as it was already shown by Zhu.[4,8]

1,3-Oxazol-2-oxime revealed to be unstable molecules with isomerization of the oxime, especially when the oxazole ring was substituted at the 4-position, and formation of decomposition products. Although we have fully characterized them, they cannot be stored for long time (even at 0 °C) but they have to be immediately used.

At the beginning, we attempted a one-pot procedure for the conversion of 1,3-oxazol-2-oximes into aryl-*α*-ketoamides.

Hydrolysis of these intermediates in the presence of HCl, at room temperature, afforded the oxime−dipeptide analogue **48**, favoring, at the same time, the partial isomerization of the oxime. When the reaction was heated, we did observe the hydrolysis of the oxime and also the formation of several byproducts, which

decrease the yield and make difficult the chromatographic purification. For these reasons, we opted to use milder catalysts as a Lewis acid, and we identified the copper(II) chloride[9] as the reagent of choice. After the aminooxazole ring was opened with HCl, the deoximation reaction in the presence of copper(II) chloride was carried out. Both reactions proceeded well and only a purification step was required (Scheme 4).



Scheme 4. Acid hydrolysis and deoximation of 1,3-oxazol-2-oximino derivatives.

By using this protocol, we prepared different aryl-*α*-ketoamide amides (**50-66**) in good yields (Figure 4).

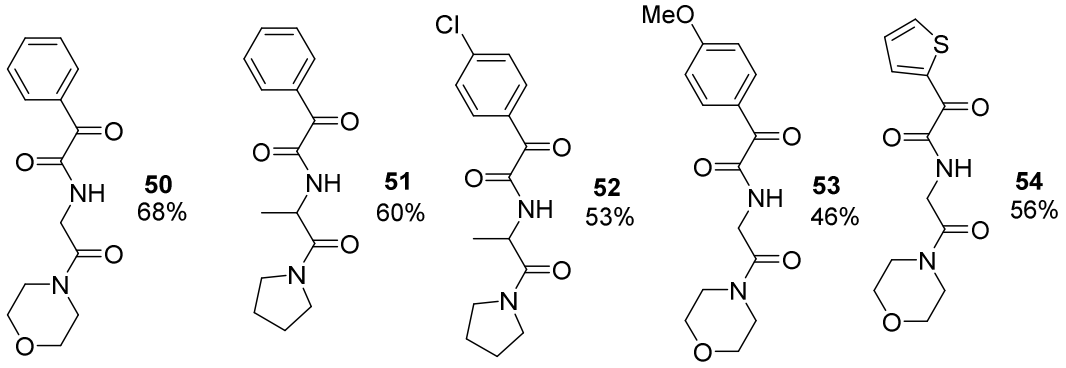


Figure 4. Synthesized aryl-*α*-ketoamides.

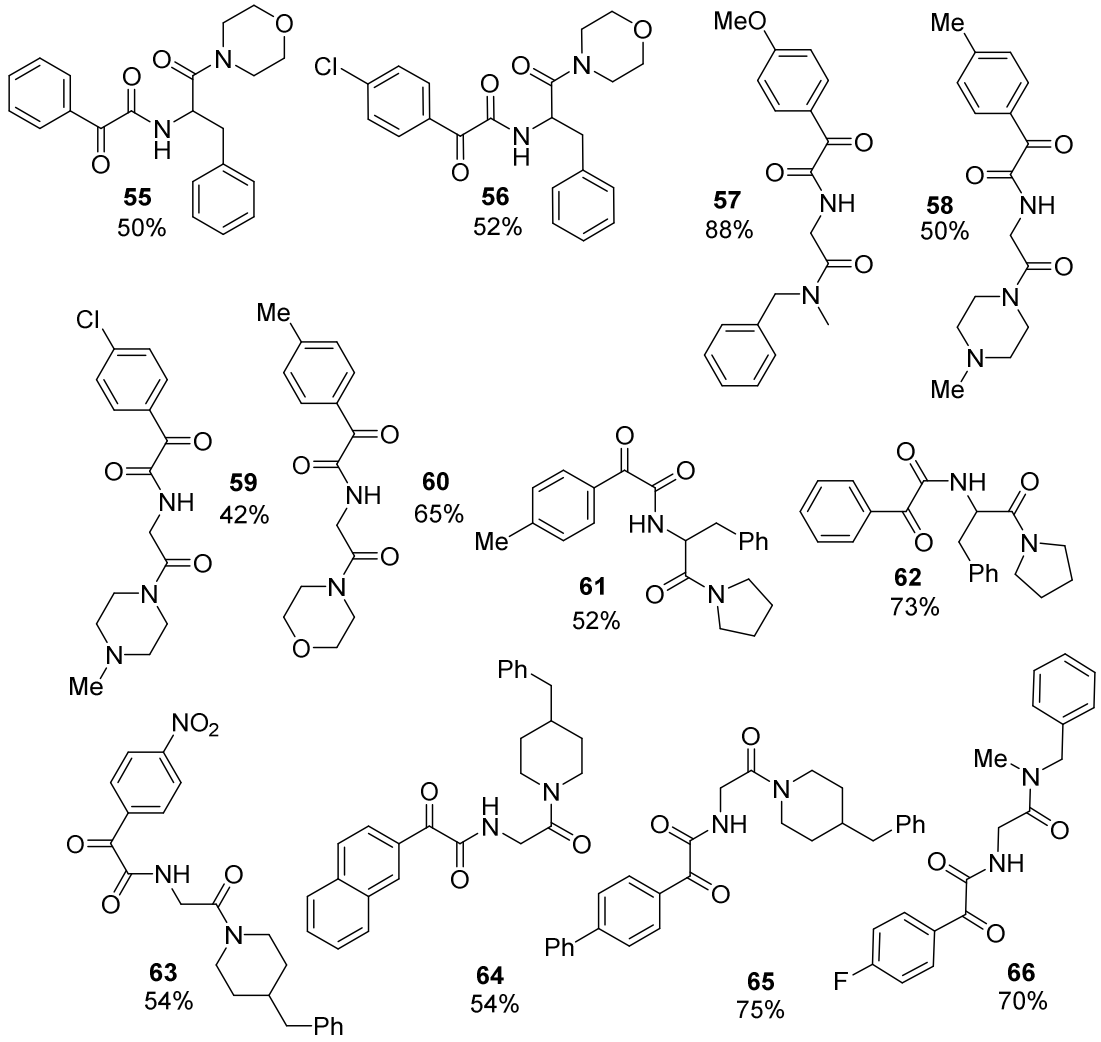


Figure 4. Synthesized aryl-*α*-ketoamides (*Continued).*

5.2 Conclusions

In conclusion a general and straightforward methodology to structurally diverse aryl *α*-ketoamide amides has been demonstrated. These latter are privileged scaffolds in medicinal chemistry due to their ability to act as inhibitors reacting with the key cysteine or lysine residues in protease,[10,11] lipase[12] and histone deacetylase[13] or as useful intermediates for a variety of transformations in organic chemistry.

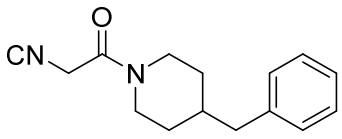
It is important to highlight that the entire sequence of reactions is realized under mild reaction conditions avoiding the use of expensive coupling agents and using simple and easily available starting materials (*Z*-arylchlorooximes and *α*-isocyanoacetamides).

This method is complementary to those previously reported for the synthesis of alkyl *α*-ketoamide amides. Indeed, Mossetti *et al.*[14] reported the reaction between acyl chlorides and *α*-isocyanoacetamides to form *α*-ketoamides via ketene intermediate. This reaction is characterized by the lack of reactivity of aroyl chlorides due to the concomitant reduced nucleophilicity of the isocyano group and the reduced electrophilicity of the aroyl chloride. Any attempts to react, in a productive way, an aroyl chloride with an *α*-isocyanoacetamides failed, and this gap is now filled by the reaction between aryl-chlorooximes and *α*-isocyanoacetamides.

5.3 Experimental section

General Methods. Commercially available reagents and solvents were used without further purification. Dichloromethane was dried by distillation from P_2O_5 and stored over activated molecular sieves (4 Å). When necessary, the reactions were performed in oven-dried glassware under a positive pressure of dry nitrogen. Melting points were determined in open glass capillaries and are uncorrected. All the compounds were characterized by IR. ^1H and ^{13}C APT NMR were recorded on a 300 MHz. Mass spectrometry was equipped with an ESI source and an ion-trap detector. HRMS were recorded on ORBITRAP mass spectrometer equipped with an ESI source. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent peak. Column chromatography was performed on silica gel (70−230 mesh ASTM) using the reported eluents. Thin-layer chromatography (TLC) was carried out on 5 × 20 cm plates with a layer thickness of 0.25 mm (silica gel 60 F_{254}). When necessary, they were developed with $KMnO_4$. Elemental analysis (C, H, N) of all of the new compounds were within ±0.4% of the calculated values. Chloroximes **12** and **15-22** are not new, and they were prepared following literature procedure.[5] Isocyanoacetamides **13** and **23-25** were prepared following Dömling's procedure,[6] while isocyanoacetammides **26-29** were prepared following Zhu's procedure.[7]

Synthesis of 4-Benzyl-1-(isocyanoacetyl)piperidine (30).



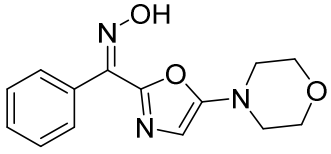
Methyl isocyanoacetate (1 eq.) was reacted with 4-benzylpiperidine (1 eq.) overnight under neat conditions. The solution was evaporated and the crude was purified by column chromatography Ex/EtOAc 7:3 to give 37 as amorphous solid (yield 75%): ^1H NMR (400 MHz, $CDCl_3$) δ 7.26.7.09 (m, 5H), 4.45 (br d, 1H), 4.24 (br d, 2H), 3.45 (br d, 1H), 2.93 (br t, 1H), 2.51.2.49 (m, 3H), 1.73.1.64 (m, 3H), 1.17.1.10 (m, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 160.4, 139.7, 129.1, 128.3, 126.1, 45.6, 44.6, 42.8, 42.6, 37.7, 32.0, 31.3; HRMS (ESI) m/z (M + H)+ calcd for $C_{15}H_{18}N_2O$ 242.1419, found 242.1422.

General Preparation of 1,3-Oxazol-2-oximes (14, 31-49).

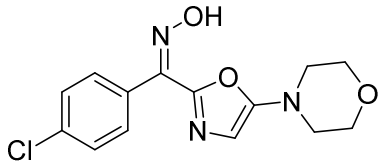
The chlorooxime (1 eq.) was dissolved in dry dichloromethane, and α-isocyanoacetamide (1 eq.) was added dropwise or portionwise at room temperature. Finally, TEA (1 eq.) was added dropwise (the reaction is slightly exothermic and on a large scale the addition should be done at 0 °C), and the reaction was stirred at room temperature under a nitrogen atmosphere until all the chlorooxime was consumed (typically 2−3 h as judged by TLC). The reaction mixture was concentrated under reduced pressure, and the crude material was purified by column chromatography.

(*Z*)-(5-Morpholinooxazol-2-yl)phenylmethanone Oxime (14).



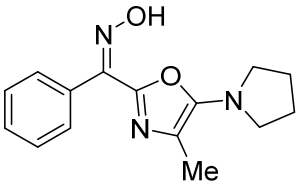
Starting material: chlorooxime 150 mg (0.96 mmol), isocyanoacetamide 148 mg (0.96 mmol). The crude material was purified by column chromatography (PE/EtOAc 7:3) to give 195 mg of product as yellow solid (yield 74%). ^{1}H NMR (300 MHz, CDCl3) δH 7.66−7.62 (m, 2H), 7.44−7.40 (m, 3H), 6.26 (br s, 1H), 3.78 (br t, 4H), 3.16 (br t, 4H); ^{13}C NMR (75 MHz, CDCl3) δC 156.2, 146.9, 141.9, 133.0, 129.5, 128.4 (2C), 101.5, 65.8, 47.3; HRMS (ESI) *m/z:* $(M+Na)^+$ Calcd for $C_{14}H_{15}N_3NaO_3$ 296.1011, found 296.1012.

(*Z*)-(4-chlorophenyl)(5-morpholinooxazol-2-yl)methanone oxime (31).



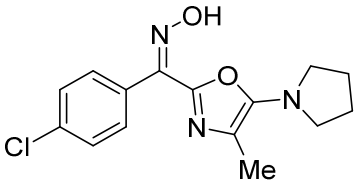
Starting material: chlorooxime 150 mg (0.79 mmol), isocyanoacetamide 122 mg (0.79 mmol). The crude material was purified by column chromatography (PE/EtOAc 6:4) to give 187 mg of product as yellow solid (yield 78%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.60-7.56 (m, 2 H, AA′XX′), 7.44-7.36 (m, 2 H, AA′XX′), 6.26 (br s, 1H), 3.80-3.77 (m, 4H), 3.18-3.15 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 156.2, 146.5, 141.0, 135.6, 131.5, 129.7, 128.7, 101.6, 65.7, 47.2; HMRS (ESI) *m/z*: $(M+H)^+$ Calcd for $C_{14}H_{14}ClN_3O_3$ 307.0724; Found 307.0727.

(*Z*)-(4-methyl-5-(pyrrolidin-1-yl)oxazol-2yl)(phenyl)methanone oxime (32).



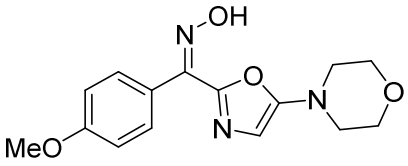
Starting material: chlorooxime 150 mg (0.96 mmol), isocyanoacetamide 147 mg (0.96 mmol). The crude material was purified by column chromatography (PE/EtOAc 7:3) to give 180 mg of product as yellow solid (yield 69%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.69-7.66 (m, 2H), 7.40-7.38 (m, 3H), 3.42-3.38 (m, 4H), 2.27 (s, 3H), 1.95-1.91 (m, 4H);^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 150.2, 143.9, 141.4, 133.3, 129.2, 128.4, 128.3, 108.4, 48.8, 25.4, 11.7; HMRS (ESI) *m/z*: $(M+H)^+$ Calcd for $C_{15}H_{17}N_3O_2$ 271.1321; Found 271.1321.

(*Z*)-(4-chlorophenyl)(4-methyl-5-(pyrrolidin-1-yl)oxazol-2-yl)methanone oxime (33).



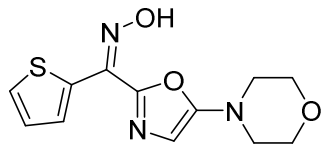
Starting material: chlorooxime 150 mg (0.79 mmol), isocyanoacetamide 120 mg (0.79 mmol). The crude material was purified by column chromatography (PE/EtOAc 6:4) to give 190 mg of product as orange solid (yield 79%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.65-7.62 (m, 2H, AA′XX′), 7.40-7.37 (m, 2H, AA′XX′), 3.45-3.43 (m, 4H), 2.29 (s, 3H), 1.98-1.92 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 150.3, 143.7, 140.5, 135.3, 131.9, 129.8, 128.6, 108.5, 48.9, 25.5, 11.7; HMRS (ESI) *m/z*: $(M+H)^+$ Calcd for $C_{15}H_{16}ClN_3O_2$ 305.0931; Found 305.0933.

(*Z*)-(4-methoxyphenyl)(5-morpholinooxazol-2-yl)methanone oxime (34).



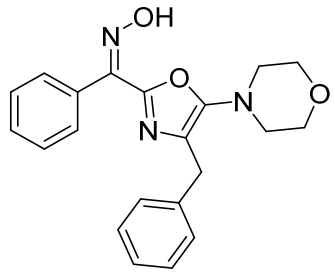
Starting material: chlorooxime 150 mg (0.81 mmol), isocyanoacetamide 125 mg (0.81 mmol). The crude material was purified by column chromatography (PE/EtOAc 5:5) to give 196 mg of product as yellow solid (yield 80%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.60-7.56 (m, 2H, AA′XX′), 6.97-6.91 (m, 2H, AA′XX′), 6.25 (br s, 1H), 3.81-3.78 (m, 7H), 3.17-3.15 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 160.6, 156.1, 147.1, 141.5, 129.7, 125.5, 113.8, 101.5, 65.8, 55.4, 47.3; HMRS (ESI) *m/z*: $(M+Na)^+$ Calcd for $C_{15}H_{17}N_3NaO_4$ 326.1117; Found 326.1120.

(*E*)-(5-morpholinooxazol-2-yl)(thiophen-2-yl)methanone oxime (35).



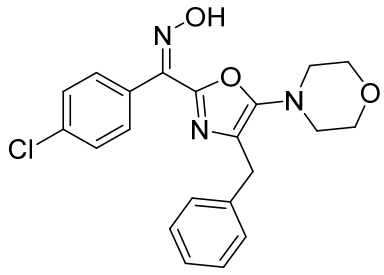
Starting material: chlorooxime 150 mg (0.93 mmol), isocyanoacetamide 143 mg (0.93 mmol). The crude material was purified by column chromatography (PE/EtOAc 6:4) to give 108 mg of product as brown solid (yield 42%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.60-7.58 (m, 1H), 7.36-7.34 (m, 1H), 7.10-7.06 (m, 1H), 6.26 (br s, 1H), 3.87-3.83 (m, 4H), 3.28-3.26 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 156.2, 146.1, 137.1, 135.6, 127.6, 127.3, 127.2, 101.4, 65.8, 47.3; $(M+H)^+$ Calcd for $C_{12}H_{13}N_3O_3S$ 279.0678; Found 279.0677.

(*Z*)-(4-benzyl-5-morpholinooxazol-2-yl)(phenyl)methanone oxime (36).



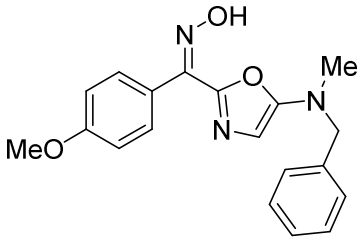
Starting material: chlorooxime 150 mg (0.96 mmol), isocyanoacetamide 236 mg (0.96 mmol). The crude material was purified by column chromatography (PE/EtOAc 7:3) to give 169 mg of product as yellow oil (yield 55%). Mixture of *E/Z* isomers, signals are referred to the main isomer: ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.69-7.66 (m, 2H), 7.45-7.39 (m, 3H), 7.35-7.21 (m, 5H), 3.94 (s, 2H), 3.75-3.71 (m, 4H), 3.10-3.06 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 151.2, 148.3, 141.9, 138.3, 132.8, 129.5, 128.7, 128.4, 128.3, 128.0, 126.7, 121.4, 66.5, 49.9, 31.80; $(M+H)^+$ Calcd for $C_{21}H_{21}N_3O_3$ 363.1583; Found 363.1583.

(*Z*)-(4-benzyl-5-morpholinooxazol-2-yl)(4-chlorophenyl)methanone oxime (37).



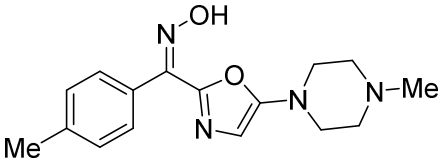
Starting material: chlorooxime 150 mg (0.79 mmol), isocyanoacetamide 193 mg (0.79 mmol). The crude material was purified by column chromatography (PE/EtOAc 7:3) to give 200 mg of product as white solid (yield 64%). Mixture of *E/Z* isomers, signals are referred to the main isomer: ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.65-7.58 (m, 2H), 7.43-7.36 (m, 2H), 7.32-7.18 (m, 5H), 3.96 (s, 2H), 3.75-3.67 (m, 4H), 3.09-3.06 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 151.3, 147.7, 141.2, 138.3, 135.5, 131.4, 129.6, 128.8, 128.59, 128.32, 126.65, 121.3, 66.6, 49.8, 31.81; $(M+H)^+$ Calcd for $C_{21}H_{20}ClN_3O_3$ 397.1193; Found 397.1197.

(*Z*)-(5-(benzyl(methyl)amino)oxazol-2-yl)(4-methoxyphenyl)methanone oxime (38).



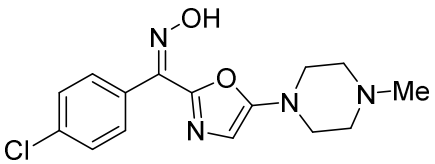
Starting material: chlorooxime 150 mg (0.81 mmol), isocyanoacetamide 152 mg (0.81 mmol). The crude material was purified by column chromatography (PE/EtOAc 7:3) to give 210 mg product as yellow solid (yield 77%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.61-7.56 (m, 2H, AA′XX′), 7.37-7.27 (m, 3H), 7.25-7.19 (m, 2H), 6.94-6.90 (m, 2H, AA′XX′), 6.15 (br s, 1H), 4.37 (s, 2H), 3.85 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 160.5, 156.1, 145.8, 141.3, 136.1, 129.7, 128.8, 127.9, 127.7, 125.6, 113.7, 55.5, 55.3, 36.6; $(M+H)^+$ Calcd for $C_{19}H_{19}N_3O_3$ 337.1426; Found 337.1426.

(*Z*)-(5-(4-methylpiperazin-1-yl)oxazol-2-yl)(p-tolyl)methanone oxime (39).



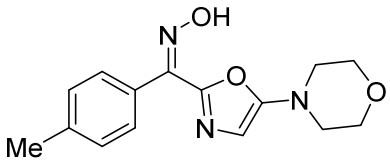
Starting materials: chlorooxime 150 mg (0.88 mmol), isocyanoacetamide 147 mg (0.88 mmol). The crude material was purified by column chromatography (DCM/MeOH 95:5) to give 232 mg product as yellow solid (88% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.56 (d, *J* = 7.8 Hz, 2H), 7.23 (m, 2H) partially overlapped to the solvent, 6.23 (s, 1H), 3.22 (br t, 4H), 2.50 (br t, 4H), 2.39 (s, 3H), 2.33 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 156.2, 146.7, 142.0, 139.3, 130.4, 128.9, 128.1, 101.4, 53.6, 46.9, 46.0, 21.3; $(M+H)^+$ Calcd for $C_{16}H_{20}N_4O_2$ 300.1586; Found 300.1590.

(*Z*)-(4-chlorophenyl)-(5-(4-methylpiperazin-1-yl)oxazol-2-yl)methanone oxime (40).



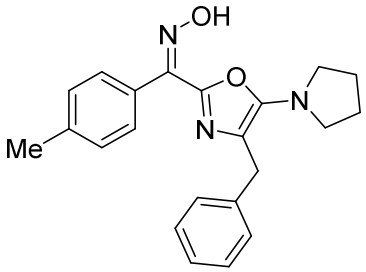
Starting materials: chlorooxime 150 mg (0.79 mmol), isocyanoacetamide 132 mg (0.79 mmol). The crude material was purified by column chromatography (DCM/MeOH 97:3) to give the product as yellow solid (195 mg, 77% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 7.57-7.55 (m, 2H, AA′XX′), 7.36-7.34 (m, 2H, AA′XX′), 6.23 (s, 1H), 3.23 (br t, 4H), 2.52 (br t, 4H), 2.33 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C 156.3, 146.2, 141.2, 135.3, 131.9, 129.5, 128.5, 101.7, 53.6, 46.9, 46.0; $(M+H)^+$ Calcd for $C_{15}H_{17}ClN_4O_2$ 320.1040; Found 320.1042.

(*Z*)-(5-morpholinooxazol-2-yl)(p-tolyl)methanone oxime (41).



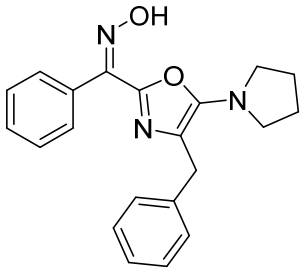
Starting materials: chlorooxime 150 mg (0.88 mmol), isocyanoacetamide 136 mg (0.88 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 7:3) to give the product as yellow solid (197 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.54 (m, 2H, AA′XX′), 7.23 (m, 2H, AA′XX′), 6.26 (s, 1H), 3.80 (m, 4H), 3.17 (m, 4H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.0, 147.0, 141.7, 139.4, 130.0, 129.0, 128.2, 101.3, 65.7, 47.2, 21.3; $(M+H)^+$ Calcd for $C_{15}H_{17}N_3O_3$ 287.1270; Found 287.1268.

(4-benzyl-5-(pyrrolidin-1-yl)oxazol-2-yl)(p-tolyl)methanone oxime (42).



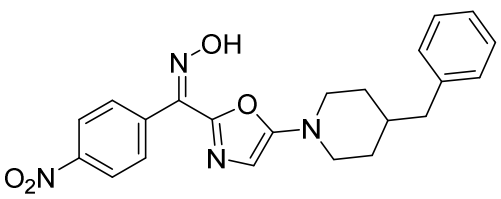
Starting materials: chlorooxime 150 mg (0.88 mmol), isocyanoacetamide 202 mg (0.88 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 7:3) to give the product as yellow solid (168 mg, 53% yield). Mixture of *E/Z* isomers, signals are referred to the main isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61 (m, 2H, AA'XX'), 7.31-7.22 (m, 7H) partially overlapped to the solvent, 3.99 (s, 2H), 3.42 (br t, 4H), 2.40 (s, 3H), 1.93 (br t, 4H); ^{13}C NMR (100 MHz, CDCl3) δ_C 150.3, 144.3, 141.3, 140.0, 139.1, 130.3, 128.9, 128.6, 128.2, 128.1, 126.3, 110.7, 48.8, 31.8, 25.3, 21.3; $(M+H)^+$ Calcd for $C_{22}H_{23}N_3O_2$ 361.1790; Found 361.1793.

(*Z*)-(4-benzyl-5-(pyrrolidin-1-yl)oxazol-2-yl)(phenyl)methanone oxime (43).



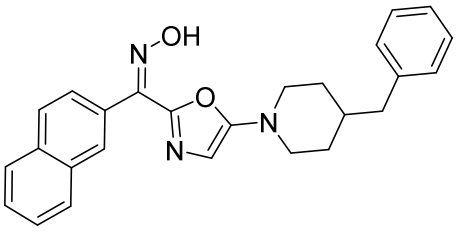
Starting materials: chlorooxime 150 mg (0.96 mmol), isocyanoacetamide 219 mg (0.96 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 7:3) to give the product as yellow solid (233 mg, 70% yield). Mixture of *E/Z* isomers, signals are referred to the main isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71 (br d, 2H), 7.63-7.57 (m, 1H), 7.43-7.41 (m, 3H), 7.33-7.20 (m, 4H) partially overlapped to the solvent, 4.00 (s, 2H), 3.41 (br t, 4H), 1.92 (br t, 4H); ^{13}C NMR (100 MHz, CDCl3) δ_C 150.3, 144.1, 141.4, 140.0, 133.2, 129.1, 128.6, 128.3, 128.2, 128.1, 126.3, 110.7, 48.7, 31.8, 25.3; $(M+H)^+$ Calcd for $C_{21}H_{21}N_3O_2$ 347.1634; Found 347.1637.

(*Z*)-(5-(4-benzylpiperidin-1-yl)oxazol-2-yl)(4-nitrophenyl)methanone oxime (44).



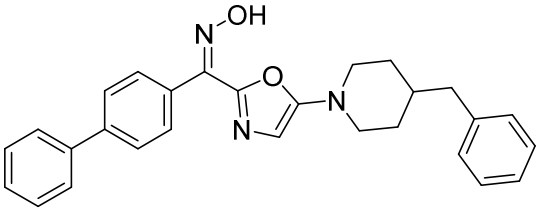
Starting materials: chlorooxime 150 mg (0.75 mmol), isocyanoacetamide 182 mg (0.75 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 9:1) to give the product as bright-yellow solid (97 mg, 32% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.28 (d, *J* = 8.7 Hz, 2H), 7.89 (d, *J* = 8.6 Hz, 2H), 7.29-7.12 (m, 6H), 6.23 (s, 1H), 3.54 (br d, 2H), 2.83 (br t, 2H), 2.58 (br d, 2H), 1.77-1.73 (m, 3H), 1.39-1.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.5, 148.2, 145.2, 139.9, 139.5, 139.2, 129.1, 129.0, 128.3, 126.1, 123.5, 100.7, 47.5, 42.8, 37.3, 30.7 ; $(M+H)^+$ Calcd for $C_{22}H_{22}N_4O_4$ 406.1641; Found 406.1646.

(*Z*)-(5-(4-benzylpiperidin-1-yl)oxazol-2-yl)(naphthalen-2-yl)methanone oxime (45).



Starting materials: chlorooxime 150 mg (0.73 mmol), isocyanoacetamide 178 mg (0.73 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 9:1) to give the product as yellow solid (177 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.18 (s, 1H), 7.89-7.85 (m, 3H), 7.79 (br d, 1H), 7.52-7.50 (m, 2H), 7.30-7.25 (m, 3H), 7.21 (br d, 1H), 7.13 (br d, 2H), 6.23 (s, 1H), 3.54 (br d, 2H), 2.79 (br t, 2H), 2.56 (br d, 2H), 1.72-1.70 (m, 3H), 1.38-1.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.5, 146.2, 141.7, 139.7, 133.6, 133.0, 130.5, 129.1, 128.5, 128.3, 128.2, 127.9, 127.6, 126.8, 126.4, 126.1, 125.6, 100.6, 47.5, 42.8, 37.3, 30.7; $(M+H)^+$ Calcd for $C_{26}H_{25}N_3O_2$ 411.1947; found 411.1950.

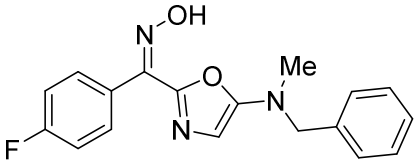
(*Z*)-[1,1'-biphenyl]-4-yl(5-(4-benzylpiperidin-1-yl)oxazol-2-yl)methanone oxime (46).



Starting materials: chlorooxime 150 mg (0.65 mmol), isocyanoacetamide 158 mg (0.73 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 9:1) to give the product as yellowish solid (142 mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.76 (br d, 2H), 7.67-7.63 (m, 4H), 7.47-7.44 (m, 3H), 7.38 (br d,

1H), 7.31-7.27 (m, 2H), 7.22 (br d, 1H), 7.14 (br d, 2H), 6.22 (s, 1H), 3.56 (br d, 2H), 2.81 (br t, 2H), 2.58 (br d, 2H), 1.75-1.72 (m, 3H), 1.41-1.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 156.5, 146.2, 142.0, 141.4, 140.3, 139.7, 132.0, 129.1, 128.8, 128.7, 128.3, 127.6, 127.1, 127.0, 126.1, 100.6, 47.6, 42.9, 37.4, 30.7; $(M+H)^+$ Calcd for $C_{26}H_{25}N_3O_2$ 411.1947; found 411.1948.

***(Z)*-(5-(benzyl(methyl)amino)oxazol-2-yl)(4-fluorophenyl)methanone oxime (47).**

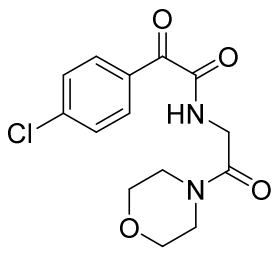


Starting material: chlorooxime 150 mg (0.87 mmol), isocyanoacetamide 163 mg (0.81 mmol). The crude material was purified by column chromatography (PE/EtOAc 7:3) to give 198 mg product as yellow solid (yield 70%). Mixture of *E/Z* isomers, signals are referred to the main isomer: ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 7.65-7.53 (m, 3H), 7.37-7.19 (m, 3H), 7.10-7.02 (m, 3H), 6.18 (br s, 1H), 4.38 (s, 2H), 2.90 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 164.9, 161.7, 156.2, 140.8, 136.0, 131.8, 130.3, 128.7, 128.6, 127.8, 115.4, 99.5, 55.3, 36.6; $(M+H)^+$ Calcd for $C_{18}H_{16}FN_3O_2$ 325.1227; found 325.1229.

General preparation of aryl-*α*-ketoamide amides (49-66)

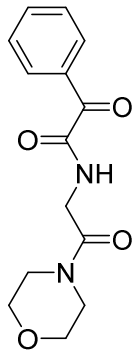
The 1,3-oxazol-2-oxime was dissolved in THF (0.8 M), concentrated HCl (1 eq.; 2 eq. for oxazoles **39** and **40**) was added and the reaction was stirred at room temperature for 30 minutes. The reaction mixture was diluted with water and extracted with EtOAc (x 3). The organic phase was washed with $NaHCO_3$ std. sln. (x1) and brine (x1), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude was dissolved in acetonitrile (0.25 M), water (55 eq) and copper (II) chloride (2 eq) were added. The solution was stirred for 1 hour at 75 °C. The reaction mixture was diluted with water and extracted with EtOAc (x2). The organic phase was washed with brine (x1), dried over sodium sulfate, filtered, and concentrated under reduced pressure and the crude material was purified by column chromatography.

2-(4-chlorophenyl)-*N*-(2-morpholino-2-oxoethyl)-2-oxoacetamide (49).



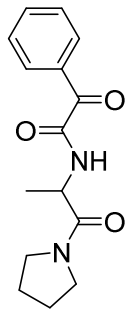
Starting material: 1,3-oxazol-2-oxime 150 mg (0.49 mmol). The crude material was purified by column chromatography (PE/EtOAc 2:8) to give 100 mg of product as white solid (yield 66%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 8.21-8.18 (m, 2H, AA′XX′), 8.03 (br s, NH), 7.41-7.38 (m, 2H, AA′XX′), 4.12 (d, J = 4.6 Hz, 2H), 3.65-3.59 (m, 6H), 3.44.3.41 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 185.8, 165.8, 161.9, 141.1, 132.4, 131.6, 128.9, 66.6, 66.3, 44.9, 42.4, 40.9; *m/z* 311 $(M+H)^+$; IR ν_{max}/cm^{-1} (KBr) 3239, 3096, 1670, 1652, 1533, 1465, 1246, 855 ; mp 122-123 °C. Anal. Calcd for $C_{14}H_{15}ClN_2O_4$: C, 54.12; H, 4.87; N, 9.02. Found: C, 53.95; H, 4.80; N, 9.31.

***N*-(2-morpholino-2-oxoethyl)-2-oxo-2-phenylacetamide (50).**



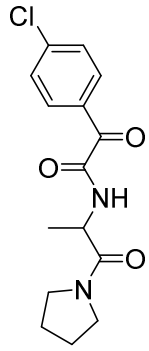
Starting materials: 1,3-oxazol-2-oxime 150 mg (0.55 mmol). The crude material was purified by column chromatography (*n*-hexane/EtOAc 5:5) to give the product as yellowish solid (103 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.28 (br d, 2H), 7.93 (br s, NH), 7.62 (br t, 1H), 7.47 (br t, 2H), 4.18 (d, J = 4.0 Hz, 2H), 3.72-3.66 (m, 6H), 3.47-3.45 (m, 2H); ^{13}C NMR (100 MHz, CDCl3) δ_C 187.1, 165.8, 162.2, 134.4, 133.1, 130.9, 128.5, 66.6, 66.3, 44.9, 42.3, 40.8; *m/z* 277 $(M+H)^+$; IR ν_{max}/cm^{-1} (KBr) 3380, 1687, 1667, 1642, 1505, 1474, 1275, 745; mp 164-165 °C. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.95; H, 5.97; N, 10.01.

***N*-(1-morpholino-1-oxopropan-2-yl)-2-oxo-2-phenylacetamide (51).**



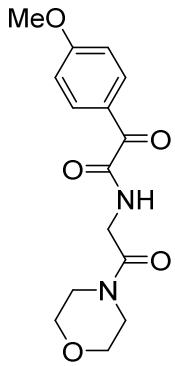
Starting material: 1,3-oxazol-2-oxime 150 mg (0.55 mmol). The crude material was purified by column chromatography (PE/EtOAc 3:7) to give 92 mg of product as yellow oil (yield 60%). Mixture of rotamers, signals are referred to the main rotamer:^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 8.20-8.17 (m, 2H), 8.03 (br d, NH), 7.56-7.38 (m, 3H), 4.80-4.72 (m, 1H), 3.64-3.35 (m, 4H), 1.98-1.78 (m, 4H), 1.39 (d, J = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 187.5, 169.9, 161.6, 134.2, 133.23, 130.9, 128.4, 46.9, 46.4, 46.2, 26.0, 24.1, 17.9; *m/z* 275 $(M+H)^+$; IR ν_{max}/cm^{-1} (KBr) 3253, 3062, 1638, 1667, 1510, 1449, 1264, 715. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.66; H, 6.65; N, 10.25.

2-(4-chlorophenyl)-*N*-(1-morpholino-1-oxopropan-2-yl)-2-oxoacetamide (52).



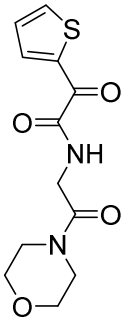
Starting material: 1,3-oxazol-2-oxime 150 mg (0.49 mmol). The crude material was purified by column chromatography (PE/EtOAc 4:6) to give 80 mg of product as colorless oil (yield 53%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 8.25-8.23 (m, 2H, AA′XX′), 7.97 (br d, NH), 7.43-7.40 (m, 2H, AA′XX′), 4.77-4.72 (m, 1H), 3.66-3.39 (m, 4H), 2.03-1.83 (m, 4H), 1.42 (d, J = 7.0 Hz, 3H);^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 186.1, 169.9, 161.0, 141.1, 132.6, 131.8, 129.0, 47.1, 46.5, 46.3, 26.2, 24.2, 18.1; *m/z* 309 $(M+H)^+$; IR ν_{max}/cm^{-1} (KBr) 3239, 3062, 1670, 1668, 1586, 1455, 856. Anal. Calcd for $C_{15}H_{17}ClN_2O_3$: C, 58.35; H, 5.55; N, 9.07. Found: C, 58.23; H, 5.21; N, 9.2.

2-(4-methoxyphenyl)-*N*-(2-morpholino-2-oxoethyl)-2-oxoacetamide (53).



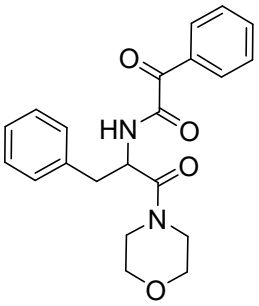
Starting material: 1,3-oxazol-2-oxime 150 mg (0.49 mmol). The crude material was purified by column chromatography (PE/EtOAc 2:8) to give 70 mg of product as white solid (yield 46%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 8.33-8.8.30 (m, 2H, AA′XX′), 7.97 (br s, NH), 6.94-6.91 (m, 2H, AA′XX′), 4.16 (br d, 2H), 3.87 (s, 3H), 3.71-3.65 (m, 6H), 3.46-43 (m, 2H);^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 185.3, 165.9, 164.8, 162.8, 133.8, 126.3, 114.0, 66.8, 66.4, 55.7, 45.0, 42.4, 41.0; *m/z* 307 $(M+H)^+$; IR ν_{max}/cm^{-1} (KBr) 3349, 3078, 1682, 1647, 1594, 1474, 1257, 861; mp 169-169.5 °C. Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: 58.93; H, 6.24; N, 9.36.

***N*-(2-morpholino-2-oxoethyl)-2-oxo-2-(thiophen-2-yl)acetamide (54).**



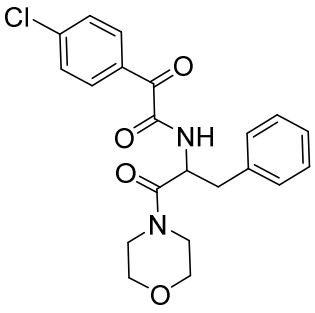
Starting material: 1,3-oxazol-2-oxime 150 mg (0.54 mmol). The crude material was purified by column chromatography (PE/EtOAc 2:8) to give 85 mg of product as white solid (yield 56%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 8.36 (d, J = 4.0 Hz, 1H), 8.19 (br s, NH), 7.80 (d, J = 4.8 Hz, 1H), 7.18-7.15 (m, 1H), 4.15 (d, J = 4.5 Hz, 2H), 3.71-3.66 (m, 6H), 3.53-3.42 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 177.6, 165.7, 161.0, 138.5, 138.0, 136.9, 128.4, 66.6, 66.40, 42.5, 41.1, 40.7; *m/z* 283 $(M+H)^+$; IR ν_{max}/cm^{-1} (KBr) 3371, 3071, 1691, 1658, 1495, 1359, 1275, 737; mp 193-194 °C. Anal. Calcd for $C_{12}H_{14}N_2O_4S$: C, 51.05; H, 5.00; N, 9.92. Found: C, 51.34; H, 5.36; N, 10.10.

_N_-(1-morpholino-1-oxo-3-phenylpropan-2-yl)-2-oxo-2-phenylacetamide (55).



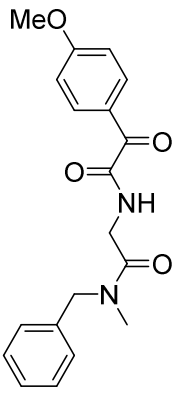
Starting material: 1,3-oxazol-2-oxime 150 mg (0.41 mmol). The crude material was purified by column chromatography (PE/EtOAc 4:6) to give 76 mg of product as white solid (yield 50%). Mixture of rotamers, signals are referred to the main rotamer: ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 8.21 (d, J = 8.2 Hz, 2H), 7.87 (br d, NH), 7.64-7.59 (br t, 1H), 7.52-7.38 (br t, 2H), 7.34-7.23 (m, 5H), 5.18 (br q, 1H), 3.62-3.44 (m, 6H), 3.16-2.94 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 187.4, 169.0, 161.6, 135.8, 134.5, 131.0, 129.7, 129.6, 128.8, 128.6, 127.4, 66.4, 66.0, 49.7, 46.1, 42.4, 39.8; *m/z* 367 $(M+H)^+$; IR ν_{max}/cm^{-1} (KBr) 3277, 3027, 1665, 1642, 1524, 1486, 1211; mp 151.5-152 °C. Anal. Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.95; H, 6.40; N, 7.34.

2-(3-chlorophenyl)-_N_-(1-morpholino-1-oxo-3-phenylpropan-2-yl)-2-oxoacetamide (56).



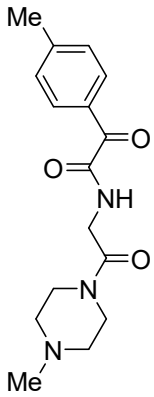
Starting material: 1,3-oxazol-2-oxime 150 mg (0.38 mmol). The crude material was purified by column chromatography (PE/EtOAc 5:5) to give 78 mg of product as white solid (yield 52%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 8.19 (d, J = 8.1 Hz, 2H), 7.93 (br d, NH), 7.42 (br d, 2H), 7.34-7.22 (m, 5H), 5.16 (br q, 1H), 3.64-3.58 (m, 2H), 3.55-3.25 (m, 4H), 3.14-2.87 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 185.8, 169.0, 160.9, 141.3, 135.7, 132.6, 131.6, 129.7, 129.0, 128.9, 127.5, 66.5, 66.1, 49.8, 46.1, 42.4, 39.9; *m/z* 401 $(M+H)^+$; IR ν_{max}/cm^{-1} (KBr) 3246, 3064, 1665, 1617, 1586, 1476, 1218, 858; mp 128-129 °C. Anal. Calcd for $C_{21}H_{21}ClN_2O_4$: C, 62.92; H, 5.28; N, 6.99. Found: C, 63.04; H, 5.46; N, 6.74.

_N_-benzyl-2-(2-(4-methoxyphenyl)-2-oxoacetamido)-_N_-methylacetamide (57).



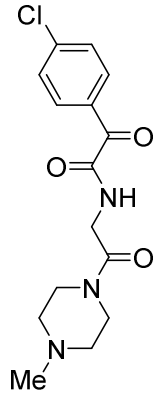
Starting material: 1,3-oxazol-2-oxime 150 mg (0.44 mmol). The crude material was purified by column chromatography (PE/EtOAc 5:5) to give 133 mg of product as colorless oil (yield 88%). Mixture of rotamers, signals are referred to the main rotamer: ^{1}H-NMR (300 MHz, $CDCl_3$) δ_H 8.35-8.31 (m, 2H), 8.05 (br s, NH), 7.38-7.14 (m, 5H), 6.94-6.89 (m, 2H), 4.61 (s, 2H), 4.24-4.20 (br t, 2H), 3.85 (s, 3H), 2.92 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ_C 185.4, 167.4, 164.7, 162.8, 136.4, 133.7, 129.2, 128.8, 127.8, 126.3, 113.9, 55.6, 51.3, 41.3, 33.7; *m/z* 341 $(M+H)^+$; IR ν_{max}/cm^{-1} (KBr) 3387, 3300, 1646, 1653, 1511, 1453, 1263, 1028. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.14; H, 6.12; N, 8.46.

_N_-(2-(4-methylpiperazin-1-yl)-2-oxoethyl)-2-oxo-2-(p-tolyl)acetamide (58).



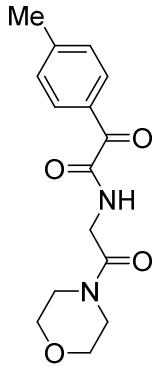
Starting material: 1,3-oxazol-2-oxime 150 mg (0.50 mmol). The crude material was purified by column chromatography (DCM/MeOH 97:3) to give the product as yellow solid (75 mg, 50% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 8.19 (br d, 2H, AA′XX′), 7.92 (br s, NH), 7.27-7.25 (m, 2H, AA′XX′) partially overlapped to the solvent, 4.17 (d, *J* = 4.2 Hz, 2H), 3.68 (br t, 2H), 3.47 (br t, 2H), 2.44 (br s, 7H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ_C 186.8, 165.5, 162.5, 145.5, 131.0, 130.7, 129.2, 54.6, 54.3, 45.8, 44.3, 41.9, 40.9, 21.8; *m/z* 304 $(M+H)^+$; IR ν_{max}/cm^{-1} (KBr) 3351, 3000, 1669, 1642, 1504, 1475, 1276, 789; mp 97-98 °C. Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.67; H, 7.12; N, 14.12.

2-(4-chlorophenyl)-_N_-(2-(4-methylpiperazin-1-yl)-2-oxoethyl)-2-oxoacetamide (59).



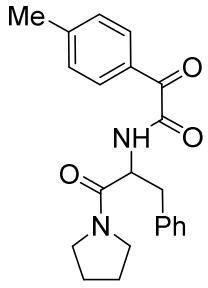
Starting material: 1,3-oxazol-2-oxime 150 mg (0.47 mmol). The crude material was purified by column chromatography (DCM/MeOH 97:3) to give the product as yellowish solid (64 mg, 42% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.23 (d, *J* = 8.4 Hz, 2H, AA′XX′), 7.98 (br s, NH), 7.41 (d, *J* = 8.4 Hz, 2H, AA′XX′), 4.12 (d, *J* = 4.0 Hz 2H), 3.63 (br t, 2H), 3.43 (br t, 2H), 2.40-2.37 (m, 4H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ_C 185.7, 165.3, 161.7, 141.0, 132.4, 131.5, 128.8, 54.7, 54.4, 46.0, 44.4, 42.0, 40.9; *m/z* 324 $(M+H)^+$; IR ν_{max}/cm^{-1} (KBr) 3344, 1673, 1645, 1586, 1443, 1273, 857; mp 127-128 °C. Anal. Calcd for $C_{15}H_{18}ClN_3O_3$: C, 55.64; H, 5.60; N, 12.98. Found: C, 55.54; H, 5.42; N, 12.78.

_N_-(2-morpholino-2-oxoethyl)-2-oxo-2-(p-tolyl)acetamide (60).



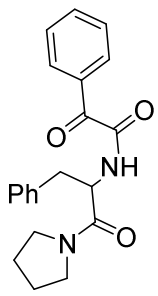
Starting material: 1,3-oxazol-2-oxime 150 mg (0.52 mmol). The crude material was purified by column chromatography (DCM/MeOH 97:3) to give the product as yellow solid (98 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.20 (d, J = 8.2 Hz, 2H), 7.92 (br s, NH), 7.28-7.25 (m, 2H) partially overlapped to the solvent, 4.17 (d, J = 4.0 Hz, 2H), 3.71-3.67 (m, 6H), 3.47-3.46 (m, 2H), 2.42 (s, 3H); ^{13}C **NMR** (100 MHz, CDCl3) δ_C 186.6, 165.8, 162.4, 145.6, 131.1, 130.7, 129.2, 66.6, 66.3, 44.9, 42.3, 40.8, 21.8; *m/z* 291 $(M+H)^+$; IR ν_{max}/cm^{-1} (KBr) 3430, 3423, 1695, 1660, 1494, 1276, 785; mp 83-84 °C. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 62.34; H, 6.43; N, 9.78.

2-oxo-_N_-(1-oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)-2-(_p_-tolyl)acetamide (61).



Starting material: 1,3-oxazol-2-oxime 150 mg (0.41 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 7:3) to give the product as a light yellow solid (78 mg, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.12 (d, J = 8.0 Hz, 2H), 7.79 (br d, NH), 7.28-7.23 (m, 7H), 4.95 (br q, 1H), 3.47-3.30 (m, 3H), 3.09 (d, J = 7.4 Hz, 2H), 2.69-2.63 (m, 1H), 2.40 (s, 3H), 1.80-1.55 (m, 4H); ^{13}C NMR (100 MHz, CDCl3) mixture of rotamers: δ_C 186.8, 168.6, 161.7, 145.5, 136.1, 132.0, 131.1, 130.7, 129.5, 128.5, 127.1, 52.4, 46.3, 45.8, 39.5, 25.8, 23.9, 21.8; *m/z* 365 $(M+H)^+$; IR ν_{max}/cm^{-1} (KBr) 3239, 3062, 1680, 1662, 1624, 1454, 1228, 763; mp 88-89 °C. Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.69. Found: C, 72.52; H, 6.65; N, 7.65.

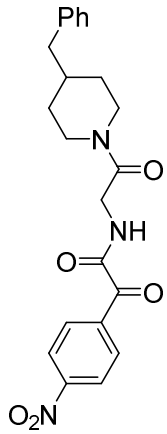
2-oxo-_N_-(1-oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-yl)-2-phenylacetamide (62).



Starting material: 1,3-oxazol-2-oxime 150 mg (0.43 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 7:3) to give the product as a yellowish solid (110 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 7.8 Hz, 2H), 7.76 (br d, NH), 7.60 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.31-7.25 (m, 6H), 4.96 (br q, 1H), 3.49-3.36 (m, 3H), 3.10 (d, J = 7.4 Hz, 2H), 2.70-2.64 (m, 1H), 1.81-1.56 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) mixture of rotamers: δ_C 187.4, 168.6, 161.6, 136.0, 134.2, 133.2, 130.8, 129.4, 128.8, 128.5, 128.4, 128.4, 127.0, 52.4, 46.3, 45.8, 39.4, 25.7, 23.9; *m/z* 351 $(M+H)^+$; IR ν_{max}/cm^{-1} (KBr) 3240, 3062, 1682,

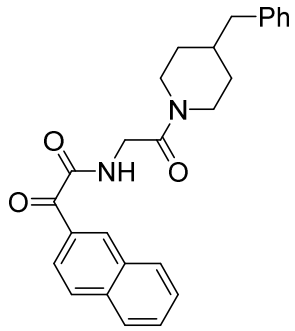
1664, 1621, 1555, 1454, 1222; mp 118-119 °C. Anal. Calcd for $C_{21}H_{22}N_2O_3$: , 71.98; H, 6.33; N, 7.99. Found: C, 72.21; H, 6.12; N, 8.21.

_N_-(2-(4-benzylpiperidin-1-yl)-2-oxoethyl)-2-(4-nitrophenyl)-2-oxoacetamide (63).



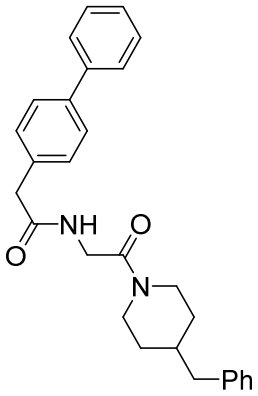
Starting material: 1,3-oxazol-2-oxime 150 mg (0.37 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 5:5) to give the product as a yellowish solid (100 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.48 (d, J = 8.6 Hz, 2H), 8.31 (d, J = 8.8 Hz, 2H), 8.08 (br s, NH), 7.31-7.12 (m, 5H), 4.59 (br d, 1H), 4.17-4.14 (m, 2H), 3.72 (br d, 1H), 3.02 (br t, 1H), 2.58-2.55 (m, 2H), 1.83-1.76 (m, 3H), 1.21-1.15 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 185.5, 164.8, 160.8, 150.8, 139.6, 137.9, 132.1, 129.0, 128.4, 126.2, 123.4, 44.8, 42.8, 42.6, 41.0, 38.0, 32.2, 31.5; *m/z* 410 $(M+H)^+$; IR ν_{max}/cm^{-1} (KBr) 3280, 1665, 1651, 1602, 1519; mp 78-79 °C. Anal. Calcd for $C_{22}H_{23}N_3O_5$: C, 64.54; H, 5.66; N, 10.26. Found: C, 64.78; H, 5.84; N, 10.02.

_N_-(2-(4-benzylpiperidin-1-yl)-2-oxoethyl)-2-(naphthalen-2-yl)-2-oxoacetamide (64).



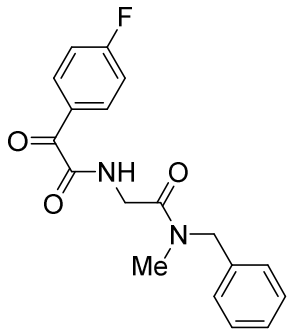
Starting material: 1,3-oxazol-2-oxime 150 mg (0.36 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 5:5) to give the product as a sticky solid (81 mg, 54% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.06 (s, 1H), 8.18 (br d, AA'XX', 1H), 8.06 (br s, NH), 7.98 (d, J = 8.1 Hz, 1H), 7.90-7.85 (m, 2H), 7.64-7.60 (m, 1H), 7.56-7.53 (m, 1H), 7.31-7.19 (m, 3H), 7.13 (br d, 2H), 4.60 (br d, 1H), 4.22-4.19 (m, 2H), 3.75 (br d, 1H), 3.01 (br t, 1H), 2.61-2.55 (m, 2H), 1.82-1.72 (m, 3H), 1.25-1.14 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 186.9, 165.1, 162.3, 139.6, 136.1, 134.5, 132.3, 130.5, 130.2, 129.2, 129.0, 128.3, 128.3, 127.7, 126.7, 126.1, 125.1, 44.8, 42.8, 42.6, 41.0, 38.0, 32.2, 31.5; *m/z* 415 $(M+H)^+$; IR ν_{max}/cm^{-1} (KBr) 3280, 1665, 1651, 1602, 1519. Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76. Found: C, 75.36; H, 6.46; N, 6.73.

2-([1,1'-biphenyl]-4-yl)-*N*-(2-(4-benzylpiperidin-1-yl)-2-oxoethyl)-2-oxoacetamide (65).



Starting material: 1,3-oxazol-2-oxime 150 mg (0.34 mmol). The crude material was purified by column chromatography (*n*-hexane/AcOEt 5:5) to give the product as a white solid (112 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.38 (br d, AA'XX', 2H), 8.01 (br s, NH), 7.70 (br d, AA'XX', 2H), 7.64 (br d, AA'XX', 2H), 7.49-7.38 (m, 3H), 7.31-7.19 (m, 3H), 7.13 (br d, AA'XX', 2H), 4.60 (br d, 1H), 4.24-4.12 (m, 2H), 3.74 (br d, 1H), 3.01 (br t, 1H), 2.64-2.55 (m, 3H), 1.82-1.75 (m, 3H), 1.25-1.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 186.7, 165.16, 162.3, 146.9, 139.7, 139.6, 132.0, 131.6, 129.0, 128.9, 128.4, 128.3, 127.3, 127.1, 126.1, 44.8, 42.8, 42.6, 41.0, 38.0, 32.2, 31.5; *m/z* 441 $(M+H)^+$; IR ν_{max}/cm^{-1} (KBr) 3364, 2919, 1682, 1628, 1475; mp 140-141 °C. Anal. Calcd for $C_{28}H_{28}N_2O_3$: C, 76.34; H, 6.41; N, 6.36. Found: C, 76.29; H, 6.42; N, 6.78.

***N*-Benzyl-2-(2-(4-fluorophenyl)-2-oxoacetamido)-*N*-methylacetamide (66).**



Starting material: 1,3-oxazol-2-oxime 150 mg (0.46 mmol). The crude material was purified by column chromatography (PE/ EtOAc 5:5) to give 106 mg of product as yellow oil (yield 70%). Mixture of rotamers, signals are referred to the main rotamer: ^{1}H NMR (300 MHz, CDCl3) δ_H 8.37−8.29 (m, 2H), 8.11 (br s, NH), 7.34−7.21 (m, 4H), 7.19−7.05 (m, 3H), 4.59 (s, 2H), 4.20 (d, J = 4 Hz, 2H), 2.91 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ_C 185.4, 167.2, 164.8, 162.1, 136.4, 134.1, 129.7, 128.7, 128.1, 127.7, 115.9, 51.3, 41.2, 33.6; MS *m/z* 329 $(M + H)^+$; IR νmax/cm^{-1} (KBr) 3377, 2926, 1647, 1595, 1230, 1089. Anal. Calcd for $C_{18}H_{17}FN_2O_3$: C, 65.84; H, 5.22; N, 8.53. Found: C, 65.52; H, 4.98; N, 8.76.

5.4 References

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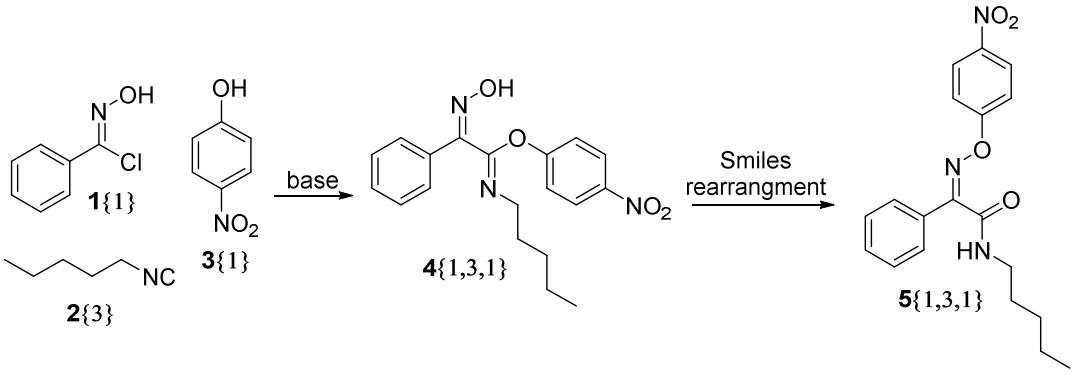
Chapter 6

Solution-phase parallel synthesis of aryloxyimino amides via a novel multicomponent reaction among aromatic *Z*-chlorooximes, isocyanides, and electron-deficient phenols

6.1 Results and discussion

As a continuation of our previous studies, we questioned whether an electron deficient phenol could be a good nucleophile third component able to intercept the nitrilium ion, generated reacting an isocyanide with a nitrile *N*-oxide to obtain aryloxyiminoamides. After formation of the imidate, the hydroxyl group of the oxime, which is properly positioned, thanks to the stereoselective addition of isocyanide to the nitrile *N*-oxide,[1] can trigger a Smiles rearrangement,[2,3] in a manner reminiscent of the Passerini−Smiles reaction developed by Prof. El Kaïm.[4,5] In this case, a six-membered transition state should occur,[6] contrary to the typical Smiles rearrangement which forms a five-membered transition state (Scheme 1).



Scheme 1. Three-component synthesis of imidate intermediate and following Smiles rearrangement.

When the reaction was carried out in the presence of 2 equivalents of triethylamine (TEA), in dichloromethane at room temperature (2 h), we obtained a mixture from which the desired product **(5) {1,3,1}** and the imidate **(4) {1,3,1}** could be separated with yields of 14% and 20%, respectively. These two compounds were easily identified via ^{13}C NMR (see Experimental section). The result did not change when the reaction was heated at reflux in toluene (6 h). We

reasoned that the difficulty in triggering the Smiles rearrangement could be due to the inability of TEA (pK_a= 10.65) to fully deprotonate the oxime (pK_a = 10.78). The use of 2 equivalents of potassium tert-butoxide (pK_a = 18) did not, however, improve the result. Under such conditions the reaction was not clean and we were able to isolate the desired compound **(5) {1,3,1}** only in very low yield (less than 10%). We therefore searched for a base stronger than TEA but weaker than *t*-BuOK, and we opted for 2 equivalents of DBU (pK_a = 12) which allowed us to isolate desired product **(5) {1,3,1**} in 20% yield and without observing the formation of the imidate.

In this case, as with TEA, heating the reaction at 80 °C in toluene (6 h) did not change the yield. Reasoning that, while the formation of the nitrile *N*-oxide species required an equimolar amount of base, the Smiles rearrangement occurring after the addition of *p*-nitrophenol to the nitrilium ion could proceed in the presence of a catalytic amount of base. Thus, by reducing the amount of DBU to 1.2 equivalents in dicloromethane (room temperature, overnight) we were able to isolate the product in 37% yield. Again, the imidate was not isolated. Such yield represented a notable advance, since *p*-nitrophenol **(3){1}** was reported to be more problematic than *o*-nitrophenol in favoring the Smiles rearrangement and El Kaïm shows it was less reactive in the Ugi-Smiles,[7,8] and completely non reactive in the Passerini-Smiles rearrangement.[4,5]

We were pleased to find the aryloxyimino amide to be stable, in particular with respect to a potential Beckmann rearrangement because of the presence of a nitrophenol leaving group. No sign of Beckmann product could be detected after refluxing in toluene for several hours. As there was in literature only one precedent for the synthesis of aryloxyimino amides,[9] with the optimized conditions for this novel multicomponent reaction in our hands, and after verifying that both the work up and the chromatographic purification were experimentally easy, we explored the

generality of this transformation by employing it in the combinatorial parallel synthesis of a library of compounds.

Three aryl-*Z*-chlorooximes **1{1−3}** bearing either electron-deficient or electro-donor substitutents, three isocyanides **2{1−3}**, and five electron-deficient arenes **3{1−5}** were used (Figure 1). By combination of these reagents in a three-component reaction a library of 45 compounds should be obtained.

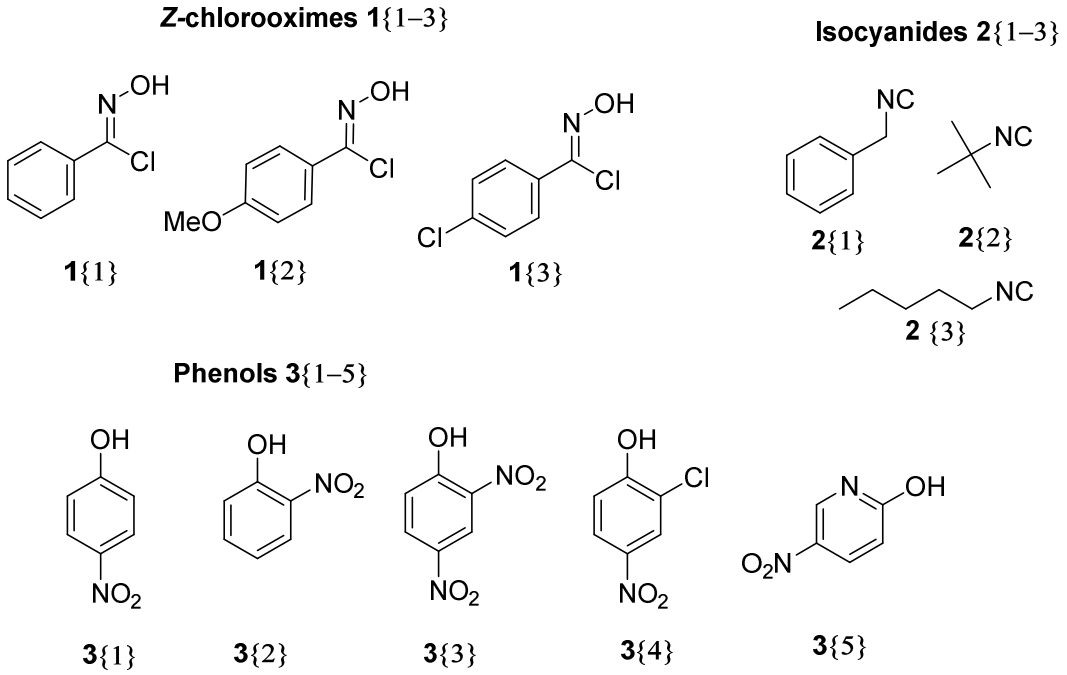


Figure 1. Building blocks used.

To optimize the management of such a large number of reactions and minimize the chances of trivial operator errors (such as miscalculations which could compromise the outcome of some of the reactions), we used a computer program, prepared by Dr. Massaroti, called MCRcombiS, able to manage large amounts of data and quickly output the correct quantities/concentrations of reagents (mmol, mg/mL, etc.) to be used in each reaction.[10]

As shown in Figure 2 the reactions proceeded efficiently (22-63% yield) and only in four cases we were not able to isolate the desired aryloxyimino amide

(compounds in red). The reaction does not seem to be very sensitive to steric or electronic factors.

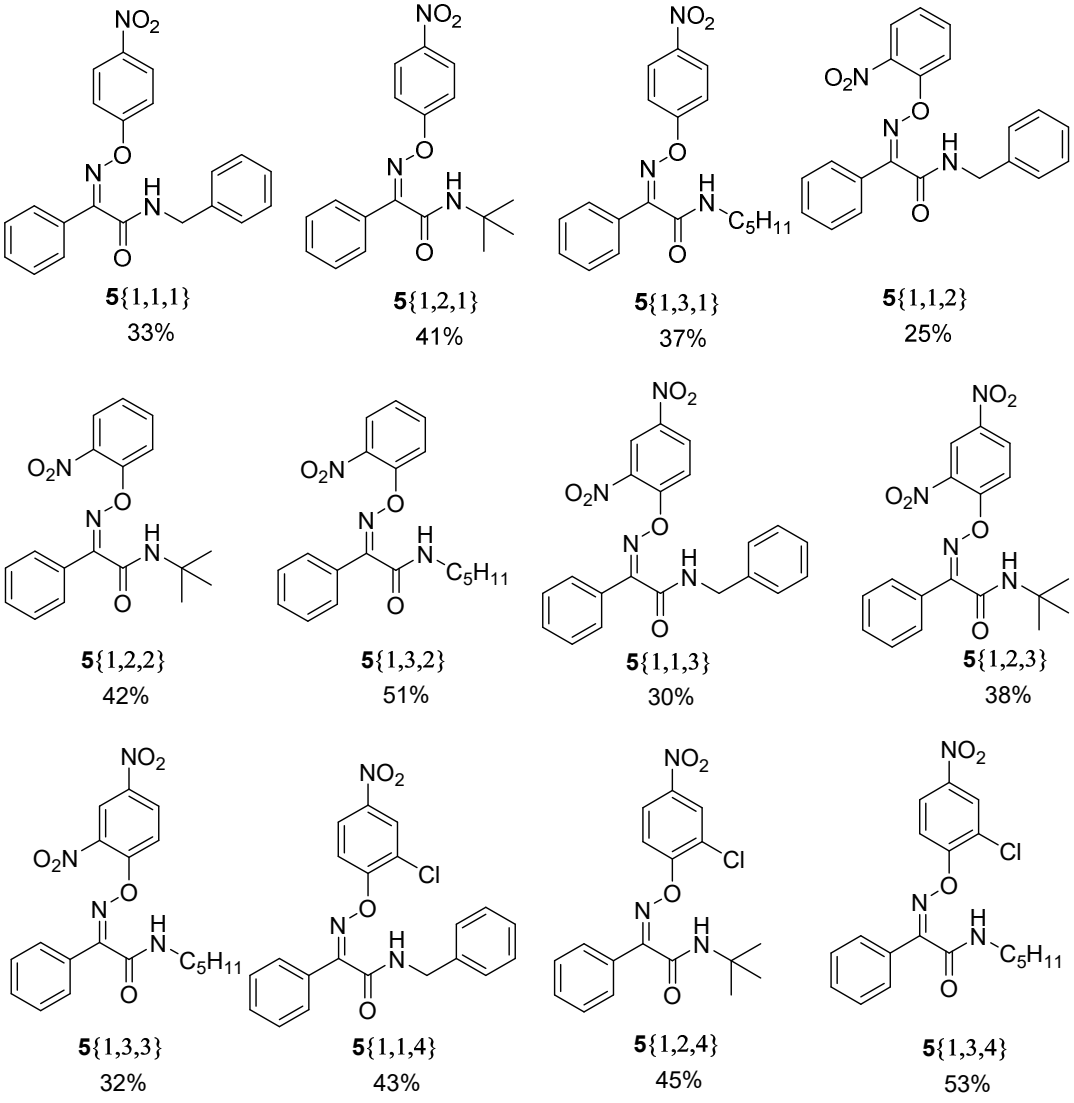


Figure 2. Aryloxymino amide synthesized (in red the products of the reactions that have not been successful).

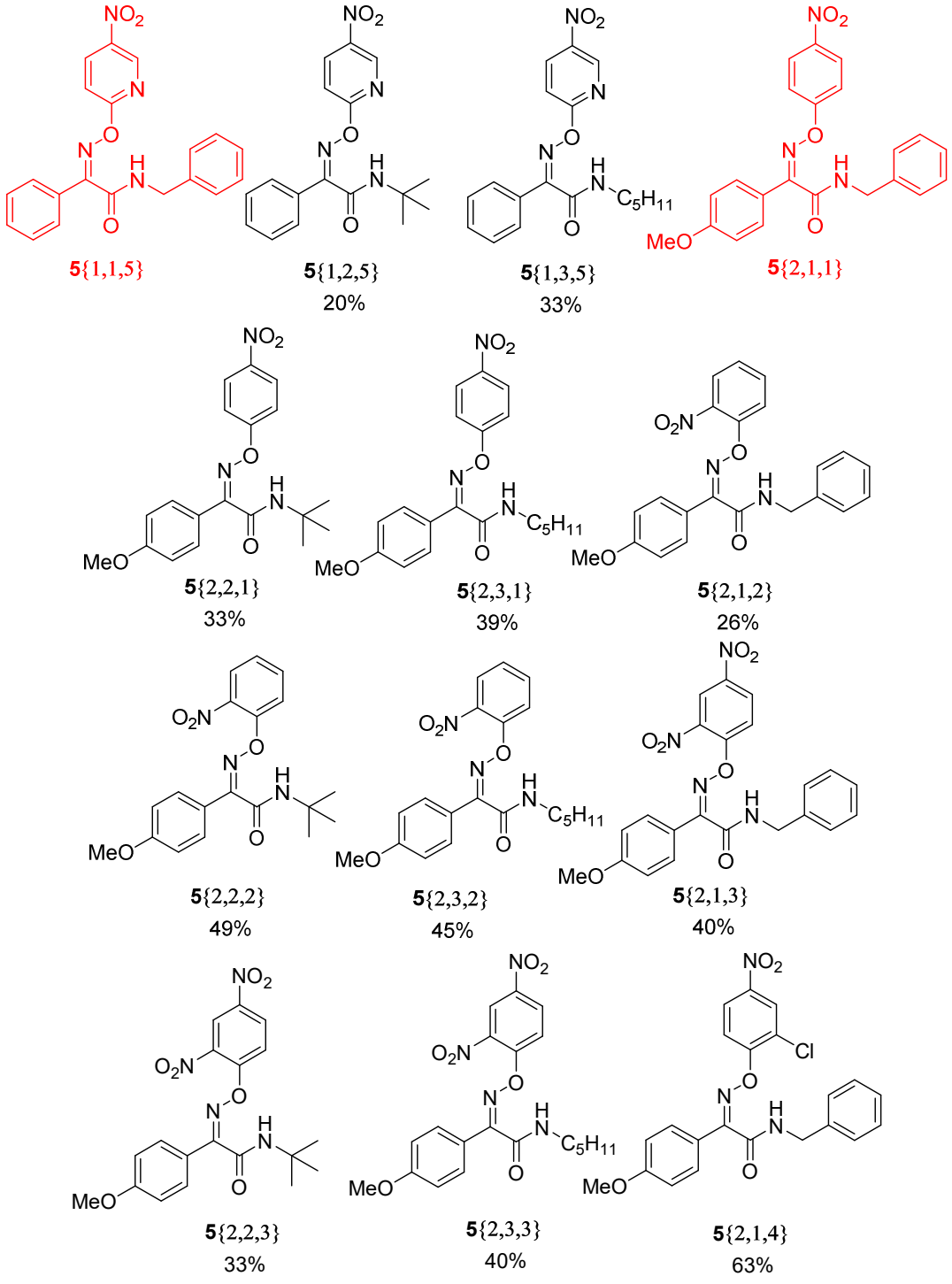


Figure 2. Aryloxymino amide synthesized (in red the products of the reactions that have not been successful) (*continued).*

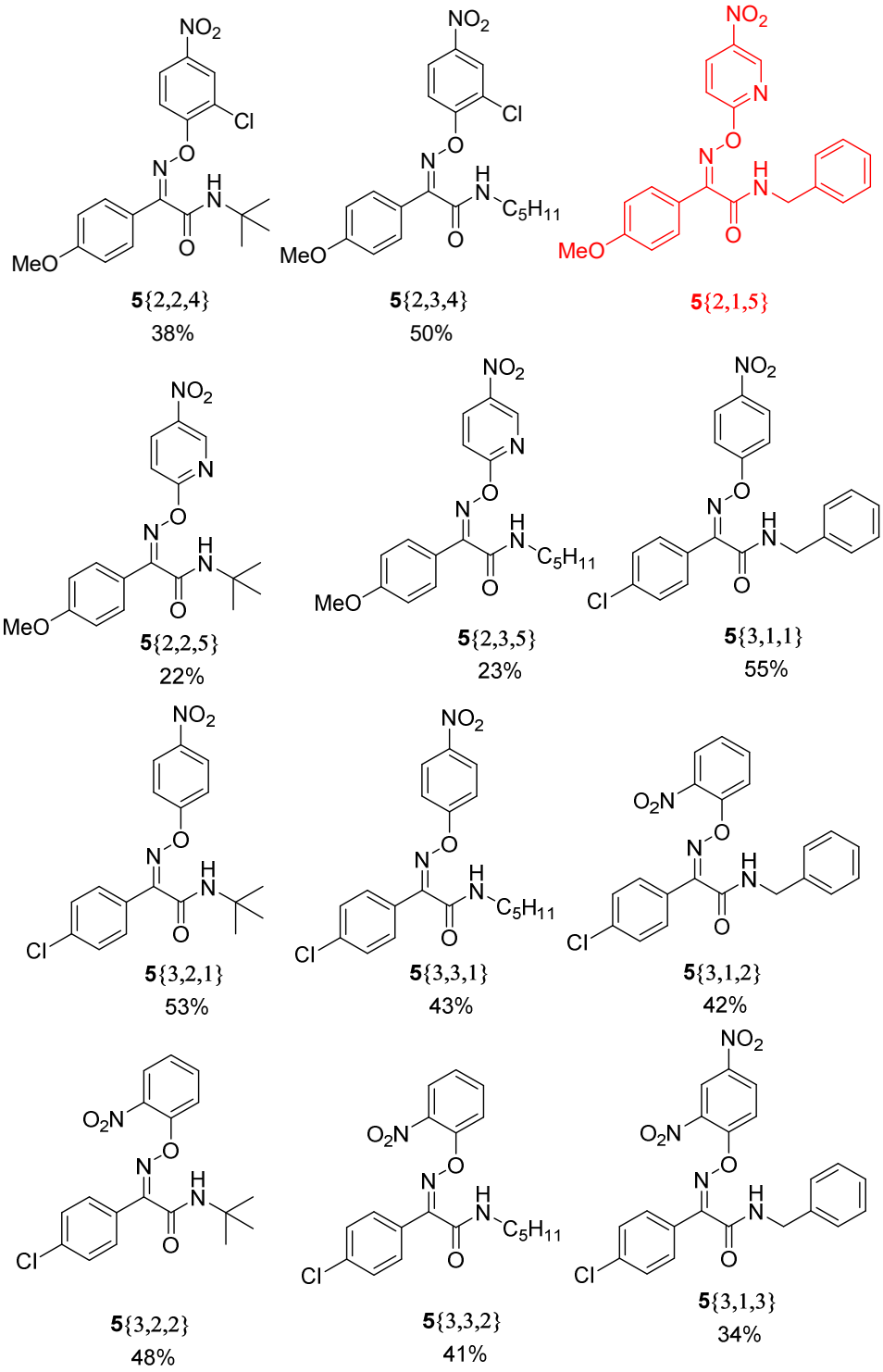


Figure 2. Aryloxymino amide synthesized (in red the products of the reactions that have not been successful) (*continued).*

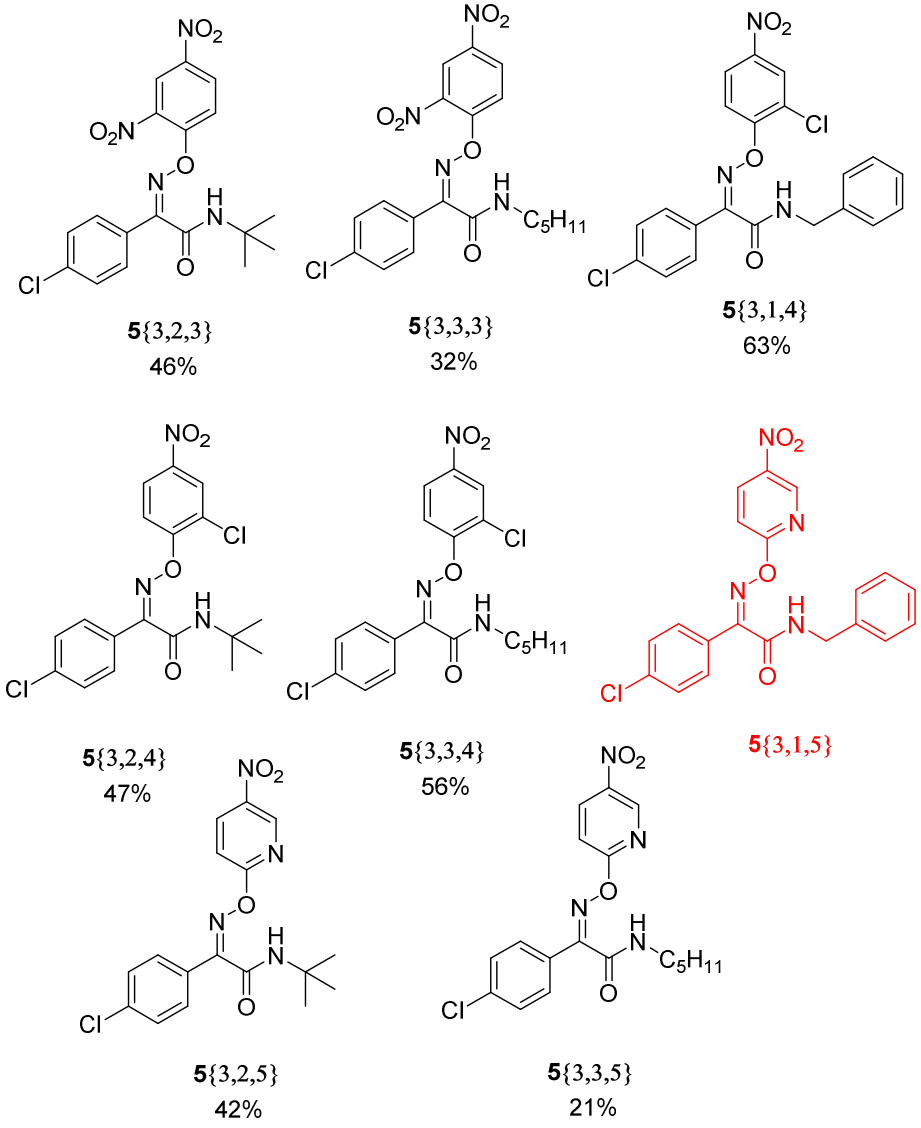


Figure 2. Aryloxymino amide synthesized (in red the products of the reactions that have not been successful) (*continued).*

The purity of all the final compounds were evaluated by HPLC-UV-MS. Thus, the application of this novel multicomponent reaction to combinatorial synthesis afforded 41 of the expected 45 compounds with an overall success rate for this library of 93% and an average purity of 93%, after a simple silica gel filtration.

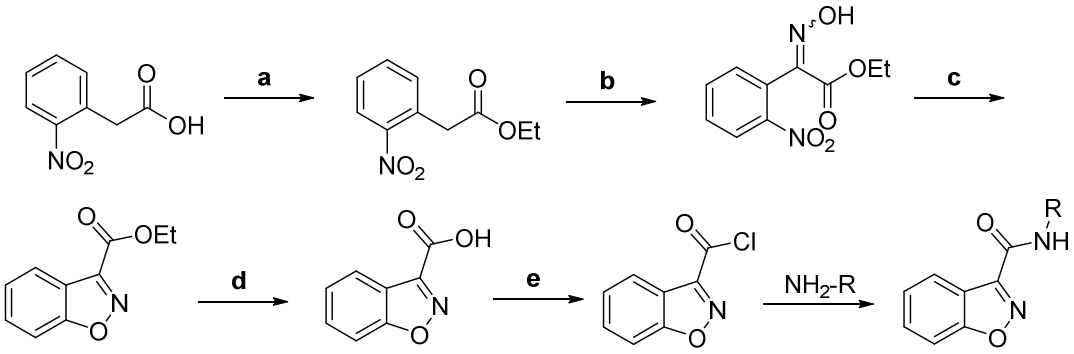
Four compounds [**5{1,3,5}**, **5{2,3,1}**, **5{2,3,5}** and **5{3,3,5}**] were found to be mixtures of *Z* and *E* isomers of the oxime, detected by both ^{1}H NMR and HPLC, while six compounds [**5{1,1,1}**, **5{1,2,1}**, **5{1,1,2}**, **5{2,2,1}**, **5{2,1,2}**, and **5{2,2,2}**] showed the presence of less than 5% of the *E* isomer visible only by HPLC. In this case, the *E*-isomer was easily removed by crystallization (Table 1).

Compound	Purity A	Purity B	Compound	Purity A	Purity B
5{1,1,1}	98.1*	98.1*	**5{2,2,2}**	96.5*	96.5*
5{1,2,1}	99.2*	98.7*	**5{2,3,2}**	93.6	95.1
5{1,3,1}	93.0	93.4			
5{1,1,2}	97.0*	99.9*	**5{2,1,3}**	79.8	80.0
5{1,2,2}	94.8	95.0	**5{2,2,3}**	83.5	84.6
5{1,3,2}	96.1	96.1	**5{2,3,3}**	86.1	85.8
5{1,1,3}	90.3	90.9	**5{2,1,4}**	90.9	90.5
5{1,2,3}	90.4	91.1	**5{2,2,4}**	89.6	89.6
5{1,3,3}	91.2	92.4	**5{2,3,4}**	91.8	91.4
5{1,1,4}	97.9	98.3	**5{2,2,5}**	85.5	86.4
5{1,2,4}	93.9	95.7	**5{2,3,5}**	85.7	90.8
5{1,3,4}	95.9	95.3	**5{3,1,1}**	90.2	89.7
5{1,2,5}	93.5	92.5	**5{3,2,1}**	94.6	94.3
5{1,3,5}	88.9*	92.4*	**5{3,3,1}**	95.5	95.6
5{2,2,1}	98.0*	96.0*	**5{3,1,2}**	93.9	95.4
5{2,3,1}	95.3*	95.3*	**5{3,2,2}**	96.6	96.6
5{2,1,2}	94.1*	92.0*	**5{3,3,2}**	97.7	97.6

Compound	Purity A	Purity B	Compound	Purity A	Purity B
5{3,1,3}	87.2	83.4			
5{3,2,3}	93.4	91.7	**5{3,3,4}**	96.6	96.5
5{3,3,3}	96.1	95.5	**5{3,2,5}**	96.9	98.5
5{3,1,4}	97.1	97.3	**5{3,3,5}**	97.4*	98.5*
5{3,2,4}	95.3	96.2			

Table 1. Purity of aryloxyimino amides synthesized. *Purity refers to the mixture of *Z* and *E* isomers

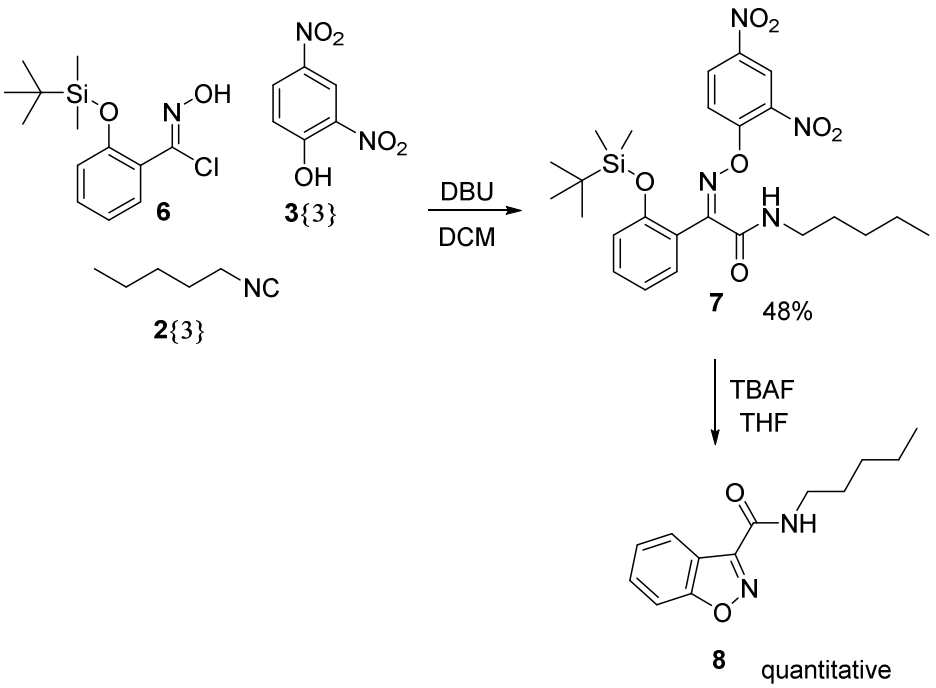
Although, aryloxyimino amides are interesting compounds per se, we were also intrigued by their potential use as intermediates for further synthetic transformations. As an example, we explored the synthesis of benzo[*d*]isoxazole-3-carboxamides, a well-known scaffold in medicinal chemistry, which usually requires a long and tedious synthesis (Scheme 2).[11]



Scheme 2. Classical synthesis of benzo[*d*]isoxazole-3-carboxamides. (**a**) EtOH, H_2SO_4, toluene reflux; (**b**) isoamyl nitrite, NaOEt, EtOH; (**c**) NaH, diglyme; (**d**) 70% H_2SO_4; (**e**) $SOCl_2$.

As it has been demonstrated that S_N2 reactions can occur at the sp*2* nitrogen of oximes,[12–14] we reasoned that the aryloxyimino amide **7**, derived from the *Z*-

chlorooxime of salicylaldeyde **6** may, after deprotection, triggers an intramolecular S_N2 type reaction affording benzo[*d*]isoxazole-3-carboxamides **8** (Scheme 3). We were pleased to find that, when TBAF was used to cleave the silyl protecting group, the desired transformation occurred in quantitative yield.



Scheme 3. Synthesis of benzo[*d*]isoxazole-3-carboxamides by MCR.

6.2 Conclusions

In conclusion, we reported in this Chapter the discovery of a novel multicomponent reaction among *Z*-chlorooximes, isocyanides and electron-deficient arenes. The oxime-mediated Smiles rearrangement drives the reaction from the less stable imidates toward the formation of stable amides.

The reaction is robust enough to be used in a combinatorial process, and one example of use as a synthetic intermediate for the preparation of a 3-substituted benzo[*d*]isoxazole was demonstrated, raising the possibility of a shorter synthetic pathway for the production of this heterocycle.

6.3 Experimental section

Solvents and Reagents. Commercially available solvents and reagents were used without further purification. Dichloromethane was dried by distillation over P_2O_5 and stored over activated molecular sieves (4 Å). When needed, the reactions were performed in oven-dried glassware under a positive pressure of dry nitrogen. **Chromatography.** Column chromatography was performed on silica gel 60 (Kieselgel 230−400 mesh ASTM) using the indicated eluents. Thin layer chromatography (TLC) was carried out on 5 × 20 cm plates with a layer thickness of 0.25 mm (Silica gel 60 F254). When needed they were visualized using $KMnO_4$ reagent.

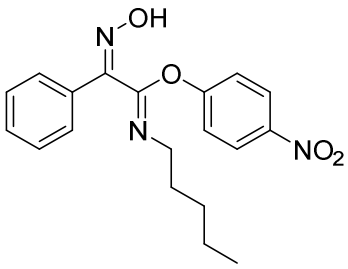
Spectra. Infrared spectra were recorded on a FT-IR with absorption maxima (νmax) recorded in wavenumbers (cm^{-1}). NMR spectra were recorded using a 300 or 400 MHz spectrometer. Chemical shifts (δ) are quoted in parts per million and referenced to the residual solvent peak. The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; hept, heptet; m, multiplet; br, broad singlet. Coupling constants (J) are reported in Hertz (Hz). HRMS were recorded on ORBITRAP mass spectrometer equipped with an ESI source. Melting points were determined and remain uncorrected. Chloroximes **1{1}**, **1{2}**, and **1{3}** are not new, and they were prepared following literature procedure.[15]

General Preparation of Aryloxyimino Amides.

The chlorooxime (1 eq.) was dissolved in dry dichloromethane and isocyanide (1 eq.), phenol (1.1 eq.), and DBU (1.2 eq.) were added. The reaction was stirred at room temperature under a nitrogen atmosphere until all the chlorooxime was consumed (typically overnight as judged by TLC). The reaction mixture was

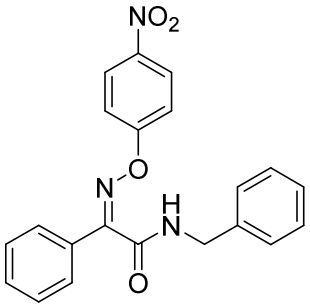
concentrated under reduced pressure, and the crude material was purified by column chromatography.

(2*Z*)-4-nitrophenyl 2-(hydroxyimino)-*N*-pentyl-2-phenylacetimidate, 4{1,3,1}



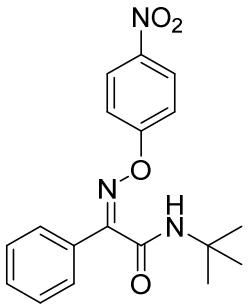
The crude material was purified by column chromatography (PE/EtOAc 95:5, 9:1) to give the product as white solid. ^{1}H-NMR (300 MHz, $CDCl_3$, CD_3OD) δ 8. 16 (d, *J* = 7.3 Hz, 2H), 7.58 (d, 2H), 7.37 (m, 5H), 7.08 (br s, NH), 3,12 (br s, 2H), 1.45-1.33 (m, 2H), 1.15 (m, 4H), 0.57 (m, 3H); ^{13}C-NMR (75 MHz, CDCl3) δ 158.3, 153.4, 148.9, 144.4, 131.2, 130.2, 129.0, 128.6, 125.9, 125.1, 122.4, 50.1, 30.2, 29.5, 22.3, 13.9.

(*Z*)-*N*-benzyl-2-((4-nitrophenoxy)imino)-2-phenylacetamide, 5{1,1,1}



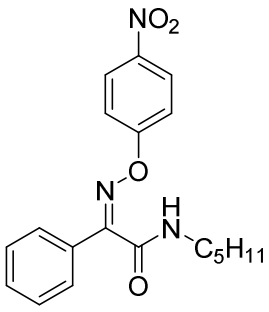
The crude material was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as yellow solid (yield 33%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.23-8.13 (m, 2H), 7.81-7.69 (m, 2H), 7.55-7.18 (m, 10H), 6.52 (br t, NH), 4.67 (d, *J* = 5.8 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 163.4, 162.2, 157.6, 142.9, 137.4, 131.8, 129.6, 129.1 (2C), 128.9, 128.0, 127.4, 125.8, 114.5, 43.6; νmax/cm^{-1} (KBr) 3412, 3258, 1646, 1591, 1342, 919; mp 151-152 °C; HRMS (EI+): *m/z*: calcd for $C_{21}H_{17}N_3O_4$: 375.1219, Found: 375.1220.

(*Z*)-*N*-(tert-butyl)-2-((4-nitrophenoxy)imino)-2-phenylacetamide, 5{1,2,1}



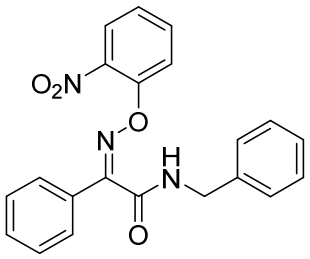
The crude material was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as white solid (yield 41%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.13-8.09 (m, 2H), 7.70-7.67 (m, 2H), 7.44-7.34 (m, 3H), 7.23-7.20 (m, 2H), 6.21 (br s, NH), 1.45 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 136.5, 161.5, 157.7, 142.5, 131.5, 129.7, 128.9, 127.3, 125.7, 114.3, 52.9, 28.7; νmax/cm-1 (KBr) 3280, 2969, 1646, 1589, 1519, 1341, 918; mp 154.3-155 °C; HRMS (EI+): *m/z*: calcd for $C_{18}H_{19}N_3O_4$: 341.1376, Found: 341.1376.

(*Z*)-2-((4-nitrophenoxy)imino)-*N*-pentyl-2-phenylacetamide, 5{1,3,1}



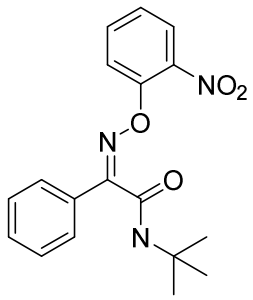
The crude material was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as yellow solid (yield 37%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.26-8.19 (m, 2H), 7.81-7.76 (m, 2H), 7.53-7.26 (m, 5H), 5.97 (br s, NH), 3.56-3.49 (m, 2H), 1.69-1.64 (m, 2H), 1.42-1.38 (m, 4H), 0.95-0.90 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 163.5, 162.1, 157.9, 142.9, 131.7, 129.8, 129.1, 127.4, 125.8, 114.5, 39.7, 29.2, 29.1, 22.4, 14.1; νmax/cm^{-1} (KBr) 3233, 2932, 1650, 1589, 1517, 1338, 921; mp 124-129.9 °C; HRMS (EI+): *m/z*: calcd for $C_{19}H_{21}N_3O_4$: 355.1532, Found: 355.1539.

(*Z*)-*N*-benzyl-2-((2-nitrophenoxy)imino)-2-phenylacetamide, 5{1,1,2}



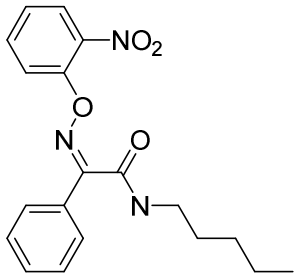
The crude material was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as brown solid (yield 25%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01-7.98 (m, 1H), 7.80-7.77 (m, 3H), 7.64-7.15 (m, 10H), 6.70 (br t, NH), 4.75 (d, *J* = 5.5 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.6, 157.9, 152.5, 138.0, 137.3, 135.0, 131.6, 129.3, 129.0, 128.9, 128.4, 127.9, 127.8, 125.9, 123.1, 118.1, 44.1; νmax/cm^{-1} (KBr) 3418, 3235, 1636, 1616, 1523, 918; mp 137.2-138 °C; HRMS (EI+): *m/z*: calcd for $C_{21}H_{17}N_3O_4$: 375.1219, Found: 375.1221.

(*Z*)-*N*-(tert-butyl)-2-((2-nitrophenoxy)imino)-2-phenylacetamide, 5{1,2,2}



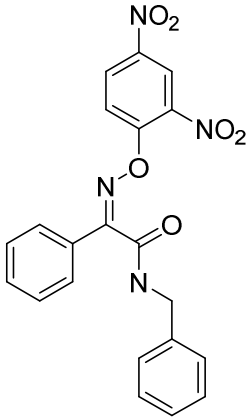
The crudematerial was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as yellow solid (yield 42%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ7.92 (dd, *J*= 8.3, 1.5 Hz, 1H), 7.78-7.72(m, 3H), 7.58 (td, *J*= 7.8, 1.5 Hz, 1H), 7.46-7.37 (m, 3H), 7.14 (td, *J*=7.8, 1.2 Hz, 1H), 6.12 (br s, NH), 1.52 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ160.9, 157.7, 152.5, 137.9, 134.7, 131.4, 130.2, 128.9, 127.5, 125.5, 122.8, 118.2, 53.2, 28.7; νmax/cm^{-1} (KBr)3270, 2964, 1647, 1519, 1563, 1354, 923; mp 139.5-139.9 °C; HRMS (EI+): *m/z*: calcd for $C_{18}H_{19}N_3O_4$: 341.1376, Found: 341.1379.

(*Z*)-2-((2-nitrophenoxy)imino)-*N*-pentyl-2-phenylacetamide, 5{1,3,2}



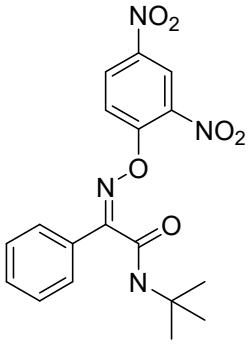
The crudematerial was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the productas yellow amorphous solid (yield 51%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.81-7.74 (m, 3H),7.59 (td, *J* = 7.9, 1.5 Hz, 1H), 7.49-7.35 (m, 3H), 7.16 (td, *J* =7.2, 1.2 Hz, 1H) 6.50 (br s, NH) 3.56-3.49 (m, 2H), 1.69-1.65(m, 2H), 1.37-1.35 (m, 4H), 0.92-0.88 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ161.6, 157.9, 152.4, 137.6, 134.8, 131.3, 130.0, 128.8, 127.6, 125.6, 122.7, 117.8,39.8, 29.1, 28.8, 22.3, 14.0; νmax/ cm^{-1} (KBr)3266, 2953, 1668, 1523, 1344, 915; HRMS (EI+):*m/z*: calcd for$C_{19}H_{21}N_3O_4$: 355.1532, Found: 355.1532.

(*Z*)-*N*-benzyl-2-((2,4-dinitrophenoxy)imino)-2-phenylacetamide, 5{1,1,3}



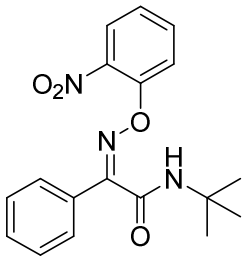
The crudematerial was purified by column chromatography (PE/EtOAc9:1, 8:2) to give the productas whitesolid (yield 30%).^{1}H-NMR (300 MHz, $CDCl_3$+ 1 gtt CD_3OD)δ 8.85 (d, *J*= 2.7 Hz, 1H), 8.44 (dd, *J*= 9.2, 2.7 Hz, 1H), 8.01 (d, *J*= 9.2 Hz, 1H),7.79-7.72 (m, 2H), 7.50-7.24 (m. 9H), 4.64(s, 2H); ^{13}C-NMR (75 MHz,$CDCl_3$+ 1 gtt CD_3OD)δ 161.8, 160.4, 156.6, 141.3, 137.0, 136.3, 132.2, 129.8, 129.3, 129.0, 128.6, 128.0, 127.6, 127.5, 121.9, 117.4, 43.5; νmax/cm^{-1} (KBr)3332, 3116, 1660,1527, 1345, 927, 902;mp155-156°C;HRMS (EI+): *m/z*: calcd for$C_{21}H_{16}N_4O_6$: 420.1070, Found: 420.1075.

(*Z*)-*N*-(tert-butyl)-2-((2,4-dinitrophenoxy)imino)-2-phenylacetamide, 5{1,2,3}



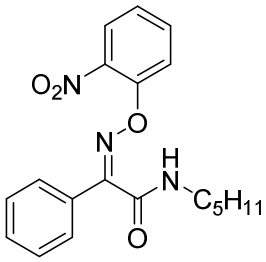
The crudematerial was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the productas yellow solid (yield 38%).^{1}H -NMR (300 MHz, $CDCl_3$) δ 8.83 (d, *J* = 2.7 Hz, 1H),8.43 (dd, *J* = 9.2 ,2.7 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.76 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.52-7.41 (m, 3H), 5.98 (br s,NH) 1.55 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.3, 159.6, 156.6, 141.3, 136.3, 132.1, 129.3, 129.2, 161.6, 157.9, 152.5, 138.0, 137.3, 135.0, 131.6, 129.3, 129.0, 128.9, 128.4, 127.9, 127.8, 125.9, 123.1, 118.1, 44.1; νmax/cm^{-1} (KBr) 3418, 3235, 1636, 1616, 1523, 918; mp 137.2-138 °C; HRMS (EI+): *m/z*: calcd for $C_{21}H_{17}N_3O_4$: 375.1219, Found: 375.1221.

(*Z*)-*N*-(tert-butyl)-2-((2-nitrophenoxy)imino)-2-phenylacetamide, 5{1,2,2}



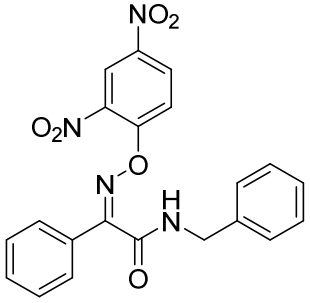
The crude material was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as yellow solid (yield 42%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.78-7.72 (m, 3H), 7.58 (td, *J* = 7.8, 1.5 Hz, 1H), 7.46-7.37 (m, 3H), 7.14 (td, *J* = 7.8, 1.2 Hz, 1H), 6.12 (br s, NH), 1.52 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.9, 157.7, 152.5, 137.9, 134.7, 131.4, 130.2, 128.9, 127.5, 125.5, 122.8, 118.2, 53.2, 28.7; νmax/cm^{-1} (KBr) 3270, 2964, 1647, 1519, 1563, 1354, 923; mp 139.5-139.9 °C; HRMS (EI+): *m/z*: calcd for $C_{18}H_{19}N_3O_4$: 341.1376, Found: 341.1379.

(*Z*)-2-((2-nitrophenoxy)imino)-*N*-pentyl-2-phenylacetamide, 5{1,3,2}



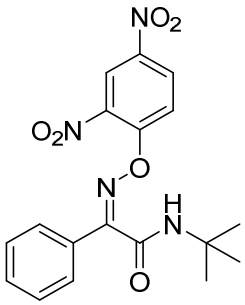
The crude material was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as yellow amorphous solid (yield 51%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.81-7.74 (m, 3H), 7.59 (td, *J* = 7.9, 1.5 Hz, 1H), 7.49-7.35 (m, 3H), 7.16 (td, *J* = 7.2, 1.2 Hz, 1H) 6.50 (br s, NH) 3.56-3.49 (m, 2H), 1.69-1.65 (m, 2H), 1.37-1.35 (m, 4H), 0.92-0.88 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.6, 157.9, 152.4, 137.6, 134.8, 131.3, 130.0, 128.8, 127.6, 125.6, 122.7, 117.8, 39.8, 29.1, 28.8, 22.3, 14.0; νmax/cm^{-1} (KBr) 3266, 2953, 1668, 1523, 1344, 915; HRMS (EI+): *m/z*: calcd for $C_{19}H_{21}N_3O_4$: 355.1532, Found: 355.1532.

(*Z*)-*N*-benzyl-2-((2,4-dinitrophenoxy)imino)-2-phenylacetamide, 5{1,1,3}



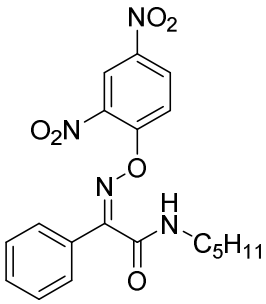
The crude material was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as white solid (yield 30%). ^{1}H-NMR (300 MHz, $CDCl_3$ + 1 gtt CD_3OD) δ 8.85 (d, *J* = 2.7 Hz, 1H), 8.44 (dd, *J* = 9.2, 2.7 Hz, 1H), 8.01 (d, *J* = 9.2 Hz, 1H),7.79-7.72 (m, 2H), 7.50-7.24 (m. 9H), 4.64 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$ + 1 gtt CD_3OD) δ 161.8, 160.4, 156.6, 141.3, 137.0, 136.3, 132.2, 129.8, 129.3, 129.0, 128.6, 128.0, 127.6, 127.5, 121.9, 117.4, 43.5; νmax/cm^{-1} (KBr) 3332, 3116, 1660, 1527, 1345, 927, 902; mp155-156 °C; HRMS (EI+): *m/z*: calcd for $C_{21}H_{16}N_4O_6$: 420.1070, Found: 420.1075.

(*Z*)-*N*-(tert-butyl)-2-((2,4-dinitrophenoxy)imino)-2-phenylacetamide, 5{1,2,3}



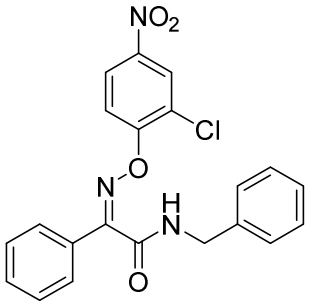
The crude material was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as yellow solid (yield 38%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.83 (d, *J* = 2.7 Hz, 1H),8.43 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.76 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.52-7.41 (m, 3H), 5.98 (br s, NH) 1.55 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.3, 159.6, 156.6, 141.3, 136.3, 132.1, 129.3, 129.2, 129.1, 127.7, 121.8, 117.7, 53.4, 28.6; νmax/cm^{-1} (KBr) 3398, 2975, 1685, 1519, 1344, 929, 901; mp 156.5-157 °C; HRMS (EI+): *m/z*: calcd for C18H18N4O6: 386.1226, Found: 386.1228.

(*Z*)-2-((2,4-dinitrophenoxy)imino)-*N*-pentyl-2-phenylacetamide, 5{1,3,3}



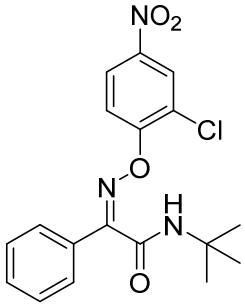
The crude material was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as yellow solid (yield 32%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.72-8.70 (m, 1H), 8.36-8.31 (m, 1H), 7.90-7.85 (m, 1H), 7.64-7.63 (m, 2H), 7.45-7.27 (m, 3H), 6.67 (br d, NH), 3.46-3.38 (m, 2H), 1.58 (br s, 2H), 1.31-1.29 (m, 4H), 0.88-0.74 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.2, 160.1, 156.5, 141.3, 136.1, 132.2, 129.4, 129.1, 128.9, 127.8, 122.0, 117.4, 40.0, 29.1, 28.8, 22.3, 14.0; νmax/cm^{-1} (KBr) 3267, 2952, 1648, 1526, 1344, 929, 904; mp 139.7-141.3 °C; HRMS (EI+): *m/z*: calcd for $C_{19}H_{20}N_4O_6$: 400.1383, Found: 400.1389.

(*Z*)-*N*-benzyl-2-((2-chloro-4-nitrophenoxy)imino)-2-phenylacetamide, 5{1,1,4}



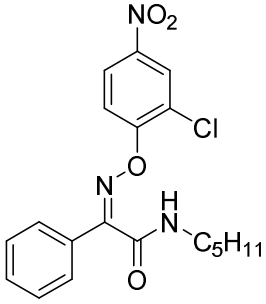
The crude material was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as white solid (yield 43%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 2.8 Hz, 1H), 8.06 (dd, *J* = 9.2, 2.1 Hz, 1H), 7.77-7.61 (m, 3H), 7.45-7.26 (m, 9H), 4.59 (br s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.8, 159.1, 158.8, 142.5, 137.0, 131.9, 129.4, 129.0, 128.8, 128.2, 127.8, 127.5, 125.9, 123.7, 120.8, 115.0, 43.6; νmax/cm^{-1} (KBr) 3249, 3084, 1653, 1584, 1351, 919, 743; mp 152.8-153 °C; HRMS (EI+): *m/z*: calcd for $C_{21}H_{16}ClN_3O_4$: 409.0829, Found: 409.0832.

(*Z*)-*N*-(tert-butyl)-2-((2-chloro-4-nitrophenoxy)imino)-2-phenylacetamide, 5{1,2,4}



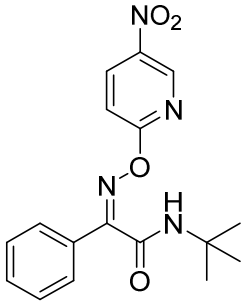
The crude material was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as white solid (yield 45%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.26 (br d, 1H), 8.13 (dd, *J* = 9.2, 1.2 Hz, 1H), 7.78-7.70 (m, 3H), 7.52-7.41 (m, 3H), 5.98 (br s, NH), 1.52 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.4, 159.3, 158.7, 142.2, 131.6, 129.6, 128.8, 127.2, 125.8, 123.7, 120.5, 114.8, 52.7, 28.4; νmax/cm^{-1} (KBr) 3263, 3085, 1654, 1583, 1365, 922, 742; mp 143-144 °C; HRMS (EI+): *m/z*: calcd for $C_{18}H_{18}ClN_3O_4$: 375.0986, Found: 375.0983.

(*Z*)-2-((2-chloro-4-nitrophenoxy)imino)-*N*-pentyl-2-phenylacetamide, 5{1,3,4}



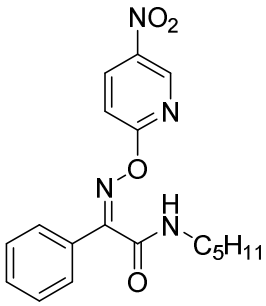
The crude material was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as white solid (yield 53%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 2.8 Hz, 1H), 8.05 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.71-7.68 (m, 2H), 7.61 (dd, *J* = 9.1, 1H), 7.48-7.35 (m, 3H), 6.54 (br t, NH), 3.42 (br q, 2H), 1.62 (br quintet, 2H), 1.38-1.31 (m, 4H), 0.90-0.86 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.7, 159.1, 158.9, 142.4, 131.8, 129.5, 129.0, 127.6, 125.9, 123.8, 120.7, 114.9, 39.9, 29.2 (2), 22.4, 14.0; νmax/cm^{-1} (KBr) 3261, 2963, 1653, 1589, 1352, 927, 742; mp 121-122 °C; HRMS (EI+): *m/z*: calcd for $C_{19}H_{20}ClN_3O_4$: 389.1142, Found: 389.1144.

(*Z*)-*N*-(tert-butyl)-2-(((5-nitropyridin-2-yl)oxy)imino)-2-phenylacetamide, 5{1,2,5}



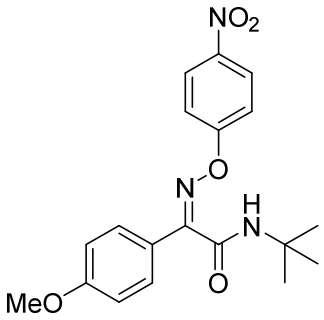
The crude material was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as white solid (yield 20%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.13 (d, *J* = 2.5 Hz, 1H), 8.49 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.79 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.56-7.36 (m, 4H), 5.88 (br s, NH), 1.53 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.7, 161.4, 159.6, 145.0, 140.7, 135.1, 131.9, 130.1, 129.1, 127.5, 109.2, 52.9, 28.7; νmax/cm^{-1} (KBr) 3290, 2970, 1674, 1516, 1347, 929; mp 169-171.2 °C; HRMS (EI+): *m/z*: calcd for $C_{17}H_{18}N_4O_4$: 342.1328, Found: 342.1327.

(*Z*)-2-(((5-nitropyridin-2-yl)oxy)imino)-*N*-pentyl-2-phenylacetamide, 5{1,3,5}



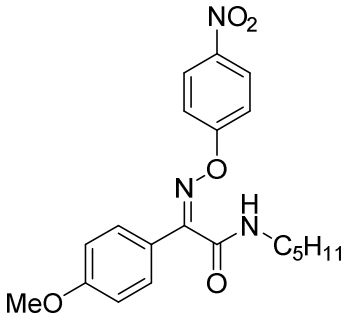
The crude material was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as brown amorphous solid (yield 33%). Mixture of E/Z isomers, signals are referred to the main isomer: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.96 (d, *J* = 2.8 Hz, 1H), 8.45 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.73-7.70 (m, 3H), 7.55-7.47 (m, 4H), 6.69 (br t, NH), 3.51 (br q, 2H), 1.69-1.59 (m, 2H), 1.43-1.33 (m, 4H), 0.92-0.82 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.7, 161.7, 159.4, 148.2, 144.9, 135.2, 133.8, 130.1, 129.3, 127.6, 109.0, 39.8, 29.5, 29.1, 22.4, 14.1; νmax/cm^{-1} (KBr) 3549, 3417, 1636, 1579, 1345, 937; HRMS (EI+): *m/z*: calcd for $C_{18}H_{20}N_4O_4$: 356.1485, Found: 356.1485.

(*Z*)-*N*-(tert-butyl)-2-(4-methoxyphenyl)-2-((4-nitrophenoxy)imino)acetamide, 5{2,2,1}



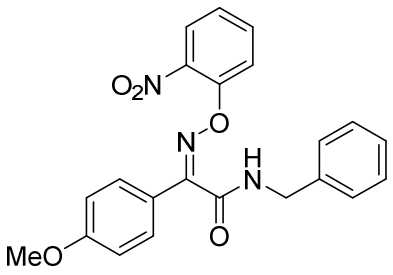
The crude material was purified by column chromatography (PE/EtOAc 95:5, 9:1) to give the product as yellow solid (yield 33%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.2 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.16 (d, *J* = 9.2 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.32 (br s, NH), 3.76 (s, 3H), 1.42 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 163.6, 162.0, 161.7, 157.3, 142.2, 128.8, 125.5, 121.9, 114.2, 114.0, 55.3, 52.7, 28.6; νmax/cm^{-1} (KBr) 3277, 2968, 1646, 1511, 1335, 1239, 914; mp 133.2-134 °C; HRMS (EI+): *m/z*: calcd for $C_{19}H_{21}N_3O_5$: 371.1481, Found: 371.1483.

(*Z*)-2-(4-methoxyphenyl)-2-((4-nitrophenoxy)imino)-*N*-pentylacetamide, 5{2,3,1}



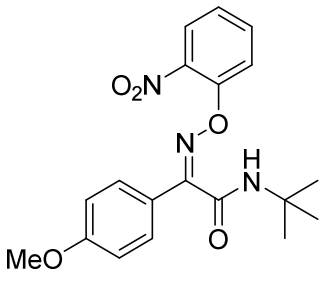
The crude material was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as yellow solid (yield 39%). Mixture of E/Z isomers, signals are referred to the main isomer: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.13-8.09 (m, 2H), 7.63-7.59 (m, 2H), 7.22-7.19 (m, 2H), 6.87-6.82 (m, 2H), 6.53 (br t, NH), 3.80 (s, 3H), 3.47-3.42 (m, 2H), 1.60-1.57 (m, 2H), 1.34-1.32 (m, 4H), 0.90-0.87 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 163.6, 162.6, 162.4, 157.5, 142.6, 129.0, 125.7, 121.9, 114.4, 114.3, 55.5, 39.7, 29.1, 29.0, 22.3, 14.0; νmax/cm^{-1} (KBr) 3266, 2930, 1650, 1515, 1337, 1180, 931; mp 116.8-117 °C; HRMS (EI+): *m/z*: calcd for $C_{20}H_{23}N_3O_5$: 385.1638, Found: 385.1640.

(*Z*)-*N*-benzyl-2-(4-methoxyphenyl)-2-((2-nitrophenoxy)imino)acetamide, 5{2,1,2}



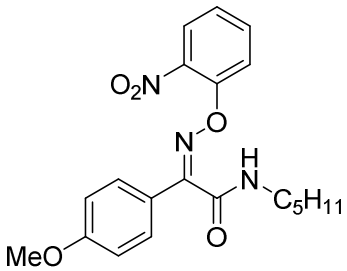
The crude material was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as yellow solid (yield 26%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.79-7.71 (m, 3H), 7.60 (td, *J* = 7.8, 1.5 Hz, 1H), 7.43-7.27 (m, 5H), 7.16 (td, *J* = 7.9, 1.2 Hz, 1H), 6.97-6.91 (m, 2H), 6.60 (br t, NH), 4.75 (d, *J* = 5.8 Hz, 2H), 3.85 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 162.4, 162.0, 157.6, 152.6, 137.3, 134.9, 129.5, 129.2, 128.9, 128.3, 127.9, 125.8, 122.7, 122.2, 117.9, 114.5, 55.6, 44.0; νmax/cm^{-1} (KBr) 3411, 3285, 1646, 1522, 1352, 1176, 924; mp 130.8-131.6 °C; HRMS (EI+): *m/z*: calcd for $C_{22}H_{19}N_3O_5$: 405.1325, Found: 405.1326.

(*Z*)-*N*-(tert-butyl)-2-(4-methoxyphenyl)-2-((2-nitrophenoxy)imino)acetamide, 5{2,2,2}



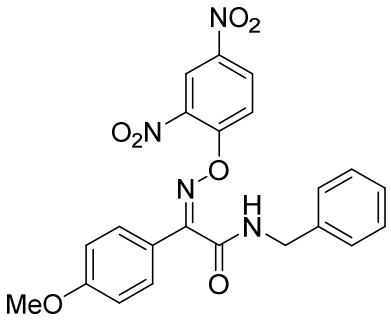
The crude material was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as yellow solid (yield 49%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.73-7.68 (m, 3H), 7.58-7.53 (m, 1H), 7.14-7.09 (m, 1H), 6.90 (dd, *J* = 8.8, 1.8 Hz, 2H), 6.07 (br s, NH), 3.82 (s, 3H), 1.51 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 162.2, 161.2, 157.6, 152.7, 138.0, 134.6, 129.2, 125.4 (2C), 122.5, 118.2, 114.4, 55.5, 53.1, 28.7; νmax/cm^{-1} (KBr) 3262, 2968, 1646, 1522, 1473, 1230, 918; mp 115.8-116.3 °C; HRMS (EI+): *m/z*: calcd for $C_{19}H_{21}N_3O_5$: 371.1481, Found: 371.1478.

(*Z*)-2-(4-methoxyphenyl)-2-((2-nitrophenoxy)imino)-*N*-pentylacetamide, 5{2,3,2}



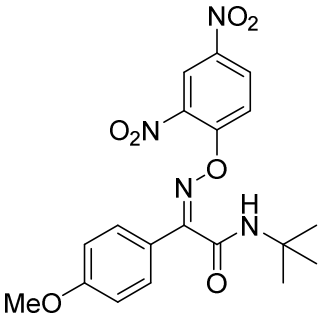
The crude material was purified by column chromatography (PE/EtOAc 9:1, 8:2) to give the product as brown solid (yield 45%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96-7.89 (m, 1H), 7.77-7.65 (m, 3H), 7.57-7.51 (m, 1H), 7.12-7.06 (m, 1H), 6.89-6.86 (m, 2H), 6.51 (br s, NH), 3.81 (s, 3H), 3.48-3.44 (m, 2H), 1.65-1.61 (m, 2H), 1.34-1.32 (m, 4H), 0.90-0.85 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 162.2, 161.9, 157.7, 152.6, 137.7, 134.7, 129.3, 125.6, 122.5, 122.3, 117.8, 114.3, 55.4, 39.9, 29.1, 28.9, 22.3, 14.0; νmax/cm^{-1} (KBr) 3244, 2936, 1645, 1558, 1344, 1179, 916; mp 105-106 °C; HRMS (EI+): *m/z*: calcd for $C_{20}H_{23}N_3O_5$: 385.1638 Found: 385.1641.

(*Z*)-*N*-benzyl-2-((2,4-dinitrophenoxy)imino)-2-(4-methoxyphenyl)acetamide, 5{2,1,3}



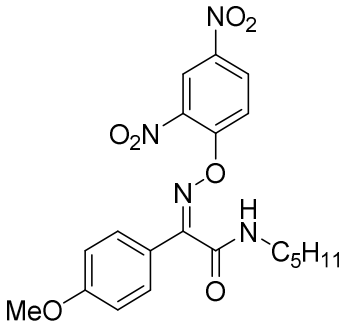
The crude material was purified by column chromatography (PE/EtOAc 8:2, 7:3) to give the product as white solid (yield 40%). ^{1}H-NMR (300 MHz, $CDCl_3$ 1 gtt DMSO-d_6) δ 8.74 (d, *J* = 2.5 Hz, 1H), 8.33 (dd, *J* = 9.5, 2.7 Hz, 1H), 7.88 (dd, *J* = 9.5, 3.9 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 2H), 7.27-7.18 (m, 5H), 6.83 (d, *J* = 8.6 Hz, 2H), 4.56 (s, 2H), 3.77 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$ + 1 gtt DMSO-d_6) δ 163.0, 160.3, 156.9 (2C), 141.5, 137.1, 136.4, 129.7, 129.5, 128.9, 128.3, 128.0, 122.2, 121.1, 117.6, 114.8, 55.6, 43.9; νmax/cm^{-1} (KBr) 3269, 1643, 1535, 1340, 1255, 927; mp 163.3-164 °C; HRMS (EI+): *m/z*: calcd for $C_{22}H_{18}N_4O_7$: 450.1175, Found: 450.1177.

(*Z*)-*N*-(*tert*-butyl)-2-((2,4-dinitrophenoxy)imino)-2-(4-methoxyphenyl)acetamide, 5{2,2,3}



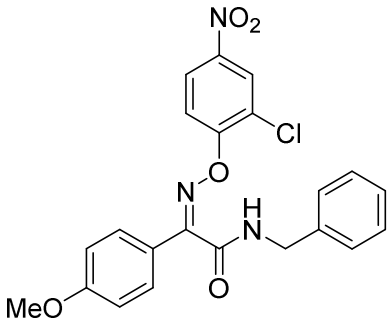
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as yellow solid (yield 33%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.45 (d, *J* = 9.0 Hz, 1H), 7.99 (d, *J* = 9.3 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 2H), 6.97 (d, *J* = 7.6 Hz, 2H), 5.80 (br s, *NH*), 3.87 (s, 3H), 1.54 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.6, 160.5, 159.2, 156.7, 141.1, 136.2, 129.4, 129.1, 121.7, 121.3, 117.6, 114.5, 55.4, 53.3, 28.5; νmax/cm^{-1} (KBr) 3295, 2971, 1666, 1526, 1340, 833; mp 148-149 °C; HRMS (EI+): *m/z*: calcd for $C_{19}H_{20}N_4O_7$: 416.1332, Found: 416.1332.

(*Z*)-2-((2,4-dinitrophenoxy)imino)-2-(4-methoxyphenyl)-*N*-pentylacetamide, 5{2,3,3}



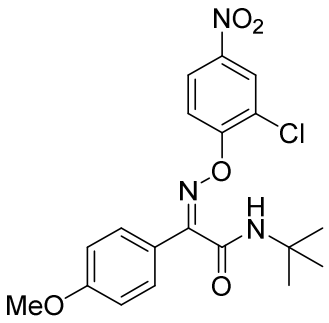
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as pale yellow solid (yield 40%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.82 (br s, 1H), 8.40 (br d, AA'XX', 1H), 7.95 (d, *J* = 9.3 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.24 (br t, *NH*), 3.84 (s, 3H), 3.53-3.48 (m, 2H), 1.67-1.63 (m, 2H), 1.37-1.35 (m, 4H), 0.92-0.89 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.8, 161.4, 159.8, 156.6, 141.1, 136.1, 129.5, 129.2, 121.9, 121.0, 117.4, 114.4, 55.4, 39.9, 29.1, 28.8, 22.2, 13.9; νmax/cm^{-1} (KBr) 3283, 2929, 1654, 1521, 1343, 1260, 833; mp 139-140 °C; HRMS (EI+): *m/z*: calcd for $C_{20}H_{22}N_4O_7$: 430.1488, Found: 430.1489.

(*Z*)-*N*-benzyl-2-((2-chloro-4-nitrophenoxy)imino)-2-(4-methoxyphenyl)acetamide, 5{2,1,4}



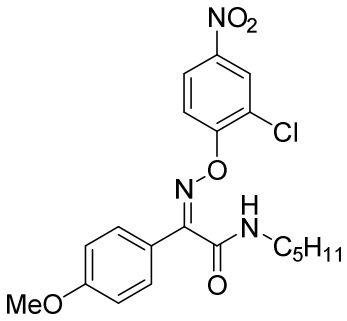
The crude material was purified by column chromatography (*n*-hexane/EtOAc 8:2) to give the product as light yellow solid (yield 63%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.16 (br d, 1H), 7.76-7.71 (m, 3H), 7.42-7.30 (m, 5H), 6.96 (d, *J*=7.7, 2H), 6.23 (br s, *NH*), 4.72 (d, *J*=5.5, 2H), 3.87 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ 162.6, 161.8, 159.8, 159.2, 142.4, 138.7, 129.5 128.7, 128.2, 127.5, 126.1, 124.9, 121.9, 119.8, 115.8, 115.1, 55.9, 42.7; νmax/cm^{-1} (KBr) 3263, 1650, 1512, 1254, 926; mp 149-150 °C; HRMS (EI+): *m/z*: calcd for $C_{22}H_{18}ClN_3O_5$: 439.0935 Found: 439.0939.

(*Z*)-*N*-(*tert*-butyl)-2-(2-chloro-4-nitrophenoxy)imino)-2-(4-methoxyphenyl)acetamide, 5{2,2,4}



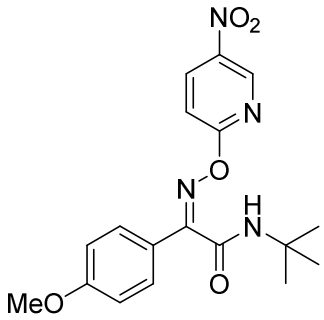
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as amorphous dark-red solid (yield 38%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 8.16 (br d, 1H), 7.75-7.72 (m, 3H), 6.95 (d, *J* = 8.7 Hz, 2H), 5.79 (br s, *NH*), 3.86 (s, 3H), 1.53 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.3, 161.0, 159.3, 158.1, 142.0, 129.1, 125.8, 123.6, 121.7, 120.5, 114.7, 114.4, 55.4, 52.9, 28.7; νmax/cm^{-1} (KBr) 3566, 1652, 1516, 1338, 1255, 920; HRMS (EI+): *m/z*: calcd for $C_{19}H_{20}ClN_3O_5$: 405.1091, Found: 405.1093.

(*Z*)-2-((2-chloro-4-nitrophenoxy)imino)-2-(4-methoxyphenyl)-*N*pentylacetamide, 5{2,3,4}



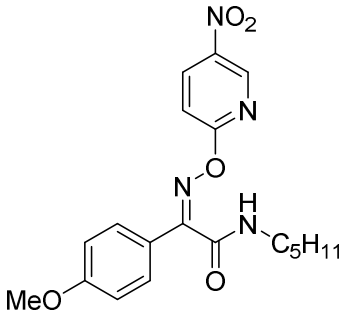
The crude material was purified by column chromatography (*n*-hexane/EtOAc 8:2) to give the product as yellowish solid (yield 50%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.15 (br d, 1H), 7.75-7.71 (m, 3H), 6.95 (d, *J* = 8.7 Hz, 2H), 5.99 (br s, *NH*), 3.86 (s, 3H), 3.55-3.50 (m, 2H), 1.69-1.66 (m, 2H), 1.40-1.36 (m, 4H), 0.93-0.90 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.5, 161.8, 159.1, 158.5, 142.3, 129.2, 125.8, 123.7, 121.5,120.6, 114.8, 114.3, 55.4, 39.8, 29.1, 29.0, 22.3, 13.9; νmax/cm^{-1} (KBr) 3261, 2958, 1646, 1582, 1335, 1255, 921; mp 124-125 °C; HRMS (EI+): *m/z*: calcd for $C_{20}H_{22}ClN_3O_5$: 419.1248, Found: 419.1248.

(*Z*)-*N*-(*tert*-butyl)-2-(4-methoxyphenyl)-2-(((5-nitropyridin-2-yl)oxy)imino)acetamide, 5{2,2,5}



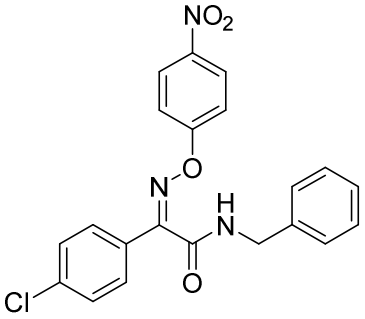
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as white solid (yield 22%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.16 (br s, 1H), 8.50 (br d, AA'XX', 1H), 7.76 (d, *J* = 7.7 Hz, 2H), 7.40 (d, *J* = 9.2 Hz, 1H), 6.96 (d, *J* = 7.9 Hz, 2H), 5.65 (br s, *NH*), 3.86 (s, 3H), 1.53 (s, 9H); ^{13}C-NMR (100 MHz, DMSO-*d*$_6$) δ 168.1, 162.4, 161.3, 159.3, 145.4, 140.8, 136.2, 129.4, 122.3, 115.1, 108.8, 55.9, 51.9, 28.9; νmax/cm^{-1} (KBr) 3419, 1613, 1515, 1347, 1258, 927; mp 174-175 °C; HRMS (EI+): *m/z*: calcd for $C_{18}H_{20}N_4O_5$: 372.1434, Found: 372.1439.

(Z)-2-(4-methoxyphenyl)-2-(((5-nitropyridin-2-yl)oxy)imino)-*N*-pentylacetamide, 5{2,3,5}



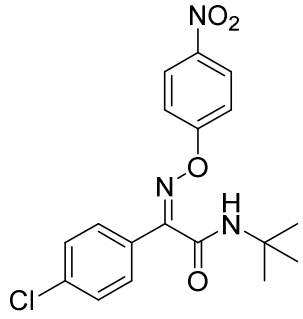
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as sticky dark-red solid (yield 39%). Mixture of E/Z isomers, signals are referred to the main isomer: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.16 (br s, 1H), 8.80 (br s, *NH*), 8.02 (br d, AA'XX', 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 3.37-3.34 (m, 2H), 1.65-1.60 (m, 2H), 1.29-1.25 (m, 4H), 0.90-0.84 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.6, 162.6, 161.0, 149.1, 136.9, 133.7, 131.9, 128.0, 123.8, 120.8, 114.1, 55.3, 52.0, 29.7, 28.9, 22.2, 13.9; νmax/cm^{-1} (KBr) 3473, 3414, 1682, 1616, 1255, 933; HRMS (EI+): *m/z*: calcd for $C_{19}H_{22}N_4O_5$: 386.1590, Found: 386.1587.

(*Z*)-*N*-benzyl-2-(4-chlorophenyl)-2((4-nitrophenoxy)imino)acetamide, 5{3,1,1}



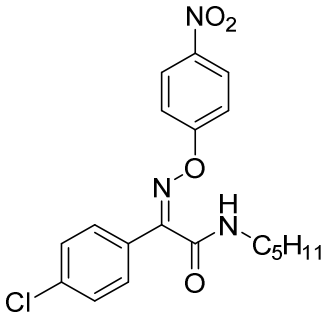
The crude material was purified by column chromatography (*n*-hexane/EtOAc 8:2) to give the product as pale yellow solid (yield 55%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 9.2 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.44-7.35 (m, 7H), 7.27-7.25 (m, 2H), 6.22 (br t, *NH*), 4.72 (br d, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.0, 161.6, 156.4, 143.0, 138.0, 137.1, 129.3, 128.9, 128.5, 128.0, 127.9, 127.9, 125.7, 114.3, 43.6; νmax/cm^{-1} (KBr) 3411, 1654, 1515, 1345, 1220, 929, 850; mp 159-160 °C; HRMS (EI+): *m/z*: calcd for $C_{21}H_{16}ClN_3O_4$: 409.0829, Found: 409.0831.

(*Z*)-*N*-(*tert*-butyl)-2-(4-chlorophenyl)-2((4-nitrophenoxy)imino)acetamide, 5{3,2,1}



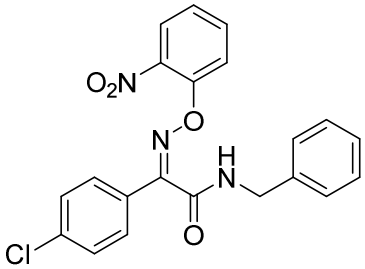
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as yellow solid (yield 53%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 9.2 Hz, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 9.2 Hz, 2H), 5.61 (br s, *NH*), 1.53 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.2, 161.0, 156.6, 142.7, 137.7, 129.2, 128.4, 128.1, 125.6, 114.2, 53.0, 28.7; νmax/cm^{-1} (KBr) 3272, 2965, 1651, 1517, 1342, 1237, 917, 841; mp 160-161 °C; HRMS (EI+): *m/z*: calcd for $C_{18}H_{18}ClN_3O_4$: 375.0986, Found: 375.0989.

(*Z*)- 2-(4-chlorophenyl)-2((4-nitrophenoxy)imino)-*N*-pentylacetamide, 5{3,3,1}



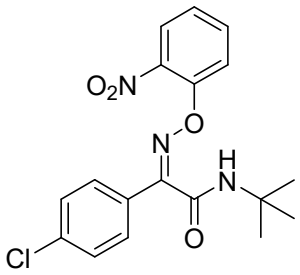
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as yellow solid (yield 43%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.23 (br d, AA'XX', 2H), 7.72 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.33 (br d, *J* = 9.2 Hz, 2H), 5.94 (br t, *NH*), 3.55-3.50 (m, 2H), 1.68-1.63 (m, 2H), 1.42-1.38 (m, 4H), 0.94-0.91 (m, 3H); ^{13}C-NMR (100 MHz, CDCl3) δ 163.1, 161.6, 156.6, 142.7, 137.7, 129.2, 128.5, 128.1, 125.6, 114.3, 39.6, 29.0, 28.9, 22.2, 13.9; νmax/cm^{-1} (KBr) 3301, 2953, 1660, 1508, 1339, 927, 854; mp 106-107 °C; HRMS (EI+): *m/z*: calcd for $C_{19}H_{20}ClN_3O_4$: 389.1142, Found: 389.1141.

(*Z*)-*N*-benzyl-2-(4-chlorophenyl)-2((2-nitrophenoxy)imino)acetamide, 5{3,1,2}



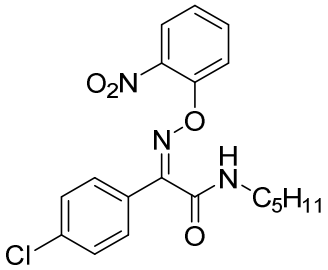
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as pale yellow solid (yield 42%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.2 Hz, 2H), 7.77-7.72 (m, 3H), 7.63 (br t, 1H), 7.42-7.29 (m, 7H), 7.22-7.18 (m, 1H), 6.80 (br s, *NH*), 4.74 (br d, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.0, 156.5, 152.1, 137.6, 137.0, 134.8, 129.1, 129.0, 128.8, 128.4, 128.1, 127.7, 125.7, 123.1, 117.9, 43.9; νmax/cm^{-1} (KBr) 3412, 3248, 1638, 1525, 1337, 1225, 926, 832; mp 145-146 °C; HRMS (EI+): *m/z*: calcd for $C_{21}H_{16}ClN_3O_4$: 409.0829, Found: 409.0832.

(*Z*)-*N*-(*tert*-butyl)-2-(4-chlorophenyl)-2((2-nitrophenoxy)imino)acetamide, 5{3,2,2}



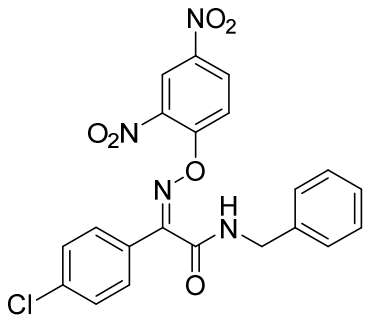
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as yellow solid (yield 48%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96 (br d, AA'XX', 1H), 7.74-7.71 (m, 3H), 7.63-7.59 (m, 1H), 7.41-7.39 (m, 2H), 7.21-7.17 (m, 1H), 6.07 (br s, *NH*), 1.53 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.4, 156.5, 152.2, 137.8, 137.4, 134.5, 129.0, 128.7, 128.6, 125.4, 122.8, 118.0, 53.1, 28.5; νmax/cm^{-1} (KBr) 3249, 2972, 1634, 1515, 1347, 1228, 915, 739; mp 125-126 °C; HRMS (EI+): *m/z*: calcd for $C_{18}H_{18}ClN_3O_4$: 375.0986, Found: 375.0983.

(*Z*)- 2-(4-chlorophenyl)-2((2-nitrophenoxy)imino)-*N*-pentylacetamide, 5{3,3,2}



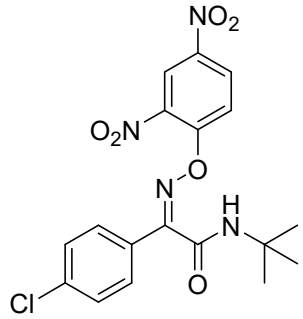
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as brown solid (yield 41%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 1H), 7.75-7.71 (m, 3H), 7.62 (br t, 1H), 7.40 (d, *J* = 8.2 Hz, 2H), 7.20 (br t, 1H), 6.52 (br s, *NH*), 3.56-3.51 (m, 2H), 1.70-1.67 (m, 2H), 1.37-1.32 (m, 4H), 0.92-0.89 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.0, 156.7, 152.1, 137.7, 137.4, 134.7, 129.0, 128.9, 128.6, 125.6, 123.0, 117.8, 39.9, 29.0, 28.8, 22.2, 13.9; νmax/cm^{-1} (KBr) 3255, 2929, 1652, 1521, 1347, 1226, 921, 833; mp 60-61 °C; HRMS (EI+): *m/z*: calcd for $C_{19}H_{20}ClN_3O_4$: 389.1142, Found: 389.1141.

(*Z*)-*N*-benzyl-2-(4-chlorophenyl)-2((2,4-dinitrophenoxy)imino)acetamide, 5{3,1,3}



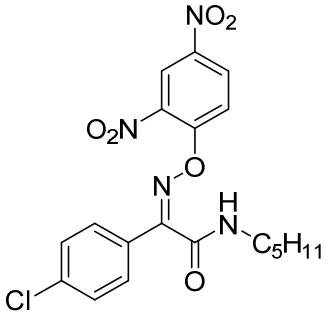
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as yellow solid (yield 34%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.92 (br s, 1H), 8.48 (br d, AA'XX', 1H), 8.00 (d, *J* = 9.4 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.46-7.37 (m, 7H), 6.42 (br s, *NH*), 4.75 (br d, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 161.0, 159.8, 155.7, 141.8, 138.2, 137.4, 136.7, 130.2, 129.9, 129.6, 128.9, 128.4, 128.0, 127.6, 122.2, 118.0, 42.9; νmax/cm^{-1} (KBr) 3236, 1604, 1533, 1342, 835; mp 142-143 °C; HRMS (EI+): *m/z*: calcd for $C_{21}H_{15}ClN_4O_6$: 454.0680, Found: 454.0683.

(*Z*)-*N*-(*tert*-butyl)-2-(4-chlorophenyl)-2((2,4-dinitrophenoxy)imino)acetamide, 5{3,2,3}



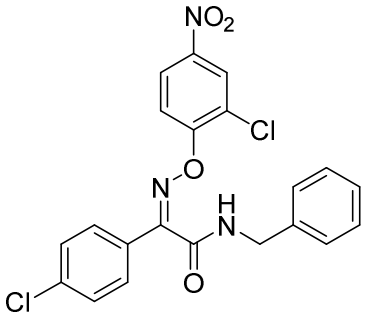
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as yellow solid (yield 46%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.46 (d, *J* = 9.3 Hz, 1H), 7.96 (d, *J* = 9.3 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 5.93 (br s, *NH*), 1.53 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 159.7, 158.5, 156.3, 141.5, 138.4, 136.4, 129.3, 129.1, 128.9, 127.7, 121.7, 117.7, 53.5, 28.5; νmax/cm^{-1} (KBr) 3275, 2972, 1660, 1540, 1344, 1283, 833, 740; mp 118-119 °C; HRMS (EI+): *m/z*: calcd for $C_{18}H_{17}ClN_4O_6$: 420.0837, Found: 420.0840.

(*Z*)- 2-(4-chlorophenyl)-2((2,4-dinitrophenoxy)imino)-*N*-pentylacetamide, 5{3,3,3}



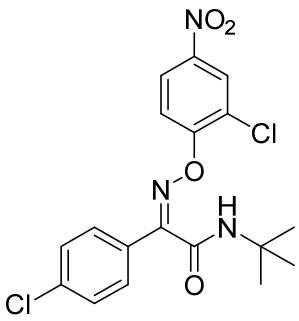
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as yellow solid (yield 32%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.90 (br s, 1H), 8.47 (br d, AA'XX', 1H), 7.98 (d, *J* = 9.3 Hz, 1H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 2H), 6.18 (br s, NH), 3.57-3.52 (m, 2H), 1.70-1.67 (m, 2H), 1.39-1.37 (m, 4H), 0.93-0.90 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.6, 158.9, 156.2, 141.5, 138.5, 136.2, 129.3, 129.3, 129.0, 127.4, 121.9, 117.4, 40.0, 29.0, 28.7, 22.2, 13.9; νmax/cm^{-1} (KBr) 3284, 1652, 1558, 1472, 1344, 834, 739; mp 156-157 °C; HRMS (EI+): *m/z*: calcd for $C_{19}H_{19}ClN_4O_6$: 434.0993, Found: 434.0995.

(Z)-*N*-benzyl-2-((2-chloro-4-nitrophenoxy)imino)-2-(4-chlorophenyl) acetamide, 5{3,1,4}



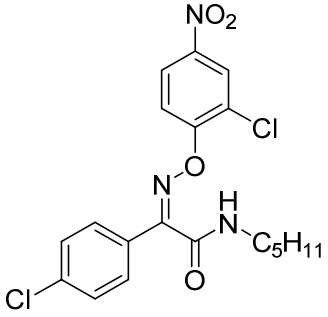
The crude material was purified by column chromatography (*n*-hexane/EtOAc 8:2) to give the product as light yellow solid (yield 63%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.22 (br s, 1H), 8.11 (br d, AA'XX', 1H), 7.69-7.65 (m, 3H), 7.38-7.25 (m, 8H), 4.61 (s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 161.2, 158.9, 158.9, 142.7, 138.4, 137.1, 129.8, 129.4, 128.8, 128.7, 128.2, 127.6, 126.1, 124.9, 119.9, 115.9, 42.8; νmax/cm^{-1} (KBr) 3353, 3104, 1676, 1523, 1344, 933, 741; mp 165-166 °C; HRMS (EI+): *m/z*: calcd for $C_{21}H_{15}Cl_2N_3O_4$: 443.0440, Found: 443.0441.

(Z)-*N*-(tert-butyl)-2-((2-chloro-4-nitrophenoxy)imino)-2-(4-chlorophenyl)acetamide, 5{3,2,4}



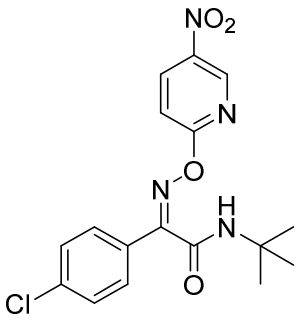
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as yellow solid (yield 47%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.18 (d, *J* = 9.0, 1H), 7.75-7.72 (m, 3H), 7.43 (d, *J* = 8.2 Hz, 2H), 5.84 (br s, *NH*), 1.53 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 160.3, 158.9, 157.3, 142.3, 137.8, 129.1, 128.6, 128.0, 125.8, 123.6, 120.5, 114.7, 53.0, 28.7; νmax/cm^{-1} (KBr) 3300, 2972, 1652, 1555, 1344, 1233, 930; mp 144-145 °C; HRMS (EI+): *m/z*: calcd for $C_{18}H_{17}Cl_2N_3O_4$: 409.0596, Found: 409.0595.

(Z)-2-((2-chloro-4-nitrophenoxy)imino)-2-(4-chlorophenyl)-*N*-pentylacetamide, 5{3,3,4}



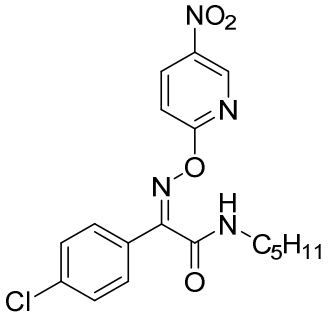
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as yellow solid (yield 56%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.29 (br s, 1H), 8.16 (br d, AA'XX', 1H), 7.74-7.69 (m, 3H), 7.42 (d, *J* = 8.6 Hz, 2H), 6.12 (br s, NH), 3.54-3.49 (m, 2H), 1.69-1.66 (m, 2H), 1.38-1.36 (m, 4H), 0.93-0.90 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 161.1, 158.8, 157.7, 142.4, 138.0, 129.1, 128.6, 127.8, 125.8, 123.6, 120.6, 114.6, 39.8, 31.5, 29.0, 22.2, 13.9; νmax/cm^{-1} (KBr) 3246, 2929, 1646, 1582, 1343, 928, 834; mp 136-137 °C; HRMS (EI+): *m/z*: calcd for $C_{19}H_{19}Cl_2N_3O_4$: 423.0753, Found: 423.0757.

(*Z*)-*N*-(*tert*-butyl)-2-(4-chlorophenyl)-2(((4-nitropyridin-2-yl)oxy)imino)acetamide, 5{3,2,5}



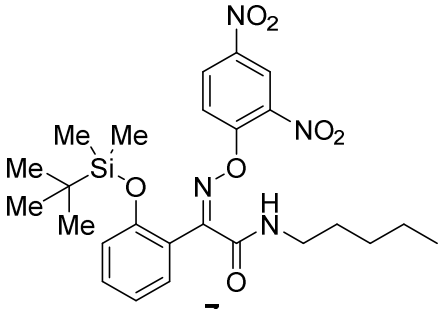
The crude material was purified by column chromatography (*n*-hexane/EtOAc 7:3) to give the product as white solid (yield 42%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.18 (br s, 1H), 8.52 (br d, AA'XX', 1H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.45-7.39 (m, 3H), 5.70 (br s, *NH*), 1.53 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.8, 160.8, 158.6, 145.4, 141.1, 136.9, 136.3, 129.7, 129.4, 129.1, 109.0, 52.1, 28.8; νmax/cm^{-1} (KBr) 3414, 3293, 1675, 1577, 1349, 935, 833; mp 193-194 °C; HRMS (EI+): *m/z*: calcd for $C_{17}H_{17}ClN_4O_4$: 376.0938, Found: 376.0939.

(Z)-2-(4-chlorophenyl)-2-(((5-nitropyridin-2-yl)oxy)imino)-*N*-pentylacetamide, 5{3,3,5}



The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as sticky dark-red solid (yield 35%). Mixture of E/Z isomers, signals are referred to the main isomer: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 9.03 (br s, *NH*), 8.05 (br d, AA'XX', 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 3.34-3.30 (m, 2H), 1.65-1.62 (m, 2H), 1.27-1.25 (m, 4H), 0.92-0.85 (m, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.2, 160.9, 148.8, 148.0, 144.9, 136.6, 135.1, 133.9, 130.0, 129.0, 127.7, 52.1, 29.7, 28.9, 22.2, 13.9; νmax/cm^{-1} (KBr) 2932, 1691, 1564, 1345, 1273, 935, 834; HRMS (EI+): *m/z*: calcd for $C_{18}H_{19}ClN_4O_4$: 390.1095, Found: 390.1098.

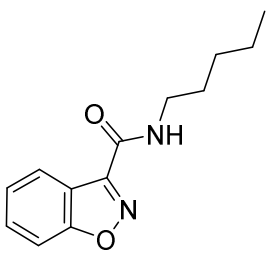
(*Z*)-2-(2-((tert-butyldimethylsilyl)oxy)phenyl)-2-((2,4-dinitrophenoxy)imino)-*N*-pentylacetamide, 7



7 48%

The crude material was purified by column chromatography (PE/EtOAc 9:1) to give the product as yellow solid (yield 48%). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.86 (d, *J* = 2.7 Hz, 1H), 8.42 (dd, *J* = 6.7, 2.4 Hz, 1H), 7.99 (d, *J* = 9.5 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.5 Hz , 1H), 6.99-6.85 (m, 3H), 3.42-3.38 (m, 2H), 1.67-1.62 (m, 2H), 1.33-1.31 (m, 4H), 0.90 (s, 12H), 0,19 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.7, 159.4, 156.5, 154.3, 141.6, 136.1, 132.1, 131.0, 129.5, 122.5, 122.1, 121.3, 119.6, 117.9, 40.3, 29.2, 28.7, 25.8, 22.3, 18.4, 14.0, -4.0; m/z 532 $(M+H)^+$; νmax/cm^{-1} (KBr) 3292, 1607, 1537, 1486, 1260, 914; mp 110.8-111.2°C; HRMS (EI+): *m/z*: calcd for $C_{25}H_{34}N_4O_7Si$: 530.2197, Found: 530.2201.

N-pentylbenzo[d]isoxazole-3-carboxamide, 8



8 quantitative

The crude material was purified by column chromatography (PE/EtOAc 9:1) to give the product as yellow amorphous solid (yield quantitative). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8. 26 (d, *J* = 9.3 Hz, 1H), 7.56 (br d, 2H), 7.36 (m, 1H), 7.08 (br s, NH), 3.49 (m, 2H), 1.65-1.61 (m, 2H), 1.36-1.33 (m, 4H), 0.89-0.87 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 164.15, 159.3, 152.0, 130.4, 124.9, 124.0, 120.0, 109.7, 39.5, 29.2, 29.1, 22.4, 14.0; m/z 233 $(M+H)^+$; νmax/ cm^{-1} (KBr) 3271, 1672, 1548, 1254, 913; HRMS (EI+): *m/z*: calcd for $C_{13}H_{16}N_2O_2$: 232.1212, Found: 232.1212.

HPLC data

The HPLC-UV analyses were performed using two different chromatographic methods on 200 ppm methanolic solution of each compound, setting the temperature of the column at 35 °C and the UV detection at 254 nm.

METHOD A: X-Terra Phenyl 3.5um 3.0*150 mm; isocratic elution water: methanol 30 : 70, run time 20 min; injection volume 3 µl; flow rate 500 µl/min

METHOD B: Syncronis C18 5 u 4.6*150 mm; isocratic elution water : methanol 15 : 85, run time 20 min; injection volume 5 µl; flow rate 800 µl/min

6.4 References

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dimethoxypyrazolo[4,5,1-Hi]indole-5-Carboxylates. *Tetrahedron* **2008**, *64* (14), 3183–3189.

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Chapter 7

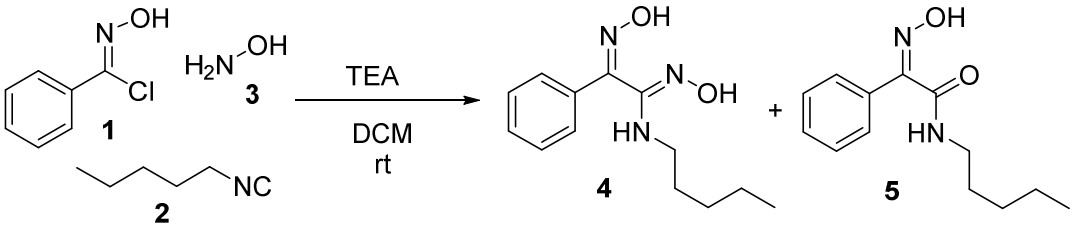
A multicomponent reaction among *Z*-chlorooximes, isocyanides and hydroxylamines as hypernucleophilic traps. A one-pot route to aminodioximes and their transformation into 5-amino-1,2,4-oxadiazoles by Mitsunobu−Beckmann rearrangement

7.1 Results and discussion

We envisaged a novel multicomponent reaction using a hyper-nucleophile, like hydroxylamine as the third component, even though literature reports on the isocyanide-mediated multicomponent processes involving hydroxylamine were somewhat discouraging. Indeed, the reactive nature of hydroxylamine, due to its three nucleophile sites, renders poor yields and several side products in the Ugi reaction.[1–3]. Moreover, hydroxylamines have been shown to react very quickly with the nitrile *N*-oxides, and low temperatures were necessary to give satisfactory yields.[4,5]

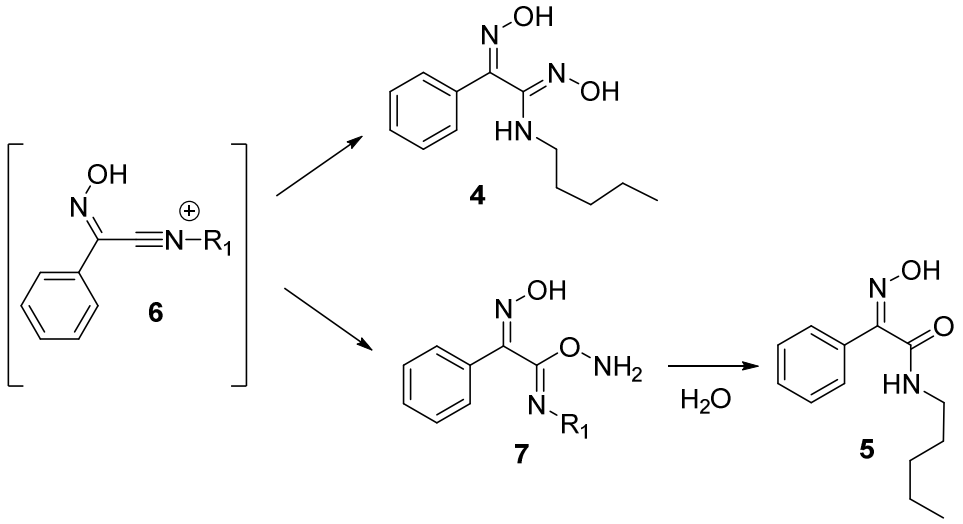
In order to demonstrate the untamed nature of the reaction between hydroxylamine and nitrile *N*-oxides at room temperature, we carried out a two-component reaction between *Z*-phenychlorooxime and hydroxylamine in dichloromethane in the presence of TEA. The result was a plethora of spots on TLC and we were able to isolate only trace amounts of the desired compound. After these preliminary results, we set up a three-component reaction among *Z*-phenylchlorooxime **1**, pentylisocyanide **2**, and hydroxylamine **3** in dichloromethane using 1 equiv of TEA at room temperature. Hydroxylamine was used as free base, prepared starting from its hydrochloric salt as reported in literature.[6]

In this case, we observed a clean reaction and the smooth formation of two products. ^{1}H NMR analysis revealed the formation of the desired aminodioxime **4** in 45% yield and the amide **5** in 15% yield (Scheme 1).



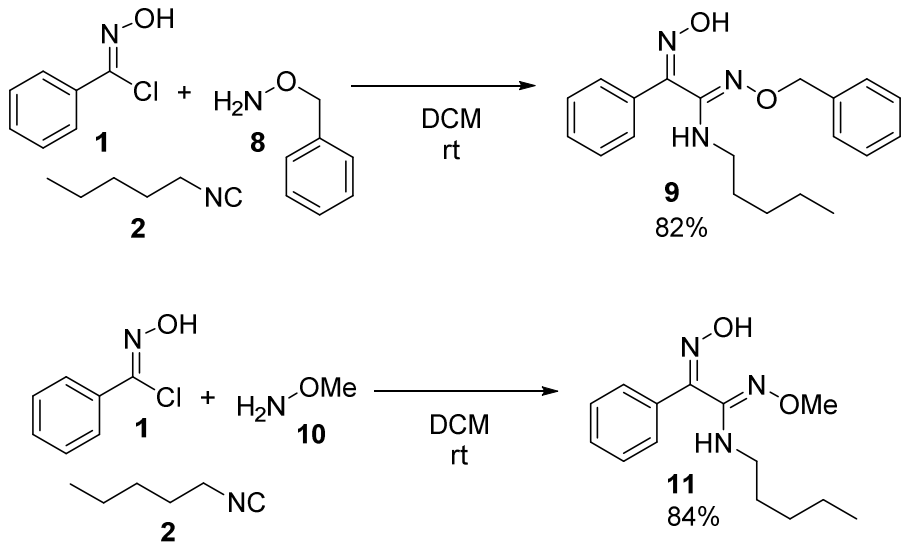
Scheme 1. The novel three component reaction with hydroxylamine.

We rationalized the formation of the amide **5** due to the reaction between the nitrilium ion and the hydroxyl group of hydroxylamine to give an unstable imidate **7** prone to undergo hydrolysis to the amide (Scheme 2).



Scheme 2. Proposed mechanism for the formation of the amide **5**.

In order to verify this hypothesis, the reaction was run using either *o*-benzylhydroxylamine **8** or *o*-methylhydroxylamine **10**. The corresponding aminodioxime **9** and **11** were obtained in 82 and 84% yield, respectively, without observable formation of the amide byproduct (Scheme 3).



Scheme 3. Multicomponent reaction using *o*-benzylhydroxylamine **9** or *o*-methylhydroxylamine **11**.

Motivated by these preliminary results, and with the goal of suppressing/reducing the formation of the undesired amide, and hence decrease the formation of the alcholate of hydroxylamine, we decided to screen different bases in dichloromethane. The results are shown in Table 1.

Entry	Base	eq.	Yield % **4**	Yield % **5**
1	*N*-methylmorpholine	1	65%	11%
2	TEA	3	47%	10%
4	imidazole	1	67%	8%
5	**$NaHCO_3$**	**1**	**72%**	**10%**
6	*N*-methylmorfoline	2	18%	16%
7	2,6-Lutidine	1	52%	9%

Table 1. Optimization of the reaction conditions.

We observed that the use of the less basic sodium bicarbonate (entry 5) was able to reduce the formation the amide probably due to the reduced ionization to the corresponding alcoholate and it increased the yield of aminodioxime to 72%.

With such optimized conditions in hand, we explored the scope of this novel multicomponent reaction using different *Z*-chlorooximes (**1** and **12-19**) and isocyanides (**2** and **20-22**) (Figure 1).

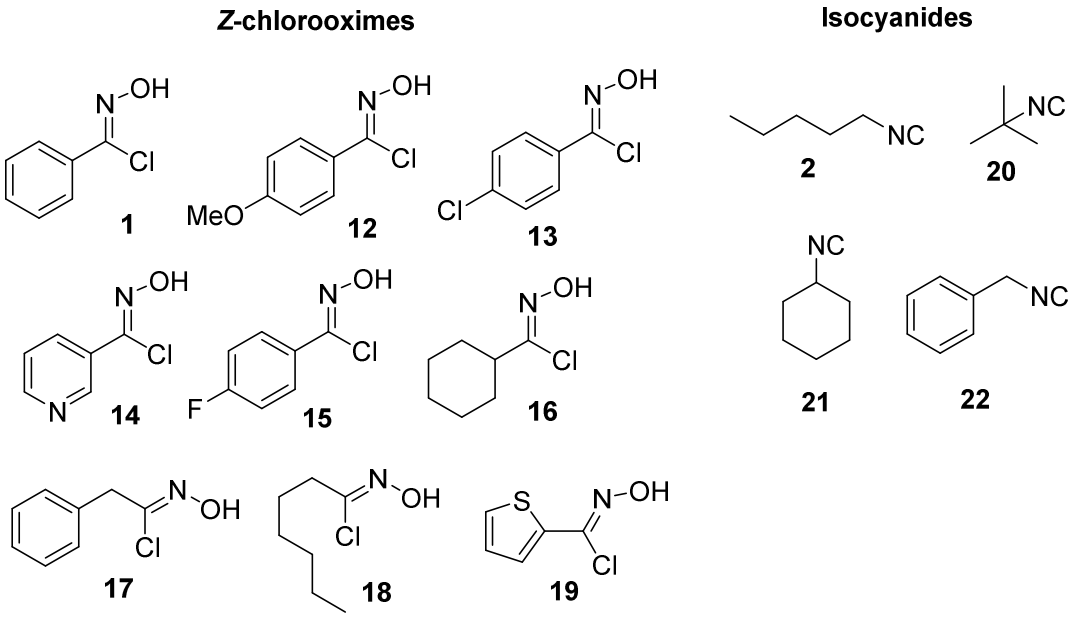


Figure 1. Building blocks used.

The library of compounds synthesized is shown in Figure 2.

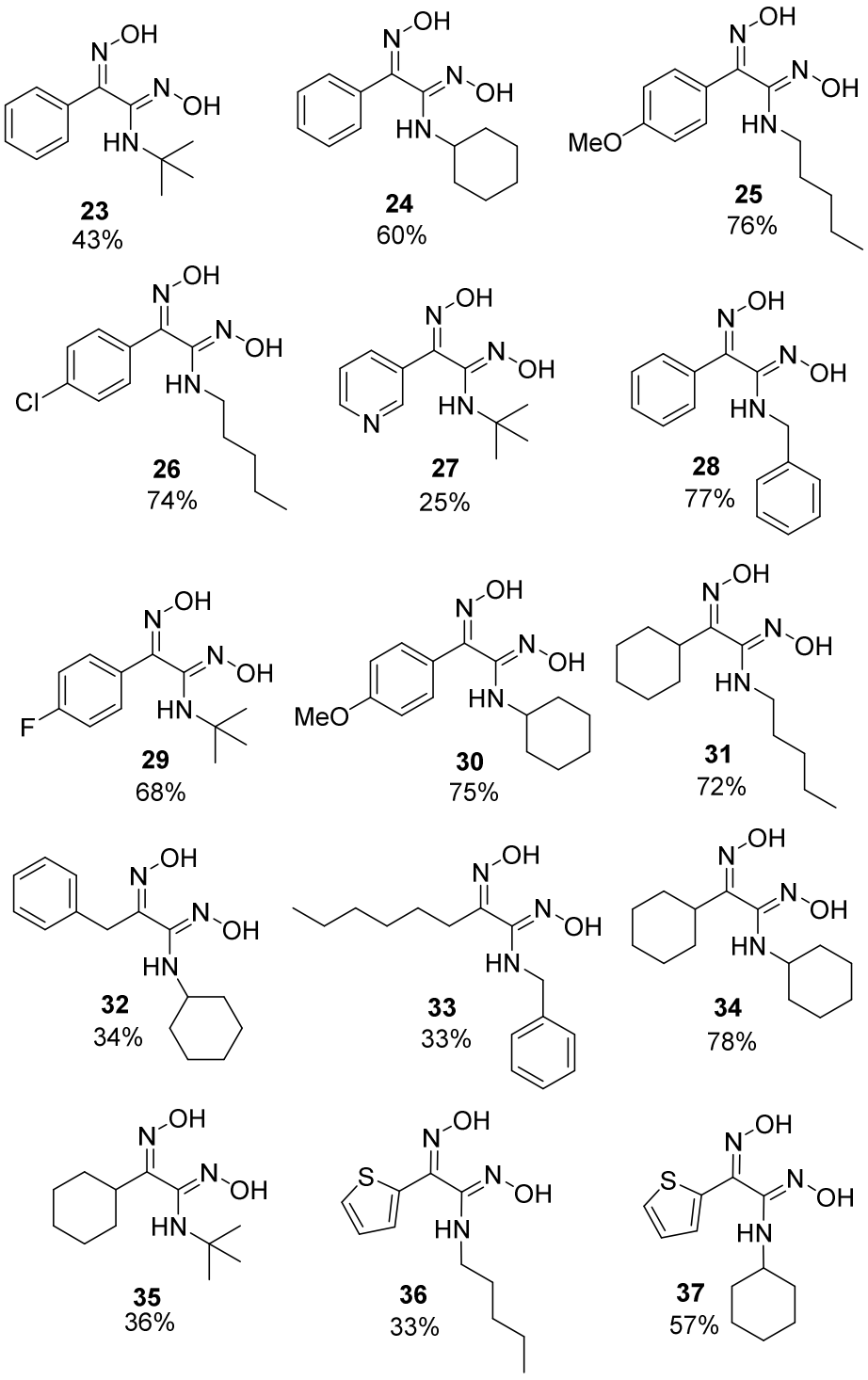
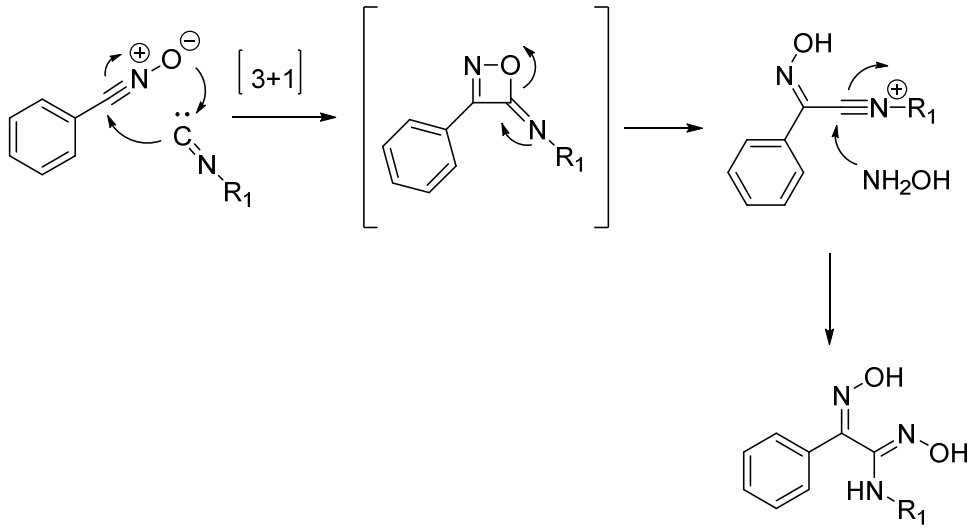


Figure 2. Aminodioximes synthesized (amide by-product was always isolate in less then 10% yield).

As show in Figure 2, the reaction is quite general: primary, secondary, tertiary isocyanides are able to initiates the multicomponent process while the reaction fails with the less reactive aromatic isocyanides. Aromatic, heteroaromatic and aliphatic *Z*-chlorooximes were successfully used as generators of the nitrile *N*-oxide species.

The ^{1}H and ^{13}C NMR spectra of the aminodioximes **4**, recorded in DMSO-d_6, revealed the presence of an equilibrium between the imino and the amino forms, which is shifted prevalently toward the amino tautomer.[7,8]

In the most plausible mechanistically scenario from the [3+1] cycloaddition of isocyanide and nitrile *N*-oxide should be obtained a four-membered ring, which readily opens, in order to relieve the ring strain, affording the nitrilium intermediate which could now be attacked by a third nucleophile, the hydroxylamine, finally forming the novel product (Scheme 4).



Scheme 4. Proposed mechanism for the selective addition of isocyanides to nitrile *N*-oxide in the presence of a third nucleophile.

On the basis of the proposed reaction mechanism and considering that the transition from one oxime geometrical isomer to another requires either high temperature or acid or base catalysis or ultraviolet light,[9] it is reasonable to assume that the first oxime retains the *syn* configuration while the amidoxime moiety can,

in principle, exist as a mixture of tautomers. As one major isomer is always formed, it is reasonable to think that it is the more stable *amphi* form (*Z*,*Z*).

In order to unambiguously establish the stereochemistry of the aminodioximes synthesized, a single-crystal X-ray diffraction analysis on derivative **23** was carried out and its crystallographic structure is presented in Figure 3 confirm the *amphi* form.

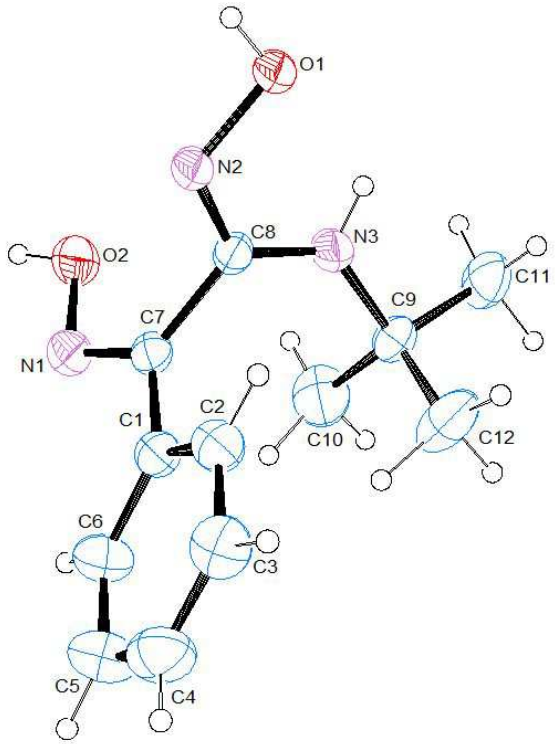


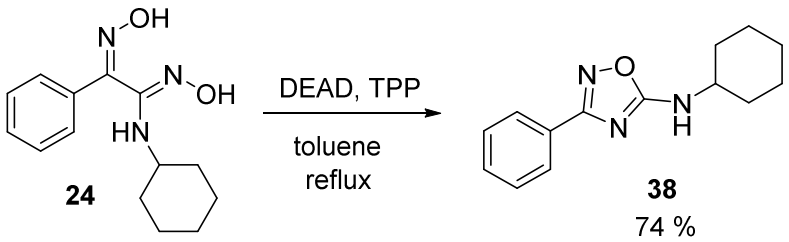
Figure 3. ORTEP[19] view of **23**, showing the arbitrary atom-labeling scheme. Atomic displacement parameters for non-H atoms are at 40% probability level.

The overall molecular conformation is determined by the "*Z*" conformation of the C7=N1 double bond, as shown by the value of the torsional angle C8-C7-N1-O2 of 7(1)°, and by the "*E*" conformation of the C8=N2 moiety, characterized by the torsional angle C7-C8-N2-O1 of 180(1)°. The orientation of the benzene ring with respect to the oxime groups is defined by dihedral angles of 24.0(2)° and 80.3(2)°between the ring and the C7-N1-O2-H21 and C8-N2-O1-H12 planes,

respectively. In the solid state are present only intermolecular interactions and a hydrogen-bond pattern is observed, in agreement with the crystal data of oximes previously published[10,11] (see Experimental section).

Aminodioxines are also pivotal reagent for the synthesis of 2-aminofurazans[12,13] under dehydrative conditions (4 M NaOH). Depending on the substrate functionalization such strong basic conditions are not always viable, rendering this transformation poor in scope. We recently demonstrated that for sensitive substrates mild dehydrative conditions using the Mitsunobu reaction on vicinal bis-oximes can afford furazans.[14] We therefore decided to employ the same dehydrative conditions with the newly formed aminodioximes.

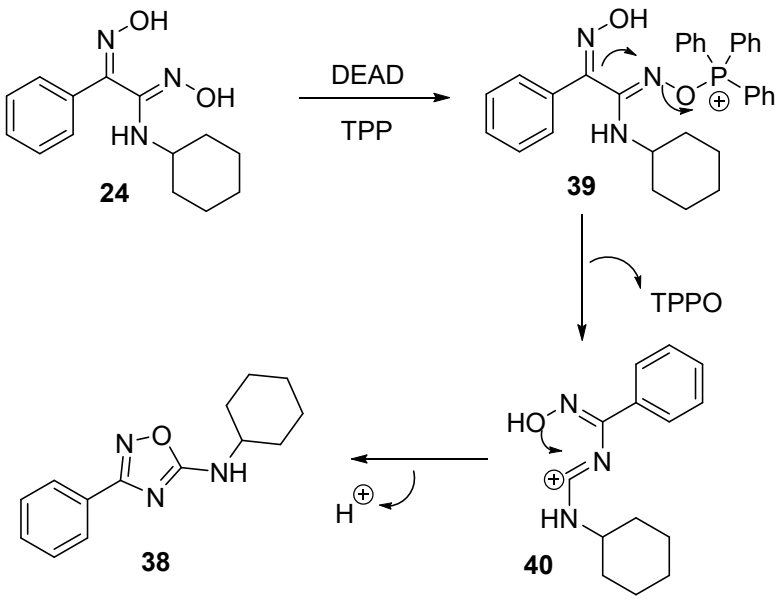
In particular, we tried dehydrative Mitsunobu conditions on the compound **24**. Serendipitously, we did not obtain the expected 2-aminofurazan but the corresponding 5-amino-1,2,4-oxadiazole **38** in 74% yield (Scheme 5). The reaction was completely chemoselective as no other isomers were detected. In order to confirm the proposed structure, the same compound was prepared according a literature procedure reacting amidoximes with carbodiimides and the spectroscopic data were in agreement with those reported.[15,16]



Scheme 5. Formation of the 5-amino-1,2,4-oxadiazole starting from the aminodioxime **24.**

To explain this result, we propose the following mechanistic scenario. The TPP−DEAD Morrison−Brunn−Huisgen betain extracts the proton of the aminooxime. Subsequently, the resulting alcoholate reacts with the TPP−DEAD adduct to give the intermediate **39**, which spontaneously undergoes a Beckmann

rearrangement with the concomitant expulsion of TPPO. Finally the hydroxyl group of hydroxylamine, properly positioned, quenches the carbocationic species to afford the 1,2,4-oxadiazole nucleus (Scheme 6). A different mechanism involving a cycloaddition between cyanamides and nitrile *N*-oxides deriving from a Beckmann fragmentation was also considered but readily ruled out because when the reaction was run in the presence of a strong dipolarophile such as phenylacetylene the formation of the corresponding isooxazole deriving from the reaction between phenylacetylene and the nitrile *N*-oxide was not detected.[17–19]



Scheme 6. Proposed mechanism for the formation of 5-amino-1,2,4-oxadiazoles starting from aminodioxides using Mistunobu conditions.

We therefore applied this novel transformation to afford a small library of 5-amino-1,2,4-oxadiazoles (**41-51**) (Figure 4).

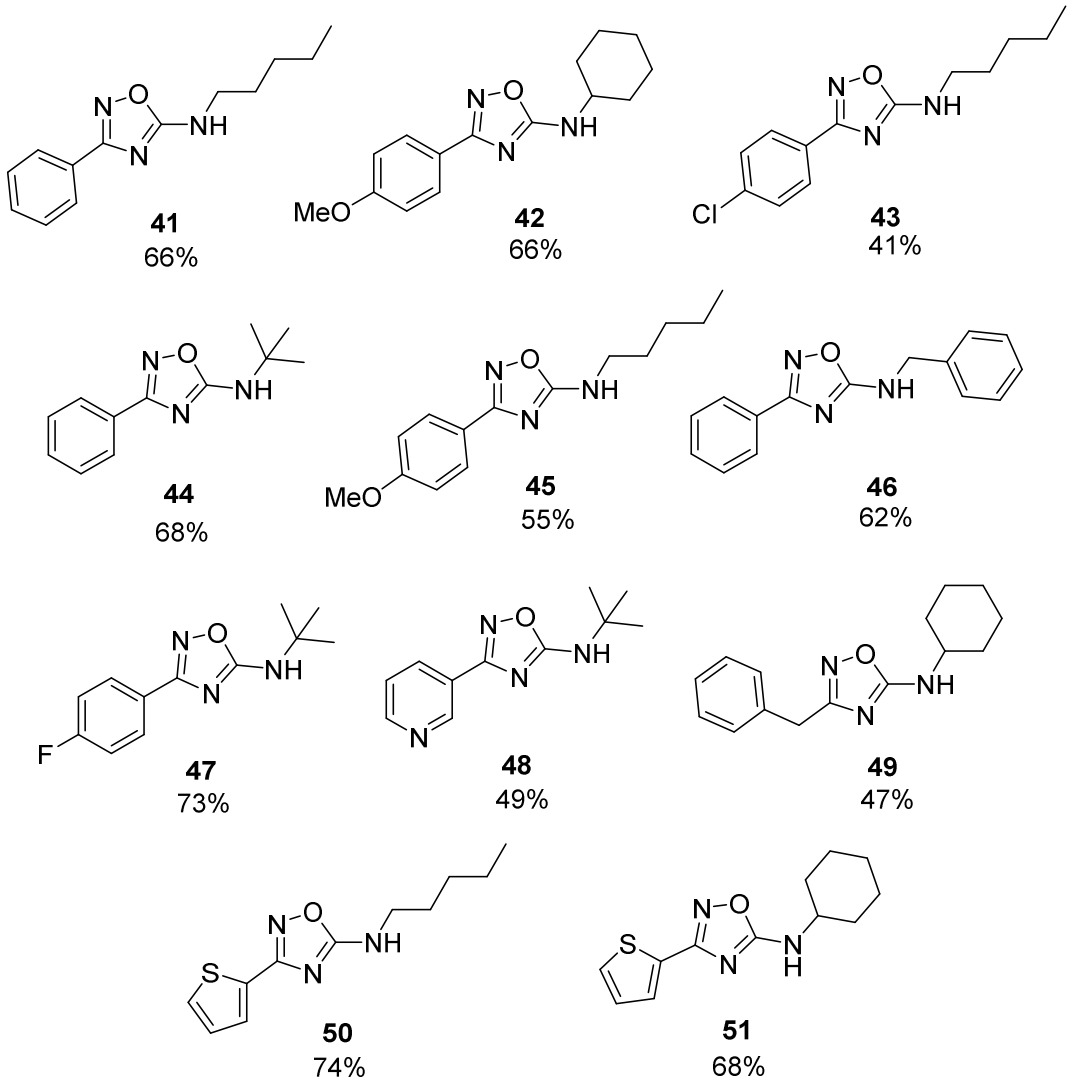


Figure 4. 5-amino-1,2,4-oxadiazoles synthesized.

The reaction appears to be general in scope irrespective of which isomer prevails on the synthesized amidoximes. The unprecedented transformation of aminodioximes into 5-amino-1,2,4-oxadiazoles through a Beckmann rearrangement was also confirmed by a few reports where 3,5-diaryl-1,2,4- oxadiazoles were prepared from symmetrical 1,2-aryldioximes of α-aryl diketones.[20,21]

7.2 Conclusions

In conclusion, with this work we have established a straightforward synthetic route which with only two synthetic steps affords at first aminodioximes and then 5-aminosubstituted 1,2,4-oxadiazoles which, until now, required long syntheses. Both these class of compounds play important roles in several branches of chemistry[22].

Apart from their undisputed role in analytical chemistry, the obtained aminodioximes (also known as *vic*-dioximes) are an important class of ligands able to form complexes with several transition metals. Such complexes have been shown to be useful in different fields of chemistry,[23] and some were also found to exhibit semiconducting properties.[24,25] Their preparation by means of a one-pot multicomponent reaction constitutes a significant improvement on the previous methods, which typically require at least four to six reaction/purification steps when starting from acetophenones.

7.3 Experimental section

General Methods. Commercially available reagents and solvents were used without further purification. Dichloromethane was dried by distillation from P_2O_5 and stored over activated molecular sieves (4 Å). When necessary the reactions were performed in oven-dried glassware under a positive pressure of dry nitrogen. Melting points were determined in open glass capillaries and are uncorrected. All the compounds were characterized by IR. ^{1}H and ^{13}C APT NMR were recorded on a 300 MHz. High-resolution ESI-MS spectra were performed on a Thermo LTQ Orbitrap XL mass spectrometer. The spectra were recorded by infusion into the ESI source using MeOH as the solvent. Chemical shifts (δ) are reported in part per million (ppm) relative to the residual solvent peak. Column chromatography was performed on silica gel 70–230 Mesh ASTM or silica gel 230–400 Mesh ASTM when it was used Biotage Isolera. Thin layer chromatography (TLC) was carried out on 5 x 20 cm plates with a layer thickness of 0.25 mm (Silica gel 60 F_{254}). When necessary they were developed with $KMnO_4$.

General preparation of hydroxylamine solution.

Hydroxylamine hydrochloride (15 mmol) in methanol (10 mL), was added to a stirred solution of potassium hydroxide (15 mmol) in methanol (4 mL) at 0 °C. The mixture was stirred for 30 min at room temperature and the precipitate potassium chloride was removed and the filtrate was used as such.[16]

General preparation of *C*-oximinoimidamides (4, 9, 11, 23-37)

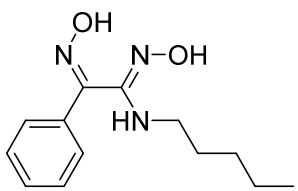
The chlorooxime (1 eq.) was dissolved in dry dichloromethane. Isocyanide (1 eq.), hydroxylamine (solution 1M in methanol, 1.2 eq.) and sodium bicarbonate (1

eq.) were added and the reaction was stirred at room temperature under a nitrogen atmosphere until all the chlorooxime was consumed (typically 16 hours as judged by TLC). The reaction mixture was concentrated under reduced pressure and the crude material was purified by column chromatography.

General preparation of oxadiazoles (38, 41-51)

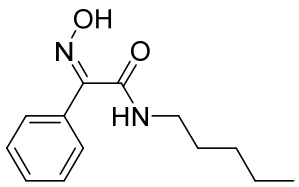
To a cooled (0 °C) suspension of *C*-oximinoimidamide (1 eq.) in dry toluene was added triphenylphosphine (2 eq.). Diethyl azodicarboxylate (DEAD, 2 eq.) was then added dropwise and the resulting solution was heated at reflux under a nitrogen atmosphere. When reagents were consumed (typically 16 hours as judged by TLC) the reaction mixture was concentrated under reduced pressure and the crude material was purified by column chromatography.

(1Z,2Z)-*N*'-hydroxy-2-(hydroxyimino)-*N*-pentyl-2-phenylacetimidamide (4).



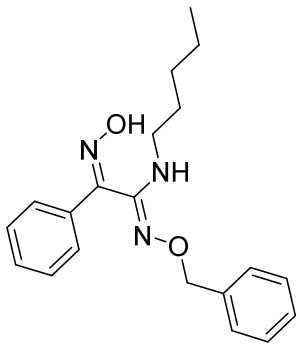
(Z)-N-hydroxybenzimidoyl chloride 100 mg (0.643 mmol), 1-pentil isocyanide 0.081 mL (0.643 mmol), hydroxylamine 0.720 mL (solution 1M in methanol, 0.772 mmol), sodium bicarbonate 54 mg (0.643 mmol), DCM dry 1 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 8:2, 6:4) to give the product as white solid (114 mg, yield 71.6%).
Signals are referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.67 (s, OH), 9.38 (s, OH), 7.60 (m, 2H), 7.37 (m, 3H), 5.89 (t, NH, J = 6.4 Hz), 2.77 (br q, 2H) 1.31 (m, 2H), 1.09 (m, 4H), 0.73 (t, 3H, J = 6.7 Hz); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 148.8, 148.4, 135.0, 129.7, 128.9, 126.5, 42.4, 30.6, 28.8, 22.7, 14.3; IR (KBr) 3265, 1653, 1442, 1409, 948, 897, 691 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{13}H_{19}N_3O_2$: 249.1477; Found: 272.1370 $[M+Na]^+$.

(*Z*)-2-(hydroxyimino)-*N*-pentyl-2-phenylacetamide (5).



White solid; yield 11.5%; ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 11.45 (s, OH), 8.44 (t, NH, *J* = 5.5 Hz), 7.62 (m, 2H), 7.39 (m, 3H), 3.21 (br q, 2H) 1.46 (m, 2H), 1.30 (m, 4H), 0.87 (t, 3H, *J* = 6.7 Hz); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 163.9, 153.5, 133.0, 129.9, 129.2, 126.2, 40.1 (peak overlaps with DMSO-d$_6$), 38.7, 29.1, 22.3, 14.5; IR (KBr) 3330, 2955, 1633, 1560, 1430, 1258, 946 ν_{max}/cm^{-1}; MS (ESI) *m/z* (M+H)$^+$ Calcd for $C_{13}H_{18}N_2O_2$: 234.1368; Found: 235.1341 [M+H]$^+$.

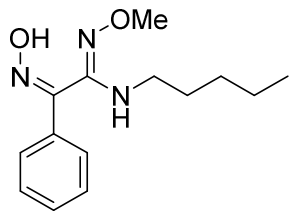
(1Z,2Z)-*N*'-(benzyloxy)-2-(hydroxyimino)-*N*-pentyl-2-phenylacetimidamide (9).



(Z)-N-hydroxybenzimidoyl chloride 100 mg (0.643 mmol), 1-pentyl isocyanide 0.081 mL (0.643 mmol), *O*-benzylhydroxylamine 0.720 mL (solution 1M in methanol, 0.772 mmol), sodium bicarbonate 54 mg (0.643 mmol), DCM dry 1 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 8:2) to give the product as white solid (179 mg, yield 82%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 11.78 (s, OH), 7.50-7.30 (m, 10H), 6.33 (br t, NH), 4.93 (s, 2H), 2.78 (m, 2H), 1.30 (m, 2H), 1.07 (m, 4H), 0.71 (br t, 3H); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 148.5, 147.5, 139.2, 133.9, 129.2, 128.4, 128.0, 127.6, 127.2, 125.8, 74.0, 42.6, 30.0, 28.2, 21.6, 13.7; IR (KBr) 3110, 1630, 1439, 1053, 955, 944, 726 ν_{max}/cm^{-1}; MS (ESI) *m/z* (M+H)$^+$ Calcd for $C_{20}H_{25}N_3O_2$: 339.1947; Found: 340.2011 [M+H]$^+$.

(1Z,2Z)-2-(hydroxyimino)-*N*'-methoxy-*N*-pentyl-2-phenylacetimidamide (10).

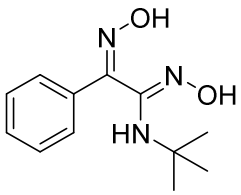


(Z)-N-hydroxybenzimidoyl chloride 100 mg (0.645 mmol), 1-pentyl isocyanide 0.086 mL (0.645 mmol), methoxyl amine 0.772 mL (solution 1M in methanol, 0.772 mmol), sodium bicarbonate 54 mg (0.645 mmol), DCM dry 1 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 8:2) to give the product as white solid (141.8 mg, yield 84%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 11.78 (s, OH), 7.61 (m, 2H), 7.40 (m, 3H), 6.18 (br t, NH), 3.65 (s, 3H), 2.78 (m, 2H), 1.30 (m, 2H), 1.09 (m, 4H), 0.75 (br t, 3H); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 147.9,

147.6, 134.1, 129.3, 128.5, 125.8, 60.4, 42.6, 29.9, 28.2, 21.7, 13.7; IR (KBr) 3137, 1630, 1439, 1414, 1052, 955, 693 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{14}H_{21}N_3O_2$: 263.1634; Found: 286.1518 $[M+Na]^+$.

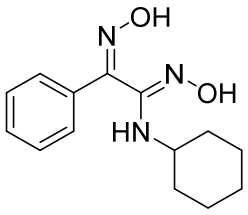
(1Z,2Z)-*N*-(tert-butyl)-*N*'-hydroxy-2-(hydroxyimino)-2-phenylacetimidamide (23).



(Z)-N-hydroxybenzimidoyl chloride 250 mg (1.61 mmol), *tert*-butyl isocyanide 0.182 mL (1.61 mmol), hydroxylamine 1.8 mL (solution 1M in methanol, 1.93 mmol), sodium bicarbonate 135 mg (1.61 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 7:3, 6:4) to give the product as white solid (162.5 mg, yield 43%).

Signals are referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.72 (s, OH), 9.79 (s, OH), 7.65 (br d, 2H), 7.38 (m, 3H), 5.36 (s, NH), 1.08 (s, 9H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 149.7, 145.7, 135.2, 129.0, 128.4, 126.1, 50.8, 30.7; IR (KBr) 3062, 1638, 1404, 1370, 949, 900, 694 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{12}H_{17}N_3O_2$: 235.1321; Found: 258.1219 $[M+Na]^+$.

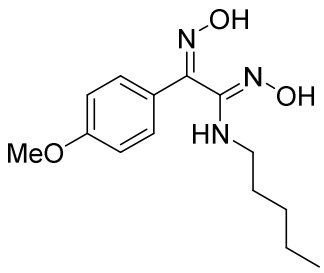
(1Z,2Z)-*N*-cyclohexyl-*N*'-hydroxy-2-(hydroxyimino)-2-phenylacetimidamide (24).



(Z)-N-hydroxybenzimidoyl chloride 250 mg (1.61 mmol), cyclohexyl isocyanide 0.200 mL (1.61 mmol), hydroxylamine 1.8 mL (solution 1M in methanol, 1.93 mmol), sodium bicarbonate 135 mg (1.61 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 7:3, 6:4) to give the product as white solid (250.5 mg, yield 60%).

Signals are referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.66 (s, OH), 9.40 (s, OH), 7.65 (m 2H), 7.37 (m, 3H), 5.73 (br d, NH), 2.71 (m, 1H), 1.64 (m, 4H), 1.44 (m, 1H), 1.19 (m, 2H), 1.00 (m, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 148.3, 146.9, 134.6, 129.2, 128.5, 125.9, 51.8, 40.1 (peak overlaps with DMSO-d_6), 34.5, 24.9; IR (KBr) 3263, 1660, 1449, 1412, 950, 903, 694 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{14}H_{19}N_3O_2$: 261.1477; Found: 262.1542 $[M+H]^+$.

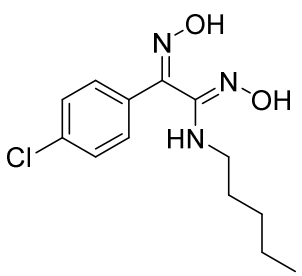
(1Z,2Z)-*N′*-hydroxy-2-(hydroxyimino)-2-(4-methoxyphenyl)-*N*-pentylacetimidamide (25).



(Z)-*N*-hydroxy-4-methoxybenzimidoyl chloride 250 mg (1.34 mmol), 1-pentyl isocyanide 0.168 mL (1.34 mmol), hydroxylamine 1.5 mL (solution 1M in methanol, 1.61 mmol), sodium bicarbonate 113 mg (1.34 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 5:5, 4:6) to give the product as white solid (286 mg, yield 76%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.40 (s, OH), 9.34 (s, OH), 7.55 (d, J = 8.8 Hz, 2 H, AA′XX′), 6.97 (d, J = 8.8 Hz, 2 H, AA′XX′), 5.85 (br t, NH), 3.77 (s, 3H), 2.78 (m, 2H), 1.31 (m, 2H), 1.10 (m, 4H), 0.74 (br t, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 160.1, 148.2, 148.0, 127.4, 127.0, 114.0, 55.3, 42.4, 30.2, 28.3, 21.8, 13.8; IR (KBr) 3274, 1652, 1255, 1182, 947, 899, 833 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{14}H_{21}N_3O_3$: 279.1583; Found: 280.1646 $[M+H]^+$.

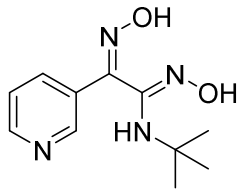
(1*Z*,2*Z*)-2-(4-chlorophenyl)-*N*'-hydroxy-2-(hydroxyimino)-*N*-pentylacetimidamide, (26).



(*Z*)-4-chloro-*N*-hydroxybenzimidoyl chloride 250 mg (1.31 mmol), cyclohexyl isocyanide 0.166 mL (1.31 mmol), hydroxylamine 1.46 mL (solution 1M in methanol, 1.57 mmol), sodium bicarbonate 110 mg (1.31 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 7:3, 6:4) to give the product as white solid (274 mg, yield 74%).

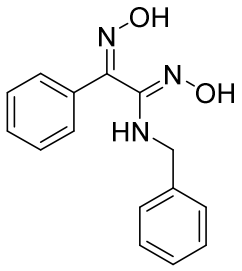
Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.86 (br s, OH), 9.48 (br s, OH), 7.62 (d, J = 8.6 Hz, 2H, AA′XX′), 7.49 (d, J = 8.6 Hz, 2H, AA′XX′), 6.01 (br s, NH), 2.77 (m, 2H), 1.27 (m, 6H), 0.75 (m, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 148.1, 147.9, 134.4, 133.9, 129.2, 128.1, 42.9, 30.7, 28.8, 22.2, 14.3; IR (KBr) 3292, 1640, 1493, 1449, 1093, 946, 832 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{13}H_{18}ClN_3O_2$: 283.1088; Found: 284.1142 $[M+H]^+$.

(1Z,2Z)-*N*-(tert-butyl)-*N′*-hydroxy-2-(hydroxyimino)-2-(pyridin-3-yl)acetimidamide (27).



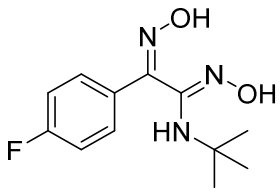
(*Z*)-*N*-hydroxynicotinimidoyl chloride 200 mg (1.28 mmol), *tert*-butyl isocyanide 0.145 mL (1.28 mmol), hydroxylamine 1.4 mL (solution 1M in methanol, 1.53 mmol), sodium bicarbonate 107.5 mg (1.28 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 6:4, 5:5) to give the product as white solid (75.4 mg, yield 25%).
Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 11.46 (s, OH), 9.95 (s, OH), 8.63 (s, 1H), 8.55 (br d, 1H), 7.84 (br d, 1H), 7.43 (m, 1H), 5.26 (s, NH), 1.32 (s, 9H); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 149.5, 149.1, 147.0, 145.2, 132.9, 129.4, 123.6, 50.8, 28.5; IR (KBr) 3137, 1642, 1504, 1415, 1243, 961, 918 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{11}H_{16}N_4O_2$: 236.1273; Found: 237.1349 $[M+H]^+$.

(1Z,2Z)-*N*-benzyl-*N*'-hydroxy-2-(hydroxyimino)-2-phenylacetimidamide (28).



(*Z*)-*N*-hydroxybenzimidoyl chloride 250 mg (1.6 mmol), benzyl isocyanide 0.197 mL (1.6 mmol), hydroxylamine 1.77 mL (solution 1M in methanol, 1.9 mmol), sodium bicarbonate 134 mg (1.6 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 7:3) to give the product as white solid (331.1 mg, yield 77%).
Signals are referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 11.77 (s, OH), 9.55 (s, OH), 7.53 (m, 2H), 7.32 (m, 4H), 7.17 (m, 4H), 6.41 (t, NH, *J* = 6.7 Hz), 4.04 (d, 2H, *J*= 6.7 Hz); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 148.1, 147.7, 140.1, 134.4, 129.0, 128.3, 128.0, 127.3, 126.6, 126.0, 46.2; IR (KBr) 3265, 1658, 1494, 1452, 1093, 944, 902 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{15}H_{15}N_3O_2$: 269.1164; Found: 270.1240 $[M+H]^+$.

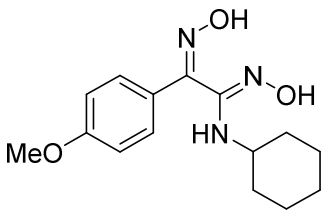
(1Z,2Z)-*N*-(tert-butyl)-2-(4-fluorophenyl)-*N′*-hydroxy-2-(hydroxyimino)acetimidamide (29).



(*Z*)-4-fluoro-*N*-hydroxybenzimidoyl chloride 250 mg (1.4 mmol), *tert*-butyl isocyanide 0.158 mL (1.4 mmol), hydroxylamine 1.6 mL (solution 1M in methanol, 1.7 mmol), sodium bicarbonate 118 mg (1.4 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 8:2, 7:3) to give the product as white solid (248.1 mg, yield 68%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 11.75 (s, OH), 9.84 (s, OH), 7.66 (m, 2H), 7.25 (m, 2H), 5.36 (br s, NH), 1.08 (s, 9H); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 163.1 (d, *J* = 244.5 Hz), 150.2, 146.2, 132.3 (d, *J* = 2.8 Hz), 128.8 (d, *J* = 8 Hz), 116.0 (d, *J* = 21.2 Hz), 51.2, 31.4; IR (KBr) 3226, 1643, 1513, 1265, 1224, 953, 834 ν_{max}/cm^{-1}; MS (ESI) *m/z* (M+H)$^+$ Calcd for $C_{12}H_{16}FN_3O_2$: 253.1227; Found: 276.1114 [M+Na]$^+$.

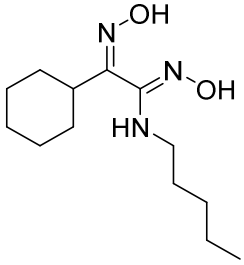
(1Z,2Z)-*N*-cyclohexyl-*N′*-hydroxy-2-(hydroxyimino)-2-(4-methoxyphenyl)acetimidamide (30).



(*Z*)-*N*-hydroxy-4-methoxybenzimidoyl chloride 250 mg (1.3 mmol), cyclohexyl isocyanide 0.161 mL (1.3 mmol), hydroxylamine 1.5 mL (solution 1M in methanol, 1.6 mmol), sodium bicarbonate 109 mg (1.35 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 5:5, 4:6) to give the product as white solid (286.2 mg, yield 75%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 11.39 (s, OH), 9.35 (s, OH), 7.56 (d, *J* = 8.6 Hz, 2 H, AA′XX′), 6.97 (d, *J* = 8.6 Hz, 2 H, AA′XX′), 5.67 (br d, NH), 3.81 (s, 3H), 2.69 (m, 1H), 1.60 (m, 4H), 1.44 (m, 1H), 1.21 (m, 2H), 1.01 (br s, 3H); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 160.1, 148.0, 147.2, 127.4, 127.2, 114.0, 55.3, 51.8, 40.2 (peak overlaps with DMSO-*d*$_6$), 34.6, 25.0; IR (KBr) 3118, 1643, 1514, 1259, 1247, 1178, 944 ν_{max}/cm^{-1}; MS (ESI) *m/z* (M+H)$^+$ Calcd for $C_{15}H_{21}N_3O_3$: 291.1583; Found: 292.1659 [M+H]$^+$.

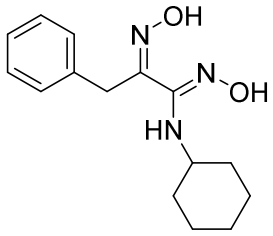
(1Z,2Z)-2-cyclohexyl-*N′*-hydroxy-2-(hydroxyimino)-*N*-pentylacetimidamide (31).



(*Z*)-*N*-hydroxycyclohexanecarbimidoyl chloride 350 mg (2.16 mmol), 1-pentyl isocyanide 0.271 mL (2.16 mmol), hydroxylamine 2.4 mL (solution 1M in methanol, 2.59 mmol), sodium bicarbonate 181 mg (2.16 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 7:3) to give the product as white solid (400.1 mg, yield 72%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 10.83 (s, OH), 9.20 (s, OH), 5.45 (br t, NH), 2.80 (m, 2H), 2.24 (m, 1H), 1.84 (m, 2H), 1.69 (m, 4H), 1.22 (m, 10H), 0.85 (t, 3H, *J* = 6.9 Hz); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 153.1, 149.4, 42.7, 42.6, 38.8 (peak overlaps with DMSO-*d*$_6$), 30.1, 30.0, 28.5, 25.7, 21.9, 13.9; IR (KBr) 3105, 1643, 1467, 1451, 964, 917, 887 ν_{max}/cm^{-1}; MS (ESI) *m/z* (M+H)$^+$ Calcd for $C_{13}H_{25}N_3O_2$: 255.1947; Found: 256.2019 [M+H]$^+$.

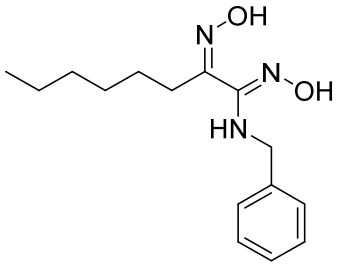
(1Z,2Z)-*N*-cyclohexyl-*N′*-hydroxy-2-(hydroxyimino)-3-phenylpropanimidamide (32).



(*Z*)-*N*-hydroxy-2-phenylacetimidoyl chloride 350 mg (2.1 mmol), cyclohexyl isocyanide 0.261 mL (2.1 mmol), hydroxylamine 2.3 mL (solution 1M in methanol, 2.5 mmol), sodium bicarbonate 176 mg (2.1 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 7:3, 6:4) to give the product as white solid (194.9 mg, yield 34%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 11.06 (s, OH), 9.35 (s, OH), 7.30-7.18 (m, 5H), 5.22 (br d, NH), 3.57 (2H, peaks overlap with DMSO-d$_6$), 2.44 (br s, 1H), 1.45 (br s, 3H), 1.15 (br s, 2H), 0.92 (m, 5H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 149.1, 148.5, 136.5, 129.4, 128.5, 126.7, 52.2, 40.7, 34.5, 25.3, 25.0; IR (KBr) 3064, 1642, 1424, 997, 941, 723, 697 ν_{max}/cm^{-1}; MS (ESI) *m/z* (M+H)$^+$ Calcd for $C_{15}H_{21}N_3O_2$: 275.1634; Found: 276.1707 [M+H]$^+$.

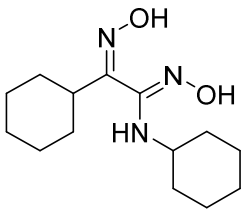
(1Z,2Z)-*N*-benzyl-*N′*-hydroxy-2-(hydroxyimino)octanimidamide (33).



(*Z*)-*N*-hydroxyheptanimidoyl chloride 350 mg (2.14 mmol), benzyl isocyanide 0.261 mL (2.14 mmol), hydroxylamine 2.4 mL (solution 1M in methanol, 2.57 mmol), sodium bicarbonate 180 mg (2.14 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 8:2, 6:4) to give the product as white solid (195.3 mg, yield 33%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-d_6) δ 10.96 (s, OH), 9.42 (s, OH), 7.35-7.18 (m, 5H), 6.20 (t, NH), 4.07 (d, 2H, J = 4.9 Hz), 1.98 (t, 2H, J = 7.5 Hz), 1.29 (m, 3H), 1.20-1.09 (m, 5H), 0.81 (br t, 3H); ^{13}C-NMR (75 MHz, DMSO-d_6) δ 149.5, 149.4, 140.9, 128.1, 127.0, 126.6, 45.9, 33.9, 31.0, 28.2, 25.3, 21.9, 13.9; IR (KBr) 3307, 1695, 1461, 1455, 1350, 921, 697 ν_{max}/cm^{-1}; MS (ESI) *m/z* (M+H)$^+$ Calcd for $C_{15}H_{23}N_3O_2$: 277.1790; Found: 278.1856 [M+H]$^+$.

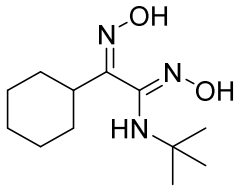
(1Z,2Z)-*N*,2-dicyclohexyl-*N′*-hydroxy-2-(hydroxyimino)acetimidamide (34).



(*Z*)-*N*-hydroxycyclohexanecarbimidoyl chloride 300 mg (1.86 mmol), cyclohexyl isocyanide 0.231 mL (1.86 mmol), hydroxylamine 2.1 mL (solution 1M in methanol, 2.23 mmol), sodium bicarbonate 156 mg (1.86 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 7:3) to give the product as white solid (388.5 mg, yield 78%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 10.81 (s, OH), 9.19 (s, OH), 5.40 (br d, NH), 2.69 (m, 1H), 2.22 (m, 1H), 1.85-1.08 (m, 20H); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 153.2, 148.4, 51.9, 42.7, 39.5 (peak overlaps with DMSO-d$_6$), 34.8, 30.1, 25.9, 25.7, 25.1; IR (KBr) 3208, 1627, 1449, 1413, 969, 933, 892 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{14}H_{25}N_3O_2$: 267.1947; Found: 268.2013 $[M+H]^+$.

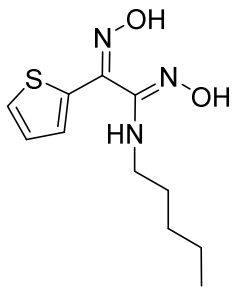
(1Z,2Z)-*N*-(tert-butyl)-2-cyclohexyl-*N′*-hydroxy-2-(hydroxyimino)acetimidamide (35).



(*Z*)-*N*-hydroxycyclohexanecarbimidoyl chloride 300 mg (1.86 mmol), *tert*-butyl isocyanide 0.210 mL (1.86 mmol), hydroxylamine 2.1 mL (solution 1M in methanol, 2.23 mmol), sodium bicarbonate 156 mg (1.86 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 7:3) to give the product as white solid (161.5 mg, yield 36%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 10.84 (s, OH), 9.69 (s, OH), 5.01 (s, NH), 2.29 (m, 1H), 1.91 (m, 4H), 1.62 (m, 6H), 1.25 (s, 9H); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 154.8, 147.6, 50.7, 40.4, 30.6, 29.5, 28.7, 25.8; IR (KBr) 3276, 1647, 1508, 1449, 1364, 969, 953 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{12}H_{23}N_3O_2$: 241.1790; Found: 264.1684 $[M+Na]^+$.

(1Z,2E)-*N′*-hydroxy-2-(hydroxyimino)-*N*-pentyl-2-(thiophen-2-yl)acetimidamide (36).

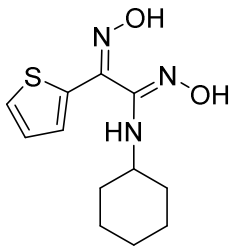


(*Z*)-*N*-hydroxythiophene-2-carbimidoyl chloride 300 mg (1.8 mmol), 1-pentyl isocyanide 0.226 mL (1.8 mmol), hydroxylamine 2.0 mL (solution 1M in methanol, 2.16 mmol), sodium bicarbonate 151 mg (1.8 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 6:4) to give the product as white solid (157.3 mg, yield 33%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz,

DMSO-*d*$_6$) δ 11.63 (s, OH), 9.50 (s, OH), 7.50 (br d, 1H), 7.09 (m, 2H), 5.87 (br t, NH), 2.80 (m, 2H), 1.29 (m, 2H), 1.11 (m, 4H), 0.73 (br t, 3H); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 147.8, 145.0, 138.7, 128.1, 127.6 (2C), 42.6, 30.3, 28.4, 21.8, 13.9; IR (KBr) 3209, 1546, 1438, 1340, 1231, 912, 701 ν_{max}/cm^{-1}; MS (ESI) *m/z* (M+H)$^+$ Calcd for $C_{11}H_{17}N_3O_2S$: 255.1041; Found: 256.1111 [M+H]$^+$.

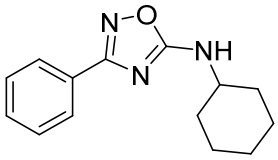
(1Z,2E)-*N*-cyclohexyl-*N'*-hydroxy-2-(hydroxyimino)-2-(thiophen-2-yl)acetimidamide (37).



(*Z*)-*N*-hydroxythiophene-2-carbimidoyl chloride 250 mg (1.5 mmol), cyclohexyl isocyanide 0.186 mL (1.5 mmol), hydroxylamine 1.7 mL (solution 1M in methanol, 1.8 mmol), sodium bicarbonate 126 mg (1.5 mmol), DCM dry 3 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 6:4) to give the product as white solid (238.1 mg, yield 57%).

Signals referred to the main isomer: ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 11.63 (s, OH), 9.54 (s, OH), 7.51 (br d, 1H), 7.09 (m, 2H), 5.64 (br d, NH), 2.72 (m, 1H), 1.62 (m, 4H), 1.44 (m, 1H), 1.18 (m, 2H), 1.02 (m, 3H); ^{13}C-NMR (75 MHz, DMSO-*d*$_6$) δ 146.8, 145.0, 138.9, 128.0, 127.6 (2C), 52.0, 40.1 (peak overlaps with DMSO-*d*$_6$), 34.6, 25.0; IR (KBr) 3275, 1658, 1442, 1008, 919, 905, 891 ν_{max}/cm^{-1}; MS (ESI) *m/z* (M+H)$^+$ Calcd for $C_{12}H_{17}N_3O_2S$: 267.1041; Found: 268.1104 [M+H]$^+$.

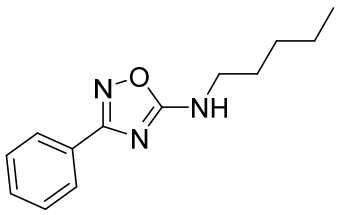
***N*-cyclohexyl-3-phenyl-1,2,4-oxadiazol-5-amine (38).**



C-oximinoimidamide 100 mg (0.383 mmol), triphenylphosphine 200.9 mg (0.766 mmol), diethyl azodicarboxylate 0.120 mL (0.766 mmol), toluene dry 1 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 95:5, 9:1) to give the product as white solid (69.2 mg, yield 74%).

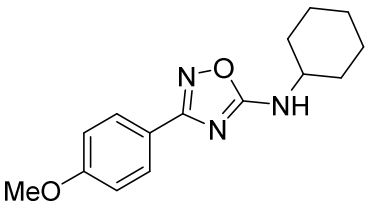
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.0 (d, *J* = 7.9 Hz, 2H,), 7.44 (m, 3H), 5.65 (br d, NH), 3.66 (m, 1H), 2.06 (m, 2H), 1.74 (m, 2H), 1.60 (m, 1H), 1.45-1.28 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.7, 168.5, 130.8, 128.7, 127.8, 127.3, 53.0, 33.3, 25.4, 24.7; IR (KBr) 3242, 1647, 1491, 1444, 1390, 1098 ν_{max}/cm^{-1}; m.p. 126.7-127.7 °C; MS (ESI) *m/z* (M+H)$^+$ Calcd for $C_{14}H_{17}N_3O$: 243.1372; Found: 244.1444 [M+H]$^+$.

_N_-pentyl-3-phenyl-1,2,4-oxadiazol-5-amine (41).



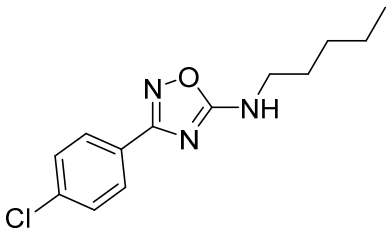
C-oximinoimidamide 70 mg (0.281 mmol), triphenylphosphine 81 mg (0.308 mmol), diethyl azodicarboxylate 0.048 mL (1.11 mmol), toluene dry 1 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1) to give the product as white solid (43 mg, yield 66%).
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.0 Hz, 2H), 7.45 (m, 3H), 6.24 (br s, NH), 3.43 (q, 2H, *J* = 7.0 Hz), 1.61 (m, 2H), 1.32 (m, 4H), 0.88 (br t, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.5, 168.5, 130.9, 128.7, 127.7, 127.3, 43.8, 29.5, 28.8, 22.3, 14.0; IR (KBr) 3244, 1654, 1527, 1462, 1386, 1301 ν_{max}/cm^{-1}; m.p. 68.1-69.0 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{13}H_{17}N_3O$: 231.1372; Found: 232.1451 $[M+H]^+$.

_N_-cyclohexyl-3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-amine (42).



C-oximinoimidamide 150 mg (0.515 mmol), triphenylphosphine 270.2 mg (1.03 mmol), diethyl azodicarboxylate 0.162 mL (1.03 mmol), toluene dry 2 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 85:15) to give the product as yellow solid (93 mg, yield 66%).
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.8 Hz, 2 H, AA′XX′), 6.92 (d, *J* = 8.8 Hz, 2 H, AA′XX′), 5.82 (br d, NH), 3.81 (s, 3H), 3.62 (m, 1H), 2.02 (m, 2H), 1.68 (m, 2H), 1.45 (m, 1H), 1.42-1.10 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.5, 168.1, 161.6, 128.8, 120.2, 114.0, 55.4, 52.9, 33.2, 25.3, 24.7; IR (KBr) 3307, 1634, 1390, 1259, 1177, 839 ν_{max}/cm^{-1}; m.p. 110.6-111.0 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{15}H_{19}N_3O_2$: 273.1477; Found: 296.1360 $[M+Na]^+$.

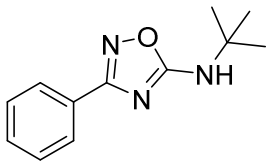
3-(4-chlorophenyl)-_N_-pentyl-1,2,4-oxadiazol-5-amine (43).



C-oximinoimidamide 144 mg (0.507 mmol), triphenylphosphine 266 mg (1.014 mmol), diethyl azodicarboxylate 0.159 mL (1.014 mmol), toluene dry 2 mL. The crude material was purified by column chromatography eluents: PE/EtOAc 95:5, 9:1) to give the product as white solid (55 mg, yield 41%).
^{1}H-NMR (300 MHz, $CDCl_3$δ 7.92 (d, *J* = 8.8 Hz, 2 H, AA′XX′), 7.41 (d, *J* = 8.8 Hz, 2 H, AA′XX′), 5.81 (br s, NH), 3.43 (q, 2H, *J* = 7.0 Hz), 1.60 (m, 2H), 1.33 (m, 4H), 0.89 (br t, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.4, 167.6, 136.9, 129.0,

128.6, 126.2, 43.9, 29.5, 28.8, 22.3, 14.0; IR (KBr) 3232, 1637, 1413, 1099, 1013, 841 ν_{max}/cm^{-1}; m.p. 105.0-106.3 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{14}H_{16}ClN_3O$: 265.0982; Found: 266.1642 $[M+H]^+$.

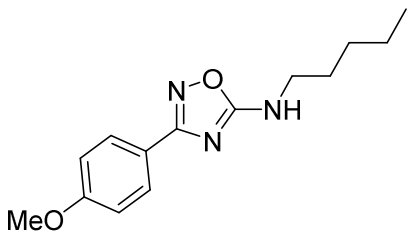
_N_-(tert-butyl)-3-phenyl-1,2,4-oxadiazol-5-amine (44).



C-oximinoimidamide 100 mg (0.425 mmol), triphenylphosphine 223 mg (0.850 mmol), diethyl azodicarboxylate 0.290 mL (0.850 mmol), toluene dry 2 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 95:5, 9:1) to give the product as white solid (62.7 mg, yield 68%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01 (m, 2H), 7.43 (m, 3H), 5.59 (br s, NH), 1.45 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.5, 168.3, 130.9, 128.8, 128.0, 127.4, 52.9, 29.2; IR (KBr) 3263, 1622, 1379, 1219, 1141, 751 ν_{max}/cm^{-1}; m.p. 87.1-88.3 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{12}H_{15}N_3O$: 217.1215; Found: 218.1279 $[M+H]^+$.

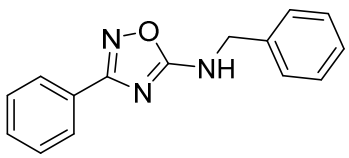
3-(4-methoxyphenyl)-_N_-pentyl-1,2,4-oxadiazol-5-amine (45).



C-oximinoimidamide 60 mg (0.215 mmol), triphenylphosphine 112.8 mg (0.430 mmol), diethyl azodicarboxylate 0.067 mL (0.430 mmol), toluene dry 2 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 95:5, 9:1) to give the product as yellow solid (30.7 mg, yield 55%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.8 Hz, 2 H, AA′XX′), 6.95 (d, *J* = 8.8 Hz, 2 H, AA′XX′), 5.89 (br s, NH), 3.84 (s, 3H), 3.42 (q, *J* = 6.7 Hz, 2H), 1.62 (m, 2H), 1.33 (m, 4H), 0.90 (br t, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.3, 168.2, 161.7, 128.9, 120.2, 114.1, 55.5, 43.9, 29.6, 28.9, 22.4, 14.1; IR (KBr) 3244, 1655, 1393, 1257, 1175, 846 ν_{max}/cm^{-1}; m.p. 72.6-73.5 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{14}H_{19}N_3O_2$: 261.1477; Found: 284.1355 $[M+Na]^+$.

_N_-benzyl-3-phenyl-1,2,4-oxadiazol-5-amine (46).

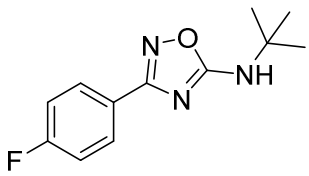


C-oximinoimidamide 110 mg (0.408 mmol), triphenylphosphine 114.3 mg (0.817 mmol), diethyl azodicarboxylate 0.128 mL (0.817 mmol), toluene dry 2 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 95:5, 9:1) to give the product as white solid (63.6 mg, yield 62%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 6.8 Hz, 2H), 7.43 (m, 3H), 7.34 (m, 5H), 6.71 (br s, NH), 4.63 (d, *J* = 6.1 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.4,

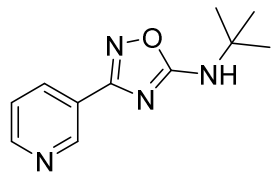
168.5, 137.2, 130.9, 128.9, 128.7, 128.1, 127.6, 127.5, 127.3, 47.7; IR (KBr) 3242, 1655, 1494, 1446, 1398, 1350 ν_{max}/cm^{-1}; m.p. 115.5-116.0 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{15}H_{13}N_3O$: 251.1059; Found: 252.1135 $[M+H]^+$.

_N_-(tert-butyl)-3-(4-fluorophenyl)-1,2,4-oxadiazol-5-amine (47).



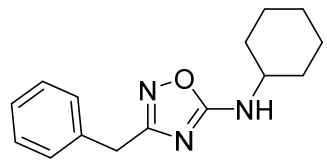
C-oximinoimidamide 110 mg (0.434 mmol), triphenylphosphine 227.8 mg (0.868 mmol), diethyl azodicarboxylate 0.136 mL (0.868 mmol), toluene dry 2 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 98:2, 95:5) to give the product as white solid (74.6 mg, yield 73%).
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98 (m, 2H), 7.10 (m, 2H), 5.58 (br s, NH), 1.44 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.4, 167.5, 164.0 (d, *J* = 248.5), 129.4 (d, *J* = 8.6), 124.1, 115.8 (d, *J* = 21.7), 52.8, 29.0 (3C); IR (KBr) 3302, 1632, 1410, 1374, 1222, 840 ν_{max}/cm^{-1}; m.p. 108.1-109.2 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{12}H_{14}FN_3O$: 235.1121; Found: 236.1185 $[M+H]^+$.

_N_-(tert-butyl)-3-(pyridin-3-yl)-1,2,4-oxadiazol-5-amine (48).



C-oximinoimidamide 60 mg (0.254 mmol), triphenylphosphine 133 mg (0.508 mmol), diethyl azodicarboxylate 0.080 mL (0.508 mmol), toluene dry 1 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 9:1, 7:3) to give the product as white solid (27 mg, yield 49%).
^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.36 (br s, 1H), 8.70 (br s, 1H), 8.28 (m, 1H), 7.42 (m, 1H), 5.71 (br s, NH), 1.51 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.8, 166.4, 151.5, 148.9, 134.7, 124.5, 123.7, 53.0, 29.2; IR (KBr) 3210, 2987, 1750, 1372, 1276, 1226, 1101 ν_{max}/cm^{-1}; m.p. 140.8-141.7 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{11}H_{21}N_4O$: 218.1168; Found: 219.1246 $[M+H]^+$.

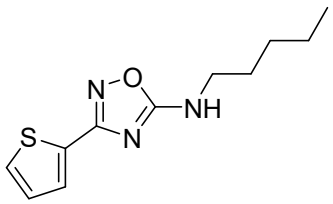
3-benzyl-_N_-cyclohexyl-1,2,4-oxadiazol-5-amine (49).



C-oximinoimidamide 100 mg (0.383 mmol), triphenylphosphine 200 mg (0.765 mmol), diethyl azodicarboxylate 0.120 mL (0.765 mmol), toluene dry 2 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 95:5, 9:1) to give the product as white solid (46.6 mg, yield 47%).
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 3H), 7.30 (m, 2H), 5.65 (br d, NH), 3.87 (s, 2H), 3.52 (m, 1H), 1.98 (m, 2H), 1.74-1.57 (m, 3H), 1.41-1.20 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.6, 169.7, 136.0, 129.0, 128.7, 127.0, 52.7, 33.3, 32.7, 25.3,

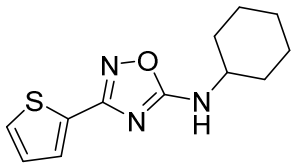
24.7; IR (KBr) 3211, 3088, 1636, 1537, 1397, 718 ν_{max}/cm^{-1}; m.p. 90.9-91.7 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{15}H_{19}N_3O$: 257.1528; Found: 258.1601 $[M+H]^+$.

_N_-pentyl-3-(thiophen-2-yl)-1,2,4-oxadiazol-5-amine (50).



C-oximinoimidamide 110 mg (0.39 mmol), triphenylphosphine 205 mg (0.78 mmol), diethyl azodicarboxylate 0.122 mL (0.78 mmol), toluene dry 2 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 95:5, 9:1) to give the product as yellow solid (68.3 mg, yield 74%).
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.67 (dd, 1H, *J* = 3.8, 1.2 Hz), 7.42 (dd, 1H, *J* = 4.9, 1.2 Hz), 7.10 (dd, 1H, *J* = 4.9, 3.8 Hz), 6.27 (br s, NH), 3.43 (q, 2H, *J* = 6.7 Hz), 1.61 (m, 2H), 1.31 (m, 4H), 0.87 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.2, 164.4, 129.3, 128.8, 128.6, 127.8, 43.8, 29.5, 28.8, 22.3, 14.0; IR (KBr) 3255, 2951, 1654, 1434, 1389, 1319 ν_{max}/cm^{-1}; m.p. 75.8-76.6 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{11}H_{15}N_3OS$: 237.0936; Found: 238.0892 $[M+H]^+$.

_N_-cyclohexyl-3-(thiophen-2-yl)-1,2,4-oxadiazol-5-amine (51).



C-oximinoimidamide 120 mg (0.449 mmol), triphenylphosphine 235 mg (0.898 mmol), diethyl azodicarboxylate 0.141 mL (0.898 mmol), toluene dry 2 mL. The crude material was purified by column chromatography (eluents: PE/EtOAc 95:5, 9:1) to give the product as yellow solid (76.7 mg, yield 68%).
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.69 (dd, 1H, *J* = 3.8, 1.2 Hz), 7.42 (dd, 1H, *J* = 4.9, 1.2 Hz), 7.11 (dd, 1H, *J* = 1.2, 3.8 Hz), 5.35 (br d, NH), 3.66 (m, 1H), 2.04 (m, 2H), 1.72 (m, 2H), 1.60 (m, 2H), 1.46-1.07 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.5, 164.5, 129.3, 128.8, 128.5, 127.7, 52.9, 33.2, 25.3, 24.6; IR (KBr) 3229, 2932, 1640, 1554, 1508, 1433, 1389, 1317 ν_{max}/cm^{-1}; m.p. 131.9-132.5 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{12}H_{15}N_3OS$: 249.0936; Found: 250.1008 $[M+H]^+$.

X-Ray data

Crystals of **23** were obtained by slow evaporation of a 1:1 methanol/water solution at room temperature, as colourless elongated prisms.

The preliminary check on the X-ray diffraction quality of the sample showed that all selected crystals were twinned crystals characterized by a non-merohedral twinning. The twin operation relating the two domains forming the composite crystal results a rotation of 180° about the *c* axis.

X-ray diffraction data in the θ range 2-25° were collected acquiring 4 sets of 600 bidimensional CCD frames with the following operative conditions: omega rotation axis, scan width 0.3°, acquisition time 30 s, sample-to-detector distance 60 mm, phi angle fixed at four different values (0°, 90°, 180°, 270°) for each of the four different sets.

Omega-rotation frames were processed with the SAINT software (Bruker: SAINT Software Reference Manual. Version 6, Bruker AXS Inc., Madison, Wisconsin, USA, **2003)** operating in a "twinning mode" with two components for data reduction (including intensity integration, background, twin overlaps, Lorentz and polarization corrections) and for determination of accurate unit-cell dimensions, obtained by least-squares refinement of the positions of 1557 independent reflections with $I > 10\sigma(I)$ in the θ range 3-20°. Absorption effects were empirically evaluated by the TWINABS software (G. M. Sheldrick, TWINABS. University of Gottingen, Gottingen, Germany, **1999**) and absorption correction was applied to the data (0.861 and 0.997 min and max transmission factor).

The structure was solved by direct methods[26] and the refinement was carried out with SHELX-97.[27] All non-H-atoms were refined anisotropically. Hydrogen atoms were detected in a difference Fourier synthesis and refined with isotropic thermal factors. CCDC-1037831 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge

Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: ++44 1223 336 033; or deposit@ccdc.cam.ac.uk).

Crystal data for 23: C12H17N4O2, *M*r = 235.3 g/mol, Monoclinic, Space group P21/c, *a* = 14.624(3) A, *b* = 6.308(1) A, *c* = 14.588(3) A, *β* = 105.522(5)°, *V* = 1296.64(4) A3, *Z* = 4, *Dcalc* = 1.21 Mg/m3, *R* = 0.056 (2307 reflections/1528 obs), *wR2* = 0.135, *T* = 293(2)K, *GOF* = 1.078. The reflections were collected in the range 1.5° ≤ θ ≤ 25.1° employing a 0.44 x 0.18 x 0.04 crystal.

The intermolecular hydrogen bonds network is highly effective in forming a polymeric chain approximately parallel to the *b* axis, thereby consolidating the crystal structure. In details, the molecules form dimers by centrosymmetric hydrogen bonds between O1-H12···N2' ('at -x, -y, -z), distance 1.92(4) A, angle 157(1)°, which are in turns interconnected by O2-H21···O1'' ('' at x, y+1, z) interactions at distance 1.91(4) A, angle 172(1)° giving rise to molecular chains along the *b* axis (Figure S1).

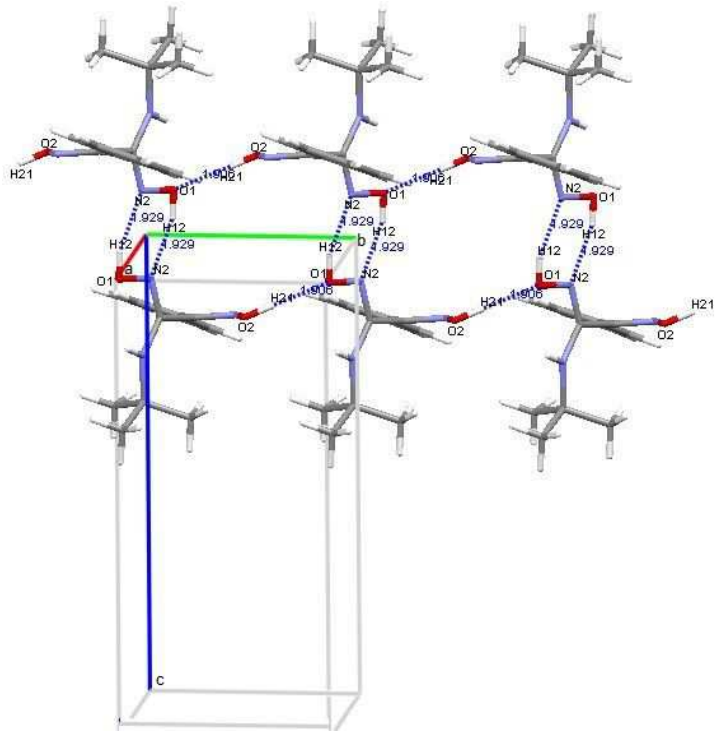


Figure S1. Intermolecular interactions viewed about down the *b* axis.

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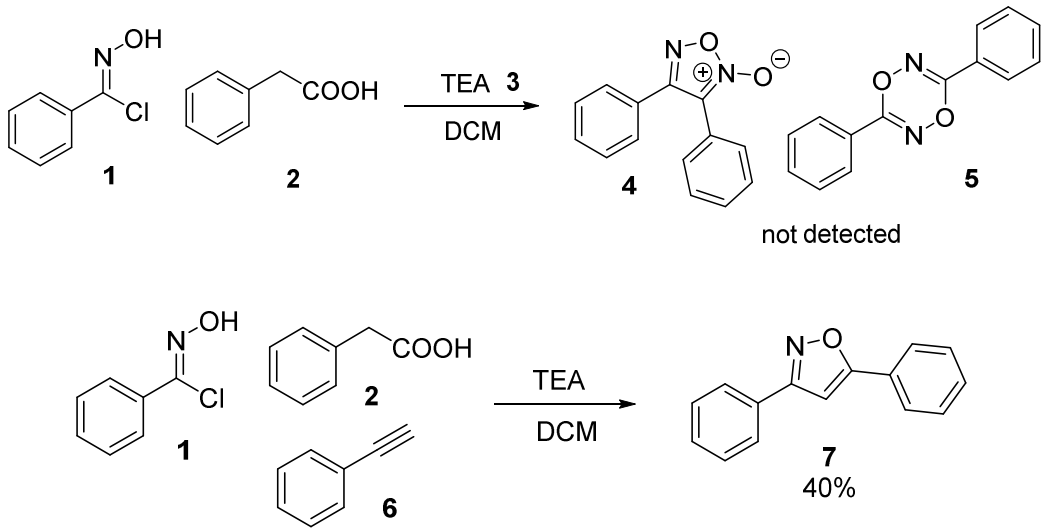
Chapter 8

General mechanism of the reaction between nitrile *N*-oxides and isocyanides

8.1 General mechanism

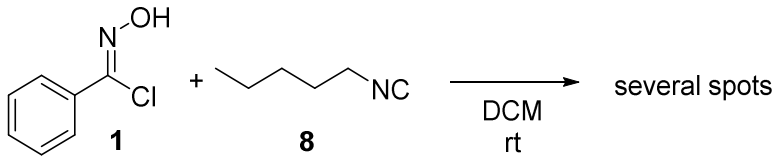
At the beginning of our research with nitrile *N*-oxide, we hypothesized the formation of an *α*-adduct between the *Z*-chlorooxime and the isocyanide, ruling out the participation of a nitrile *N*-oxide species, since, in an independent experiment, among *Z*-phenylchlorooxime **1**, phenylacetic acid **2**, and triethylamine **3**, the formation of the nitrile *N*-oxide dimerization products diphenylfuroxan **4** and/or 3,6-dipheyl-1,4,2,5-dioxadiazine **5** was not detected.[1,2]

Later, we realized that the formation of these dimerization products is actually not as easy as we thought and cannot be considered as a marker for the involvement of nitrile *N*-oxides. Indeed, when we carried out the reaction in the presence of phenylacetylene **6**, the corresponding isooxazole **7** was obtained in 40% yields, confirming that, even under these buffered conditions (TEA and carboxylic acid), the nitrile *N*-oxides can be generated (Scheme 1).



Scheme 1. Experiments to demonstrate the direct involvement of the nitrile *N*-oxide species.

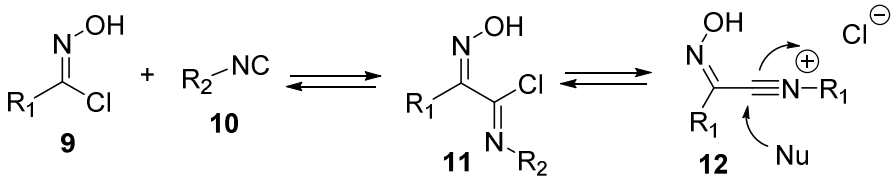
When we tried the two component reaction between *Z*-phenylchloroxime and pentyl isocyanide we were not able to isolate the corresponding cyanide and isocyanate, as reported by Olofson[3] and Vita Finzi,[1] but we only observed the formation of a complex and inseparable mixture of products. (Scheme 2)



Scheme 2. Reaction between *Z*-phenylchlorooxime and isocyanide.

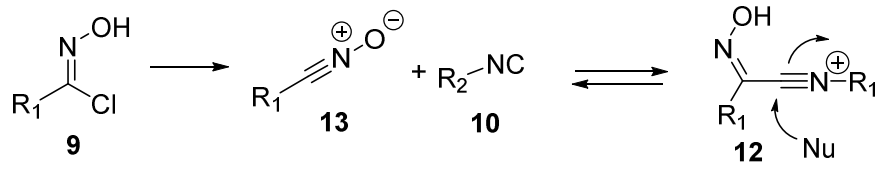
For this reason, initially, we were inclined to hypothesize an α-addition between the *Z*-chloroxime **9** and the isocyanide **10** to give the imidoyl chloride **11**, followed by the generation of the nitrilium species **12**, which can be attacked by the nucleophile (Mechanism A).

Mechanism A



Anyway, after observing the formation of nitrile *N*-oxide species even in buffered conditions (carboxylic acid and base), we hypothesized the nucleophilic attack of isocyanides to the nitrile *N*-oxides with the formation of the nitrilium ion which can be intercepted by a third nucleophile (Mechanism B).

Mechanism B

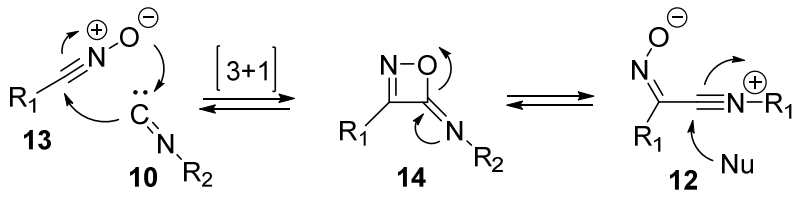


Anyway during our research activity, we noted that independently from the strength of the nucleophile used as third component: carboxylate[4], phenate (Chapter 6), primary and secondary amines (Chapter 4, 7) and hydroxylamine (Chapter 7) (in order of increasing nucleophilicity), we observed that the reaction between isocyanides and nitrile *N*-oxides always overruled the possible attack of the nucleophile to the nitrile *N*-oxide. The unexpected nitrile *N*-oxide behavior prompted us to re-examine the reaction mechanism. Indeed, it should be logic to consider that nitrile *N*-oxides are better electrophilic partners for phenates and amines than isocyanides which are usually considered as poor nucleophiles.[5] It follows that the reaction between nitrile *N*-oxides and isocyanides cannot be interpreted as a simple nucleophilic addition.

However, if we consider the isocyanides involved in these transformations in their carbenic nature and not in their ionic resonance form, a concerted [3+1] cycloaddition reaction between isocyanide and nitrile *N*-oxide could take place to give an oxazetidine ring **14**[6]. A recent paper corroborates this hypothesis, demonstrating that isocyanides exist predominantly in the carbenic form.[7] Although [3+1] cycloaddition reactions between isocyanides and azomethine imines, nitrile ylides, and azomethine ylides have already been reported,[6–9] there are no examples for a [3+1] cycloaddition reaction between nitrile *N*-oxides and isocyanides.[10] Nitrile *N*-oxides **13**, as well as all the 1,3-dipolar species, are ambiphilic dipoles characterized by a low energy difference between their HOMO or LUMO frontier orbitals1 and they can hence react both with electron-rich or electron-poor dipolarophiles, as in this case the isocyanide in its carbenic nature.

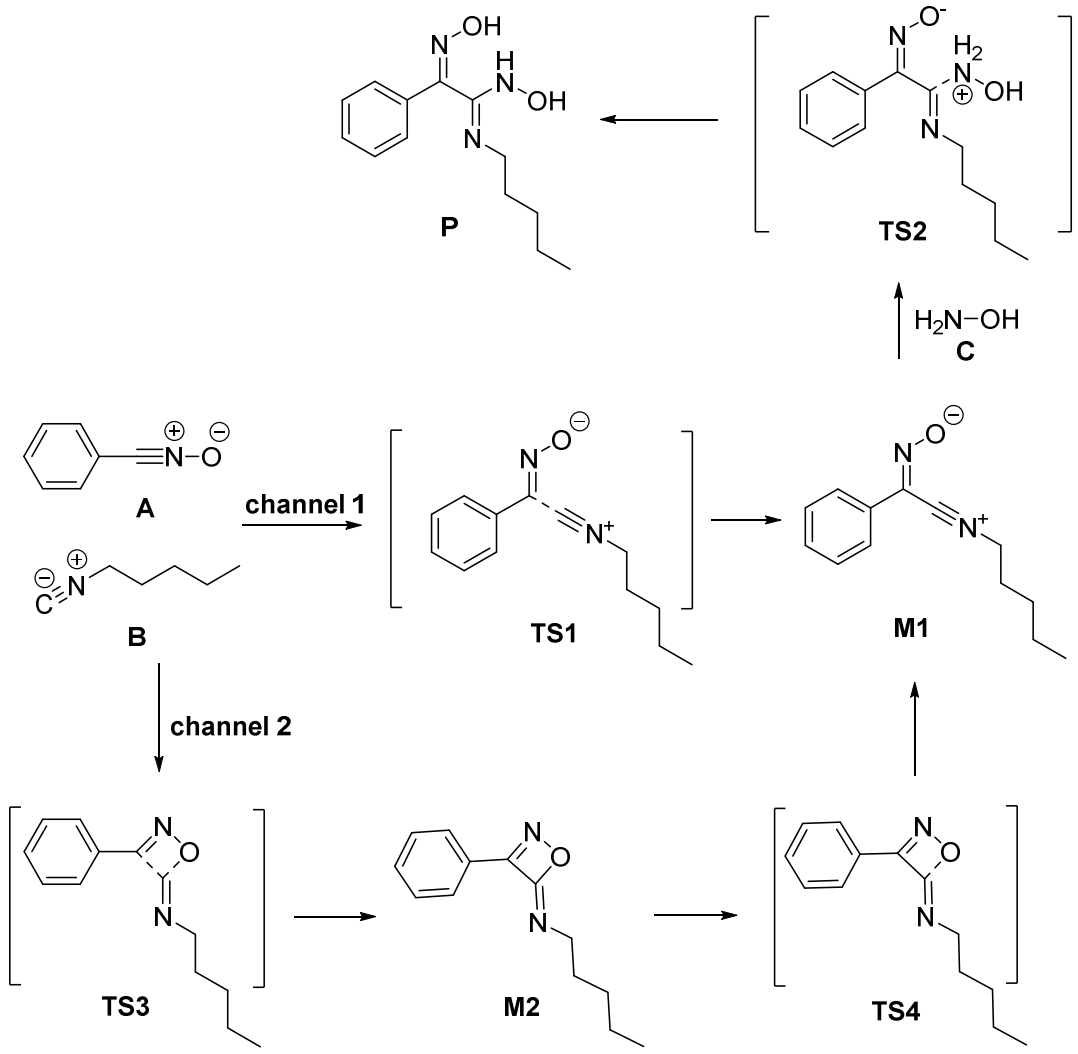
A four-membered ring should be obtained from the reaction between nitrile *N*-oxides and the electron-poor dipolarophiles isocyanides. The so-formed oxazetidine ring **14**, undergoes ring opening, in order to relieve the ring strain, unveiling the ephemeral nitrilium ion **12**, which could now be attacked by a third nucleophile and finally form the novel product (Mechanism C).

Mechanism C



In order to verify if Mechanism C was the more plausible, *ab initio* calculations were performed by Dr. Alberto Massarotti, to compare the energies involved in either the [3 + 1] cycloaddition or the ionic addition between the isocyanide and the nitrile *N*-oxide and in the reaction between the nucleophile (hydroxylamine) and the nitrile *N*-oxide.

The model reaction between phenyl nitrile oxide **A**, pentyl isocyanide **B**, and hydroxylamine **C**, which generates product **P**, was chosen for this theoretical investigation. The detailed reaction mechanisms were interpreted using density functional theory (DFT), which was widely employed to study organic reaction mechanisms.[11] Two possible reaction pathways were investigated in detail (Scheme 3).

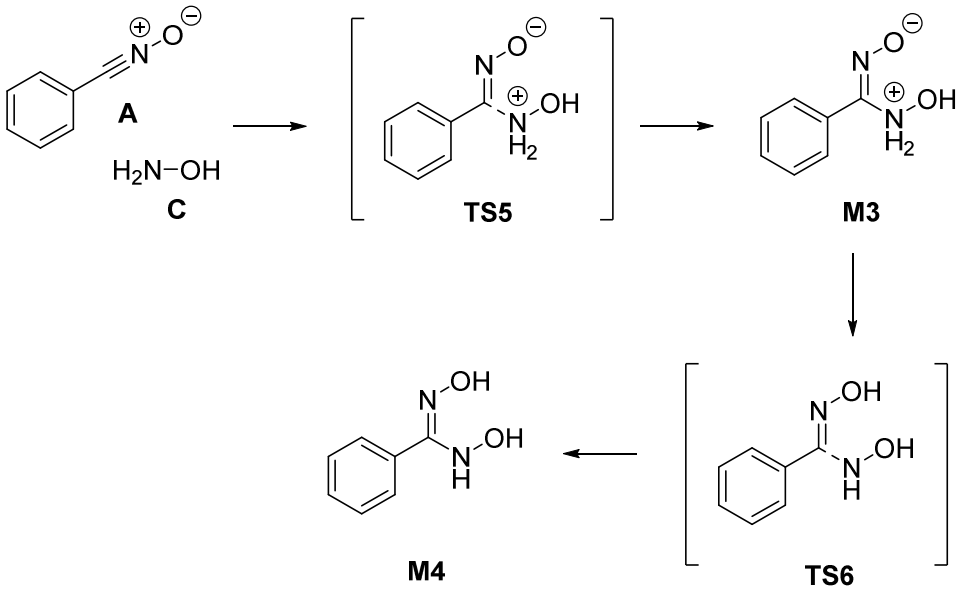


Scheme 3. Possible reaction pathways 1 and 2.

In reaction path 1, the isocyanide carbon atom behaves as a nucleophile attacking the nitrile *N*-oxide species to generate intermediate **M1**. In the second step, the nitrilium ion is attacked by the nitrogen atom of hydroxylamine. Subsequently, a prototropic exchange gives the final compound **P**. We set the energies of the three reactants (**A + B + C**) as 0.00 kcal/mol as reference in the energy profile. The calculated energy barrier for traversing **TS1** was 16.88 kcal/mol (depicted in Figure 1A). In reaction path 2, the isocyanide behaves as carbene giving a [3 + 1] cycloaddition with the nitrile *N*-oxide species in the first step. Subsequently, the

resulting oxatedine ring opens due to ring strain via the transition state **TS4** to generate intermediate **M1**. The calculated energy barrier for path 2 for traversing **TS3** was 11.11 kcal/mol, while the rate-limiting step is traversing **TS4** that requires 23.66 kcal/mol (depicted in Figure 1A).

In addition to paths 1 and 2, we also evaluated the direct attack of hydroxylamine **C** to the phenyl nitrile oxide **A** (pathway 3, Scheme 4). The energy barrier for traversing **TS5** was 26.67 kcal/mol (Figure 1B), which indicates that reactant **C** cannot compete with the isocyanide **B** in the reaction with nitrile *N*-oxides.



Scheme 4. The competitive reaction channel investigated (pathway 3).

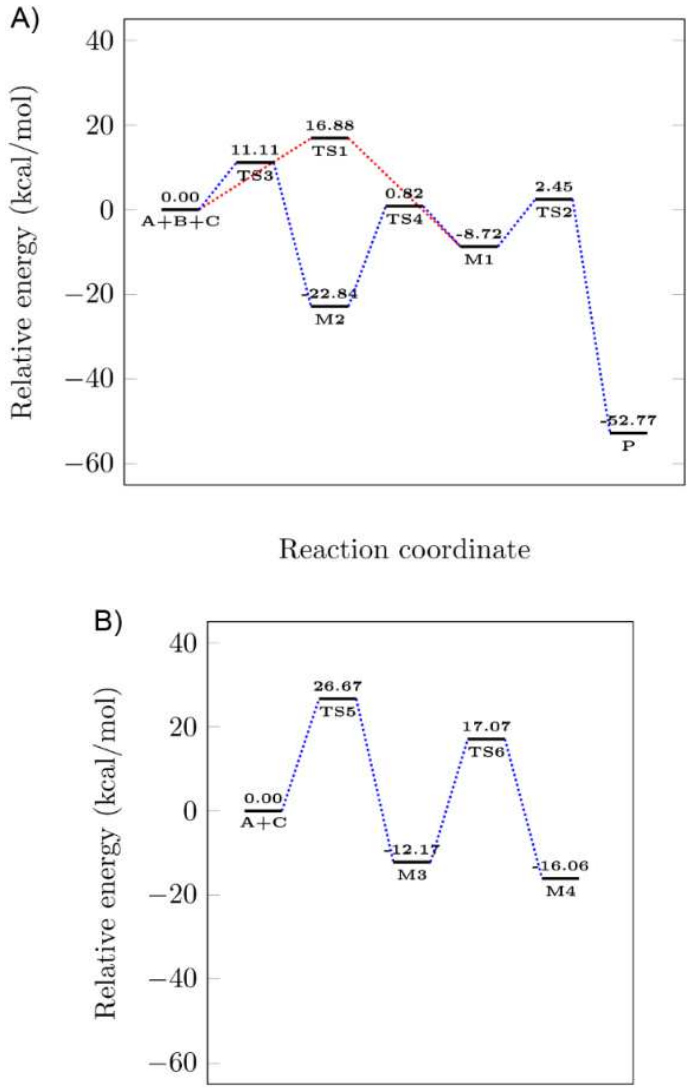


Figure 1. The energy profile of reactions at the M06-2X/6-31G(d, p) level in dichloromethane (unit: kcal/mol). The energy reference is the sum of the reactant energies computed separately. A) Pathway 1 and 2 are depicted in red and blue respectively. B) Pathway 3.

In summary, the energy barriers of pathways 1, 2, and 3 are 16.88, 11.11, and 26.67 kcal/mol, respectively, indicating that path 2 is the most energetically favorable. Moreover, the energy barrier of path 2 is not too high to be accessible under room temperature reaction conditions.

8.2 Conclusions

In this Chapter, we showed that the presence of the third component is pivotal in diverging the course of the two component reaction between the 1,3-dipolar species and isocyanides, which is sometimes messy and unable to afford a single main product.

The detailed mechanism of the reaction between nitrile *N*-oxides and isocyanides has been studied indicating a [3+1] cycloaddition between nitrile *N*-oxide and isocyanides as the most energetically favorable step, thus preventing the direct attack of the third nucleophile to nitrile *N*-oxides.

These quantum mechanical studies further validation the use of such 1,3-dipolar species in isocyanide-mediated multicomponent processes.

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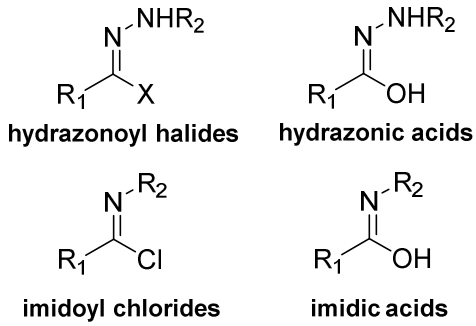
Chapter 9

Prologue (II): Nitrile imines as electrophilic partners in IMCRs

9.1 Introduction

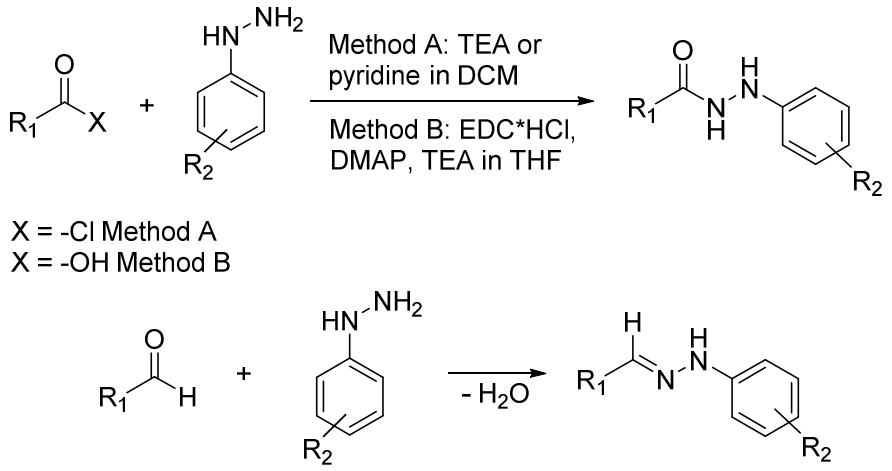
Hydrazonoyl halides are a class of compounds with the general formula -C(X)NNH-, where X represents a chlorine or bromine group. These compounds are the halides of the so-called hydrazonic acids as imidoyl chlorides are the chlorides of imidic acids (Scheme 1).[1]



Scheme 1. General formula of hydrazonoyl halides, hydrazonic acids, imidoyl chlorides and imidic acids.

The hydrazonoyl chlorides can be readily synthesized either using acylhydrazines or the hydrazones as a starting materials.

Acylhydrazines can be obtained from phenylhydrazines and acyl chlorides (Method A, using dichloromethane as a solvent and pyridine), or from phenylhydrazines and carboxylic acids (Method B, using THF as a solvent, EDC*HCl, DMAP and triethylamine).[2–4] While, hydrazones are prepared by reacting aliphatic or aromatic aldehydes with a phenylhydrazines in alcohol at room temperature[5] (Scheme 2).



Scheme 2. General preparation of acylhydrazies and hydrazones.

Then, the acylhydrazines or the hydrazones are transformed in hydrazonoyl chloride using different condition methods as exemplified in Table 1.

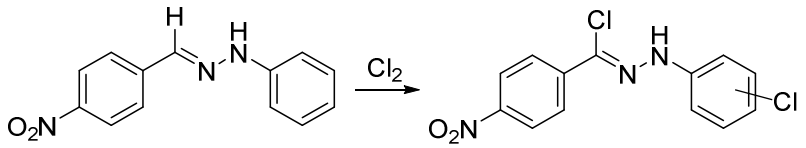
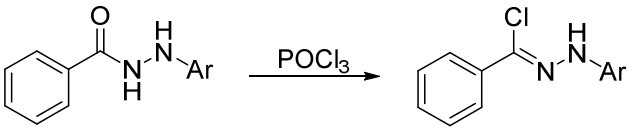
Chattaway *et al.* in 1925[6]	 Disadvantage: generally accompanied by halogenation in the *N*-aryl part of the hydrazine in the 2, 4, 6-positions
Vukov *et al.* in *1977*[3]	 Disadvantage: can only be applied to aromatic hydrazonyl chlorides and to specific substrates.

Table 1. General preparation of hydrazonoyl chlorides.

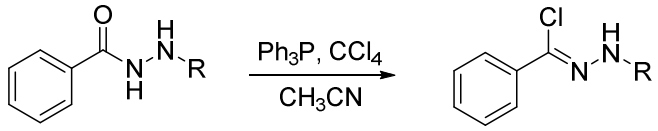
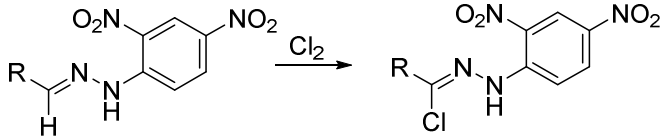
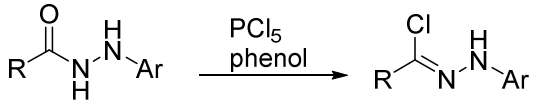
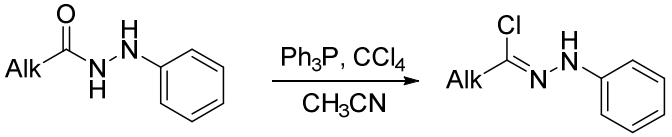
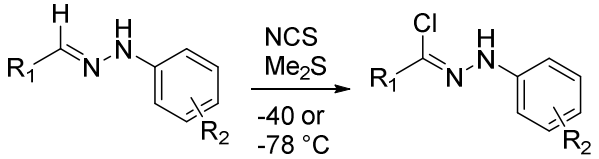
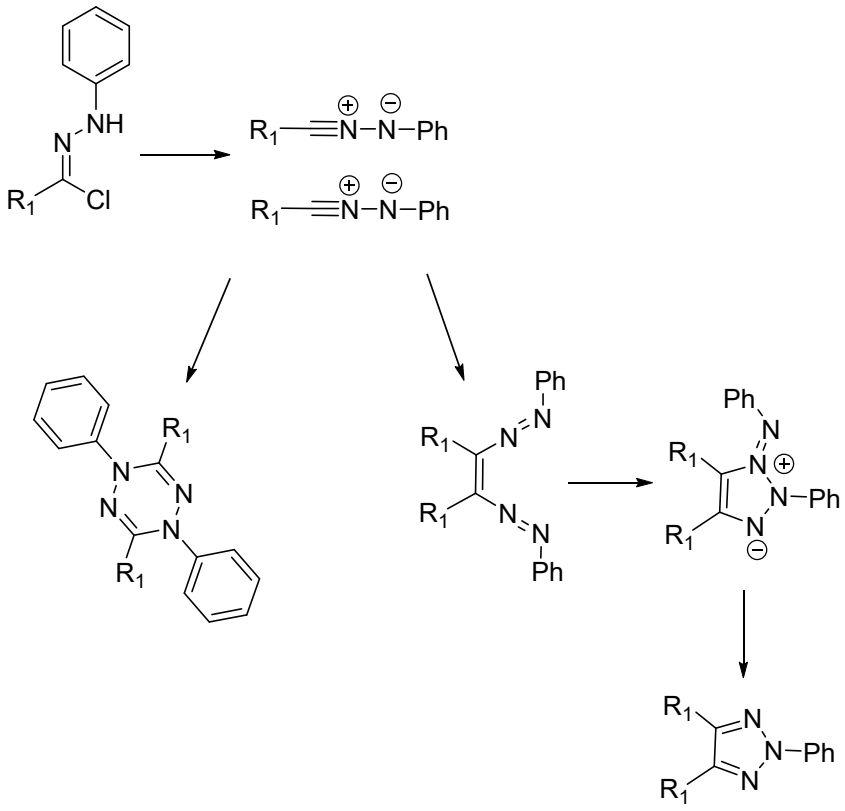
Appel *et al* and Wolkoff, in 1973 and 1975[7,8]	 R = Alk or Ar Advantage: applicable to aromatic hydrazonyl halides and aliphatich on the side of hydrazine. Disadvantage: in case ofelectron rich aryl or heteroaryl rings, the chlorination can also occur on the ring.
Tewari et al. in 1981[9]	 R = Alk or Ar Disadvantage: using only if the aromatic part has two nitro group in position 2 and 4.
Ghiglieri-Bertez *et al.* in 1987[10]	 Disadvantage: can only be applied substrates.
Sakamoto *et al.* in 1988[11]	 Extension of PPh_3-CX_4 method to *N*-phenylalkanehydrazonoyl chlorides.
Patel *et al.* and Paulvann *et al.* in 1996[12], 2000[13]	 R1 = Alk or Ar Advantage: halogen does not enter in the aromatic nucleus Disadvantage: the procedure requires a low temperature.

Table 1. General preparation of hydrazonoyl chlorides (*Continued).*

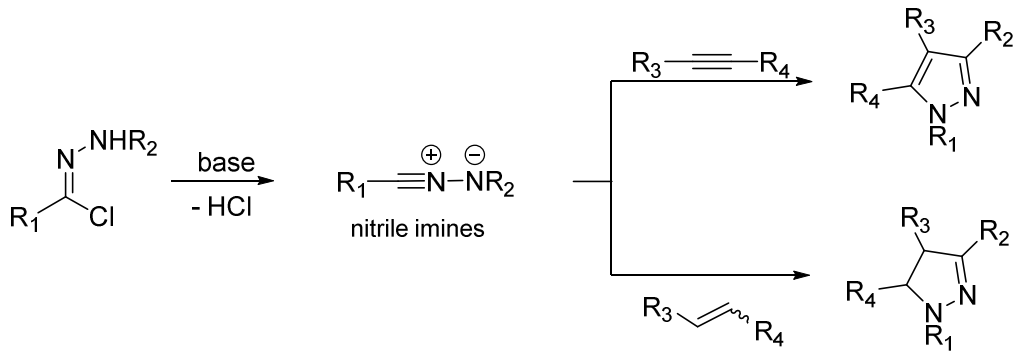
The most general method appears to us to be the formation of acylhydrazines and the the subsequent transformation into hydrazonoyl chlorides using PPh_3, CCl_4 in acetonitrile.

Respect to the reaction with nitrile *N*-oxides, two important caveats have to be highlighted for nitrile imines. The first one is that despite the fact that the reaction is stereoselective and generates only the *Z* isomers, we observed that these hydrazonoyl chlorides, as opposed to oximes, were not geometrically stable and, on standing, some of them underwent an isomerization process to afford a mixture of *E* and *Z* isomers. Furthermore hydrazonoyl chlorides have a reduced stability. They are not stable on storage, especially the aliphatic ones, with a high predisposition to dimerize[14] (Scheme 3).



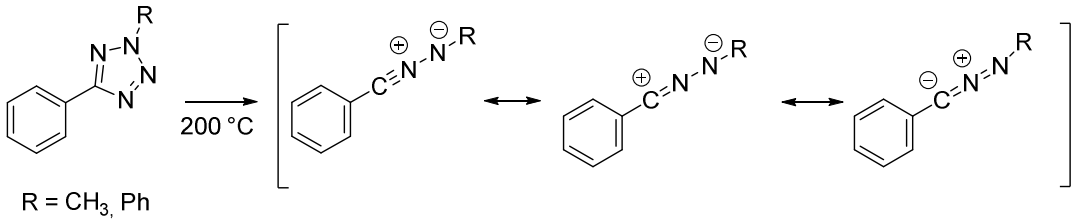
Scheme 3. Dimerization of the corresponding nitrile imine.

The use of a bases is able to dehydrohalogenation of the hydrazonoyl halides to generate the transient nitrile imines. The latter have been used in 1,3-dipolar cycloadditions with a variety of 1,3-dipolarophiles including suitable alkenes and alkynes, which afford 4,5-dihydropyrazoles and pyrazoles, respectively (Scheme 4).[15,16]



Scheme 4. Generation of nitrile imines from hydrazonoyl halides and entrapment with alkynes or alkenes.

Historically, the first nitrile imine was synthesized by Huisgen and co-workers in 1959 by thermal decomposition of 2,5-disubstituted tetrazoles (Scheme 5).[17]

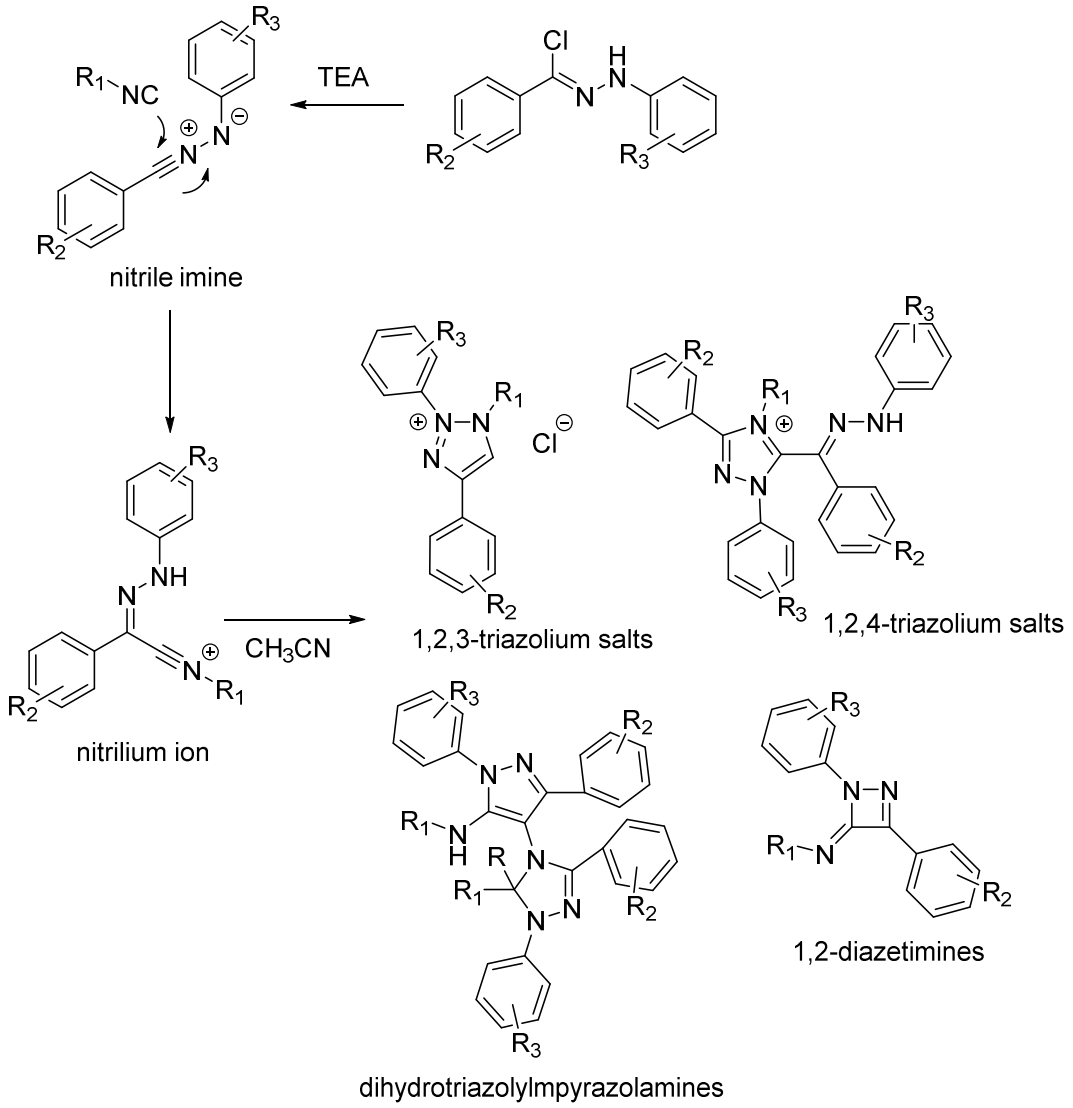


Scheme 5. Nitrile imines were first observed in the thermal decomposition of 2-tetrazoles.

The dominant structure of nitrilimine is with a C-N triple bond and with a formal positive charge on nitrogen and two lone pairs and a formal negative charge on the terminal nitrogen.

A survey of the literature showed us the works of Professor Moderack on the reaction between nitrile imines and isocyanides.[18–23] In these papers it was clearly

shown that the two-component reaction could afford several different products according to the reaction conditions, the steric and electronic nature of isocyanides and the nitrile imines used. This chaotic result can be ascribed to the formation of a nitrilium intermediate deriving from the isocyanide attack to the nitrile imine, which can follow different pathways, no one being preferred over the others (Scheme 6).



Scheme 6. Reaction between nitrile imines and isocyanides reported by Moderack.

While the diversity of obtainable products can be considered a bonus of this chemistry, the impossibility to limit the course of the reaction to a single product, or control the ratio of the various adducts under the conditions and with the reagents used, drastically reduces the generality of these transformations.

Aware the results obtained with nitrile *N*-oxide,[24,25] we reasoned that a third component present in the flask might quench the nitrilium ion, obtained from isocyanide and nitrile imines, channelling the reaction toward the formation of a single product.

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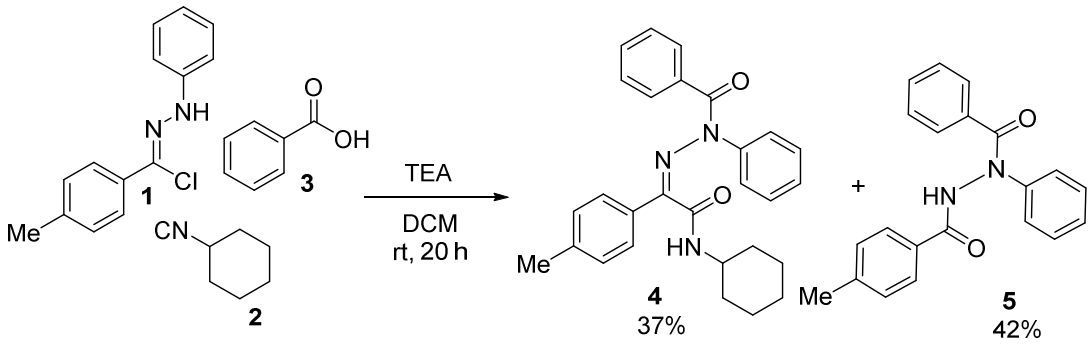
Chapter 10

Synthesis of aminocarbonyl *N*-acylhydrazones by a three- component reaction of isocyanides, hydrazonoyl chlorides, and carboxylic acid

10.1 Results and discussion

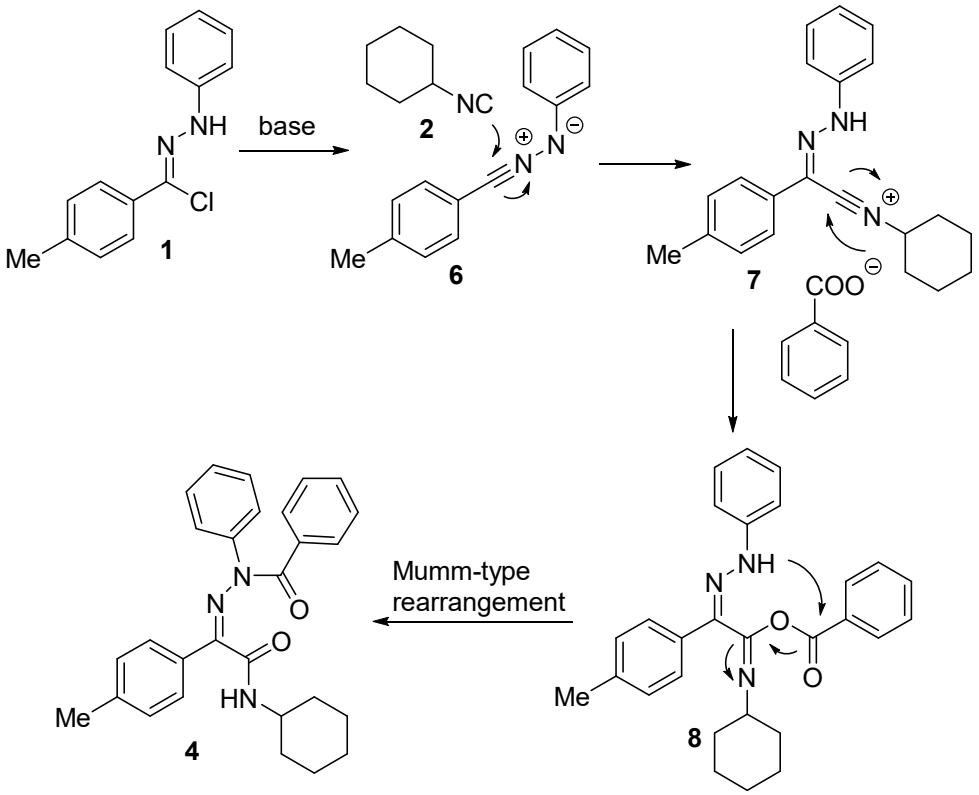
Based on the consideration discussed in the Prologue II (Chapter 9), we carried out the reaction between a hydrazonoyl chloride **1**, cyclohexylisocyanide **2** and benzoic acid **3** as third component, in dichloromethane (0.2 M) at room temperature overnight, and with two equivalents of triethylamine (one needed to generate the nitrile imine and the other to form the carboxylate). We were pleased to observe the formation of the multicomponent adduct *α*-aminocarbonyl *N*-acylhydrazone **4** in 37% yield, along with the adduct **5** in 42% yield deriving from a two-component reaction between the hydrazonoyl chloride **1** and the carboxylic acid **3** (Scheme 1).



Scheme 1. Three-component reaction between a hydrazonoyl chloride, cyclohexylisocyanide and benzoic acid.

To explain the formation of these two products the following mechanistic scenario is proposed. The hydrazonoylchloride **1**, under basic conditions, forms the ephemeral nitrilimine species **6**[1,2] bearing an electrophilic carbon suitable for the isocyanide attack. At this point, the generated nitrilium ion **7** would be ready to undergo the transformations reported by Moderack.[3–7] Instead the presence of the

carboxylate ion prevents the other reaction pathways by generating, in a stereoselective way,[8] the iminoanhydride intermediate **8**, which affords the desired product by undergoing a Mumm type rearrangement thanks to the properly positioned hydrazine nitrogen atom (Scheme 2).



Scheme 2. Proposed mechanism.

Additionally, nitrile imines are highly reactive species which can react directly with carboxylic acids[9] and undergo an acyl migration to generate the by-product compound **5**. It is important to highlight that we did not observe any of the compounds described by Moderack, proving that the use of the carboxylate as third component suppresses all the competing reactions between nitrile imines and isocyanides. Stimulated by this early result and with the goal to suppress/reduce the formation of the product **5**, we decided to screen the reaction conditions in order to

improve the **4**:**5** ratio and increase the yield of *α*-aminocarbonyl *N*-acylhydrazones (Table 1).

Entry	Solvent	Isocyanide (eq)	Yield (**4**)	yield (**5**)
1	DCM (1 M)	1	44%	54%
2	**Neat**	**1**	**52%**	**18%**
3	DCM (1 M)	1.5	44%	56%
4	Neat	1.5	54%	41%
5	Neat	2	56%	19%
6	DCM (0.2 M)	2	37%	42%
7	DCM (1 M)	2	38%	23%
8	Neat	2	52%	42%
9	Neat	1.5	53%	18%
10	Neat	2	55%	16%
11	DCM (1 M)	2	39%	58%

Table 1. Optimization of the reaction conditions.

To our delight, the solvent-free reaction conditions (Entry 2) with equimolar amount of hydrazonoyl chloride, isocyanide and carboxylic acid, and two equivalents of TEA gave the *α*-aminocarbonyl *N*-acylhydrazone **4** in 52% yield and compound **5** in 18% yield, increasing the desired/undesired product ratio.

With these optimized conditions in hand, we planned to explore the scope and the limitations of this novel multi-component process by casually combining one of six hydrazonoylchlorides (**1**, **9**-**13**) with one of five isocyanides (**2**, **14**-**17**) and one of ten carboxylic acids (**18**-**27**) (Figure 1). The starting hydrazonoyl chlorides (**1**, **9**-**13**) were readily synthesized in two steps with quite good yields (43-77%), starting from hydrazines.

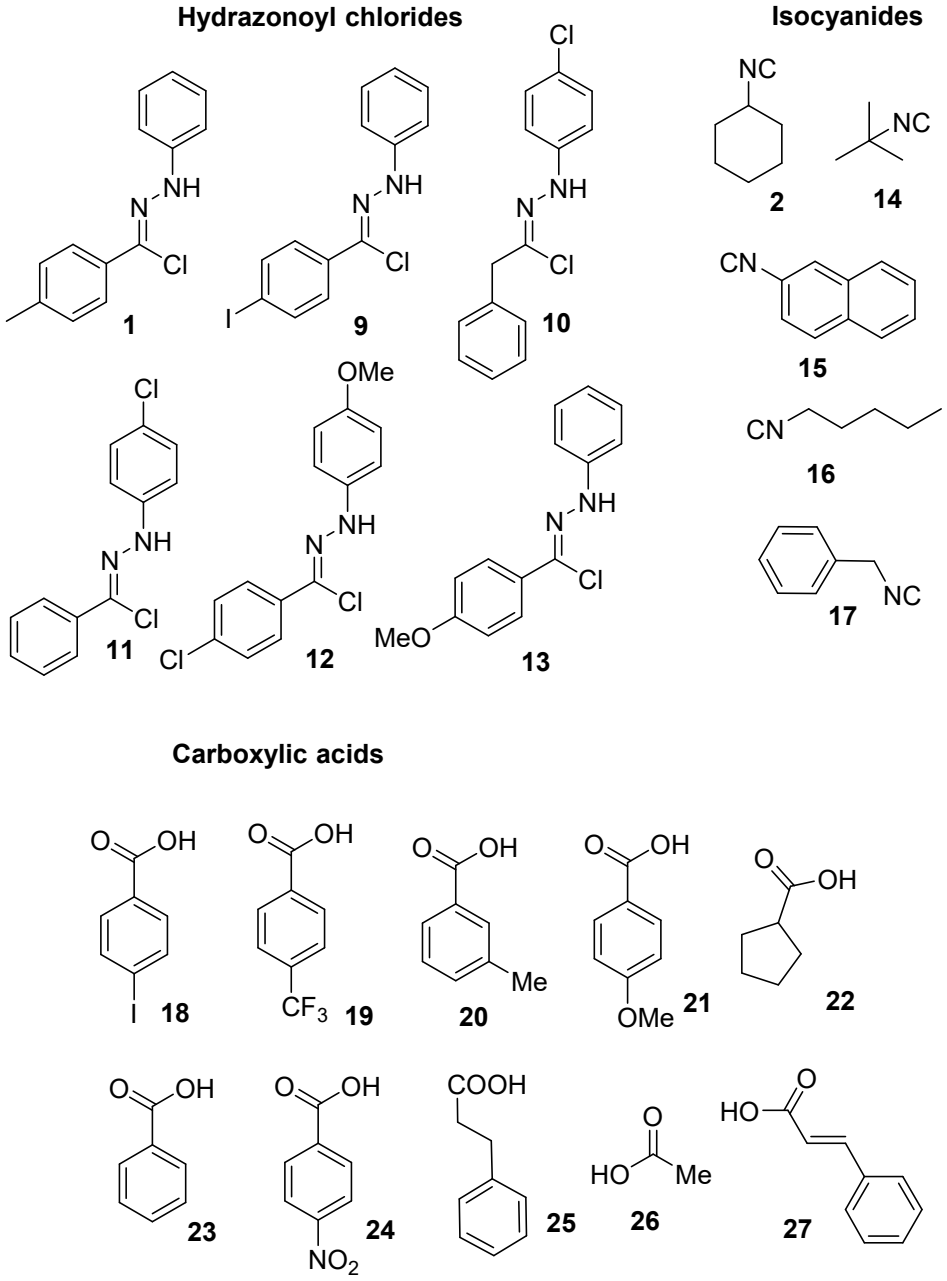


Figure 1. Building blocks used.

A library of 14 α-aminocarbonyl *N*-acylhydrazones was thus generated (**28**-**40**, Figure 2) with yields ranging from 83% to 27%, indicating the generality and the versatility of the process. In particular we observed that the reaction proceeded well

when the carboxylic acids were solid. When they were liquid (e.g. cyclopentancarboxylic acid) the formation of the undesired product was preponderant (86% yield). In this case prior salification to afford a solid was used with success affording the desired 3-CR product in 67% yield (**34**).

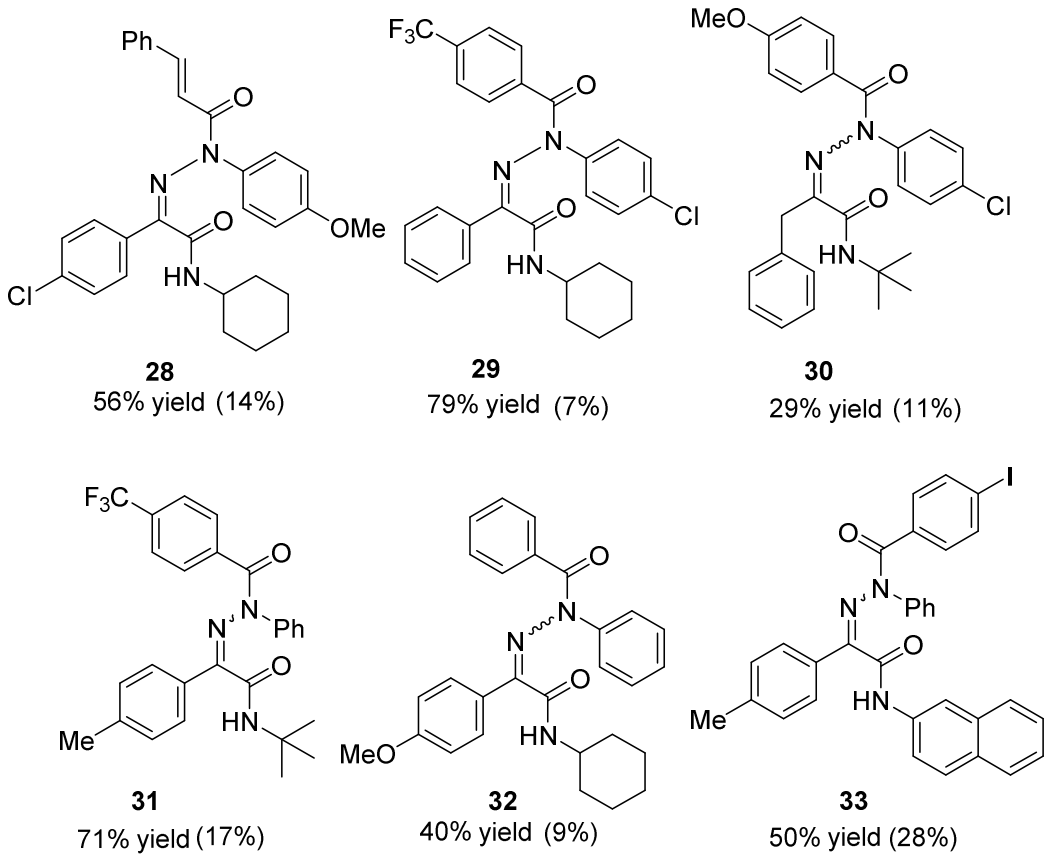


Figure 2. Synthesized *α*-aminocarbonyl *N*-acylhydrazones. Yields in parentheses refer to the competing reaction between nitrile imines and carboxylic acids.

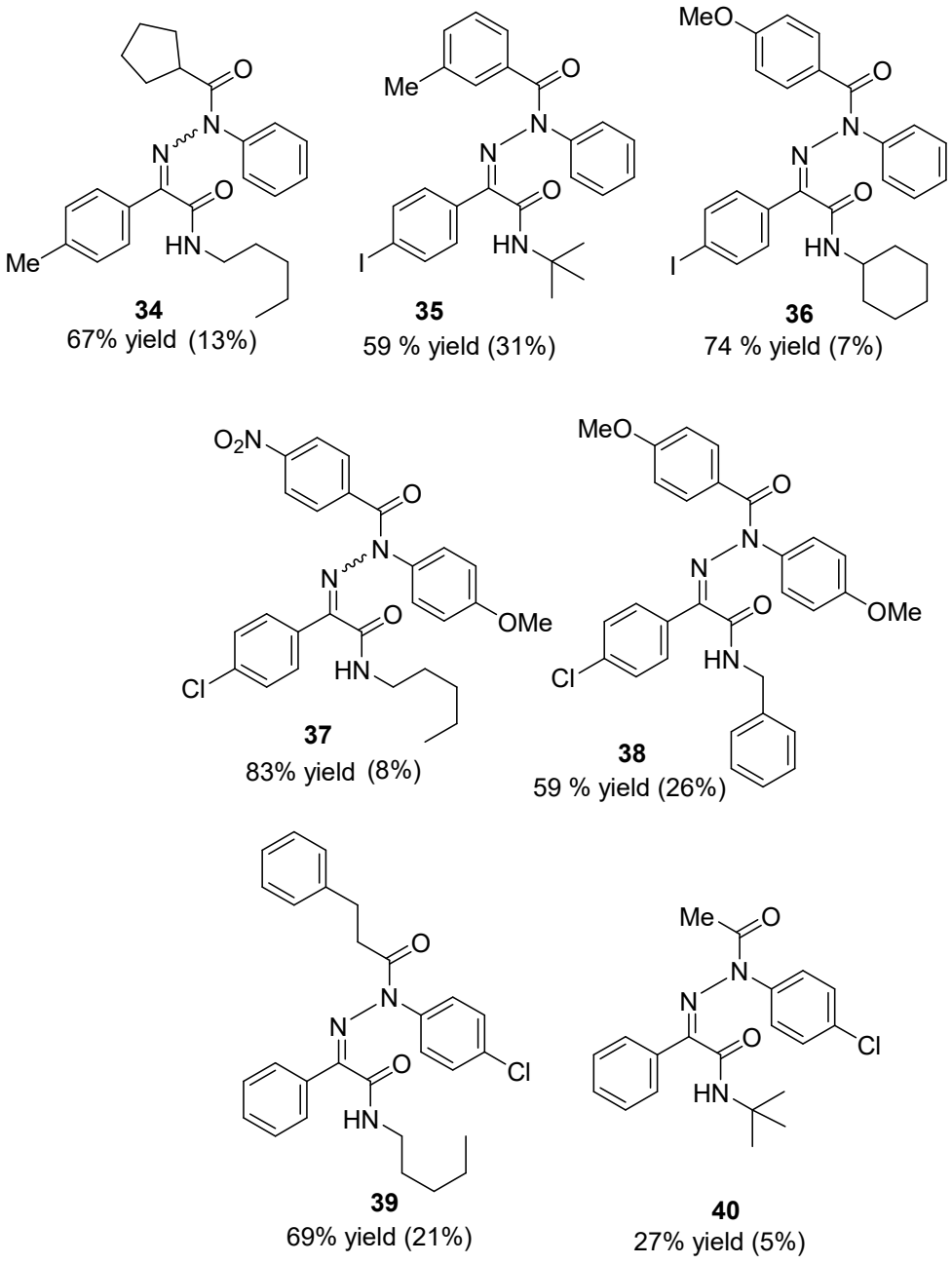


Figure 2. Synthesized *α*-aminocarbonyl *N*-acylhydrazones Yields in parentheses refer to the competing reaction between nitrile imines and carboxylic acids (*Continued).*

Although the reaction stereoselectively generates the *Z* isomer, we observed that these acylhydrazones were not always geometrically stable and, on standing, some

of them underwent an isomerization process to afford a mix of *E* and *Z* isomers. In order to provide a detailed structure assignment of the proposed structures, a single crystal X-ray diffraction analysis on derivative **4** has been carried out. The established solid state structure is represented in Figure 3, together with the relative arbitrary atom-numbering scheme.

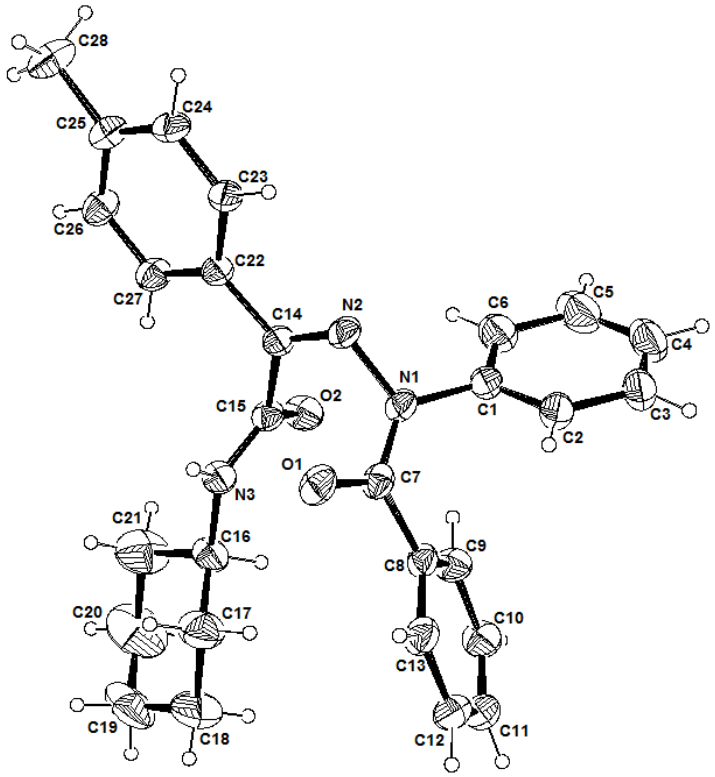
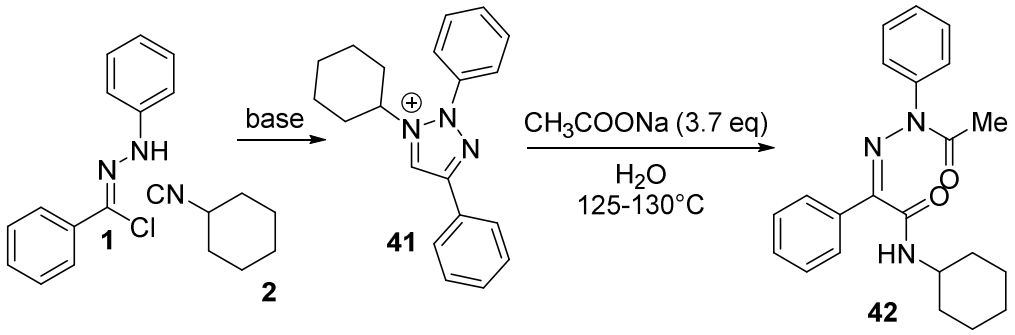


Figure 3. ORTEP[10,11] view of **4** and the relative arbitrary atomnumbering scheme (thermal ellipsoids at 40% probability).

It is noteworthy that we could only find in the literature *one example* of *α*-aminocarbonyl *N*-acylhydrazone, produced by a two-step reaction involving hydrazonoylchloride **1**, cyclohexylisocyanide **2** and sodium acetate (Scheme 3).[4] This reaction is however *conceptually different* from the one we report here, as it involves first the attack of isocyanide **2** to the hydrazonoyl chloride **1** to form a 1,2,3-triazolium salt **41**, followed by a challenging purification step consisting of several recrystallizations. The purified intermediate then undergoes a ring opening

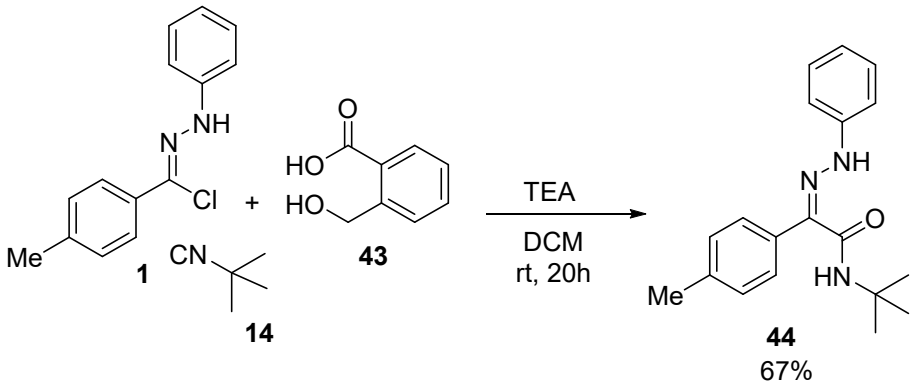
reaction with 3.7 equivalents of sodium acetate at 125-130 °C to give the *α*-aminocarbonyl *N*-acylhydrazones **42** in 33% yields (overall yield after a further purification step).



Scheme 3. The only two-step synthesis of α-aminocarbonyl *N*-acylhydrazones reported to date.

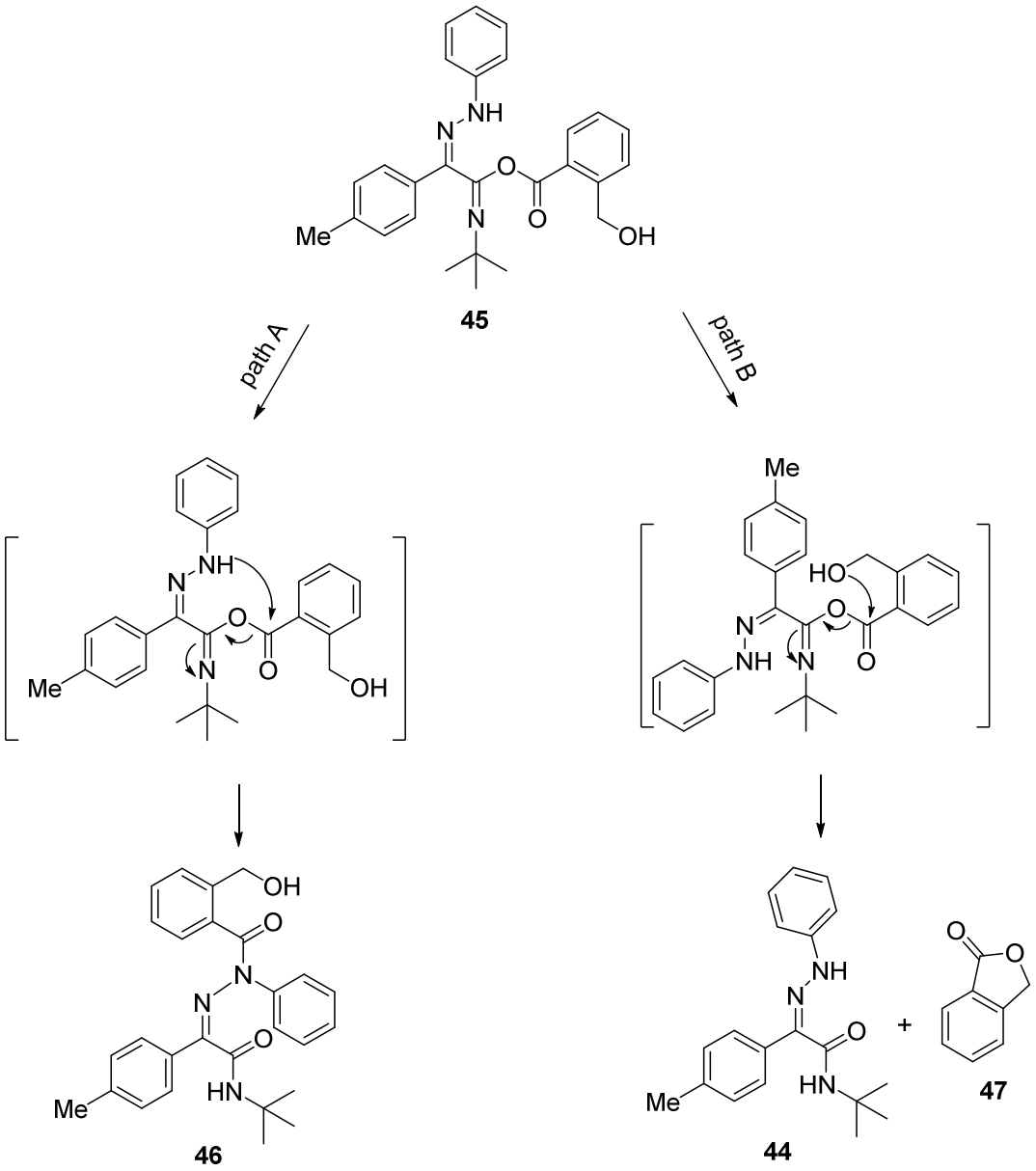
Therefore, such two-component reaction is not deemed suitable for the fast and efficient synthesis of libraries of *α*-aminocarbonyl *N*-acylhydrazone due to the low yield of product, the formation of several by-products and the need for several purification steps. In order to widen the scope of this novel 3-CR and to further explore the reactivity of the nitrilimine nitrogen atom towards a Mumm-type rearrangement we decided to react nitrilimine **1**, *tert*-butylisocyanide **14** and 2-hydroxymethylbenzoic acid **43** ("sacrificial acid").

The use of the substituted benzoic acid has been already reported by our laboratory[12] for the synthesis of unsimmetrical bis (*β*-aminoamides). The presence of a hydroxymethyl function at the *orto* position of benzoic acid engenders an alternative reaction path leading to the formation of phtalide and a formal addition of water to the final compound. It should be noted that water itself would not be nucleophilic enough to intercept the nascent nitrilium ion. With our satisfaction the reaction was clean and we observed a marked increase in yield in the presence of solvent. Whereas the desired α-amino-carbonylhydrazone **44** was produced with 67% yield in the presence of CH_2Cl_2 (Scheme 4), under neat conditions the yield was only 18%.



Scheme 4. Multicomponent synthesis of α-amino-carbonylhydrazone using the sacrificial acid **43**.

A possible reaction mechanism accounting for the formation of **47** is depicted in Scheme 5. Here the *α*-adduct **45** could in principle follow two different reaction pathways: path A, which via a Mumm-type rearrangement gives a 6-membered transition state leading to compound **46**, and path B, which following the intramolecular attack of the hydroxyl function on the iminoanhydride gives the adduct **44** (via a five-membered transition state) and phtalide **47**. Since only **44** is obtained we speculate that the formation of the five-membered intermediate has a lower activation energy than in the six-membered case.



Scheme 5. Possible paths of 3-CR with "sacrificial acid".

It is important to highlight that the "sacrificial acid" **43** is not able to accomplish the formal addition of water when an Ugi-type reaction with primary amine is attempted, due to the higher nucleophilicity of the secondary amine formed in situ, which leads to Mumm rearrangement.

To further prove the generality of such mechanism and the selectivity towards path B, the synthesis of a small collection of *α*-aminocarbonylhydrazones was attempted. In all cases the *α*-aminocarbonylhydrazone (**48**-**52**) was the only reaction product and medium-high yields were obtained (Figure 4). We were therefore enthusiastic in discovering the possibility, in our new 3-CR, to tune the reactivity of the nitrilimine nitrogen atom.

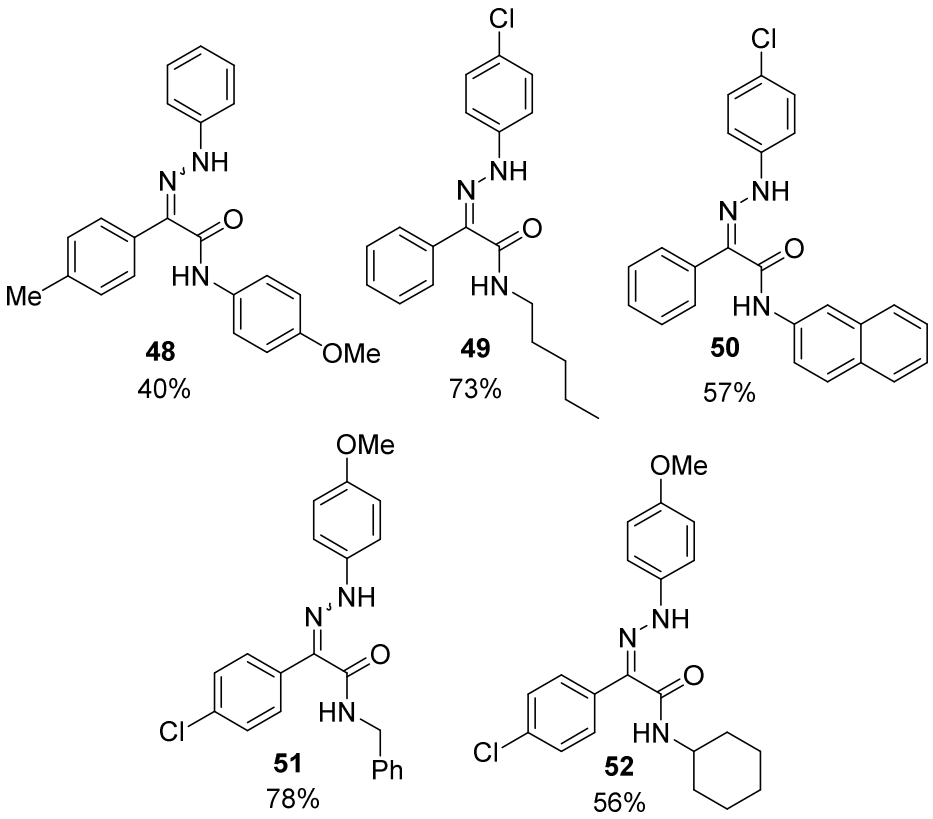


Figure 4. *α*-Aminocarbonyl *N*-acylhydrazones synthesized.

Some of them undergo a rapid isomerization, during the chromatographic purification. We were able to isolate the two different isomers, but they both underwent a rapid isomerization at room temperature to give a 1:1 *E/Z* mix.

In Figure 5 are shown the superimposition of a first spot (green), a second spot (red), and the second spot after 20 hours (blue). The second spot shows

dichloromethane traces (5.30 ppm), but during the evaporation of the solvent, the attempt to dry it at high vacuum pump overnight at room temperature gave the spectrum in blue, which clearly shows isomerization (Figure 5).

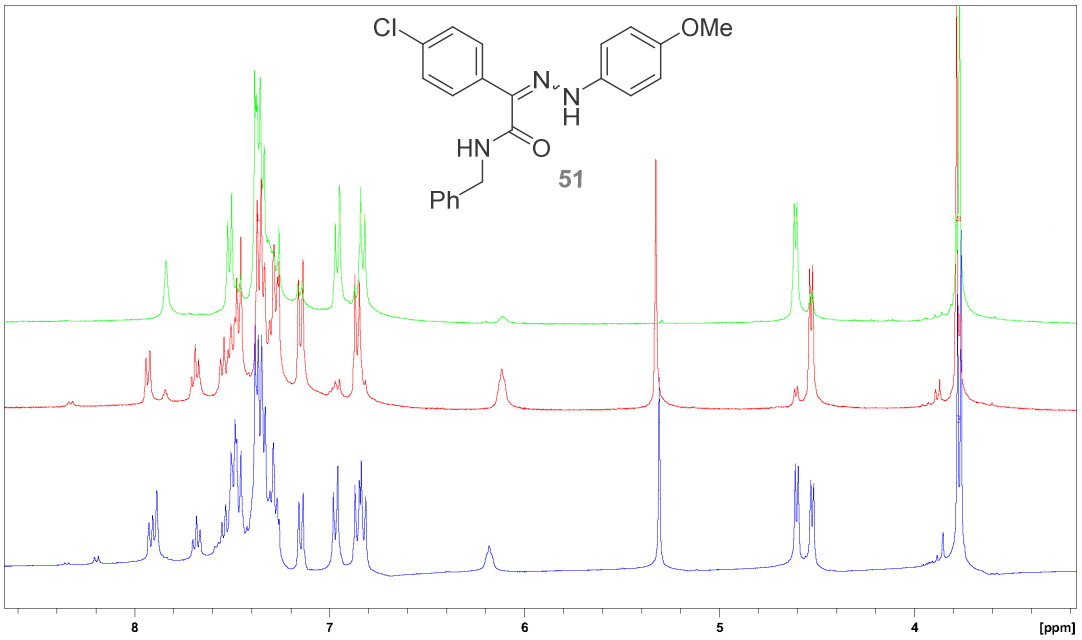


Figure 5. Isomerization of compound **51**.

10.2 Conclusions

In conclusion, starting from an erratic two component reaction between nitrile imines and isocyanides, we discovered a novel 3-CR between nitrile imines, isocyanides and carboxylic acids and applied it to the synthesis of the first reported library of α-aminocarbonyl *N*-acylhydrazones and some related *α*-aminocarbonylhydrazones. In addition, our novel MCR with "sacrificial acid" allows to obtain in the *α*-aminocarbonylhydrazones, with a NH group that enables further derivatization, opening up the way to a variety of post-MCR modifications and thus enlarging the scope of the reaction.

The compounds obtained could also be seen as aza-homologues of the Ugi scaffold, in which case the hydrazonoyl chlorides, hence their nitrilimine activated form would represent a valuable substitute for the imines.

In fact, although obtained in a completely different way, the novel 3-CR molecular scaffold shows the atom connectivity NCCNNC and an evident peptidomimetic nature, similarly to the four-component Ugi scaffold with a NCCNC connectivity. Additionally the different chemical functionalities present (hydrazone, amide, and acyl groups) enable a potentially large number of post-trasformation reactions, similarly to the Ugi adducts.[13]

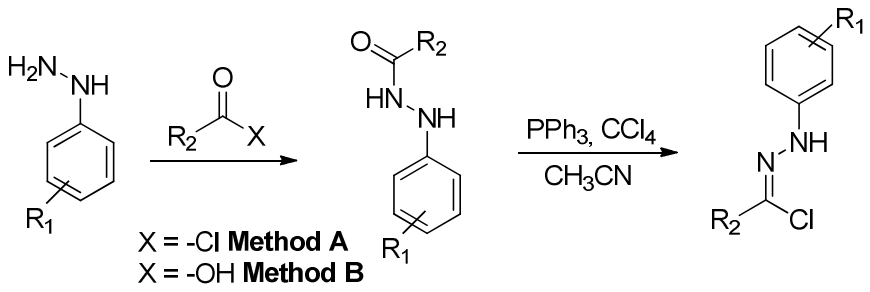
Finally, we reckon that other 1,3 dipolar species lay dormant still, since their multicomponent reaction with isocyanides has not been investigated so far, and are ready to be successfully used for the discovery of novel multicomponent reactions.[14,15]

10.3 Experimental section

General Methods. Commercially available reagents and solvents were used without further purification. Dichloromethane was dried by distillation from P_2O_5 and stored over activated molecular sieves (4 Å). When necessary the reactions were performed in oven-dried glassware under a positive pressure of dry nitrogen. Melting points were determined in open glass capillaries and are uncorrected. All the compounds were characterized by IR. ^1H and ^{13}C APT NMR were recorded on a 400 MHz. High-resolution ESI-MS spectra were performed on a Thermo LTQ Orbitrap XL mass spectrometer. The spectra were recorded by infusion into the ESI source using MeOH as the solvent. Chemical shifts (δ) are reported in part per million (ppm) relative to the residual solvent peak. Column chromatography was performed on silica gel (70–230 mesh ASTM) using the reported eluents. Thin layer chromatography (TLC) was carried out on 5 x 20 cm plates with a layer thickness of 0.25 mm (Silica gel 60 F_{254}). When necessary they were developed with $KMnO_4$.

General preparation of hydrazonoyl chlorides (1, 9-13).[16–18]

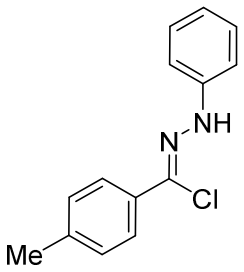
The hydrazonoyl chlorides were readily synthesized in two steps:



Preparation of acylhydrazines. Method A: To a stirred solution of phenylhydrazine on 5 mmol scale in dichloromethane (1 M, 5 mL) was slowly added pyridine (0.403 mL, 5 mmol, 1 eq.) in an ice bath. Then, to this, well-stirred reaction mixture was added dropwise a solution of acyl chloride (5 mmol, 1 eq.) in dichloromethane (4 M, 1.25 mL). Upon completion of addition, ice bath was taken away, and stirring was continued overnight at the room temperature. The reaction was poured in water and the two layers were separated. The organic phase was washed with water (x1) and brine (x1), dried over sodium sulfate, concentrated under reduced pressure and purified by chromatography. **Method B:** To a stirred solution of acid on a 5 mmol scale in THF (0.2 M, 10 mL) were added EDC HCl (1.05 g, 5.5 mmol, 1.1 eq.), DMAP (0.122 g, 1 mmol, 0.2 eq.), triethylamine (1.4 mL, 10 mmol, 2 eq.) and hydrazine (5 mmol, 1 eq.) at 0 °C. The resulting mixture was allowed to warm to room temperature over 24 h. The crude reaction mixture was washed with HCl 1M sol. (x2), $NaHCO_3$ sat. sol. (x2) and brine (x1), evaporated to dryness and used in the next step without further purification.

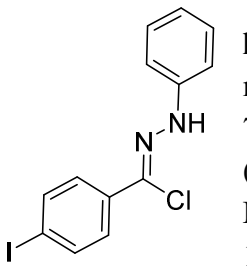
Preparation of hydrazonoyl chlorides (1, 9-13).[16–18] The corresponding acylhydrazine (2.5 mmol) was dissolved in CH_3CN (0.5 M, 5 mL) and triphenylphosphine (0.787 g, 3 mmol, 1.2 eq.) and carbon tetrachloride (0.289 mL, 3 mmol, 1.2 eq.) were added. The reaction was stirred at room temperature until all the acylhydrazine was consumed as judged by TLC (typically 8-12 hours). The reaction was concentrated under reduced pressure and purified by column chromatography (*n*-hexane/EtOAc 30:1) and stored below 0 °C.

(*Z*)-4-methyl-*N*'-phenylbenzohydrazonoyl chloride (1).



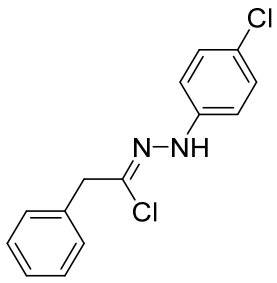
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 30:1) to give the product as a yellowish solid (391 mg, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (br s, NH), 7.85 (d, *J* = 8.2 Hz, 2H), 7.36-7.32 (m, 2H), 7.25-7.20 (m, 4H), 6.97 (t, *J* = 7.3 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 139.4, 131.8, 129.4, 129.1, 126.3, 125.0, 121.0, 113.4, 21.3. IR (KBr) 3297, 1586, 1492, 1232, 1129, 938 νmax/cm^{-1}; Mp 133-134 °C.

(*Z*)-4-iodo-*N*'-phenylbenzohydrazonoyl chloride (9).



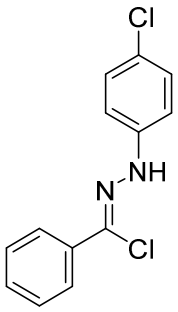
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 30:1) to give the product as a white solid (570 mg, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (br s, NH), 7.73 (br d, AA'XX', 2H), 7.64 (br d, AA'XX', 2H), 7.34-7.30 (m, 2H), 7.17 (br d, 2H), 6.96 (t, *J* = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 137.5, 134.0, 129.4, 127.9, 123.7, 121.4, 113.5, 95.1. IR (KBr) 3307, 1577, 1503, 1231, 1146, 938 νmax/cm^{-1}; Mp 160-161 °C.

(*Z*)-*N*'-(4-chlorophenyl)-2-phenylacetohydrazonoyl chloride (10).



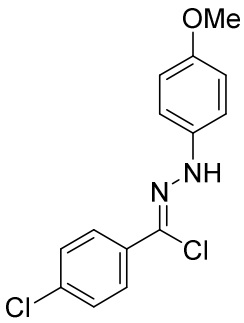
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 30:1) to give the product as a white solid (419 mg, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (br s, NH), 7.38-7.31 (m, 5H), 7.24 (br d, AA'XX', 2H), 7.00 (br d, AA'XX', 2H), 3.92 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 135.6, 129.3, 129.2, 128.8, 127.4, 127.0, 125.5, 114.5, 45.0. IR (KBr) 3329, 1593, 1492, 1256, 1185, 1075, 825 νmax/cm^{-1}; Mp 80-81 °C.

(*Z*)-*N*'-(4-chlorophenyl)benzohydrazonoyl chloride (11).



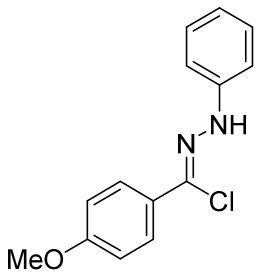
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 30:1) to give the product as a light yellow solid (495 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (br s, NH), 7.93 (br d, AA'XX', 2H), 7.44-7.39 (m, 3H), 7.28 (br d, AA'XX', 2H), 7.11 (br d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 134.2, 129.4, 129.3, 128.5, 126.5, 125.8, 125.5, 114.6. IR (KBr) 3322, 1592, 1495, 1232, 1129, 1085, 947 νmax/cm^{-1}; Mp 108-109 °C.

(*Z*)-4-chloro-*N*'-(4-methoxyphenyl)benzohydrazonoyl chloride (12).



The crude material was purified by column chromatography (*n*-hexane/ EtOAc 30:1) to give the product as a light yellow solid (457 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (br s, NH), 7.83 (br d, AA'XX', 2H), 7.36 (br d, AA'XX', 2H), 7.11 (br d, AA'XX', 2H), 6.89 (br d, AA'XX', 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 137.2, 134.8, 133.1, 128.6, 127.3, 122.6, 114.8, 114.7, 55.6. IR (KBr) 3329, 1569, 1396, 1242, 1091, 943 νmax/cm^{-1}; Mp 108-109 °C.

(*Z*)-4-methoxy-N'-phenylbenzohydrazonoyl chloride (13).



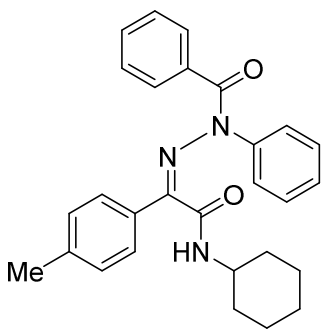
Compound **13** characterization data were compared to literature reported ones, see: G. Wang, X. Liu, T. Huang, Y. Kuang, L. Lin, X. Feng, *Org. Lett.* **2013**, *15*, 76–79

General preparation of *α*-aminocarbonyl *N*-acylhydrazones (4, 28-40).

The hydrazonoyl chloride (0.5 mmol, 1 eq.), the isocyanide (0.5 mmol, 1 eq.) the carboxylic acid (0.5 mmol, 1 eq.) and TEA (1 mmol, 2 eq.) were one-pot mixed in a screw-top vial. The reaction was stirred at room temperature under a nitrogen atmosphere overnight. The crude material was purified by column chromatography.

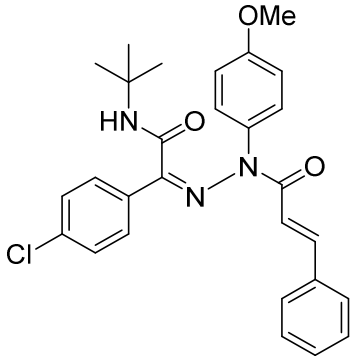
NB. In order to minimize the cis-trans amide isomerism, which complicates the NMR spectra, a simple solvent switch from $CDCl_3$ to DMSO-d_6 was employed, which was sometimes able to suppress or minimize rotamerism and enable assignment of the spectra. Although the reaction stereo-selectively generates the Z isomer, we observed that these acylhydrazones are not geometrically stable and on standing they undergo an isomerization process to afford equimolar amounts of the *Z* and *E* isomers. For compounds **30-34**, and **37** this process is so rapid that we were not able to isolate the *Z* isomer.

(*Z*)-2-(2-benzoyl-2-phenylhydrazono)-*N*-cyclohexyl-2-(*p*-tolyl)acetamide (4).



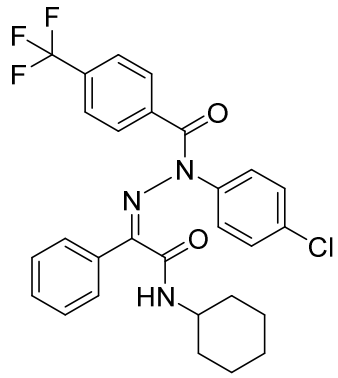
The crude material was purified by column chromatography (*n*-hexane/ EtOAc t 9:1) to give the product as light yellow solid (114 mg, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (br d, AA'XX', 2H), 7.44 (br d, AA'XX', 2H), 7. 30-7.17 (m, 10H), 6.54 (br s, NH), 3.96-3.88 (m, 1H), 2.38 (s, 3H), 1.80-1.77 (m, 2H), 1.60-1.50 (m, 3H), 1.28-1.22 (m, 2H), 1.09-1.06 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 164.0, 142.9, 142.0, 134.8, 130.6, 129.4 , 129.2, 129.1, 129.0, 128.5, 128.0 (2C), 127.9, 127.8, 48.3, 32.6, 25.2, 24.6, 21.6. IR (KBr) 3296, 2923, 1643, 1552, 1322, 1234, 899 νmax/cm^{-1}; Mp 166-167 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{28}H_{29}N_3O_2$: 439.2260; Found: 462.2130 $[M+Na]^+$

(*Z*)-*N*-(*tert*-butyl)-2-(4-chlorophenyl)-2-(2-cinnamoyl-2-(4methoxyphenyl) hydrazono)acetamide (28).



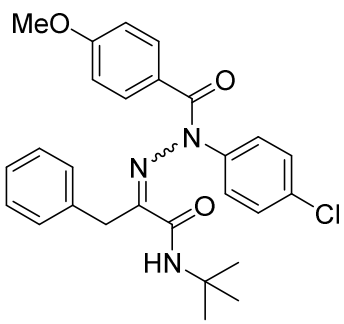
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as orange solid (137 mg, 56% yield). Signals are referred to the main rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (br d, AA'XX', 2H), 7.75 (d, *J* = 15.6 Hz, 1H), 7.41-7.33 (m, 9H), 7.05 (br s, NH), 6.96 (br d, AA'XX', 2H), 6.48 (br d, 1H), 3.84 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 (2C), 159.9, 143.0, 138.2, 134.8, 132.7, 130.0, 129.8 (2C), 129.6, 128.9, 128.8, 128.0, 117.9, 114.9, 55.5, 52.0, 28.4. IR (KBr) 3329, 2967, 1670, 1508, 1358, 1251, 836 νmax/cm^{-1}; Mp 173-174 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{28}H_{28}ClN_3O_3$: 489.1819; Found: 512.1700 $[M+Na]^+$.

(*Z*)-2-(2-(4-chlorophenyl)-2-(4-(trifluoromethyl)benzoyl)hydrazono)-*N*-cyclohexyl-2 phenylacetamide (29).



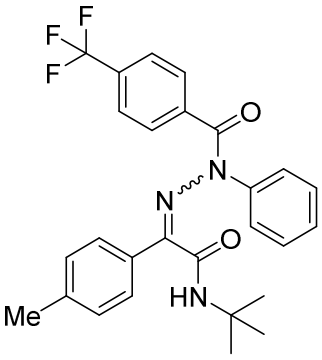
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as yellowish solid (208 mg, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (br d, AA'XX', 2H), 7. 58-7.53 (m, 5H), 7.45-7.42 (m, 2H), 7.24-7.22 (m, 4H), 6.28 (br s, NH), 3.93-3.86 (m, 1H), 1.79-1.77 (m, 2H), 1.63-1.52 (m, 3H), 1.33-1.24 (m, 2H), 1.11-1.03 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 163.5, 139.8, 138.0, 134.2, 132.5, 132.4 (q, *2JCF* = 33 Hz), 124.8 (q, *1JCF* = 270 Hz), 131.6, 129.5, 129.4, 129.3, 128.8 (2C), 128.4 (2C), 125.1 (q, *3JCF* = 3.6 Hz), 48.5, 32.5, 25.1, 24.5. IR (KBr) 3269, 2928, 1673, 1536, 1333, 1124, 847 νmax/cm^{-1}; Mp 177-178 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{28}H_{25}ClF_3N_3O_2$: 527.1587; Found: 550.1464 $[M+Na]^+$.

(*Z*)-*N*-(*tert*-butyl)-2-(2-(4-chlorophenyl)-2-(4-methoxybenzoyl)hydrazono)-3-phenylpropanamide (30).



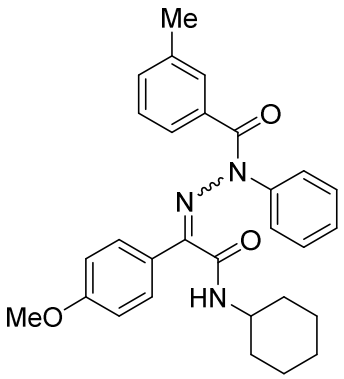
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as a colorless amorphous solid (69 mg, 29% yield). Mixture of E/Z isomers, signals are referred to the main isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.08 (m, 9H), 6.93 (br s, NH), 6.74 (br d, AA'XX', 2H), 6.70 (br d, AA'XX', 2H), 3.91 (s, 2H), 3.79 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 161.8, 161.4, 141.3, 136.0, 133.2, 133.0, 130.9, 129.8, 129.2, 128.9, 128.6, 128.4, 126.1, 113.2, 55.3, 51.2, 42.5, 28.5. IR (KBr) 3384, 2928, 1670, 1602, 1511, 1256, 834 νmax/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{27}H_{28}ClN_3O_3$: 477.1819; Found: 500.1719 $[M+Na]^+$.

(*Z*)-*N*-(*tert*-butyl)-2-(2-phenyl-2-(4-(trifluoromethyl)benzoyl)hydrazono)-2-(*p*-tolyl)acetamide (31).



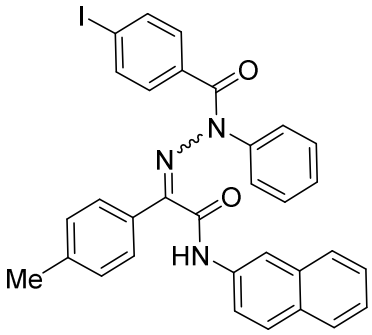
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as yellow solid (171 mg, 71% yield). Mixture of E/Z isomers, signals are referred to the main isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (br d, AA'XX', 2H), 7. 57 (br d, AA'XX', 2H), 7. 49 (br d, AA'XX', 2H), 7.30-7.22 (m, 5H), 7.13-7.11 (m ,1H), 7.00-6.93 (m, 1H), 6.34 (br s, NH), 2.40 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 162.1, 143.0, 141.5, 139.4, 138.4, 132.6, 132.1 (q, *2JCF* = 32.5 Hz), 129.6, 129.5, 129.0, 128.5, 128.2, 128.0, 125.0 (q, *3JCF* = 3.4 Hz), 123.5 (q, *1JCF* = 270 Hz), 52.2, 28.6, 21.6. IR (KBr) 3296, 2961, 1657, 1314, 1015 νmax/cm^{-1}; Mp 176-177 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{27}H_{26}F_3N_3O_2$: 481.1977; Found: 504.1853 $[M+Na]^+$.

(*Z*)-*N*-cyclohexyl-2-(4-methoxyphenyl)-2-(2-(3-methylbenzoyl)-2-phenylhydrazono)acetamide (32).



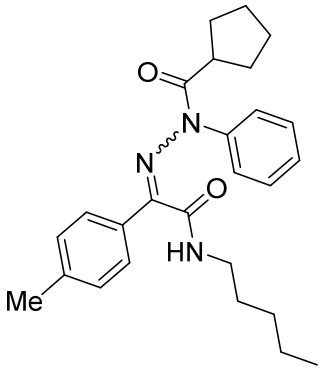
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as sticky solid (94 mg, 40% yield). Mixture of E/Z isomers, signals are referred to the main isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (br d, AA'XX', 2H), 7. 31-7.02 (m, 9H), 6.91 (br d, AA'XX', 2H), 6.58 (br d, *NH*), 3.96-3.91 (m, 1H), 3.82 (s, 3H), 2.23 (s, 3H), 1.85-1.78 (m, 2H), 1.61-1.49 (m, 3H), 1.34-1.22 (m, 2H), 1.13-1.09 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 164.1, 162.9, 142.1 (2C), 137.7, 134.8, 133.9, 131.3, 130.4, 129.7, 129.0 (2C), 128.0, 127.6, 126.2, 124.1, 114.0, 55.4, 48.3, 32.6, 25.2, 24.6, 21.2. IR (KBr) 3307, 2928, 1657, 1508, 1253, 735 νmax/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{29}H_{31}N_3O_3$: 469.2365; Found: 492.2256 $[M+Na]^+$.

(*Z*)-2-(2-(4-iodobenzoyl)-2-phenylhydrazono)-*N*-(naphthalen-2-yl)-2-(*p*-tolyl)acetamide (33).



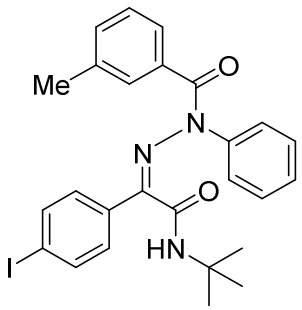
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as yellow solid (216 mg, 71% yield). Mixture of E/Z isomers, signals are referred to the main isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (br s, *NH*), 8.20 (s, 1H), 7.92-7.72 (m, 5H), 7.47-7.39 (m, 4H), 7.27-7.24 (m, 3H), 7.14-6.96 (m, 7H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 161.1, 141.3, 137.5 (2C), 135.0 (2C), 134.8, 133.9, 133.6, 131.0, 130.7, 129.7, 129.4 (2C), 128.9 (2C), 128.4, 128.0, 126.6, 125.1, 119.4, 116.0, 97.9, 21.4. IR (KBr) 3346, 3032, 1676, 1536, 1220, 1006 νmax/cm^{-1}; Mp 202-203 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{32}H_{24}IN_3O_2$: 609.0913; Found: 632.0814 $[M+Na]^+$.

(*Z*)-2-(2-(cyclopentanecarbonyl)-2-phenylhydrazono)-*N*-pentyl-2-(*p*-tolyl)acetamide (34).



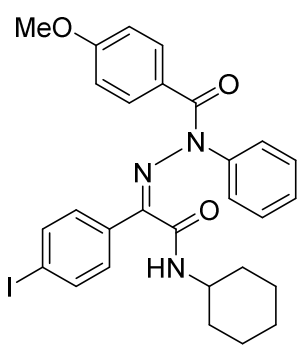
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as sticky solid (140 mg, 67% yield). Mixture of E/Z isomers, signals are referred to the main isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (br d, NH), 7.71 (br d, 2H), 7.41-6.83 (m, 7H), 3.35 (br q, 2H), 2.35 (s, 3H), 2.24-2.22 (m, 1H), 1.81-1.25 (m, 14H), 0.90-0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4, 162.0, 145.5, 131.4, 131.0 (2C), 129.3, 129.2, 128.4, 128.1, 42.1, 39.2, 29.1, 29.1, 29.0, 26.2, 22.3, 21.5, 13.9. IR (KBr) 3247, 2928, 1684, 1377, 1185, 694 νmax/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{26}H_{33}N_3O_2$: 419.2573; Found: 442.2436 $[M+Na]^+$.

(*Z*)-*N*-(*tert*-butyl)-2-(4-iodophenyl)-2-(2-(3-methylbenzoyl)-2-phenylhydrazono)acetamide (35).



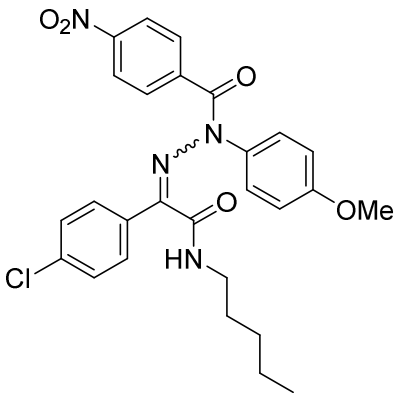
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as yellow solid (159 mg, 59% yield). Signals are referred to the main rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (br d, AA'XX', 2H), 7. 65 (br d, AA'XX', 2H), 7.33 (s, 1H), 7.26-7.06 (m, 8H), 6.51 (br s, NH), 2.25 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 163.6, 142.0, 138.0, 137.8, 134.4, 131.5, 129.9 (2C), 129.1 (2C), 128.0, 128.0, 127.7, 126.4, 99.3, 52.2, 28.5, 21.2. IR (KBr) 3285, 2967, 1659, 1489, 1215, 735 νmax/cm^{-1}; Mp 142-143 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{26}H_{26}IN_3O_2$: 539.1070; Found: 562.0911 $[M+Na]^+$.

(*Z*)-*N*-cyclohexyl-2-(4-iodophenyl)-2-(2-(4-methoxybenzoyl)-2-phenylhydrazono)acetamide (36).



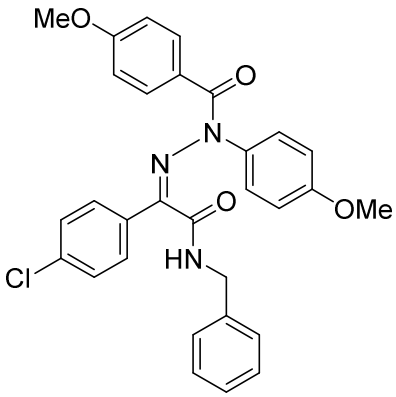
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as white solid (215 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7. 63 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.25-7.20 (m, 5H), 6.71 (d, *J* = 8.5 Hz, 2H), 6.52 (br d, NH), 3.89-3.84 (m ,1H), 3.77 (s, 3H), 1.75-1.72 (m, 2H), 1.60-1.51 (m, 3H), 1.40-1.21 (m, 2H), 1.07-0.99 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 163.4, 161.5, 142.3, 137.9, 131.5, 131.4, 129.8, 129.2, 128.0, 127.8 (2C), 126.5, 113.2 (2C), 99.2, 55.2, 48.2, 32.4, 25.1, 24.6. IR (KBr) 3269, 2928, 1657, 1506, 1251, 1001 νmax/cm^{-1}; Mp 174-175 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{28}H_{28}IN_3O_3$: 581.1175; Found: 604.1022 $[M+Na]^+$.

(*Z*)-2-(4-chlorophenyl)-2-(2-(4-methoxyphenyl)-2-(4-nitrobenzoyl)hydrazono)-*N*-pentyl-acetamide (37).



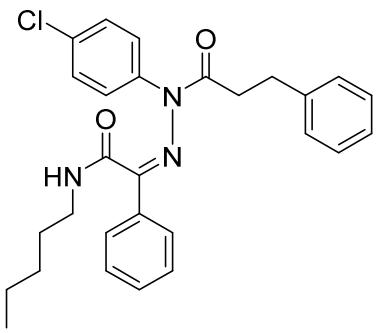
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as a sticky solid (217 mg, 83% yield). Mixture of E/Z isomers, signals are referred to the main isomer: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27-8.21 (m, 4H), 7.87-7.85 (m, 2H), 7.43-7.40 (m, 2H), 7.26 (br d, AA'XX', 2H), 7.16 (br s, NH), 6.91 (br d, AA'XX', 2H), 3.75 (s, 3H), 2.83-2.76 (m, 2H), 1.37-1.04 (m, 6H), 0.81-0.77 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.7, 163.0, 159.6, 148.6, 142.7, 134.1, 131.5, 130.8, 130.3, 129.6 , 129.2 (2C), 123.4 (2C), 114.3, 55.8, 39.0, 29.1, 28.4, 22.1, 14.1. IR (KBr) 3296, 2934, 1662, 1508, 1245, 831 νmax/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{27}H_{27}ClN_4O_5$: 522.1670; Found: 545.1545 $[M+Na]^+$.

(*Z*)-*N*-benzyl-2-(4-chlorophenyl)-2-(2-(4-methoxybenzoyl)-2-(4-methoxyphenyl)hydrazono) acetamide (38).



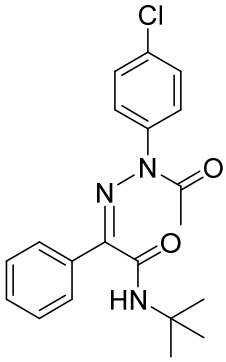
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as yellowish solid (155.5 mg, 59% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.89 (br s, NH), 7.57-7.44 (m, 6H), 7.24-7.14 (m, 7H), 6.91-6.89 (m, 4H), 3.99 (m, 2H), 3.78 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 163.5 (2C), 161.5, 159.0, 138.4, 135.7, 133.3, 132.0, 130.7, 129.2, 129.0, 128.7, 128.1 (2C), 127.6, 127.5, 114.3, 113.4, 55.8, 55.7, 42.7. IR (KBr) 3230, 3054, 2835, 1665, 1294, 1026, 836 νmax/cm^{-1}; Mp 173-174 °C; MS (ESI) *m/z* (M+H)$^+$ Calcd for $C_{30}H_{26}ClN_3O_4$: 527.1612; Found: 550.1464 [M+Na]$^+$.

(*Z*)-2-(2-(4-chlorophenyl)-2-(3-phenylpropanoyl)hydrazono)-*N*-pentyl-2-phenylacetamide (39).



The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as yellowish solid (164 mg, 69% yield). ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.28 (br t, NH), 7.62 (br d, AA'XX', 2H), 7.47-7.37 (m, 5H), 7.29-7.26 (m, 4H), 7.18-7.13 (m, 3H), 3.13-3.05 (m, 2H), 2.94-2.90 (m, 2H), 2.67-2.59 (m, 2H), 1.25-1.13 (m, 6H), 0.83 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 191.3, 163.4, 141.7, 138.2, 134.8, 132.6, 131.0, 130.0, 129.1, 128.8, 128.8, 128.6 (2C), 127.2 (2C), 126.4, 38.7, 36.2, 30.8, 29.1, 28.3, 22.2, 14.3. IR (KBr) 3263, 2934, 1687, 1624, 1163, 721 νmax/cm^{-1}; Mp 142-143 °C; MS (ESI) *m/z* (M+H)$^+$ Calcd for $C_{28}H_{30}ClN_3O_2$: 475.2027; Found: 498.1873 [M+Na]$^+$.

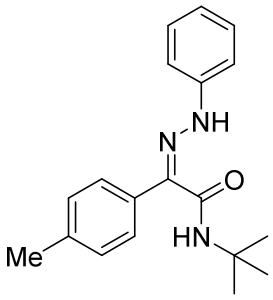
(*Z*)-2-(2-acetyl-2-(4-chlorophenyl)hydrazono)-*N*-(*tert*-butyl)-2-phenylacetamide (40).



The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as a yellow solid (50 mg, 27% yield). Signals are referred to the main rotamer: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (br s, NH), 7.73 (br d, AA'XX', 2H), 7.51-7.26 (m 7H), 2.31 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 189.8, 163.0, 143.0, 139.0, 134.7, 131.9, 129.5, 129.1, 128.8 (2C), 127.7 (2C), 51.6, 28.5, 23.2. IR (KBr) 3247, 2972, 1695, 1550, 1366, 919, 688 νmax/cm^{-1}; MP 159-160 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{20}H_{22}ClN_3O_2$: 371.1401; Found: 394.1299 $[M+Na]^+$.

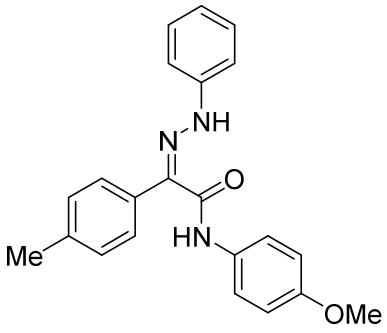
General preparation of α-aminocarbonylhydrazones (44, 48-52). The hydrazonoyl chloride (0.5 mmol, 1 eq.), the isocyanide (0.5 mmol, 1 eq.), the 2-hydroxymethylbenzoic acid (0.5 mmol, 1 eq.) and TEA (1 mmol, 2 eq.) were one-pot mixed in DCM (0.5 M, 1 mL). The reaction was stirred at room temperature under a nitrogen atmosphere overnight. After evaporation of the solvent, the crude material was purified by column chromatography.

(*Z*)-*N*-(*tert*-butyl)-2-(2-phenylhydrazono)-2-(*p*-tolyl)acetamide (44).



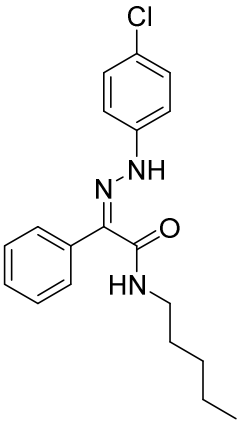
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 30:1) to give the product as a sticky solid (104 mg, 67% yield). Signals are referred to the main rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.61 (br s, NH), 7.45 (d, *J* = 7.9 Hz, 2H), 7.30-7.21 (m, 6H), 6.94-6.90 (m, 1H), 5.80 (br s, NH), 2.41 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 144.0, 138.2, 134.2, 132.1, 129.5, 128.5, 121.1, 113.5, 51.9, 28.8, 21.3. IR (KBr) 3318, 2972, 1626, 1530, 1245, 1157, 817 νmax/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{19}H_{23}N_3O$: 309.1841; Found: 332.1727 $[M+Na]^+$.

(*Z*)-*N*-(4-methoxyphenyl)-2-(2-phenylhydrazono)-2-(*p*-tolyl)acetamide (48).



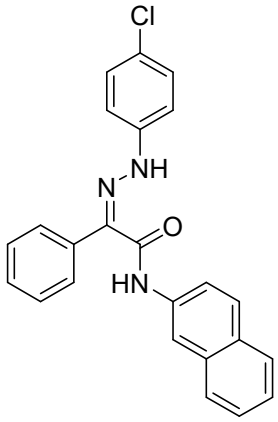
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 30:1) to give the product as a sticky solid (72 mg, 40% yield). Mixture of E/Z isomers, signals are referred to the main isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (br s, NH), 8.12 (br s, NH), 7.62 (br d, AA'XX', 2H), 7.46-7.27 (m, 6H), 7.09 (br d, AA'XX', 2H), 6.98 (br t, 1H), 6.90 (br d, AA'XX', 2H), 3.80 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 156.0, 142.8, 139.8, 137.6, 131.4, 130.0, 129.4, 129.1, 125.7, 122.0, 121.0, 114.2, 113.7, 55.6, 21.5. IR (KBr) 3373, 3225, 2923, 1654, 1508, 1242, 823 νmax/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{22}H_{21}N_3O_2$: 359.1634; Found: 382.1512 $[M+Na]^+$.

(*Z*)-2-(2-(4-chlorophenyl)hydrazono)-*N*-pentyl-2-phenylacetamide (49).



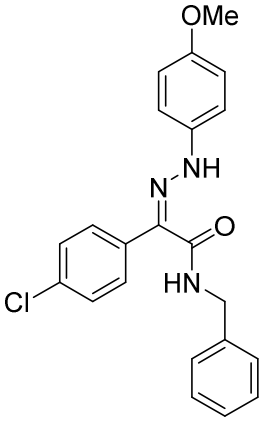
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 30:1) to give the product as a sticky solid (125 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.79 (br s, NH), 7.53 (br d, AA'XX', 2H), 7.46-7.39 (m, 3H), 7.22 (br d, AA'XX', 2H), 7.12 (br d, AA'XX', 2H), 5.90 (br s, NH), 3.35-3.30 (m, 2H), 1.57-1.50 (m, 2H), 1.36-1.26 (m, 4H), 0.92-0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 142.4, 136.5, 131.7, 129.1, 128.9, 128.7, 128.5, 126.0, 114.7, 39.3, 29.1, 29.0, 22.3, 14.0. IR (KBr) 3291, 2923, 1624, 1541, 1245, 820, 688 νmax/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{19}H_{22}ClN_3O$: 343.1451; Found: 366.1341 $[M+Na]^+$.

(*Z*)-2-(2-(4-chlorophenyl)hydrazono)-*N*-(naphthalen-2-yl)-2-phenylacetamide (50).



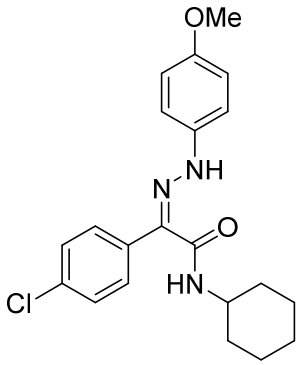
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as dark yellow solid (114 mg, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10 (br s, NH), 8.40 (br s, NH), 8.08 (s, 1H), 7.84 (br d, AA'XX', 1H), 7.80 (br d, AA'XX', 2H), 7.63-7.38 (m, 8H), 7.30 (br d, AA'XX', 2H), 7.06 (br d, AA'XX', 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 141.2, 138.1, 135.3, 134.0, 130.5, 130.0, 129.5, 129.2, 128.8 (2C), 128.4, 127.7, 127.6, 127.0, 126.5, 124.8, 119.7, 116.0, 114.9. IR (KBr) 3296, 1753, 1651, 1530, 1489, 1251, 1146, 814 νmax/cm^{-1}; Mp 164-165 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{24}H_{18}ClN_3O$: 399.1138; Found: 422.2436 $[M+Na]^+$.

(*Z*)-*N*-benzyl-2-(4-chlorophenyl)-2-(2-(4-methoxyphenyl)hydrazono)acetamide (51).



The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as dark yellow solid (153 mg, 78% yield). Mixture of E/Z isomers, signals are referred to the main isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (br s, NH), 7.51-7.26 (m, 10H), 6.97 (br d, AA'XX', 2H), 6.85 (br d, AA'XX', 2H), 4.60 (br d, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 155.1, 138.8, 136.5, 135.5, 134.9, 130.8, 129.6, 128.7, 127.7, 127.6, 127.4, 115.0, 114.8, 55.6, 43.4. IR (KBr) 3412, 3170, 1632, 1503, 1234, 1078, 823 νmax/cm^{-1}; Mp 123-124 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{22}H_{20}ClN_3O_2$: 393.1244; Found: 416.1122 $[M+Na]^+$.

(*Z*)-2-(4-chlorophenyl)-*N*-cyclohexyl-2-(2-(4-methoxyphenyl) hydrazono)acetamide (52).



The crude material was purified by column chromatography (*n*-hexane/ EtOAc 30:1) to give the product as a dark yellow solid (108 mg, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.70 (br s, NH), 7.47 (br d, AA'XX', 2H), 7.38 (br d, AA'XX', 2H), 7.12 (br d, AA'XX', 2H), 6.85 (br d, AA'XX', 2H), 5.65 (br t, NH), 3.91-3.84 (m, 1H), 3.77 (s, 3H), 1.95-1.92 (m, 2H), 1.71-1.60 (m, 3H), 1.44-1.35 (m, 2H), 1.20-1.10 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 154.9, 137.5, 135.5, 134.0, 129.8, 129.0, 128.7, 114.7, 114.7, 55.6, 48.2, 32.8, 25.4, 24.8. IR (KBr) 3401, 3175, 2928, 1626, 1508, 1229, 1039, 820 νmax/cm^{-1}; Mp 170-171 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{21}H_{24}ClN_3O_2$: 385.1557; Found: 408.1441 $[M+Na]^+$.

Single crystal X-ray diffraction analysis.

ORTEP view of 4 and the relative arbitrary atom-numbering scheme (thermal ellipsoids at 40% probability).

The overall molecular conformation is determined by the Z conformation of the C=N double bond. The two carbonyl-O1 and O2 atoms adopt an *anti* disposition. The dihedral angle between the benzene C1-C6 with the ring C8-C13 is 71.6(8)° and the equivalent angle with the phenyl C22-C27 is 83.2(7)°. The latter group forms a dihedral angle with the phenyl C8-C13 of 66.9(6)°. The cyclohexane adopts a half-chair conformation, as shown by the puckering coordinates Q = 0.564(4) Å, ϕ_2 = -137.8(1)°, θ = 177.6(5)°. The crystal packing is stabilized by centrosymmetric hydrogen bonds between N3-H3A…O1' ('at -x, -y, -z), distance 2.11(2) Å, angle 167(1)°, that link the molecules forming dimers. These latter are in turns interconnected by C10-H10…O2'' ('' at 1-x, 1-y,-z) contacts, distance 2.62(2) Å, angle 133(1)° giving rise to molecular chains along the *c* axis.

10.4 References

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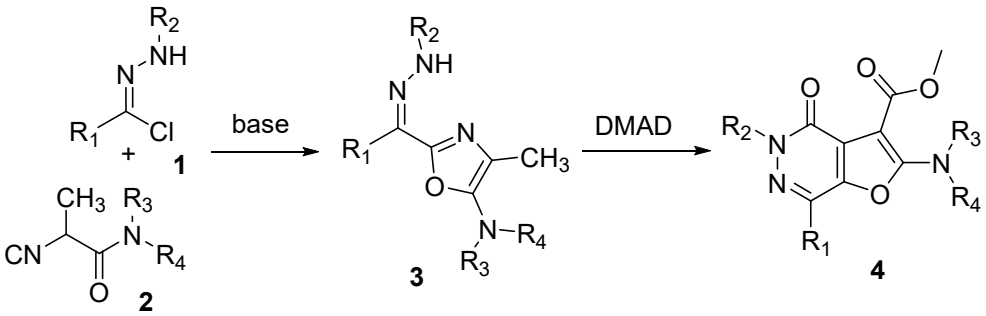
Chapter 11

Exploiting the electrophilic and nucleophilic dual role of nitrile imines: one-pot, three-component synthesis of furo[2,3-*d*]pyridazin-4(5*H*)-ones

11.1 Results and discussion

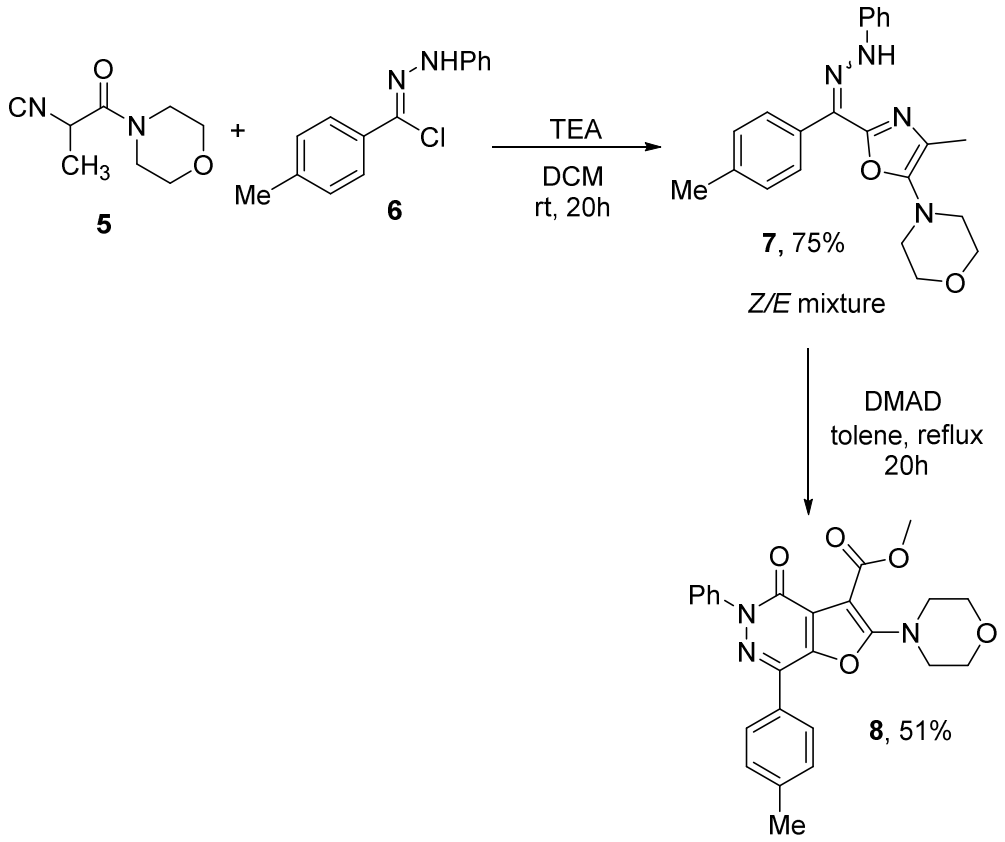
Stimulated by our first results with nitrile imines and in connection with our studies on the reactivity of α-isocyanoacetamides,[1–4] we envisaged a multicomponent synthesis of fully substituted furo[2,3-*d*]pyridazin-4(5*H*)-ones (4), starting from readily available hydrazonoyl chlorides **1** and α-methylisocyanoacetamides **2** (Scheme 1). The intermediate α-hydrazono-oxazole **3** obtained could then be intercepted in situ with dimethylacetylene dicarboxylate (DMAD), which should be able to trigger a triple-domino process consisting of a Diels−Alder cyclization, a [4 + 2] cycloreversion, and an intramolecular lactamization.



Scheme 1. General reaction sequence to get furo[2,3-d]pyridazin-4(5*H*)-ones.

According to Scheme 2, 2-isocyano-1-morpholino-propan-1-one[3] **5** and the hydrazonoyl chloride **6** were mixed in dichloromethane in the presence of 1 equivalent of TEA overnight at room temperature. Addition of isocyanide to nitrile imine was stereoselective, affording the *Z*-isomer.[5] Due to the low energy barrier required for the *Z* to *E* isomerism of this class of hydrazones, we detected a *Z/E* mixture of 1,3-oxazole-2-hydrazone **7** obtained in 75% yield after chromatographic column. Subsequent reaction of **7** with 1 equivalent of DMAD in toluene at reflux overnight afforded a novel fluorescent spot on TLC which, after purification and

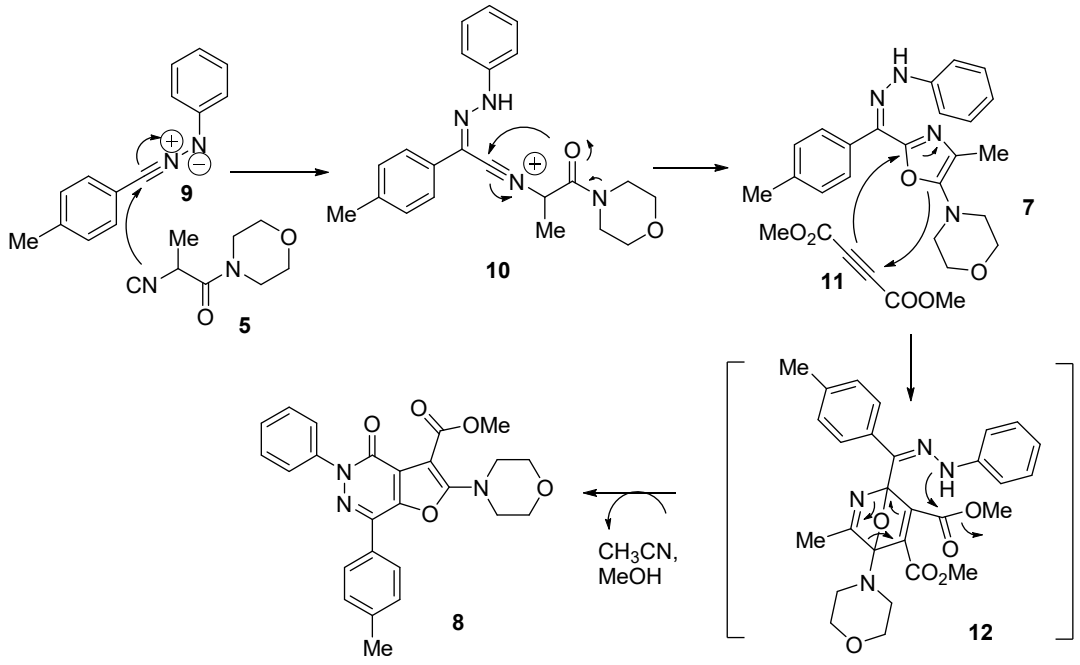
spectroscopic investigation, was shown to be the desired furo[2,3-*d*]pyridazin-4(5*H*)-one **8** obtained in 51% yield (Scheme 2).



Scheme 2. Synthetic procedure to get furo[2,3-*d*]pyridazin-4(5*H*)-ones.

After demonstrating the feasibility of this novel transformation, in a further advancement, we evaluated the possibility to perform the whole transformation in a one-pot, two-step domino fashion without isolating the 1,3-oxazole-2- hydrazone intermediate **7**. Indeed, after monitoring its formation by TLC, the dichloromethane was evaporated and the crude reaction mixture was dissolved in toluene: by simply adding DMAD the reaction proceeded smoothly toward the formation of the furo[2,3-*d*]pyridazin-4(5*H*)-one **8**. When different DMAD equivalents (1, 1.2, 1.5, and 2 equiv) were screened, a satisfactory yield of 45% was obtained when 2 equivalents was used.

The proposed reaction mechanism is reported in Scheme 3. The hydrazonoyl chloride formed in situ the dipolar nitrilimine **9** which was then attacked by the isocyanide carbon atom of isocyanoacetamide **5**. Once the nitrilium ion **10** was formed, it was intramolecularly intercepted by the oxygen of the tertiary amide to give the 1,3-oxazol-2-hydrazone **7**. The latter was then able to attack the DMAD **11** triple bond to give the unstable oxa-bridged intermediate **12** via Diels-Alder reaction, which after acetonitrile loss by means of a [4+2] cycloreversion, and simultaneous methanol loss by means of intramolecular lactamization gave the desired furo[2,3-*d*]pyridazin-4(5*H*)-one **8**.



Scheme 3. Proposed reaction mechanism for the one-pot domino formation of furo[2,3-*d*]pyridazin-4(5*H*)-ones **8**.

With these optimized one-pot reaction conditions in hand, we started to evaluate the scope of this transformation using different hydrazonoyl chlorides (**6, 13.19**) and isocyanoacetamides (**5, 20-23**) (Figure 1) and randomly combining them in order to get a library of furo[2,3-*d*]pyridazin-4(5*H*)-ones (**24-34**) (Figure 2).

Hydrazonoyl chlorides

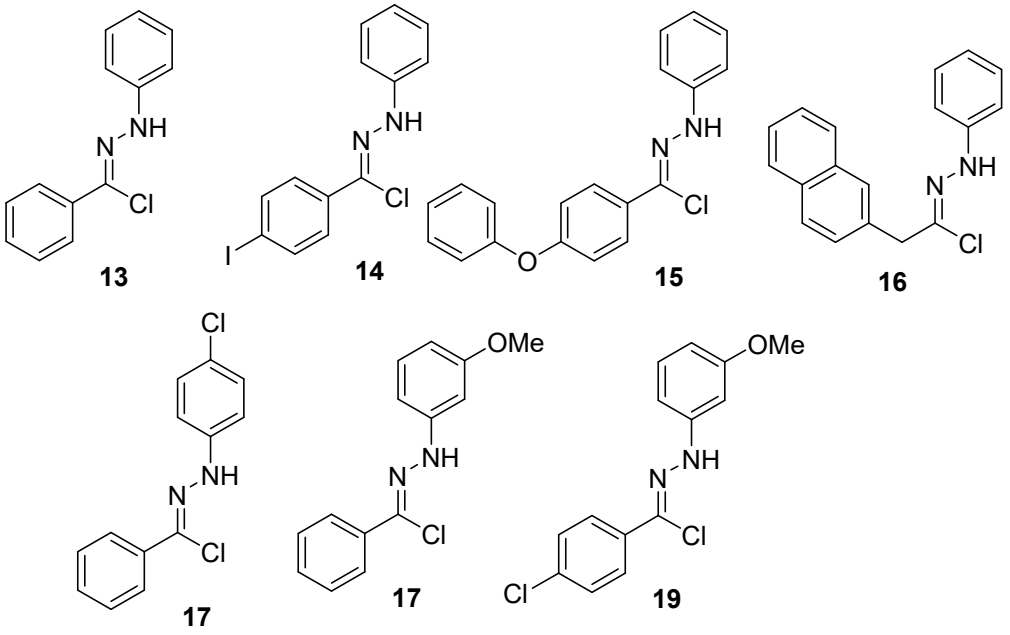


Figure 1. Building blocks used.

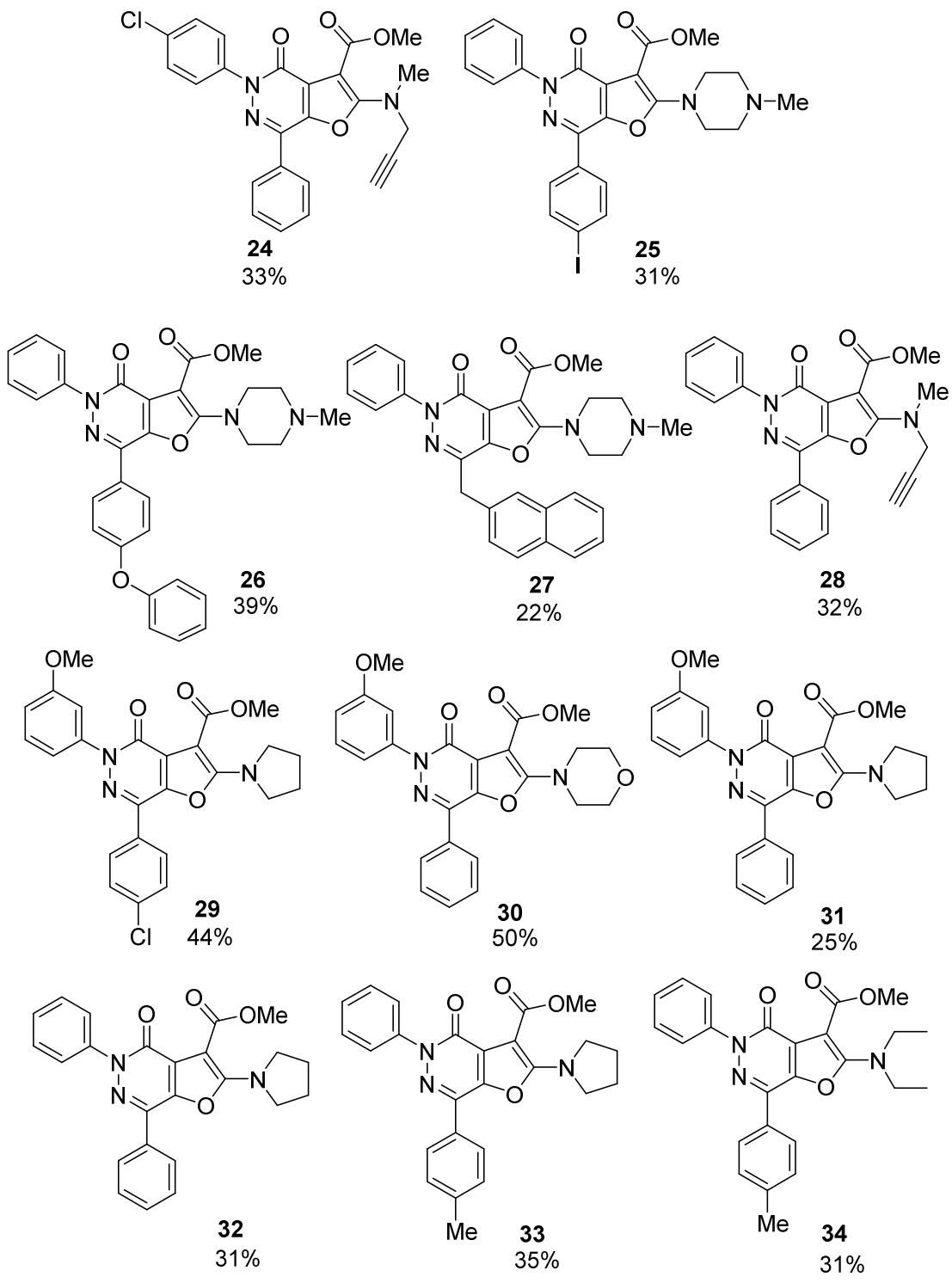
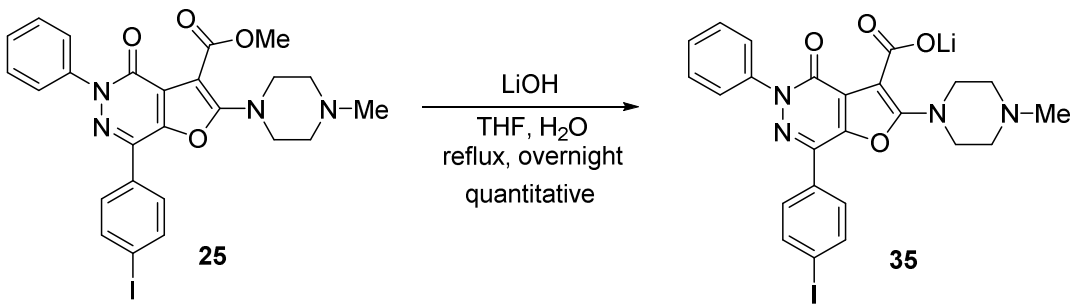


Figure 2. Library of synthesized furo[2,3-*d*]pyridazin-4(5*H*)-ones**.**

Yields ranged from 22 to 50% and were shown to be unaffected by hydrazonoyl chlorides substitution pattern as both electron-withdrawing chlorine or iodine atom (**14**, **17**, **19**, Figure 2) and electron-donor methoxy or phenoxy groups gave good yields (**15**, **18**, **19** Figure 2). Isocyanoacetamides with an additional alkyne function, considerable for further derivatizations (**21**, Figure 2) or a basic amine group (**22**, Figure 2), also worked well, allowing for the generation of widely decorated heterocyles. Notably, the yields are referred to a sequence of four different reactions (the formation of 1,3-oxazol-2-hydrazone, the Diels-Alder cyclization with DMAD, the [4+2] cycloreversion with the extrusion of acetonitrile and the intramolecular lactamization with loss of methanol), indicating an average yield of 84-67% for each synthetic step.

It is important to highlight that, to date, the chemistry of isocyanoacetamides coupled with domino sequences has been mainly explored using aldehydes, imines, and acyl chlorides as electrophilic partners.[6–11] In this case, the use of hydrazonoyl chlorides allowed for the incorporation of one more nitrogen atom in the forming heterocyclic ring, giving access to a furo[2,3-d]pyridazinone scaffold not synthesizable with the previous strategies.

Notwithstanding its vinylogous carbamic nature, the ester function can also be easily hydrolyzed without affecting the pyridazinone moiety, providing an acid group amenable to further derivatization as reported in Scheme 3 for compound **35**.



Scheme 3. Synthesis of the furo[2,3-*d*]pyridazin-3-carboxylic acid **35**.

11.2 Conclusions

In conclusion we reported a one-pot synthesis of fully substituted furo[2,3-*d*]pyridazin-4(5*H*)-ones, through a multicomponent, one-pot sequence of four different reactions: oxazole formation, Diels-Alder cyclization, [4+2] cycloreversion and intramolecular lactamization.

Furo[2,3-*d*]pyridazin-4(5*H*)-one derivatives have shown potential in medicinal chemistry as immunomodulator, antiasthmatic, and thromboxane A2 synthase inhibitors.[12] Despite their pharmaceutical relevance, their synthetic approaches had required, until now, at least 5-6 reaction steps with overall yields of 7-20%, different purifications and the use of very toxic reagents (e.g. trimethylsylildiazomethane), and harsh reaction conditions (e.g. concentrated HCl) not always compatible with other functional groups.

The reactivity of 1,3-dipolar species nitrilimines, in situ generated from hydrazonoyl chlorides, toward isocyanoacetamides was here explored for the first time in a three-center, two components reaction and in combination with a further sequence of post-condensation domino processes.

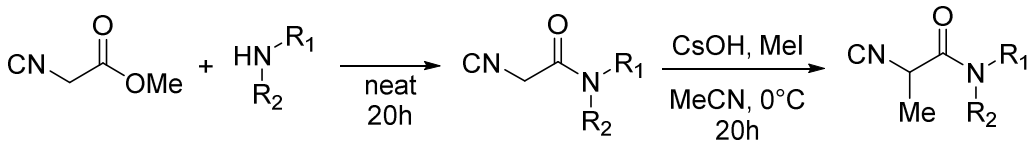
To our knowledge this is the first report enabling a fast and practical synthesis of fully decorated furo[2,3-*d*]pyridazin-4(5*H*)-ones starting from cheap and available starting materials. The suitability of the developed synthesis to combinatorial approaches, and the possibility to get multi-functionalized furo[2,3-d]pyridazin-4(5H)-ones highlighted how the fused-pyridinazinones chemical space could be better explored in order to come up with new bioactive compounds.

This method constitutes a significant advancement over previously reported strategies[13,14] and is likely to facilitate deeper medicinal chemistry studies of this class of compounds.

11.3 Experimental section

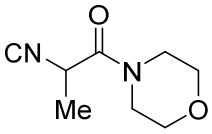
General Methods. Commercially available reagents and solvents were used without further purification. Dichloromethane was dried by distillation from P_2O_5 and stored over activated molecular sieves (4 A). When necessary the reactions were performed in oven-dried glassware under a positive pressure of dry nitrogen. Melting points were determined in open glass capillaries and are uncorrected. All the compounds were characterized by IR. ^{1}H and ^{13}C APT NMR were recorded on a 400 MHz. High-resolution ESI-MS spectra were performed on a Thermo LTQ Orbitrap XL mass spectrometer. The spectra were recorded by infusion into the ESI source using MeOH as the solvent. Chemical shifts (δ) are reported in part per million (ppm) relative to the residual solvent peak. Column chromatography was performed on silica gel (70–230 mesh ASTM) using the reported eluents. Thin layer chromatography (TLC) was carried out on 5 x 20 cm plates with a layer thickness of 0.25 mm (Silica gel 60 F254). When necessary they were developed with KMnO4.

General preparation of isocyanoacetamides (5, 20-23).[3] The α-methyl-α-isocyanoacetamides where readily synthesized in two steps starting from the commercially available methylisocyanoacetate:



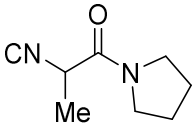
5, 20-23

2-isocyano-1-morpholinopropan-1-one (5).



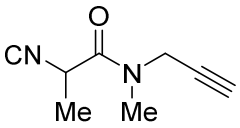
Compound **1** characterization data were compared to literature reported ones.[3]

2-isocyano-1-(pyrrolidin-1-yl)propan-1-one (20).



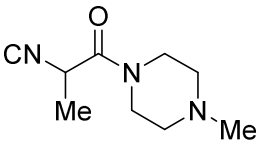
Compound **16** characterization data were compared to literature reported ones.[3]

2-isocyano-*N*-methyl-*N*-(prop-2-yn-1-yl)propanamide (21).



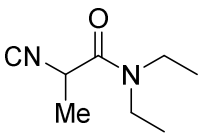
Compound **17** characterization data were compared to literature reported ones.[1]

2-isocyano-1-(4-methylpiperazin-1-yl)propan-1-one (22).



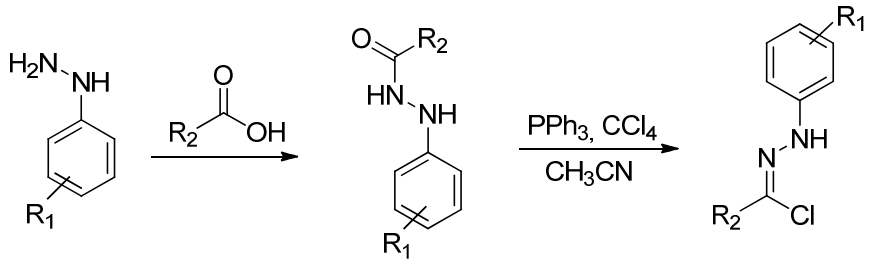
The crude material was purified by column chromatography (dichloromethane/methanol 95:5) to give the product as a colorless oil (46% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (br q, 1H), 3.62-3.34 (m, 4H), 2.35-2.29 (m, 4H),2.20 (s, 3H), 1.46 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 158.6, 54.5, 54.3, 49.5,45.8, 45.6, 42.4, 18.7. IR (KBr) 2939, 2148, 1665, 1451, 1289, 1144, 998 νmax/cm^{-1}. MS (ESI) *m/z* Calcd for $C_9H_{15}N_3O$: 181,1215; Found: 182.1290 $[M+H]^+$.

***N*,*N*-diethyl-2-isocyanopropanamide (23).**



Compound **23** characterization data were compared to literature reported ones.[15]

General preparation of hydrazonoyl chlorides (6, 13-19).[16] The hydrazonoyl chlorides were readily synthesized in two steps:

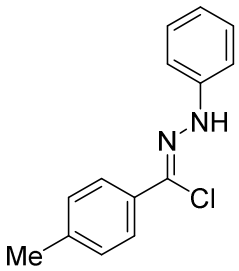


2, 9-15

Preparation of acylhydrazines. To a stirred solution of acid on a 5 mmol scale in THF (0.2 M) were added EDC HCl (5.5 mmol, 1.1 eq.), DMAP (1 mmol, 0.2 eq.), triethylamine (10 mmol, 2 eq.) and hydrazine (5 mmol, 1 eq.) at 0 °C. The resulting mixture was allowed to warm to room temperature over 24 h. The crude reaction mixture was washed with HCl 1M sol. (x2), $NaHCO_3$ at. sol. (x2) and brine (x1), evaporated to dryness and used in the next step without further purification.

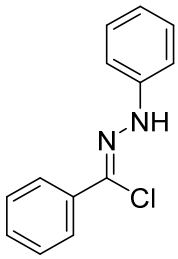
Preparation of hydrazonoyl chlorides (6, 13-19). The corresponding acylhydrazine (2.5 mmol) was dissolved in CH_3CN (0.5 M) and triphenylphosphine (3 mmol, 1.2 eq.) and carbon tetrachloride (3 mmol, 1.2 eq.) were added. The reaction was stirred at room temperature until all the acylhydrazine was consumed as judged by TLC (typically 8-12 hours). The reaction was concentrated under reduced pressure and purified by column chromatography (*n*-hexane/EtOAc 30:1) and stored below 0 °C. Due their delicate nature, neither HMRS nor elemental analyses of nitrile imines gave satisfactory results.

(*Z*)-4-methyl-*N*'-phenylbenzohydrazonoyl chloride (6).



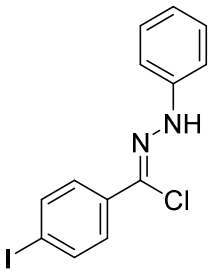
Compound **2** characterization data were compared to literature reported ones.[16]

(*Z*)-*N*'-phenylbenzohydrazonoyl chloride (13).



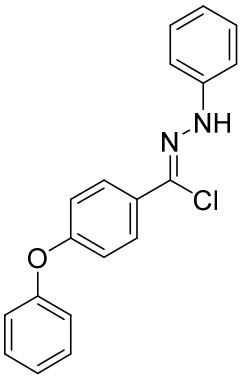
Compound **9** characterization data were compared to literature reported ones.[17]

(*Z*)-4-iodo-*N*'-phenylbenzohydrazonoyl chloride (14).



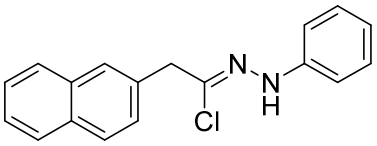
Compound **10** characterization data were compared to literature reported ones.[16]

(*Z*)-4-phenoxy-*N*'-phenylbenzohydrazonoyl chloride (15).



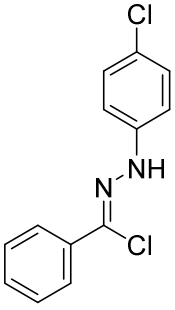
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 30:1) to give the product as an amorphous yellowish solid (59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (br s, *NH*), 7.98 (d, *J* = 8.7 Hz, 2H), 7.48- 7.39 (m, 4H), 7.27-7.23 (m, 3H), 7.18 (br d, AA'XX', 2H), 7.12 (br d, AA'XX', 2H), 7.04 (br t, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 156.6, 143.5, 130.1 (2C), 129.5 (2C), 129.4 (2C), 128.1, 124.3, 124.0, 121.2, 119.5 (2C), 118.4 (2C), 113.5 (2C).

(*Z*)-2-(naphthalen-2-yl)-*N*'-phenylacetohydrazonoyl chloride (16).



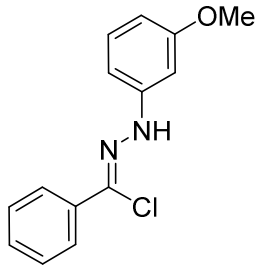
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 30:1) to give the product as a pink oil (59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.3, 1H), 7.91 (d, *J* = 7.8, 1H), 7.86-7.84 (m, 1H), 7.70 (br s, *NH*), 7.59-7.47 (m, 4H), 7.33-3.29 (m, 2H), 7.09-7.07 (m, 2H), 6.96-6.93 (m, 1H), 4.42 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 134.0, 132.3, 131.7, 129.5 (2C), 128.9, 128.4, 128.2, 126.5, 126.0, 125.9, 125.6, 124.0, 120.9, 113.3 (2C), 42.6.

(Z)-*N*'-(4-chlorophenyl)benzohydrazonoyl chloride (17).



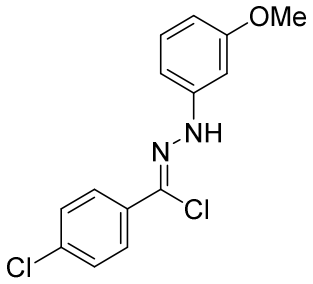
Compound **13** characterization data were compared to literature reported ones.[16]

(Z)-*N*-(3-methoxyphenyl)benzohydrazonoyl chloride (18).



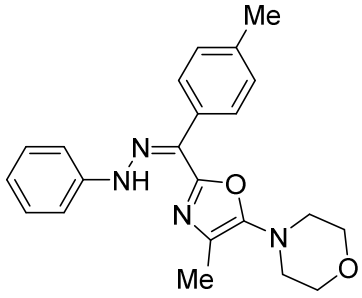
The crude material was purified by column chromatography (PE/EtOAc 95:5) to give the product as a brown solid (55% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.07 (br s, *NH*), 7.75 (br d, 2H), 7.45-7.39 (m, 3H), 7.24 (br t, 1H), 6.85 (br s, 1H), 6.75 (dd, *J* = 7.9, 1.86 Hz, 1H), 6.54 (dd, *J* = 8.1, 2.4 Hz, 1H), 3.84 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.9, 144.8, 134.5, 130.3, 129.3, 128.5 (2C), 126.5 (2C), 124.8, 106.6, 106.2, 99.6, 55.3.

(Z)-4-chloro-*N*-(3-methoxyphenyl)benzohydrazonoyl chloride (19).



The crude material was purified by column chromatography (PE/EtOAc 95:5) to give the product as a brown solid (47% yield). ^{1}H-NMR (300 MHz, $CDCl_3$+CD_3OD) δ 7.79 (d, AA'XX, *J* = 8.2 Hz, 2H), 7.33 (d, AA'XX, *J* = 8.2 Hz, 2H), 7.19-7.15 (m, 1H), 6.75 (br s, 1H), 6.69 (dd, *J* = 7.9, 1.8 Hz, 1H), 6.47 (dd, *J* = 8.1, 2.4 Hz, 1H), 3.82 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$+CD_3OD) δ 160.8, 144.4, 135.1, 132.9, 130.1, 128.6, 127.5, 123.5, 106.6, 106.2, 99.6, 55.3.

Synthesis of 4-(4-methyl-2-((2-phenylhydrazono)(*p*-tolyl)methyl)oxazol-5-yl)morpholine (7).

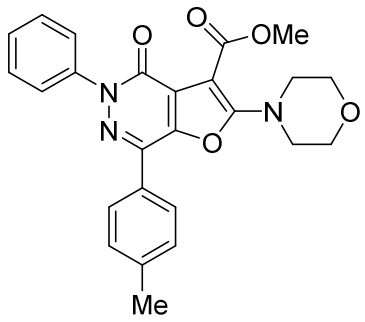


The hydrazonoyl chloride (0.8 mmol, 1 eq.), the isocyanoacetamide (0.8 mmol, 1 eq.) and TEA (0.8 mmol, 1 eq.) were one-pot mixed in DCM (0.8 M, 1 mL) and stirred at room temperature under a nitrogen atmosphere overnight. After evaporation of the solvent, the crude material was purified by column chromatograph (*n*-hexane/ EtOAc 8:2) to give the product as yellow solid (226 mg, 75% yield). Data are referred to the main isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.77 (br s, *NH*), 7.68 (br d, AA'XX', 2H), 7.31-7.22 (m, 7H), 3.81-3.79 (m, 4H), 3.12-3.10 (m, 4H), 2.40 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3,

163.4, 143.8, 138.4, 133.4, 130.8, 129.6 (2C), 129.2 (2C), 128.4 (2C), 126.0, 121.4, 113.6 (2C), 66.7, 66.5, 45.9, 42.5, 21.3, 18.8. IR (KBr) 3219, 2945, 2846, 1947, 1909, 1665, 1596, 1495, 1251 νmax/cm^{-1}; Mp 137-138 °C; MS (ESI) *m/z* Calcd for $C_{22}H_{24}N_4O_2$: 376.1899; Found: 377.1963 $[M+H]^+$.

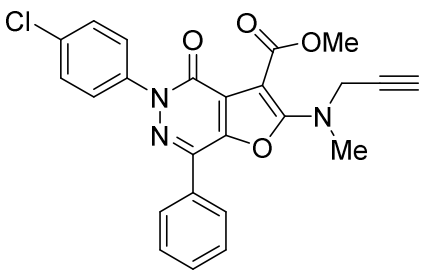
General one-pot preparation of furo[2,3-*d*]pyridazin-4(5*H*)-ones (8, 24-34). The hydrazonoyl chloride (0.8 mmol, 1 eq.), the isocyanoacetamide (0.8 mmol, 1 eq.) and TEA (0.8 mmol, 1 eq.) were one-pot mixed in DCM (0.8 M, 1 mL) and stirred at room temperature under a nitrogen atmosphere overnight. The formation of the intermediate oxazole was monitored by TLC, and after evaporation of the solvent, toluene (0.2M, 4 mL) and DMAD (dimethyl acetylenedicarboxylate) (1.6 mmol, 2 equiv.) were added to the crude mixture and the reaction was stirred at reflux temperature overnight. After evaporation of the solvent, the crude material was purified by column chromatography.

Methyl 2-morpholino-4-oxo-5-phenyl-7-(*p*-tolyl)-4,5-dihydrofuro[2,3-*d*]pyridazine-3-carboxylate (8).



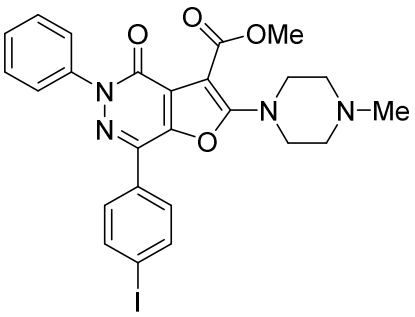
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 7:3) to give the product as yellow solid (160 mg, 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (br d, AA'XX', 2H), 7.61 (br d, AA'XX', 2H), 7.50-7.46 (m, 2H), 7.40-7.36 (m, 1H), 7.29 (br d, 2H), 3.91 (s, 3H), 3.89-3.87 (m, 4H), 3.67-3.64 (m, 4H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 161.5, 156.8, 143.6, 142.3, 139.9, 134.8, 129.5 (2C), 129.4, 128.7 (2C), 127.9, 127.4 (2C), 126.4 (2C), 123.5, 90.5, 66.3 (2C), 52.2, 48.2 (2C), 21.4. IR (KBr) 2956, 2846, 1695, 1585, 1448, 1294, 1072 νmax/cm^{-1}; Mp 211-212 °C; MS (ESI) *m/z* Calcd for $C_{25}H_{23}N_3O_5$: 445.1638; Found: 446.1693 $[M+H]^+$.

Methyl 5-(4-chlorophenyl)-2-(methyl(prop-2-yn-1-yl)amino)-4-oxo-7-phenyl-4,5-dihydrofuro [2,3-*d*]pyridazine-3-carboxylate (24).



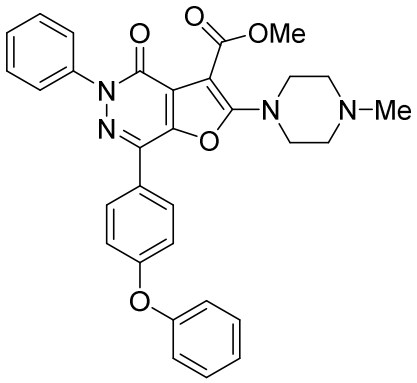
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 7:3) to give the product as yellow solid (118 mg, 33% yield). ^{1}H NMR (400 MHz,$CDCl_3$) δ 8.01 (br d, AA'XX', 2H), 7.60 (br d, AA'XX', 2H), 7.50-7.43 (m, 5H), 4.36 (s, 2H), 3.93 (s, 3H), 3.27 (s, 3H), 2.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 160.9, 156.6, 143.5, 140.8, 134.9, 133.6, 132.1, 129.7, 128.7 (4C), 127.6 (2C), 127.5 (2C), 123.8, 90.6, 77.5, 73.6, 52.2, 42.3, 38.1. IR (KBr) 3214, 2945, 1673, 1591, 1489, 1286, 1067 νmax/cm^{-1}; Mp 86-87 °C; MS (ESI) *m/z* Calcd for $C_{24}H_{18}ClN_3O_4$: 447.0986; Found: 448.1036 $[M+H]^+$.

Methyl 7-(4-iodophenyl)-2-(4-methylpiperazin-1-yl)-4-oxo-5-phenyl-4,5-dihydrofuro[2,3-*d*]pyridazine-3-carboxylate (25).



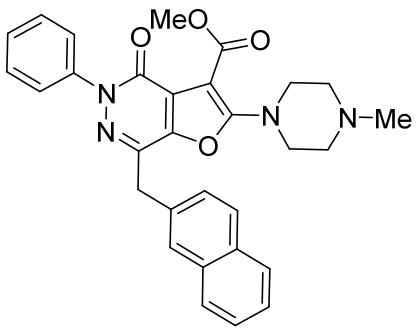
The crude material was purified by column chromatography (dichloromethane/methanol 95:5) to give the product as yellow solid (141 mg, 31% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (br d, AA'XX', 2H), 7.71 (br d, AA'XX', 2H), 7.59 (br d, 2H), 7.50-7.46 (m, 2H), 7.41-7.37 (m, 1H), 3.90 (s, 3H), 3.72-3.69 (m, 4H), 2.66-2.62 (m, 4H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 161.5, 156.7, 143.1, 142.2, 138.0, 133.7, 131.8, 129.1, 128.8, 128.1, 126.4, 123.8, 96.0, 90.2, 54.3 (2C), 52.3, 47.9 (2C), 46.0. IR (KBr) 2939, 2802, 1681, 1575, 1451, 1275, 1072 νmax/cm^{-1}; Mp 236-237 °C; MS (ESI) *m/z* Calcd for $C_{25}H_{23}IN_4O_4$: 570.0764; Found: 571.0777 $[M+H]^+$.

Methyl 2-(4-methylpiperazin-1-yl)-4-oxo-7-(4-phenoxyphenyl)-5-phenyl-4,5-dihydrofuro[2,3-*d*]pyridazine-3-carboxylate (26).



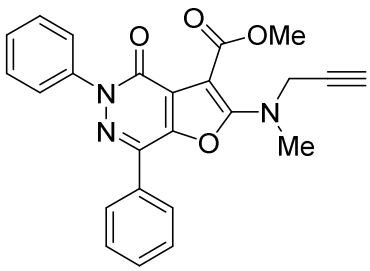
The crude material was purified by column chromatography (dichloromethane/methanol 95:5) to give the product as yellow solid (167 mg, 39% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (br d, AA'XX', 2H), 7.60 (br d, AA'XX', 2H), 7.49-7.45 (m, 2H), 7.39- 7.35 (m, 3H), 7.16 (br t, 1H), 7.09-7.05 (m, 4H), 3.90 (s, 3H), 3.75-3.71 (m, 4H), 2.71-2.66 (m, 4H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 161.3, 158.9, 156.7, 156.4, 143.4, 142.4, 134.1, 129.9 (2C), 129.0 (2C), 128.6 (2C), 127.8, 127.0, 126.3 (2C), 124.0, 123.6, 119.6 (2C), 118.5 (2C),94.1, 54.2 (2C), 52.1, 47.8 (2C), 45.7. IR (KBr) 2945, 2796, 1681, 1585, 1486, 1237, 1155, 1067 νmax/cm^{-1}; Mp 193-194 °C; MS (ESI) *m/z* Calcd for $C_{31}H_{28}N_4O_5$: 536.2060; Found: 537.2079 $[M+H]^+$.

Methyl 2-(4-methylpiperazin-1-yl)-7-(naphthalen-2-ylmethyl)-4-oxo-5-phenyl-4,5-dihydrofuro[2,3-*d*]pyridazine-3-carboxylate (27).



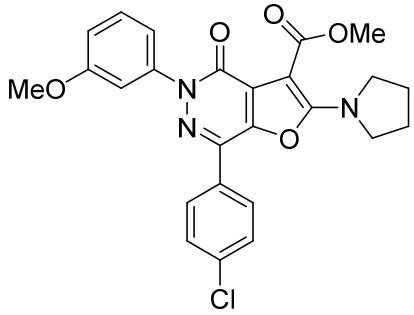
The crude material was purified by column chromatography (dichloromethane/methanol 98:2) to give the product as light yellow solid (89.5 mg, 22% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.58-7.47 (m, 7H), 7.43-7.37 (m, 2H), 4.61 (s, 2H), 3.83 (s, 3H), 3.40-3.38 (m, 4H), 2.41-2.39 (m, 4H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 161.6, 156.9, 144.3, 142.3, 136.0, 134.0, 132.6, 132.1, 128.8 (3C), 128.0, 127.9, 127.6, 126.5 (2C), 126.3, 125.8, 125.2, 124.0, 123.3, 89.5, 54.3 (2C), 52.0, 48.0 (2C), 46.0, 35.1. IR (KBr) 2939, 2796, 1670, 1583, 1448, 1253, 1144, 1061 νmax/cm^{-1}; Mp 202-203 °C; MS (ESI) *m/z* Calcd for $C_{30}H_{28}N_4O_4$: 508.2111; Found: 509.2176 $[M+H]^+$.

Methyl 2-(methyl(prop-2-yn-1-yl)amino)-4-oxo-5,7-diphenyl-4,5-dihydrofuro[2,3-*d*]pyridazine-3-carboxylate (28).



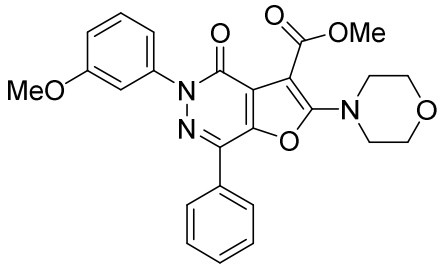
The crude material was purified by column chromatography (*n*-hexane/ EtOAc 7:3) to give the product as yellowish solid (106 mg, 32% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (br d, AA' XX', 2H), 7.62 (br d, AA' XX', 2H), 7.52-7.46 (m, 5H), 7.41-7.37 (m, 1H), 4.37 (br d, 2H), 3.93 (s, 3H), 3.27 (s, 3H), 2.36 (br t, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 161.0, 156.8, 143.6, 142.3, 134.7, 132.2, 129.7, 128.8 (2C), 128.7 (2C), 127.9, 127.5 (2C), 126.4 (2C), 123.7, 90.5, 73.6, 52.4, 42.3 (2C), 38.2. IR (KBr) 3252, 1703, 1668, 1610, 1215, 1070 νmax/cm^{-1}; Mp 146-147 °C; MS (ESI) *m/z* Calcd for $C_{24}H_{19}N_3O_4$: 413.1376; Found: 414.1458 $[M+H]^+$.

Methyl 7-(4-chlorophenyl)-5-(3-methoxyphenyl)-4-oxo-2-(pyrrolidin-1-yl)-4,5-dihydrofuro[2,3-*d*]pyridazine-3-carboxylate (29).



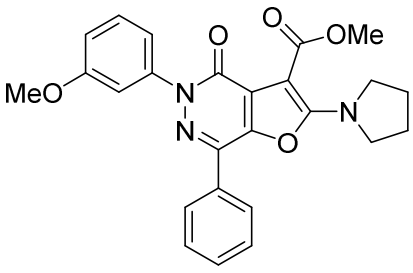
The crude material was purified by column chromatography (PE/EtOAc 7:3) to give the product as yellowish solid (169 mg, 44% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95 (d, AA'XX', *J* = 8.2 Hz, 2H), 7.43 (d, AA'XX', *J* = 8.2 Hz, 2H), 7.40-7.45 (m, 1H), 7.18-7.13 (m, 2H), 6.93 (dd, *J* = 8.2, 2.1 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.67 (br t, 4H), 2.05 (br t , 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 163.7, 160.0, 159.9, 156.9, 143.5, 142.6, 135.6, 133.2, 131.0, 129.5, 129.0, 128.8, 124.4, 119.0, 114.1, 112.4, 86.8, 55.6, 52.1, 49.8, 25.6; IR (KBr) 2952, 2873, 1738, 1683, 1589, 1489, 1271, 1089, 835 νmax/cm^{-1}; Mp 162.2-163.1 °C; MS (ESI) *m/z* Calcd for $C_{25}H_{22}ClN_3O_5$: 479.1248; Found: 480.1327 $[M+H]^+$.

Methyl 5-(3-methoxyphenyl)-2-morpholino-4-oxo-7-phenyl-4,5-dihydrofuro[2,3-*d*]pyridazine-3-carboxylate (30).



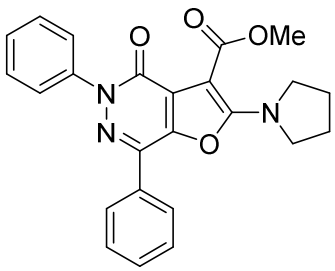
The crude material was purified by column chromatography (PE/EtOAc 6:4) to give the product as white solid (185 mg, 50% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.99 (br d, 2H), 7.47-7.33 (m, 4H), 7.21-7.15 (m, 2H), 6.92 (dd, *J* = 8.1, 2.1 Hz, 1H), 3.91 (s, 3H), 3.82 (s, 3H), 3.66 (br t, 4H), 2.02 (br t, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 163.8, 160.0, 159.9, 156.9, 143.6, 142.9, 134.4, 132.5, 129.5, 129.4, 128.7, 127.5, 124.2, 119.0, 114.0, 112.4, 86.7, 55.5, 52.0, 49.7, 25.5; IR (KBr) 2955, 2877, 1687, 1601, 1580, 1491, 1270, 1087, 767 νmax/cm^{-1}; Mp 194.7-195.8 °C; MS (ESI) *m/z* Calcd for $C_{25}H_{23}N_3O_6$: 461.1587; Found: 462.1664 $[M+H]^+$.

Methyl 5-(3-methoxyphenyl)-4-oxo-7-phenyl-2-(pyrrolidin-1-yl)-4,5-dihydrofuro[2,3-*d*]pyridazine-3-carboxylate (31).



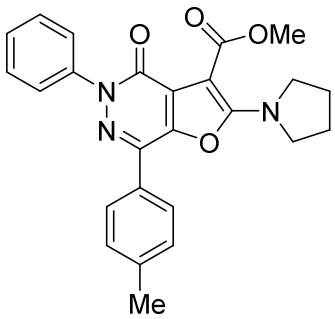
The crude material was purified by column chromatography (PE/EtOAc 6:4) to give the product as white solid (89 mg, 25% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.6 Hz, 2H), 7.48-7.35 (m, 4H), 7.20-7.14 (m, 2H), 6.94 (br d, 1H), 3.91 (s, 3H), 3.89-3.86 (m, 4H), 3.83 (s, 3H), 3.67-3.34 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 163.9, 161.6, 160.0, 156.8, 143.6, 143.5, 134.7, 132.3, 129.8, 129.6, 128.9, 127.6, 123.7, 119.0, 114.2, 112.5, 90.7, 66.4, 55.6, 52.4, 48.4; IR (KBr) 2952, 2857, 1687, 1673, 1577, 1492, 1288, 1070, 1031, 773 νmax/cm^{-1}; Mp 184.2-184.8 °C; MS (ESI) *m/z* Calcd for $C_{25}H_{23}N_3O_5$: 445.1638; Found: 446.1676 $[M+H]^+$.

Methyl 4-oxo-5,7-diphenyl-2-(pyrrolidin-1-yl)-4,5-dihydrofuro[2,3-*d*]pyridazine-3-carboxylate (32).



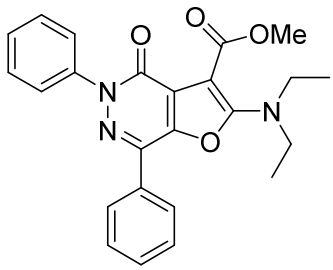
The crude material was purified by column chromatography (PE/EtOAc 7:3) to give the product as white solid (103 mg, 31% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.50-7.42 (m, 5H), 7.39-7.35 (m, 1H), 3.90 (s, 3H), 3.70-3.66 (m, 4H), 2.06-2.02 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 163.9, 160.1, 157.2, 143.0, 142.6, 134.6, 132.6, 129.6, 128.8, 127.9, 127.6, 127.3, 126.6, 124.2, 86.8, 52.1, 49.8, 25.6; IR (KBr) 2972, 2875, 1709, 1670, 1613, 1585, 1496, 1263, 1080, 912, 773 νmax/cm^{-1}; Mp 231.1-231.6 °C; MS (ESI) *m/z* Calcd for $C_{24}H_{21}N_3O_4$: 415.1532; Found: 416.1614 $[M+H]^+$.

Methyl 4-oxo-5-phenyl-2-(pyrrolidin-1-yl)-7-(*p*-tolyl)-4,5-dihydrofuro[2,3-*d*]pyridazine-3- carboxylate (33).



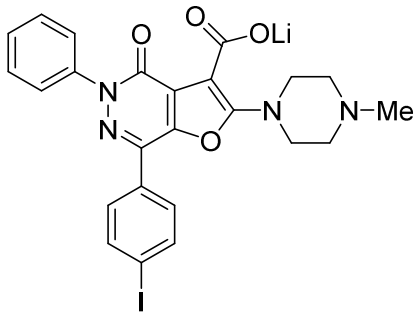
The crude material was purified by column chromatography (PE/EtOAc 7:3) to give the product as white solid (120 mg, 35% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.88 (d, AA'XX', *J* = 8.2 Hz, 2H), 7.63 (d, AA'XX', *J* = 8.2 Hz, 2H), 7.50-7.46 (m, 2H), 7.43-7.33 (m, 1H), 7.27-7.25 (m, 2H), 3.92 (s, 3H), 3.68-3.67 (m, 4H), 2.40 (br s, 3H), 2.05-2.03 (m,4H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 163.8, 160.0, 157.0, 142.9, 142.6, 139.6, 134.5, 129.7, 129.4, 128.6, 127.8, 126.5, 124.1, 86.7, 52.0, 49.6, 25.5, 21.4; IR (KBr) 2968, 2862, 1680, 1565, 1442, 1078, 988 νmax/cm^{-1}; Mp 220.2-220.9 °C; MS (ESI) *m/z* Calcd for $C_{25}H_{23}N_3O_4$: 429.1689; Found: 430.1735 $[M+H]^+$.

Methyl 2-(diethylamino)-4-oxo-5,7-diphenyl-4,5-dihydrofuro[2,3-*d*]pyridazine-3-carboxylate (34).



The crude material was purified by column chromatography (PE/EtOAc 7:3) to give the product as white solid (104 mg, 31% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.8 Hz, 2H), 7.67 (d, *J* = 7.8 Hz, 2H), 7.53-7.39 (m, 6H), 3.96 (s, 3H), 3.65 (q, *J* = 7.0 Hz, 4H), 1.31 (t, *J* = 7.0 Hz, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 164.4, 160.3, 157.1, 142.8, 142.6, 134.6, 132.7, 129.6, 128.8, 128.0, 127.6, 126.6, 124.7, 87.9, 52.5, 45.3, 13.5; IR (KBr) 2865, 1698, 1667, 1611, 1572, 1487, 1315, 891, 801 νmax/cm^{-1}; Mp 225.2-226.1 °C; MS (ESI) *m/z* Calcd for $C_{24}H_{23}N_3O_4$: 417.1689; Found: 418.1769 $[M+H]^+$.

Preparation of: Lithium 7-(4-iodophenyl)-2-(4-methylpiperazin-1-yl)-4-oxo-5-phenyl-4,5-dihydrofuro[2,3-*d*]pyridazine-3-carboxylate (35).



The furo[2,3-*d*]pyridazin-4(5*H*)-one **25** (0.05 mmol, 1 eq.) was dissolved in THF/H_2O 3:1 (0.2M), lithium hydroxide (0.05 mmol, 1 eq.) was added and the rection mixture was stirred at 100 °C overnight. The hydrolysis of the ester function was monitored by TLC (95:5 DCM/MeOH). The conversion as revealed by NMR of the crude reaction mixture was quantitative. ^{1}H-NMR (400 MHz, D_2O-DMSO-d_6) δ 7.86 (br d, AA'XX', 2H), 7.71 (br d, AA'XX', 2H), 7.52-7.37 (m, 5H), 3.51-3.48 (m, 4H), 2.43-2.39 (m, 4H), 2.16 (s, 3H); ^{13}C-NMR (100 MHz, D_2O-DMSO-d_6) δ 167.7, 166.4, 158.6, 158.4, 142.6, 141.9, 138.2 (2C), 134.1, 132.0, 129.8 (2C), 129.1 (2C), 128.4, 126.8 (2C), 124.9, 96.7, 54.2 (2C), 47.2 (2C), 45.9; IR (KBr) 2934, 2780, 17111, 1569, 1489, 1358, 1144, 998 νmax/cm^{-1}; Mp 204-205 °C; MS (ESI) *m/z* Calcd for $C_{24}H_{21}IN_4O_4$: 556.0607; Found: 557.0647 $[M+H]^+$.

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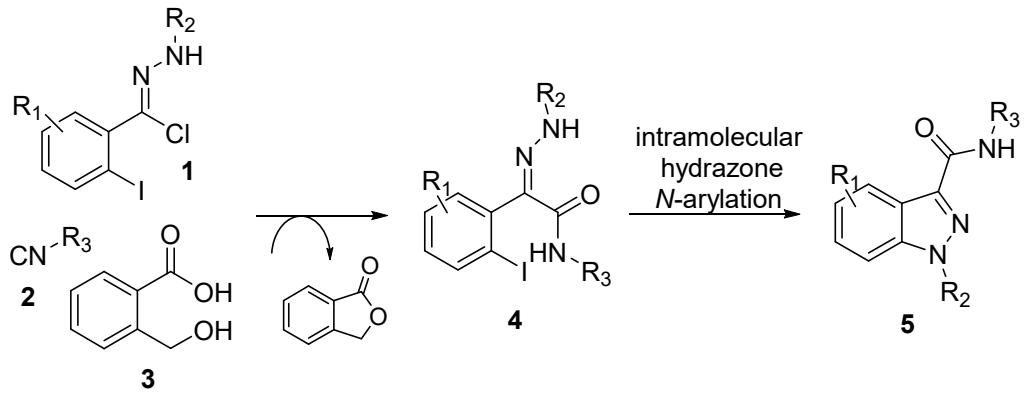
Chapter 12

An efficient synthesis of 1-arylindazole-3-carboxamides using nitrile imines, isocyanides and 2-hydroxymethylbenzoic acid, followed by a chemoselective Buchwald–Hartwig intramolecular cyclization

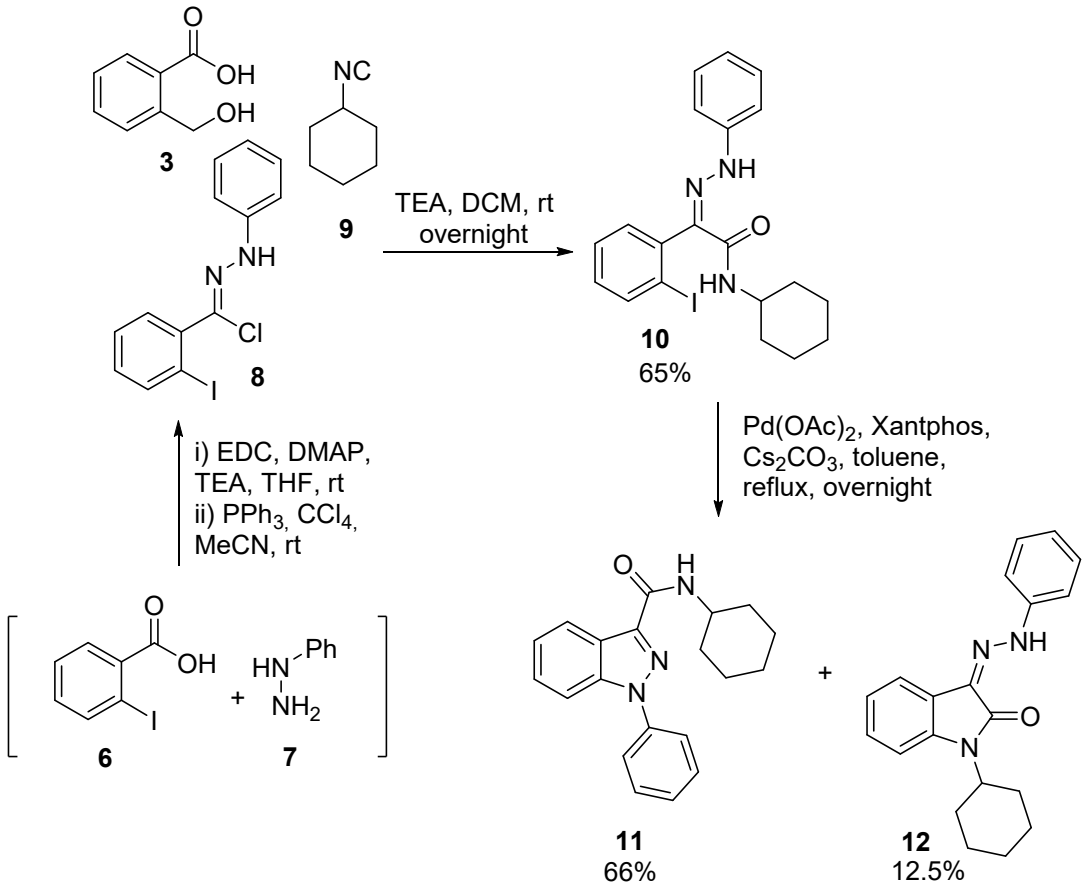
12.1 Results and discussion

Continuing to use the chemistry developed in Chapters 10 and 11, we recognized that *α*-aminocarbonyl hydrazones **1**,[1] thanks to their atom connectivity and the presence of the hydrazone functional group could be exploited in a post-condensation modification using a Buchwald–Hartwing intramolecular amination to generate the substituted indazole ring **5** in two operationally simple reaction steps (Scheme 1).



Scheme 1. General structure of α-aminocarbonyl hydrazones and cyclic indazole derivatives.

In order to test our hypothesis, we reacted 2-iodo-*N'*-phenylbenzohydrazonoyl chloride **8**, cyclohexylisocyanide **9** and 2-hydroxymethylbenzoic acid ("sacrificial acid") **3** in DCM at room temperature overnight to obtain *α*-aminocarbonyl hydrazone **10** in 65%. The multicomponent reaction is triggered by the *in situ* generation of nitrile imine by a base-induced dehydrochlorination of hydrazonoyl chloride. The 2-hydroxymethylbenzoic acid behaves like a pseudo water molecule in order to overpass the poor reactivity of water on the nitrilium ion.[2] Subsequently, this linear intermediate was then reacted in classic Buchwald-Hartwing conditions to evaluate indazole **11** formation (Scheme 2).



Scheme 2. 3-CR affording α-aminocarbonyl hydrazones and test reaction for the formation of indazole derivatives.

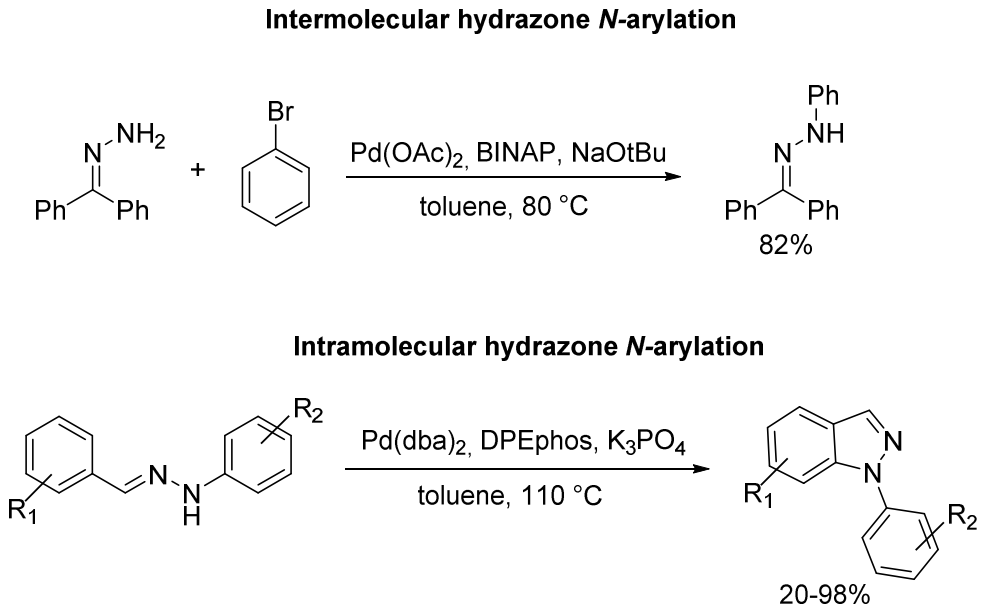
It is important to highlight that *a priori* both the hydrazone and the amide function could cyclize to give either the indazole or the indolone derivatives,[3] both being at a suitable distance (5 centers) from the aromatic iodine atom of intermediate **10**. Refluxing **10** in toluene, and in the presence of palladium acetate, Xantphos and cesium carbonate gave indeed the desired indazole **11** in 66% yield (Entry 1, Table 1), and 12.5 % of indolone derivative **12** coming from intramolecular amidation.

Entry	Solvent	Catalyst	Ligand	Yield of 11 (yield of 12)
1	Toluene	$Pd(OAc)_2$	Xantphos	66% (12,5%)
2	Toluene	$Pd(dppf)Cl_2$	Xantphos	48% (4%)
3	Toluene	CuI	*N,N'*-dimehtylethylene diamine	22% (10%)
4	Toluene	$Pd(dppf)Cl_2$	XPhos	38% (20%)
5	Toluene	$Pd(PPh_3)_2Cl_2$	Tri-o-tolyl-phosphine	78% (traces)
6	1,4-dioxan	$Pd(PPh_3)_2Cl_2$	Tri-o-tolyl-phosphine	97% (traces)

Table 1. Optimization of indazole cyclization conditions.

In order to optimize indazole formation we screened different palladium sources (Entries 2, 4-6), ligands (Entries 3-6), and solvents (Entry 6), and we also tried copper catalyst in place of palladium (Entry 3). With palladium catalysts (Entries 1, 2 and 4–6) 1 equivalent of cesium carbonate was used as base. With our satisfaction, we were able to obtain indazole **12** in 97% yields, which means a highly regioselective formation of indazole derivatives over indolone one, when intermediate **10** was refluxed in 1,4-dioxan in the presence of tri-*o*-tolylphosphine (0.1 equiv.), cesium carbonate (1 equiv.) and bis(triphenylphosphine)palladium(II) dichloride (0.07 equiv.).

Despite the reported examples of both intermolecular[4] and intramolecular[5] hydrazone *N*-arylation (Scheme 3), to our knowledge this is the first example of a regioselective hydrazone palladium catalyzed cyclization in the presence of an amide bond.



Scheme 3. Examples of inter- and intra-molecular hydrazine *N*-arylation reported in literature.

To evaluate the scope of this cyclization, we synthesized five different hydrazonoyl chlorides (**8, 13-16**) and we selected six isocyanides (**9, 17-21**) as starting inputs (Figure 1).

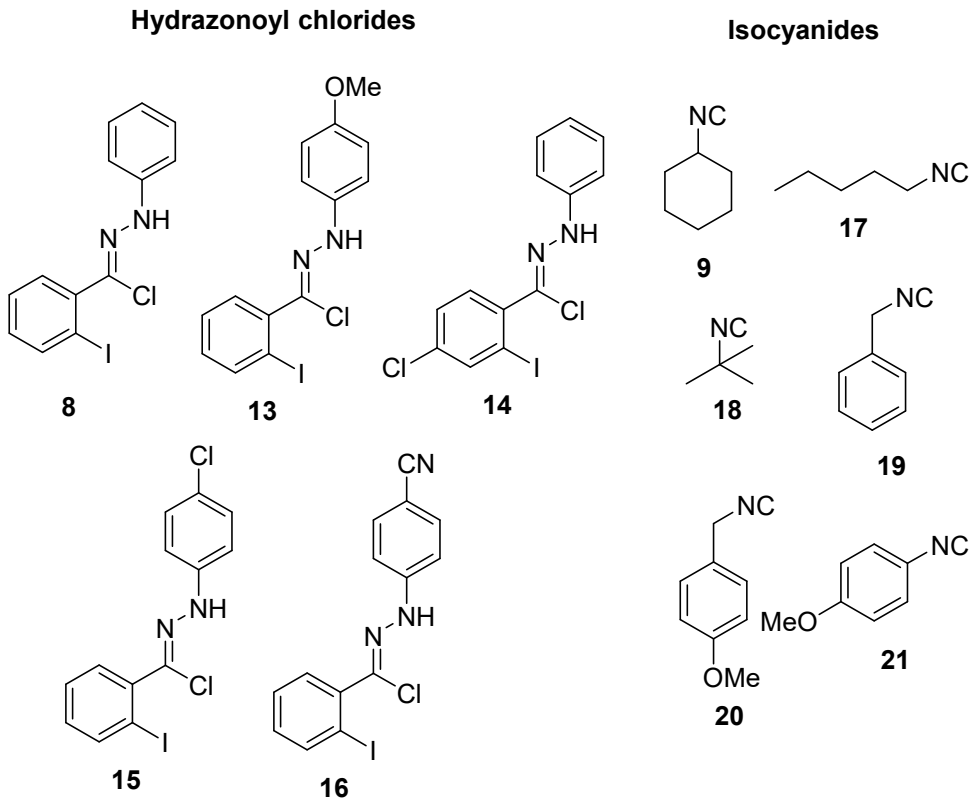


Figure 1. Starting materials for the synthesis of α-aminocarbonyl hydrazones.

A library of *α*-aminocarbonyl hydrazones (31-74% yields) was obtained (Figure 2). Aliphatic hydrazonoyl chlorides are much less stable than aromatic ones and did not react successfully in this reaction (poor yield, byproducts formation and difficult purification procedure).

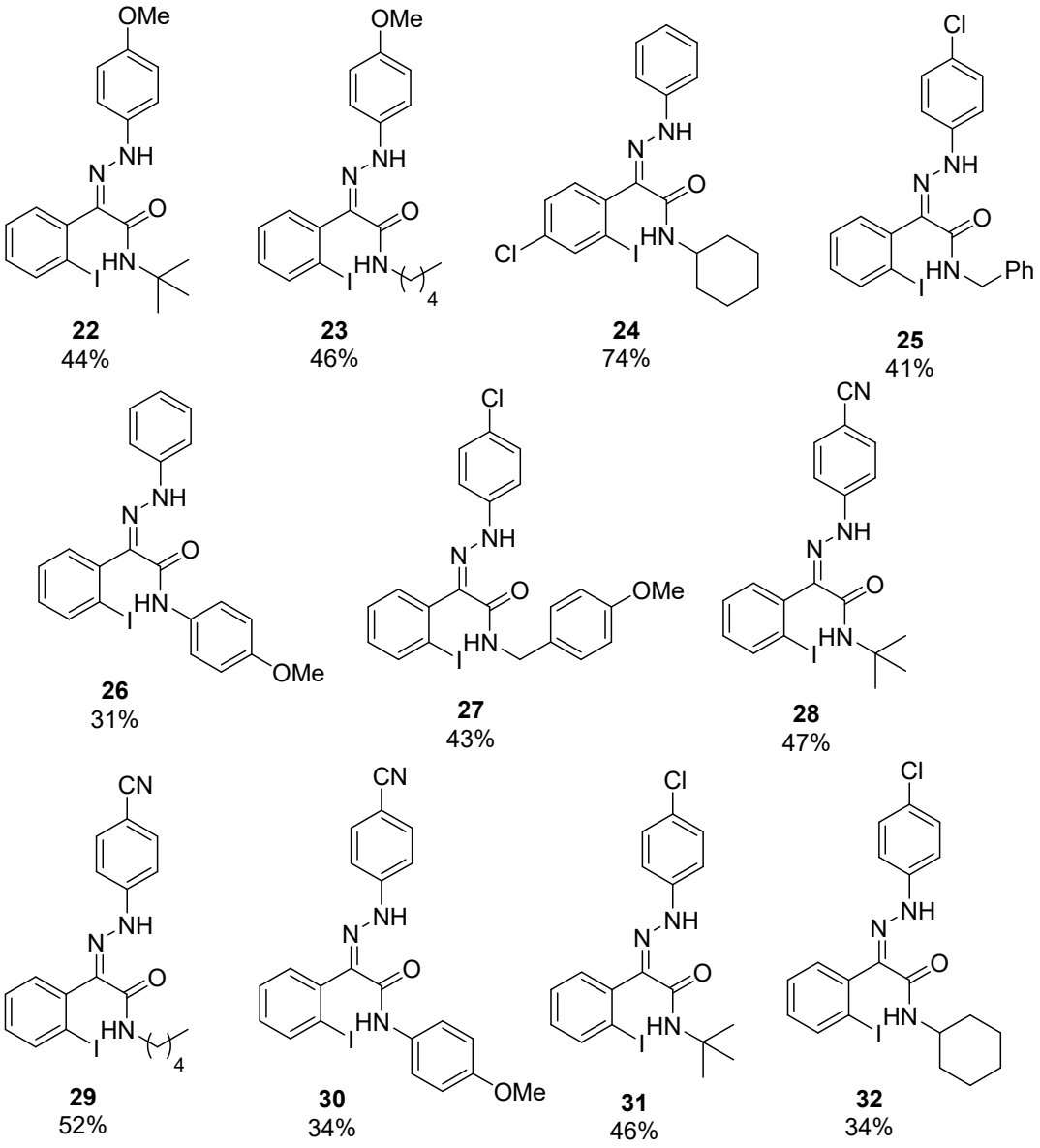


Figure 2. Synthesized library of linear *α*-aminocarbonyl hydrazones.

We then reacted the intermediate hydrazones using the optimized conditions to get eleven different substituted 1-arylindazole-3-carboxamides in excellent yields (48-98%) (Figure 3).

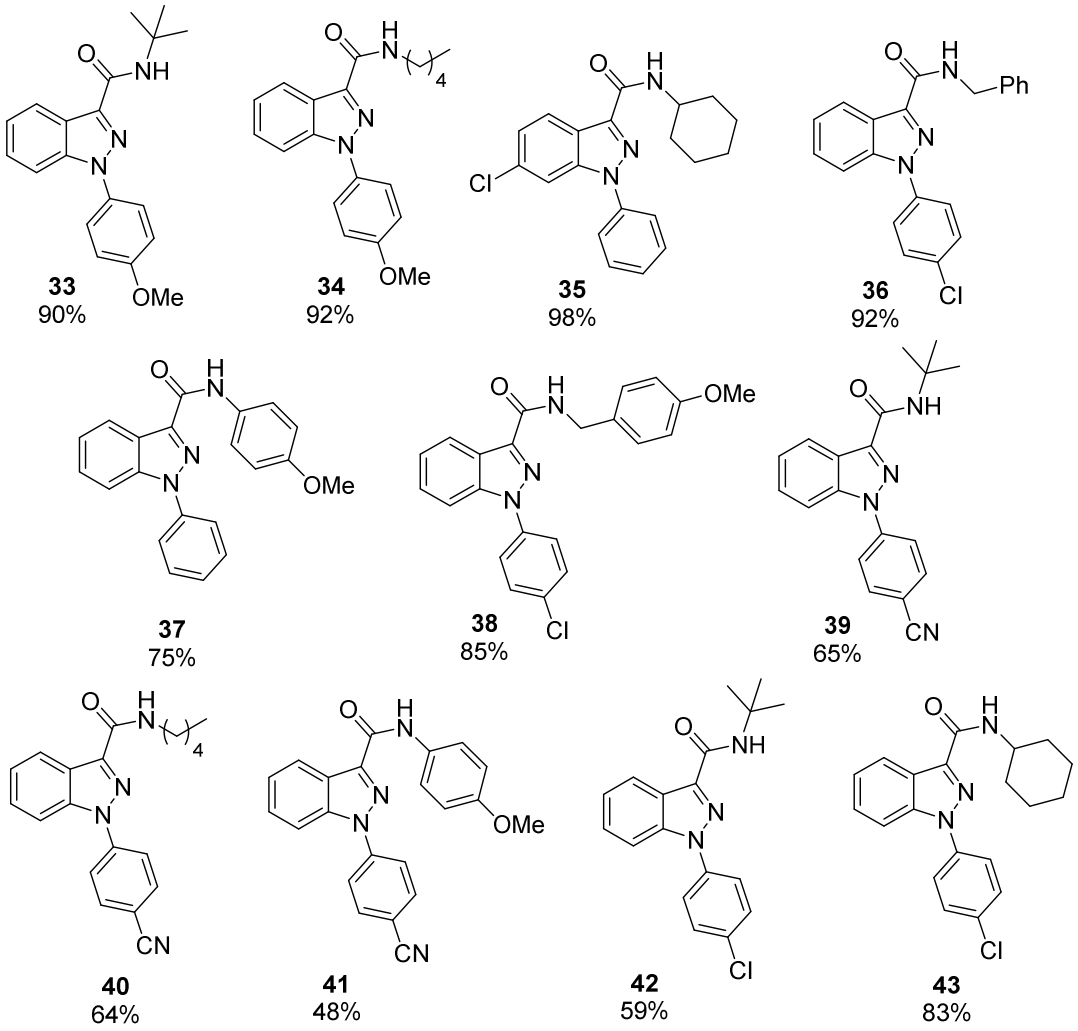
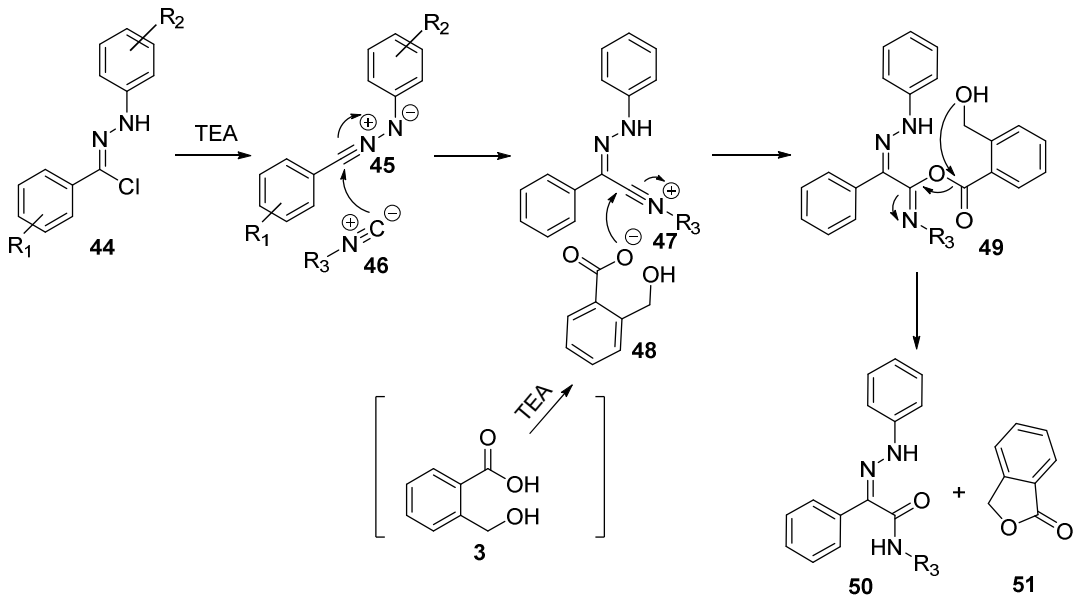


Figure 3. Synthesized library of indazole cyclic derivatives.

The reaction proved to be quite general in scope as the presence of both aliphatic (**33-36**, **38-40**, **42** and **43**) and aromatic (**37, 41**) carboxamides gave good yields. Only electron-withdrawing nitrile group on the hydrazone aromatic ring in derivatives **39, 40** and **41** showed to decrease yields to 65, 64 and 48%, respectively (Figure 3).

A working hypothesis for the formation of hydrazone derivatives is depicted in Scheme 4. The hydrazonoyl chlorides **44** readily form the nitrilimine, which is the active 1,3-dipolar species and is attacked by the isocyanide carbon atom to form a nitrilium ion. The latter is then attacked by the carboxylate function of sacrificial acid **3** to give an unstable imidate: the hydroxy-function cyclize into the C=O carbonyl to give the *N*-arylhydrazono-acetamides **50** and phthalide. In this reaction sacrificial acid **3** enables to overcome the poor nucleophilicity of water towards the nitrilium ion. **3** behaves indeed like a pseudo water molecule, as it traps the nitrilium ion and then undergoes an intramolecular cyclization to deliver one oxygen atom to the product, as water would, and the aromatic lactone phthalide.

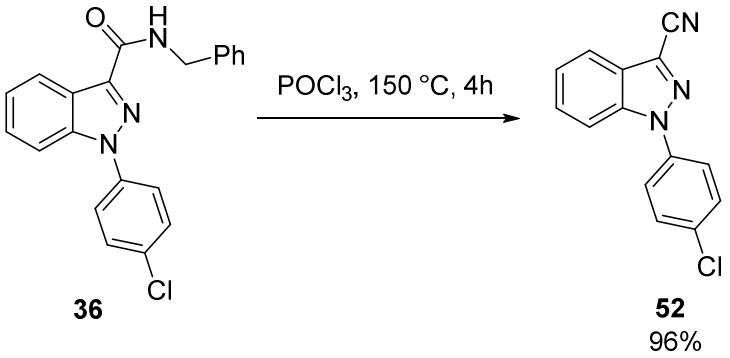


Scheme 4. Proposed mechanism for the synthesis of hydrazono-acetamide derivate **50**.

In order to further expand the scope of the reaction we tried a direct conversion of *N*-arylindazole-3-carboxamides to *N*-arylindazole-3-carbonitriles. The synthesis of such derivatives is usually accomplished in two or more synthetic steps, with overall yields of 26 to 44% and the use of harsh reaction conditions, with Zn- or Cu-containing waste[6,7] or promoted by tri-*n*-butyltin chloride and palladium.[8,9] An alternative two-step route, based on a primary amide formation and subsequent

dehydration to nitrile (overall yield 63%) has been reported for the synthesis of p38 kinase inhibitors.[10] Dealing with their biological activities, *N*-arylindazole-3-carbonitrile derivatives have been described also as xanthine oxidase inhibitors[6,7] and as low nanomolar bradykinin receptor antagonists.[8,9] We speculated indeed that a one-step conversion of the reported *N*-arylindazole-3-carboxamides to *N*-arylindazole-3-carbonitrile could be useful to further enlarge the size and the variability of the synthesizable libraries. So, reacting *N*-arylindazole-3-carboxamide **36** in $POCl_3$ at 150 °C in a sealed tube for 4h we were able to get *N*-arylindazole-3-carbonitrile **52** in 96% yield (Scheme 5).

To our knowledge, this transformation accounts for the first application of benzylisocyanide as a convertible isocyanide.



36 **52** 96%

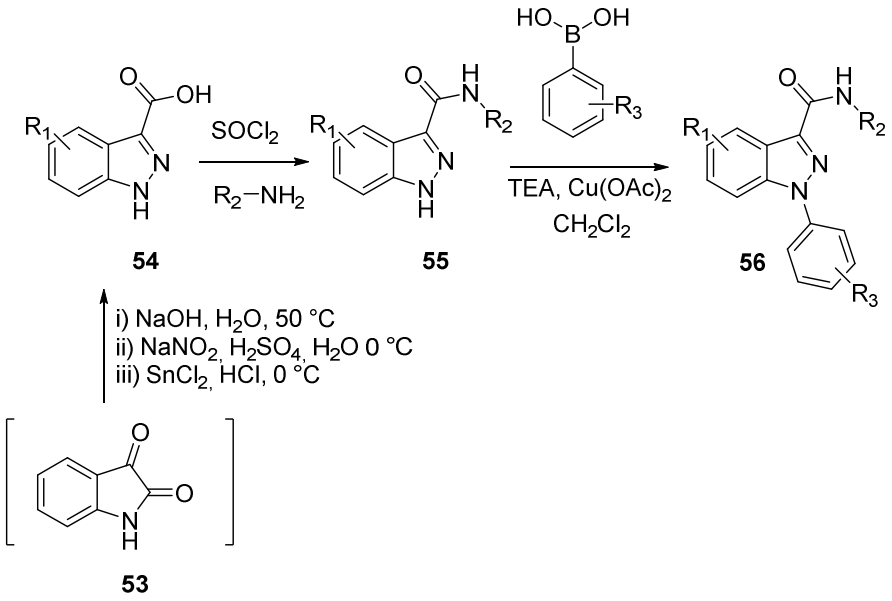
Scheme 5. Conversion of *N*-arylindazole-3-carboxamides to *N*-arylindazole-3-carbonitriles.

12.2 Conclusions

In conclusion we developed a novel, concise two-step synthesis for the construction of 1-aryl-indazoles-3-carboxamides performing a three component reaction between isocyanides, 2-iodo-*N*-arylbenzohydrazonoyl chlorides and 2-hydroxymethylbenzoic and a Buchwald-Hartwig cyclization.

A regioselective intramolecular hydrazone palladium catalyzed cyclization in the presence of aliphatic amide functional groups was reported for the first time with high yields and broad substrate scope. Furthermore benzyl-isocyanide was unconventionally employed as a convertible isocyanide for the synthesis of biologically interesting *N*-arylindazole-3-carbonitriles.

It is important highlight that the classic methods of preparations reported in literature depend on the pattern of substitution of the indazole ring.[5,11–14] In particular 1-arylindazole-3-carboxamides **56** are prepared starting from the corresponding 1*H*-indazole-carboxylic acids **54** which are coupled with amines and then subjected to a Pd or Cu *N*-arylation. One disadvantage of this synthetic plan is that aryl substituted 1*H*-indazole-carboxylic acids require a multistep synthesis with poor overall efficiency (Scheme 6).[15,16] Our novel strategy provides an additional indazole synthesis to those already reported in literature both in the type of substrate as well as the substitution pattern obtainable in the products.



Scheme 6. Conventional synthesis of *N*-arylindazoles-3-carboxamides.

12.3 Experimental section

General Method. Commercially available reagents and solvents were used without further purification. Dichloromethane was dried by distillation from P_2O_5 and stored over activated molecular sieves (4 Å). When necessary the reactions were performed in oven-dried glassware under a positive pressure of dry nitrogen. Melting points were determined in open glass capillaries and are uncorrected. All the compounds were characterized by IR. ^{1}H and ^{13}C APT NMR were recorded on a 400 MHz. High-resolution ESI-MS spectra were performed on a Thermo LTQ Orbitrap XL mass spectrometer. The spectra were recorded by infusion into the ESI source using MeOH as the solvent. Chemical shifts (d) are reported in part per million (ppm) relative to the residual solvent peak. Column chromatography was performed on silica gel (70–230 mesh ASTM) using the reported eluents. Thin layer chromatography (TLC) was carried out on 5 x 20 cm plates with a layer thickness of 0.25 mm (silica gel 60 F_{254}). When necessary they were developed with $KMnO_4$.

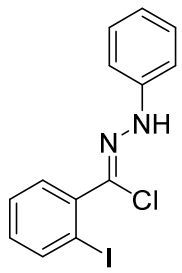
General preparation of hydrazonoyl chlorides (8, 13-16).[11a]

The hydrazonoyl chlorides were readily synthesized in two steps:

***Preparation of acylhydrazines*.** To a stirred solution of 2- iodobenzoic acids on a 5 mmol scale in THF (0.2 M, 10 mL) were added EDC HCl (1.05 g, 5.50 mmol, 1.1 eq.), DMAP (0.12 g, 1 mmol, 0.2 eq.), triethylamine (1.40 mL, 10 mmol, 2 eq.) and hydrazine (5 mmol, 1 eq.) at 0 °C. The resulting mixture was allowed to warm to room temperature over 24 h. The crude reaction mixture was washed with HCl 1 M sol. (x2), sat. $NaHCO_3$ (x2) and brine (x1), evaporated to dryness and used in the next step without further purification.

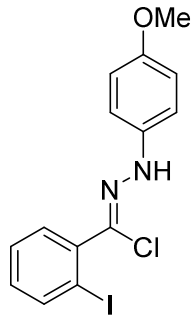
Preparation of hydrazonoyl chlorides. The corresponding acylhydrazine (2.50 mmol) was dissolved in CH_3CN (0.5 M, 5 mL) and triphenylphosphine (0.79 g, 3 mmol, 1.2 eq.) and carbon tetrachloride (0.29 mL, 3 mmol, 1.2 eq.) were added. The reaction was stirred at room temperature until all the acylhydrazine was consumed as *J*udged by TLC (typically 8–12 hours). The reaction was concentrated under reduced pressure and purified by column chromatography (*n*-hexane/EtOAc) and stored below 0 °C.

(*Z*)-2-Iodo-*N'*-phenylbenzohydrazonoyl chloride (8).



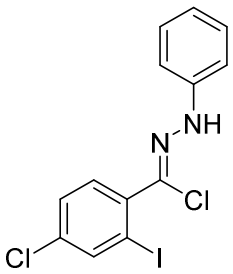
The crude material was purified by column chromatography (*n*-hexane/EtOAc 30:1) to give the product as a white solid (0.41 g, 46% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (br s, NH), 8.05 (d, *J* = 7.8 Hz, 1H), 7.64 (br d, 1H), 7.48–7.41 (m, 3H), 7.35–7.33 (m, 2H), 7.14–7.07 (m, 2H). 13C NMR (100 MHz, $CDCl_3$) δ 143.3, 140.5, 139.9, 130.9, 130.7, 129.6, 128.3, 123.0, 121.6, 113.7, 96.8.

***(Z)*-2-Iodo-*N'*-(4-methoxyphenyl)benzohydrazonoyl chloride (13).**



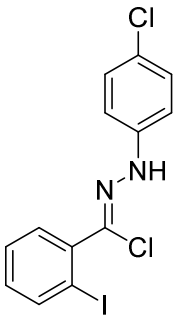
The crude material was purified by column chromatography (*n*-hexane/EtOAc 30:1) to give the product as a yellowish solid (0.43 g, 44% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.9 Hz, 1H), 7.90 (br s, NH), 7.54 (d, *J* = 7.7 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 8.8 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.9 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 154.7, 140.5, 139.9, 137.2, 130.8, 130.5, 128.2, 122.0, 114.8 (4C), 96.6, 55.7.

(*Z*)-4-Chloro-2-iodo-*N'*-phenylbenzohydrazonoyl chloride (14).



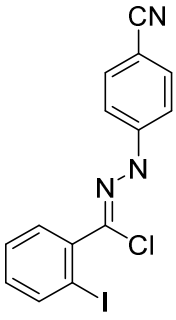
The crude material was purified by column chromatography (*n*-hexane/EtOAc 30:1) to give the product as a light yellow solid (0.69 g, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, NH), 7.97 (s, 1H), 7.47 (br d, 1H), 7.39 (br d, AA'XX', 1H), 7.33–7.29 (m, 2H), 7.22–7.20 (m, 2H), 6.96 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 139.8, 138.2, 135.5, 131.2, 129.4, 128.4, 121.6, 121.5, 113.5, 96.3.

(*Z*)-*N'*-(4-Chlorophenyl)-2-iodobenzohydrazonoyl chloride (15).



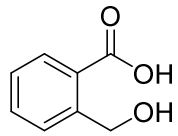
The crude material was purified by column chromatography (*n*-hexane/EtOAc 30:1) to give the product as a light yellow solid (0.33 g, 34% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (br s, NH), 7.71 (br d, AA'XX', 2H), 7.41 (br t, 1H), 7.26 (br d, AA'XX', 2H), 7.15 (br d, AA'XX', 2H), 7.08 (br t, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 140.4, 139.6, 130.8, 130.7, 129.3, 128.2, 126.1, 123.7, 114.8, 96.5.

(*Z*)-*N'*-(4-Cyanophenyl)-2-iodobenzohydrazonoyl chloride (16).



The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as a light orange solid (0.84 g, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (br s, NH), 7.98 (br d, 1H), 7.65 (br d, AA'XX', 2H), 7.59 (br d, 1H), 7.49 (br t, 1H), 7.40 (br d, AA'XX', 2H), 7.19 (br t, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 140.3, 140.2, 134.0, 131.8, 131.0, 129.0, 125.0, 120.0, 114.2, 102.2, 97.5.

Synthesis of 2-hydroxymethyl benzoic acid (3)

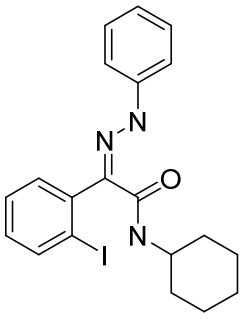


To a solution of NaOH (4.5 g, 111.9 mmol, 1.5 eq) in H_2O (100 ml), phtalide (10 g, 74.6 mmol, 1eq) was added and the mixture was refluxed for 3 h. The solution was let to reach room tempereture, and then HCl conc. was added. A white solid precipitate was formed, which was purified by filtration (90%). ^{1}H-NMR (300 MHz, CD_3OD) δ 7.96 (d, *J* = 6.6 Hz, 1H), 7.63 (d, *J* =7.9 Hz, 1H), 7.53 (t, *J* =7.7 Hz, 1H), 7.33 (t, *J* = 7.1 Hz, 1H), 4.92 (s, 2H); ^{13}C-NMR (75 MHz, CD_3OD) δ 169.5, 143.3, 132.2, 130.7, 128.6, 127.6, 126.8, 62.6; MS (ESI) *m/z* 153.4 $(M+H)^+$.

General preparation of a-aminocarbonylhydrazones (10, 22-32).

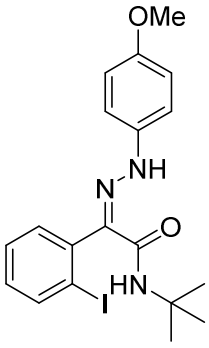
The hydrazonoyl chloride (0.5 mmol, 1 eq.), the isocyanide (0.5 mmol, 1 eq.), 2-hydroxymethylbenzoic acid (0.5 mmol, 1 eq.) and TEA (1 mmol, 2 eq.) were one-pot mixed in DCM (0.5 M, 1 mL) and stirred at room temperature under a nitrogen atmosphere overnight. After evaporation of the solvent, the crude material was purified by column chromatography.

(Z)-N-Cyclohexyl-2-(2-iodophenyl)-2-(2-phenylhydrazono)acetamide (10).



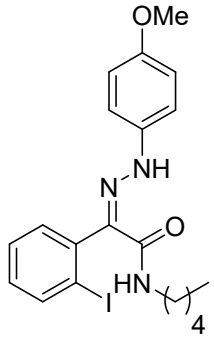
The crude material was purified by column chromatography (*n*-hexane/EtOAc 30:1) to give the product as yellow solid (0.15 g, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.25 (br s, NH), 7.93 (br d, 1H), 7.46–7.45 (m, 2H), 7.29–7.10 (m, 5H), 6.93 (br t, 1H), 5.17 (br d, NH), 3.89–3.82 (m, 1H), 1.94–1.92 (m, 2H), 1.68–1.58 (m, 3H), 1.42–1.33 (m, 2H), 1.16–1.04 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 143.5, 140.7, 140.0, 132.8, 131.8, 130.4, 129.2, 128.9, 121.7, 113.8, 100.6, 48.2, 32.7, 25.4, 24.8. IR (KBr) 3390, 2923, 2846, 1632, 1497, 1171, 760 ν_{max}/cm^{-1}; mp 121.1–122.3 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{20}H_{23}IN_3O$: 448.0886; found: 448.0895 (100%) $[M+H]^+$.

(*Z*)-*N*-(tert-Butyl)-2-(2-iodophenyl)-2-(2-(4-methoxyphenyl)-hydrazono)acetamide (22).



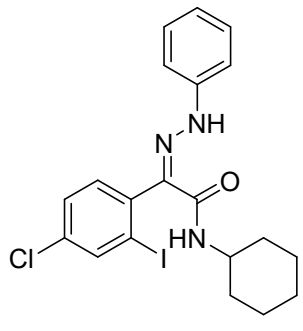
The crude material was purified by column chromatography (*n*-hexane/EtOAc 30:1) to give the product as sticky reddish solid (0.10 g, 44% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.20 (bs, NH), 7.92 (d, *J* = 7.9 Hz, 1H), 7.45–7.44 (m, 2H), 7.14 (br d, AA'XX', 2H), 7.12–7.07 (m, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 5.05 (br s, NH), 3.76 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 154.9, 141.2, 139.6, 137.6, 132.3, 131.8, 130.1, 128.9, 115.0, 114.6, 100.7, 55.6, 51.6, 28.6. IR (KBr) 3406, 2956, 1635, 1530, 1500, 1229, 1157 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{19}H_{23}IN_3O_2$: 452.0835; found: 452.0774 (100%) $[M+H]^+$.

(*Z*)-2-(2-Iodophenyl)-2-(2-(4-methoxyphenyl)hydrazono)-*N*-pentylacetamide (23).



The crude material was purified by column chromatography (*n*-hexane/EtOAc 95:5) to give the product as reddish oil (0.11 g, 46% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.19 (br s, NH), 7.94 (d, *J* = 7.9 Hz, 1H), 7.47–7.42 (m, 2H), 7.13 (br d, AA'XX', 2H), 7.11–7.08 (m, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 5.27 (br t, NH), 3.76 (s, 3H), 3.26 (q, *J* = 6.5 Hz, 2H), 1.53–1.46 (m, 2H), 1.33–1.25 (m, 4H), 0.89–0.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 155.0, 140.9, 140.0, 139.7, 137.5, 131.7, 130.2, 128.8, 115.0 (2C), 114.6 (2C), 101.0, 55.6, 39.2, 29.1, 29.0, 22.3, 14.0. IR (KBr) 3417, 2950, 2923, 1635, 1506, 1220, 1168, 823 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{20}H_{25}IN_3O_2$: 466.0991; found: 466.0956 (100%) $[M+H]^+$.

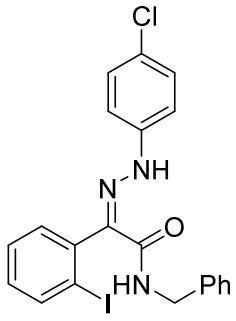
(*Z*)-2-(4-Chloro-2-iodophenyl)-*N*-cyclohexyl-2-(2-phenylhydrazono) acetamide (24).



The crude material was purified by column chromatography (*n*-hexane/EtOAc 30 : 1) to give the product as yellow solid (0.18 g, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.20 (br s, NH), 7.45 (br d, AA'XX', 1H), 7.37 (br d, AA'XX', 1H), 7.28–7.24 (m, 2H), 7.17 (br d, AA'XX', 2H), 6.94 (br t, 1H), 5.07 (br d, NH), 3.88–3.80 (m, 1H), 1.95–1.92 (m, 2H), 1.69–1.59 (m, 3H), 1.42–1.32 (m, 2H), 1.17–1.06 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 143.3, 139.4, 139.0, 135.2, 132.3, 131.5, 129.2, 129.1, 122.0, 113.9, 100.6, 48.2, 32.8, 25.4, 24.8. IR (KBr) 3395, 2928, 2851, 1635, 1495, 1245, 1168, 990, 740

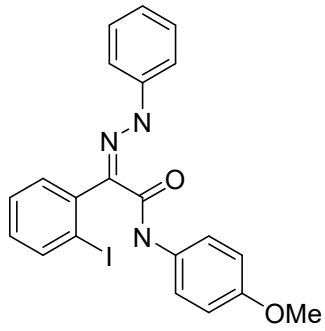
ν_{max}/cm^{-1}; mp 132.6–133.2 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for C_{20}-$H_{22}ClIN_3O$: 482.0496; found: 482.0482 (100%) $[M+H]^+$.

(*Z*)-*N*-Benzyl-2-(2-(4-chlorophenyl)hydrazono)-2-(2-iodophenyl)-acetamide (25).



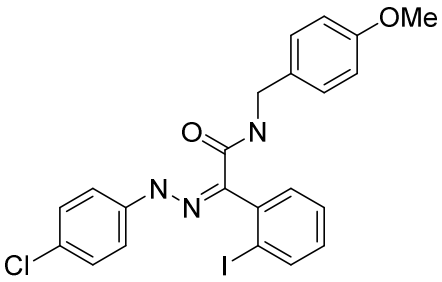
The crude material was purified by column chromatography (*n*-hexane/EtOAc 99:1) to give the product as yellowish solid (0.10 g, 41% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.24 (br s, NH), 7.92 (br d, 1H), 7.45–7.10 (m, 12H), 5.63 (br s, NH), 4.50 (d, *J* = 5.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 142.15, 140.4, 139.8, 137.3, 132.9, 131.5, 130.5, 129.2, 128.9, 128.7, 126.7, 115.2, 100.6, 43.3. IR (KBr) 3390, 1629, 1533, 1495, 1160, 823, 754 ν_{max}/cm^{-1}; mp 110.4–111.7 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{21}H_{18}ClIN_3O$: 490.0183; found: 490.0152 (100%) $[M+H]^+$.

(*Z*)-2-(2-Iodophenyl)-*N*-(4-methoxyphenyl)-2-(2-phenylhydrazono)acetamide (26).



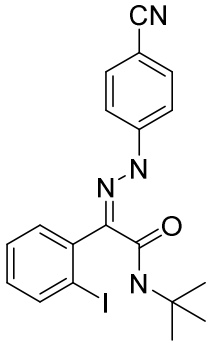
The crude material was purified by column chromatography (*n*-hexane/EtOAc 95:5) to give the product as yellow solid (0.07 g, 31% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.22 (br s, NH), 7.99 (br d, 1H), 7.57–7.50 (m, 2H), 7.34–7.15 (m, 7H), 6.96 (br t, 1H), 6.88 (br d, AA'XX', 2H), 6.83 (br s, NH), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 157.2, 143.4, 140.5, 139.9, 132.4, 132.0, 130.6, 129.5, 129.1, 123.1, 122.2, 114.3, 114.1, 100.9, 55.5. IR (KBr) 3351, 1601, 1506, 1484, 1234, 1146, 998 ν_{max}/cm^{-1}; mp 119.3–120.6 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{21}H_{19}IN_3O_2$: 472.0522; found: 472.0556 (100%) $[M+H]^+$.

(*Z*)-2-(2-(4-Chlorophenyl)hydrazono)-2-(2-iodophenyl)-*N*-(4-methoxybenzyl)acetamide (27).



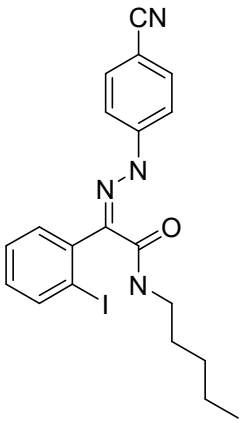
The crude material was purified by column chromatography (*n*-hexane/EtOAc 99:1) to give the product as white solid (0.11 g, 43% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.24 (br s, NH), 7.91 (br d, 1H), 7.44–7.42 (m, 2H), 7.23–7.10 (m, 7H), 6.85 (br d, AA'XX', 2H), 5.60–5.57 (m, 1H), 4.42 (br d, 2H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 159.1, 142.1, 140.3, 139.8, 132.9, 131.6, 130.5, 129.3, 129.2, 129.1, 128.9, 126.6, 115.1, 114.1, 100.6, 55.3, 42.8. IR (KBr) 3324, 3208, 1626, 1517, 1489, 1242, 1160, 1004, 825 ν_{max}/cm^{-1}; mp 143.3–144.4 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{22}H_{20}ClIN_3O_2$: 520.0289; found: 520.0292 (100%) $[M+H]^+$.

(*Z*)-*N*-(tert-Butyl)-2-(2-(4-cyanophenyl)hydrazono)-2-(2-iodophenyl)acetamide (28).



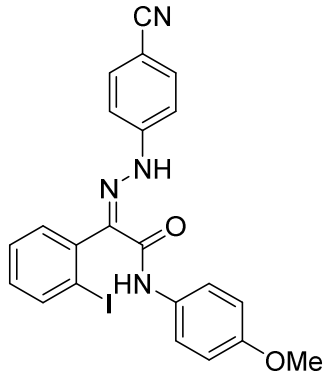
The crude material was purified by column chromatography (*n*-hexane/EtOAc 95:5) to give the product as white solid (0.11 g, 47% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.45 (br s, NH), 7.94 (br d, 1H), 7.53–7.41 (m, 4H), 7.21–7.16 (m, 3H), 5.18 (br s, NH), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 147.0, 140.2, 139.7, 136.7, 133.5, 131.5, 130.8, 129.0, 119.7, 113.8, 103.5, 99.6, 52.1, 28.4. IR (KBr) 3390, 3164, 2961, 2214, 1637, 1508, 1149, 990 ν_{max}/cm^{-1}; mp 167.8– 168.8 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{19}H_{20}IN_4O$: 447.0682; found: 447.0646 (100%) $[M+H]^+$.

(*Z*)-2-(2-(4-Cyanophenyl)hydrazono)-2-(2-iodophenyl)-*N*-pentylacetamide (29).



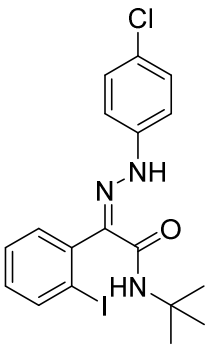
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as yellowish solid (0.12 g, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.43 (br s, NH), 7.96 (br d, 1H), 7.54–7.41 (m, 4H), 7.22–7.15 (m, 3H), 5.42 (br s, NH), 3.30–3.25 (m, 1H), 1.55–1.48 (m, 2H), 1.33–1.25 (m, 4H), 0.88 (br t, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 146.9, 139.9, 139.8, 135.9, 133.6, 131.4, 130.8, 129.0, 119.7, 113.9, 103.8, 99.9, 39.5, 29.1, 28.8, 22.3, 13.9. IR (KBr) 3329, 2923, 2214, 1646, 1508, 1149, 828 ν_{max}/cm^{-1}; mp 91.0–92.4 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{20}H_{22}IN_4O$: 461.0838; found: 461.0852 (100%) $[M+H]^+$.

(*Z*)-2-(2-(4-Cyanophenyl)hydrazono)-2-(2-iodophenyl)-*N*-(4-methoxyphenyl)acetamide (30).



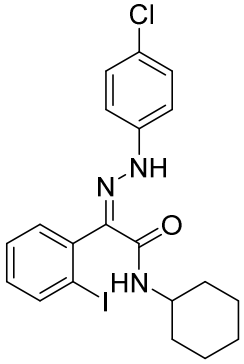
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as reddish solid (0.08 g, 34% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.40 (br s, NH), 8.00 (br d, 1H), 7.56–7.54 (m, 5H), 7.34–7.21 (m, 4H), 6.92 (br s, NH), 6.89 (br s, AA'XX', 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 157.6, 146.7, 140.0, 139.7, 135.7, 133.6, 131.8, 131.1, 129.2, 128.9, 123.1, 119.6, 114.3, 114.1, 104.2, 100.0, 55.5. IR (KBr) 3395, 2208, 1607, 1506, 1229, 1141, 825 ν_{max}/cm^{-1}; mp 111.2–112.3 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{22}H_{18}IN_4O_2$: 497.0474; found: 497.0482 (100%) $[M+H]^+$.

(*Z*)-*N*-(tert-Butyl)-2-(2-(4-chlorophenyl)hydrazono)-2-(2-iodophenyl)acetamide (31).



The crude material was purified by column chromatography (*n*-hexane/EtOAc 97:3) to give the product as yellow solid (0.11 g, 46% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.26 (br s, NH), 7.93 (br d, 1H), 7.46–7.42 (m, 2H), 7.22–7.10 (m, 5H), 5.11 (br s, NH), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 142.3, 140.8, 139.7, 134.0, 131.7, 130.4, 129.1, 128.9, 126.2, 114.9, 100.2, 51.8, 28.5. IR (KBr) 3406, 2956, 1643, 1489, 1231, 1157, 987, 823 ν_{max}/cm^{-1}; mp 139.4–140.6 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{18}H_{20}ClIN_3O$: 456.0340; found: 456.0304 (100%) $[M+H]^+$.

(*Z*)-2-(2-(4-Chlorophenyl)hydrazono)-*N*-cyclohexyl-2-(2-iodophenyl)acetamide (32).

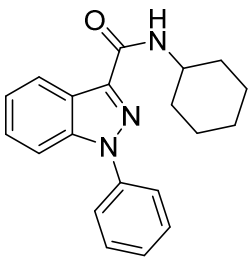


The crude material was purified by column chromatography (*n*-hexane/EtOAc 97:3) to give the product as orange solid (0.08 g, 34% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.25 (br s, NH), 7.93 (br d, 1H), 7.46–7.41 (m, 2H), 7.20 (br d, AA'XX', 2H), 7.14–7.09 (m, 4H), 5.16 (br d, NH), 3.87–3.79 (m, 1H), 1.92–1.89 (m, 2H), 1.67–1.63 (m, 3H), 1.38–1.31 (m, 2H), 1.12–1.05 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 142.2, 140.5, 139.7, 133.5, 131.7, 130.4, 129.2, 128.9, 126.3, 114.9, 100.4, 48.2, 32.7, 25.4, 24.7. IR (KBr) 3390, 2923, 2846, 1635, 1492, 1160, 993 ν_{max}/cm^{-1}; mp 134.8–135.4 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{20}H_{22}ClIN_3O$: 482.0496; found: 482.0472(100%) $[M+H]^+$.

General preparation of *N*-arylindazole-3-carboxamides (11, 33-43).

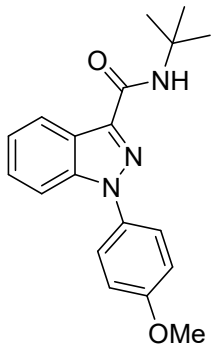
The α-aminocarbonylhydrazone (0.1 mmol, 1 eq.) is dissolved in dry 1,4-dioxan (0.3 M) and cesium carbonate (0.1 mmol, 1 eq.), tri-o-tolylphosphine (0.01 mmol, 0.1 eq.) and bis(triphenylphosphine)palladium(II) dichloride (0.007 mmol, 0.07 eq.) were added. The reaction mixture was stirred at reflux temperature overnight, evaporated and purified by chromatographic column (*n*-hexane/ EtOAc).

N-Cyclohexyl-1-phenyl-1*H*-indazole-3-carboxamide (11).



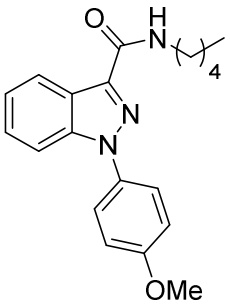
The crude material was purified by column chromatography (*n*-hexane/EtOAc 95:5) to give the product as yellow solid (0.03 g, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.1 Hz, 1H), 7.73–7.66 (m, 3H), 7.58–7.54 (m, 2H), 7.46–7.40 (m, 2H), 7.35–7.32 (m, 1H), 7.04 (br d, NH), 4.10–4.00 (m, 1H), 2.08–2.03 (m, 2H), 1.80–1.64 (m, 3H), 1.50–1.20 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 140.4, 139.7, 139.5, 129.6 (2C), 127.6 (2C), 123.9, 123.4 (2C), 123.3, 123.2, 110.4, 48.0, 33.3 (2C), 25.6, 25.0 (2C). IR (KBr) 2923, 2851, 1662, 1555, 1363, 1245, 1171, 1056 ν_{max}/cm^{-1}; mp 104.3–105.5 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{20}H_{22}N_3O$: 320.1763; found: 320.1730 (100%) $[M+H]^+$.

N-(tert-Butyl)-1-(4-methoxyphenyl)-1*H*-indazole-3-carboxamide (33).



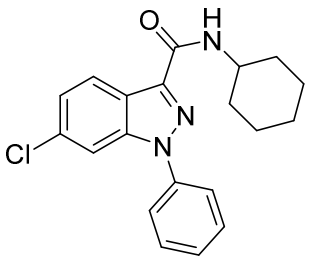
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as reddish oil (0.03 g, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 8.1 Hz, 1H), 7.60–7.56 (m, 3H), 7.42 (br t, 1H), 7.31 (br t, 1H), 7.08–7.04 (m, 3H), 3.89 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 159.0, 140.7, 139.6, 132.4, 127.4, 125.2 (2C), 123.4, 123.3, 123.0, 114.7 (2C), 110.3, 55.7, 51.3, 29.1. IR (KBr) 3406, 2956, 1668, 1533, 1508, 1196, 1028, 751 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{19}H_{22}N_3O_2$: 324.1712; found: 324.1728 (100%) $[M+H]^+$.

1-(4-Methoxyphenyl)-*N*-pentyl-1*H*-indazole-3-carboxamide (34).



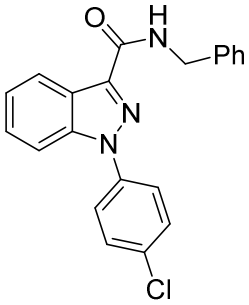
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as an off-white solid (0.03 g, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.1 Hz, 1H), 7.59–7.56 (m, 3H), 7.41 (br t, 1H), 7.31 (br t, 1H), 7.14 (br t, NH), 7.06 (br d, AA'XX', 2H), 3.87 (s, 3H), 3.52–3.47 (m, 2H), 1.66–1.61 (m, 2H), 1.39–1.35 (m, 4H), 0.92–0.88 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 159.1, 140.6, 139.0, 132.5, 127.4, 125.1 (2C), 123.5, 123.2, 123.1, 114.7 (2C), 110.3, 55.6, 39.1, 29.5, 29.2, 22.4, 14.0. IR (KBr) 3291, 2956, 1640, 1544, 1245, 1201, 1026 ν_{max}/cm^{-1}; mp 58.7–59.8 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{20}H_{24}N_3O_2$: 338.1869; found: 338.1843 (100%) $[M+H]^+$.

6-Chloro-*N*-cyclohexyl-1-phenyl-1*H*-indazole-3-carboxamide (35).



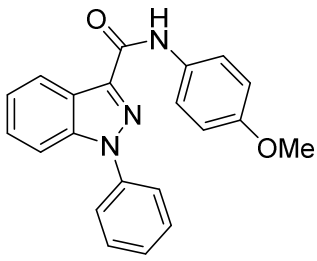
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as an off-white solid (0.03 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 8.6 Hz, 1H), 7.69–7.67 (m, 3H), 7.60–7.57 (m, 2H), 7.48–7.44 (m, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 6.99 (br d, NH), 4.08–4.00 (m, 1H), 2.08–2.05 (m, 2H), 1.80–1.66 (m, 4H), 1.49–1.17 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 140.7, 139.8, 139.0, 134.2, 129.7 (2C), 128.0, 124.4 (2C), 123.5 (2C), 122.2, 110.2, 48.0, 33.2 (2C), 25.6, 25.0 (2C). IR (KBr) 3324, 2934, 2851, 1637, 1536, 1495, 1251, 751 ν_{max}/cm^{-1}; mp 146.1–147.2 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{20}H_{21}ClN_3O$: 354.1373; found: 354.1349 (100%) $[M+H]^+$.

***N*-Benzyl-1-(4-chlorophenyl)-1H-indazole-3-carboxamide (36).**



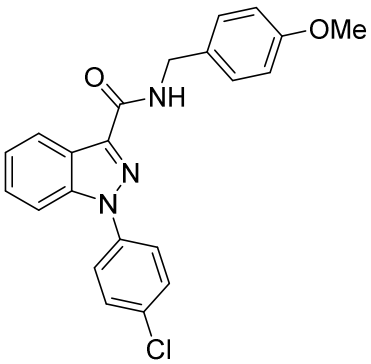
The crude material was purified by column chromatography (*n*-hexane/EtOAc 95:5) to give the product as white solid (0.03 g, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 8.1 Hz, 1H), 7.68–7.65 (m, 3H), 7.53–7.29 (m, 10H), 4.73 (br d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 140.2, 139.5, 138.2, 138.0, 133.2, 129.7 (2C), 128.7 (2C), 128.0, 127.9 (2C), 127.5, 124.4 (2C), 124.0, 123.6, 123.3, 110.3, 43.1. IR (KBr) 3302, 1648, 1539, 1492, 1196, 1086, 976 ν_{max}/cm^{-1}; mp 101.3–102.6 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{21}H_{17}ClN_3O$: 362.1060; found: 362.1030 (100%) $[M+H]^+$.

***N*-(4-Methoxyphenyl)-1-phenyl-1*H*-indazole-3-carboxamide (37).**



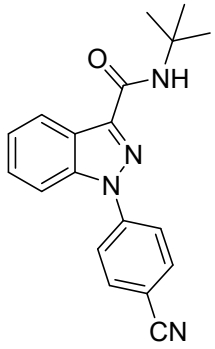
The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as red solid (0.03 g, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (br s, NH), 8.53 (d, *J* = 7.0 Hz, 1H), 7.73–7.66 (m, 5H), 7.57–7.54 (m, 2H), 7.46–7.41 (m, 2H), 7.34 (br t, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 156.3, 140.5, 139.4, 139.3, 131.0, 129.6, 127.8 (2C), 123.9, 123.5, 123.4, 123.2, 121.5, 114.2, 110.6, 55.5. IR (KBr) 3318, 2956, 1668, 1530, 1240, 1020, 823 ν_{max}/cm^{-1}; mp 116.6–117.3 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{21}H_{18}N_3O_2$: 344.1399; found: 344.1407 (100%) $[M+H]^+$.

1-(4-Chlorophenyl)-*N*-(4-methoxybenzyl)-1*H*-indazole-3-carboxamide (38).



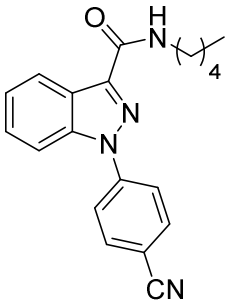
The crude material was purified by column chromatography (n-hexane/EtOAc 9:1) to give the product as orange solid (0.03 g, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (br d, 1H), 7.64–7.61 (m, 3H), 7.49–7.46 (m, 4H), 7.37–7.31 (m, 3H), 6.86 (br d, AA'XX', 2H), 4.64 (br d, 2H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 159.0, 140.2, 139.7, 138.0, 133.1, 130.4, 129.7, 129.3, 128.0, 124.3, 124.0, 123.5, 123.4, 114.1, 110.3, 55.3, 42.6. IR (KBr) 3313, 1646, 1541, 1492, 1086, 828 ν_{max}/cm^{-1}; mp 135.0–136.1 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{22}H_{19}ClN_3O_2$: 392.1166; found: 392.1133 (100%) $[M+H]^+$.

***N*-(tert-Butyl)-1-(4-cyanophenyl)-1*H*-indazole-3-carboxamide (39).**



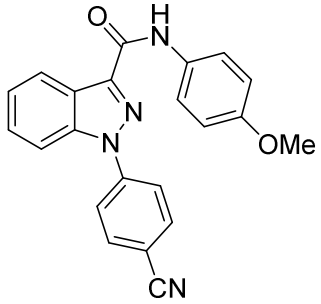
The crude material was purified by column chromatography (*n*-hexane/EtOAc 95:5) to give the product as yellowish solid (0.02 g, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (br d, 1H), 6.91 (br d, AA'XX', 2H), 7.84 (br d, AA'XX', 2H), 7.73 (br d, 1H), 7.49 (br t, 1H), 7.35 (br t, 1H), 6.99 (br s, NH), 1.53 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 143.0, 141.7, 140.0, 133.6, 128.5, 124.4, 123.9 (2C), 122.7, 118.2, 110.3, 110.3, 51.5, 29.0. IR (KBr) 3340, 2967, 2230, 1651, 1541, 1363, 850 ν_{max}/cm^{-1}; mp 131.7–133.0 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{19}H_{19}N_4O$: 319.1559; found: 319.1525 (100%) $[M+H]^+$.

1-(4-Cyanophenyl)-*N*-pentyl-1*H*-indazole-3-carboxamide (40).



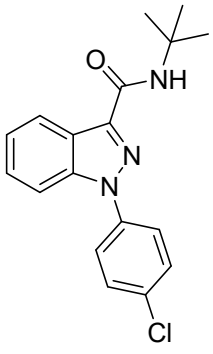
The crude material was purified by column chromatography (*n*-hexane/EtOAc 95:5) to give the product as light pink solid (0.02 g, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (br d, 1H), 7.91 (br d, AA'XX', 2H), 7.84 (br d, AA'XX', 2H), 7.75 (br d, 1H), 7.51 (br t, 1H), 7.37 (br t, 1H), 7.12 (br t, NH), 3.53–3.48 (m, 2H), 1.76–1.65 (m, 2H), 1.39–1.38 (m, 4H), 0.92–0.89 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 143.1, 141.1, 140.0, 133.6, 128.5, 124.5, 124.0, 123.8, 122.7, 118.2, 110.4, 110.3, 39.2, 29.5, 29.1, 22.4, 14.0. IR (KBr) 3285, 2934, 2225, 1646, 1555, 1421, 1179, 842 ν_{max}/cm^{-1}; mp 144.2–145.5 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{20}H_{21}N_4O$: 333.1715; found: 333.1728 (100%) $[M+H]^+$.

1-(4-Cyanophenyl)-*N*-(4-methoxyphenyl)-1*H*-indazole-3-carboxamide (41).



The crude material was purified by column chromatography (*n*-hexane/EtOAc 9:1) to give the product as pink solid (0.02 g, 48% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (br s, NH), 8.56 (br d, 1H), 7.96 (br d, AA'XX', 2H), 7.88 (br d, AA'XX', 2H), 7.78 (br d, 1H), 7.66 (br d, AA'XX', 2H), 7.56 (br t, 1H), 7.43 (br t, 1H), 6.93 (br d, AA'XX', 2H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 156.5, 142.9, 141.0, 140.2, 133.7, 130.6, 128.7, 124.5, 124.3, 123.8, 122.9, 121.6, 118.1, 114.3, 110.7, 110.4, 55.5. IR (KBr) 3302, 2225, 1648, 1599, 1506, 1237, 1168, 836 ν_{max}/cm^{-1}; mp 191.5–192.4 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{22}H_{17}N_4O_2$: 369.1352; found: 369.1341 (100%) $[M+H]^+$.

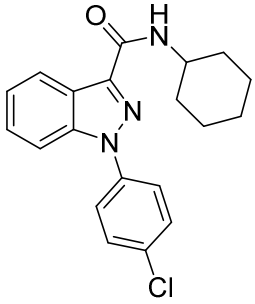
***N*-(tert-Butyl)-1-(4-chlorophenyl)-1*H*-indazole-3-carboxamide (42).**



The crude material was purified by column chromatography (*n*-hexane/EtOAc 98:2) to give the product as yellow solid (0.02 g, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (br d, 1H), 7.67–7.61 (m, 3H), 7.52 (br d, AA'XX', 2H), 7.45 (br t, 1H), 7.33 (br t, 1H), 7.01 (br s, NH), 1.53 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 140.5, 140.3, 138.0, 133.1, 129.7, 127.9, 124.5, 123.8, 123.6, 123.4, 110.1, 51.3, 29.1. IR (KBr) 3401, 3060, 2961, 1662, 1530, 1497, 1193, 1091 ν_{max}/cm^{-1}; mp 47.1–48.7 °C; MS (ESI)

m/z $(M+H)^+$ calcd for $C_{18}H_{19}ClN_3O$: 328.1217; found: 328.1224 (100%) $[M+H]^+$.

1-(4-Chlorophenyl)-*N*-cyclohexyl-1*H*-indazole-3-carboxamide (43).

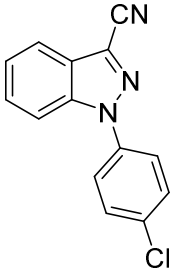


The crude material was purified by column chromatography (*n*-hexane/EtOAc 98:2) to give the product as yellow solid (0.03 g, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (br d, 1H), 7.67 (br d, AA'XX', 2H), 7.63 (br d, 1H), 7.52 (br d, AA'XX', 2H), 7.45 (br t, 1H), 7.34 (br t, 1H), 7.00 (br s, NH), 4.10–4.01 (m, 1H), 2.08–2.03 (m, 2H), 1.83–1.76 (m, 3H), 1.49–1.20 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 140.2, 140.0, 138.0, 133.1, 129.7, 127.9, 124.4, 124.0, 123.5, 123.4, 110.1, 48.0, 33.3, 25.6, 25.0. IR (KBr) 3401, 2923, 2846, 1657, 1528, 1492, 1196, 1086, 831 ν_{max}/cm^{-1}; mp 58.9–60.8 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{20}H_{21}ClN_3O$: 354.1373; found: 354.1384 (100%) $[M+H]^+$.

General preparation of N-arylindazole-3-carbonitriles (52).

N-Benzyl-1-(4-chlorophenyl)-1*H*-indazole-3-carboxamide **37** (0.07 mmol, 1 equiv.) is dissolved in phosphorous oxychloride (0.03 M) stirred at 150 °C for 4 hours. The reaction mixture is cooled at room temperature and poured into ice/ammonium hydroxide. The product is then extracted with EtOAc (x3); the organic phase is washed with brine, dried over Na_2SO4 and evaporated. The product is then purified by chromatographic column (*n*-hexane/ EtOAc).

1-(4-Chlorophenyl)-1*H*-indazole-3-carbonitrile (52).



The crude material was purified by column chromatography (*n*-hexane/EtOAc 98:2) to give the product as yellowish solid (0.02 g, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (br d, 1H), 7.75 (br d, 1H), 7.68 (br d, AA'XX', 2H), 7.57–7.55 (m, 3H), 7.44 (br t, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.0, 137.4, 134.3, 130.0, 128.9, 126.1, 124.6, 124.4, 120.6, 120.1, 113.1, 111.2. IR (KBr) 2236, 1495, 1355, 1218, 1089, 834 ν_{max}/cm^{-1}; mp 164.4–165.6 °C; MS (ESI) *m/z* $(M+H)^+$ calcd for $C_{14}H_9ClN_3$: 254.0485; found: 254.0467 (100%) $[M+H]^+$.

12.4 References

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Chapter 13

Conclusions

In this Ph.D. thesis period (2013-2016), we developed seven novel multicomponent reactions between the 1,3-dipolar species nitrile *N*-oxides and nitrile imines, generated from *Z*-chlooximes or hydrazonoyl chloride respectly, with isocyanides in the presence of a nucleophilic component.

The presence of a third component is pivotal in diverging the course of the two-component reaction between the 1,3-dipolar species and isocyanides, which is sometimes messy and unable to afford a single main product.

We have established straightforward synthetic routes which with only one or two synthetic steps allow to synthesize several important scaffolds for medicinal chemists. In particular starting from nitrile *N*-oxide we obtained *C*-oximinoamidines, aryl α-ketoamide amides, aryloxyimino amides, and 5-amino-1,2,4-oxadiazoles (Figure 1).

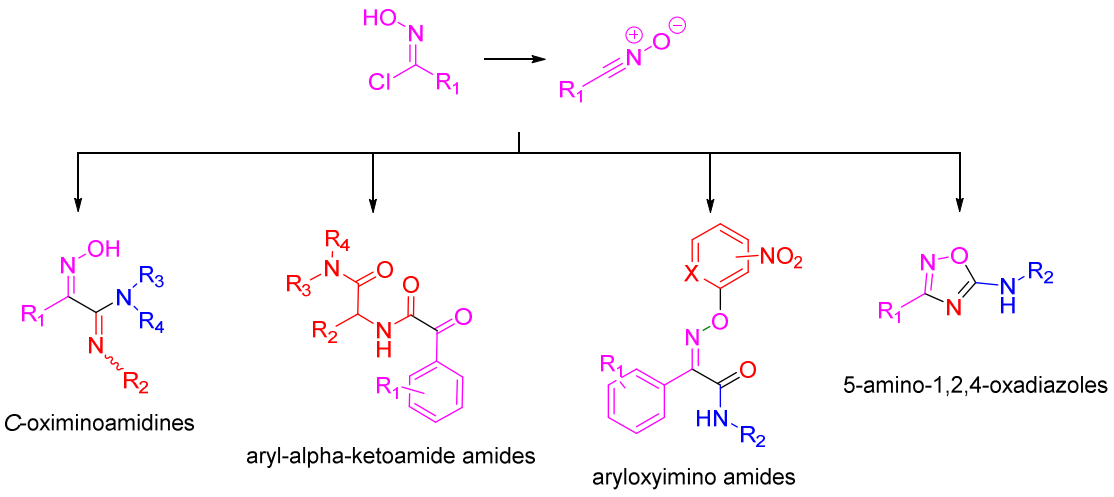

Figure 1. Scaffolds synthesized by a novel MCRs starting from *Z*-chlorooximes.

While starting from nitrile imines we synthesized aminocarbonyl *N*-acylhydrazones, furo[2,3-*d*]pyridazin-4(5*H*)-ones and 1-arylindazole-3-carboxamides (Figure 2).

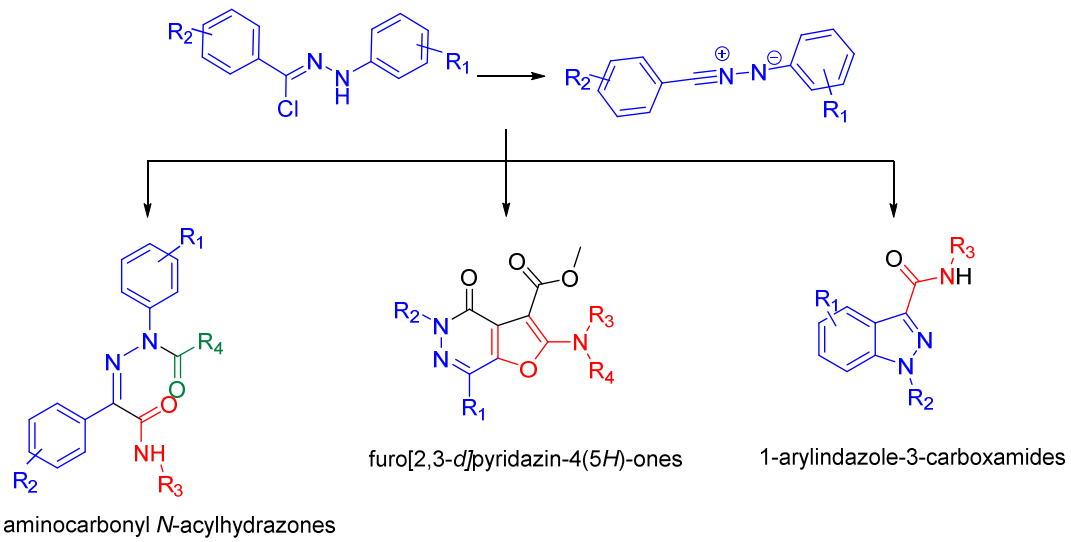

Figure 2. Scaffolds synthesized by a novel MCRs starting from hydrazonoyl chlorides.

It is important to highlight that the entire sequence of reactions is realized under mild reaction conditions avoiding the use of expensive coupling agents and using simple and easily available starting materials.

The detailed mechanism of the reaction between nitrile *N*-oxides and isocyanides has been studied indicating a [3+1] cycloaddition as the most energetically favorable step, thus preventing the direct attack of the third nucleophile to nitrile *N*-oxides. The mechanism with nitrile imines has been less well investigated leaving the possibility of a direct nucleophilic attack of isocyanide to nitrile imine or a 1,3-dipolar cycloaddition to form the strained 1,2-diazet-3(2*H*)-imine.

As several nucleophiles showed an ability to intercept the nitrilium ion generated by reacting nitrile *N*-oxide or nitrile imine with isocyanide, is it plausible that other nucleophiles besides those reported by us, can intercept the nitrilium ion in a productive manner without directly competing with the isocyanide in the reaction with the 1,3-dipolar species.

This will create novel opportunities for the synthesis of molecular scaffolds not easily accessible through conventional multistep synthesis.

Chapter 14

Publications

Research publications from thesis

- Giustiniano M., **Mercalli V.**, Novellino E., Tron G.C. An efficient synthesis of 1-arylindazole-3-carboxamides using nitrile imines, isocyanides and 2-hydroxymethylbenzoic acid, followed by a chemoselective Buchwald-Hartwig intramolecular cyclization *RSC Adv.*, **2016**, *6 (41)*, 34913-34920. DOI: 10.1039/C6RA01442A (IF: 3.289)

- **Mercalli V.**, Massarotti A., Varese M., Giustiniano M., Meneghetti F., Novellino E., Tron G.C. Multicomponent Reaction of *Z*-Chlorooximes, Isocyanides, and Hydroxylamines as Hypernucleophilic Traps. A One-Pot Route to Aminodioximes and Their Transformation into 5-Amino-1,2,4-oxadiazoles by Mitsunobu-Beckmann Rearrangement *J. Org. Chem.*, **2015**, *80 (19),* 9652-9661. DOI: 10.1021/acs.joc.5b01676 (IF: 4.785)

- Giustiniano M., **Mercalli V.**, Amato J., Novellino E., Tron G.C. Exploiting the Electrophilic and Nucleophilic Dual Role of Nitrile Imines: One-Pot, Three-Component Synthesis of Furo[2,3-*d*]pyridazin-4(5*H*)-ones *Org. Lett.*, **2015**, *17 (16)*, 3964-3967. DOI: 10.1021/acs.orglett.5b01798 (IF: 6.732)

- **Mercalli V.**, Giustiniano M., Del Grosso E., Varese M., Cassese H., Massarotti A., Novellino E., Tron G.C. Solution phase parallel synthesis of aryloxyimino amides via a novel multicomponent reaction among aromatic (*Z*)-chlorooximes, isocyanides and electron deficient phenols *ACS Comb. Sci.*, **2014**, *16 (11)*, 602-605. DOI: 10.1021/co5000882 (IF: 3.317)

- Giustiniano M., Meneghetti F., **Mercalli V.**, Varese M., Giustiniano F., Novellino E., Tron G.C. Synthesis of Aminocarbonyl *N*-Acylhydrazones by a Three-Component Reaction of Isocyanides, Hydrazonoyl Chlorides, and Carboxylic Acids *Org. Lett.*, **2014**, *16*, 5332-5335. DOI: 10.1021/ol502515b (IF: 6.732)

- Giustiniano M., **Mercalli V.**, Cassese H., Di Maro S., Galli U., Novellino E., Tron G.C. Reaction Between (*Z*)-Arylchlorooximes and alpha-Isocyanoacetamides: a Procedure For The Synthesis of Aryl-alpha-Ketoamide amides *J. Org. Chem.*, **2014**, *79 (13)*, 6006-6014. DOI: 10.1021/jo5005444 (IF: 4.785)

- **Mercalli V.**, Meneghetti F., Tron G.C. Isocyanide-Mediated Multicomponent Synthesis of *C*-Oximinoamidines *Org. Lett.*, **2013**, *15 (22)*, 5902-5905. DOI: 10.1021/ol403062m (IF: 6.732)

Research publications from allied projects

- Travelli C., Aprile S., Rahimian R., Grolla A. A., Rogati F., Bertolotti M., Malagnino F., di Paola R., Impellizzeri D., Fusco R., **Mercalli V.**, Massarotti A., Stortini G., Terrazzino S., Fahfouri G., Troiani M. P., Alisi M. A., Grosa G., Orsomando G., Cuzzocrea S., Genazzani A. A., Galli U., Tron G. C. Identification of novel triazole-based NAMPT inhibitors endowed with anti-proliferative and anti-inflammatory activity. Manuscript submitted for publication *J. Med. Chem., **2016.***

- **Mercalli V.**, Nyadanu A., Cordier M., Tron G.C., Grimaud L., El Kaïm L. N–N bond formation in Ugi processes: from nitric acid to libraries of nitramines *ChemComm*, **201**7, ASAP. DOI: 10.1039/C6CC10288C

- Giustiniano M., Basso A., **Mercalli V.**, Massarotti A., Novellino E., Tron G.C., Zhu J. To each his own: isonitriles for all flavors. Functionalized isocyanides as valuable tools in organic synthesis *Chem. Soc. Rev.*, **2017**, ASAP. DOI: 10.1039/C6CS00444J.

- Massarotti A., Aprile S., **Mercalli V.**, Del Grosso E., Grosa G., Sorba G., Tron G.C. Are 1,4- and 1,5-disubstituted-1,2,3-triazoles good pharmacophoric groups? *ChemMedChem*, **2014**, *9 (11)*, 2497-2508. DOI: 10.1002/cmdc.201402233 (IF: 2.980)

Patent

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Chapter 15

Synopsis

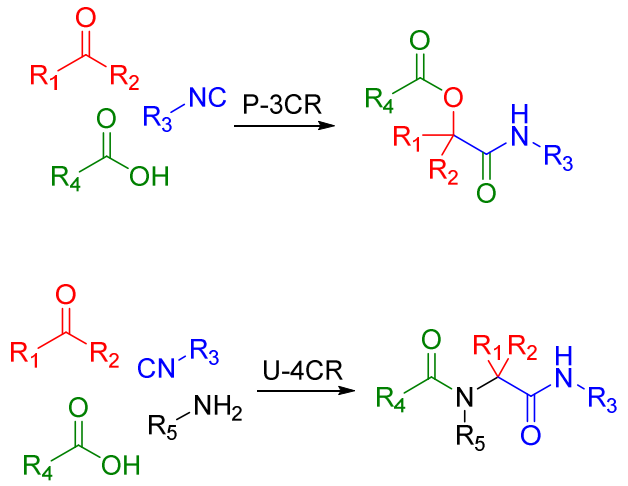
Nitrile *N*-oxides and nitrile imines as electrophilic partners for the discovery of novel isocyanides multicomponent reactions: an innovative strategy for the synthesis of molecular scaffolds useful in medicinal chemistry

1. Introduction

Multicomponent reactions (MCRs) are reactions in which three or more different starting materials are combined, in one step, to give a product that incorporates substantial portions of all the components, reducing the number of synthetic steps necessary to form the desired molecules.

Special subclasses of the MCRs are those isocyanides based. Isocyanides have a unique reactivity; indeed, no other functional group reacts with nucleophiles and electrophiles at the same carbon atom, leading to the so-called α-adduct.

Nowadays, most MCR chemistry performed with isocyanides relates to the classical reactions of Passerini and Ugi, followed by post transformation reactions (Scheme 1).

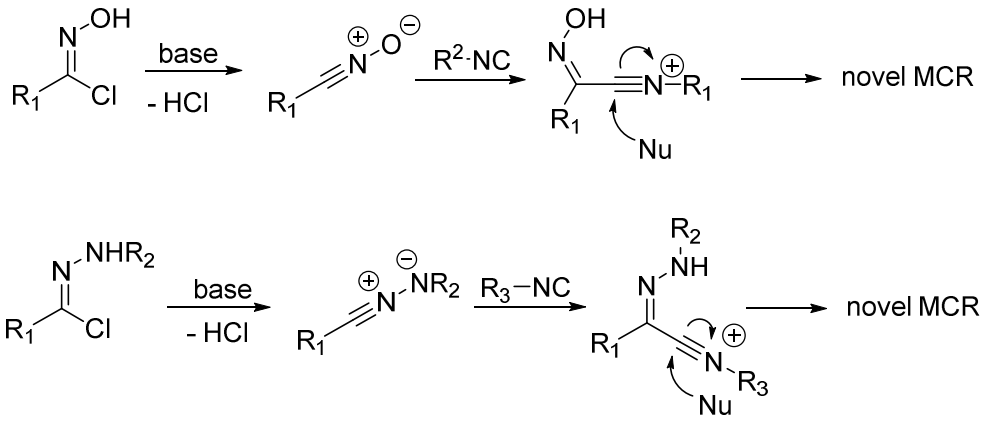


Scheme 1. Passerini reaction (P-3CR) and Ugi reaction (U-4CR).

2. Outline of the thesis

The major objective of this thesis was related to the ambitious goal of discovering new multicomponent reactions. This could be lead to the synthesis of important scaffolds in medicinal chemistry either not easily accessible via the classical two-component chemistry or never reported in literature.

The aim of this Ph.D. thesis was the search for neglected electrophilic groups that could replace the carbonyl component in the Passerini reaction. In particular, we have investigated, the role of *Z*-chlorooximes and hydrazonoyl chlorides. These two starting materials are, indeed, able to generate, under very mild reaction conditions, 1,3-dipolar species, respectively, nitrile *N*-oxides and nitrile imines which can be attacked by the isocyanide. The ephemeral nitrilium ion created can then be intercepted by a third component (Scheme 2).

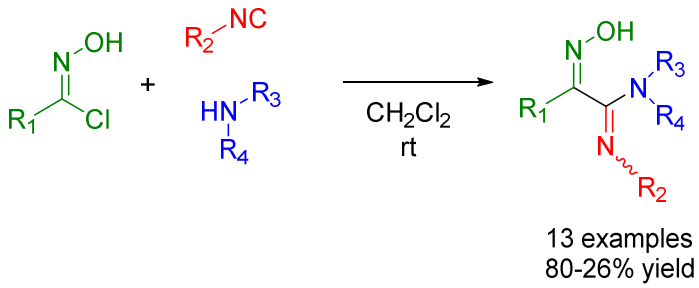


Scheme 2. Reaction between nitrile *N*-oxides or nitrile imines, isocyanides and a third nucleophile.

3. Nitrile *N*-oxides and nitrile imines as electrophilic partners in isocyanides based multicomponent reactions (IMCRs)

Over last decades was shown as the two components reactions between isocyanides and nitrile *N*-oxides or nitrile imines were inefficient forming several products. In this thesis we demonstrated that this erratic situation changes abruptly when a third component was present in the flask to driving the reaction towards the formation of a single novel product.

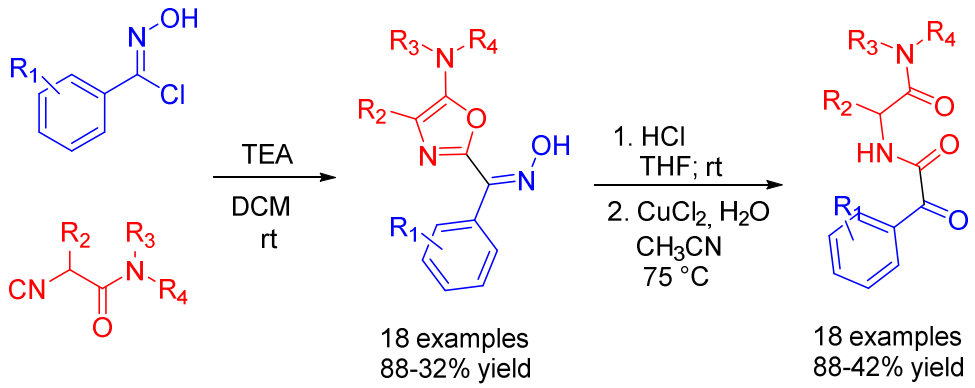
In detail, the multicomponent reaction between *N*-oxides, isocyanides and amine, has allowed to obtain *C*-oximinoamidines, a so far elusive class of compounds (Schema 3). A library of thirteen *C*-oximinoamidines was synthesized in order to demonstrated the generality of this synthetic procedure.



Scheme 3. General reaction between *Z*-chlorooximes, isocyanides and amine.

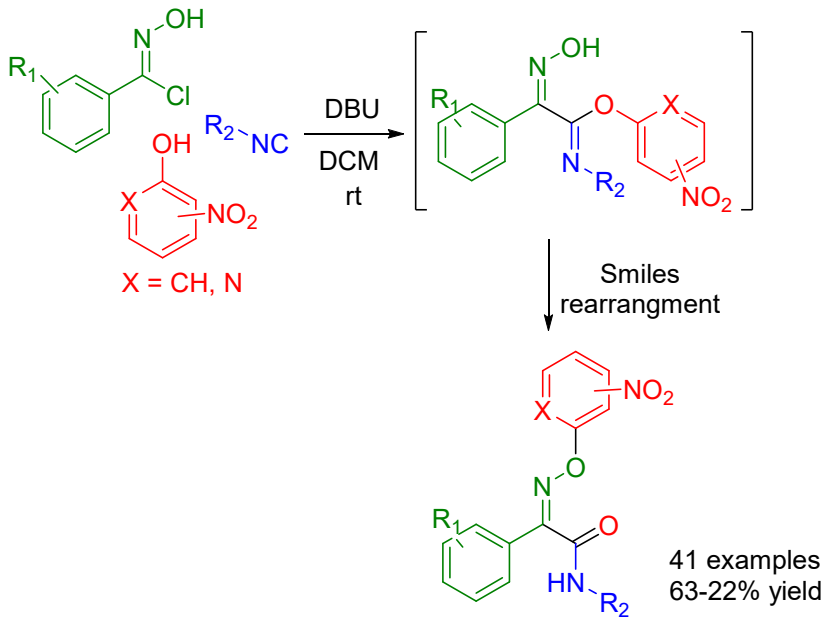
In the search of new different nucleophiles able to intercept the nitrilium intermediate, generated from the reaction between nitrile *N*-oxides and isocyanides, we reasoned that the nitrilium ion could also be intramolecularly intercepted by an internal nucleophile. To prove this hypothesis, we reacted *Z*-arylchlorooximes and α-isocyanoacetamides producing 1,3-oxazol-2-oxime derivatives in good yields. Opening of the oxazole ring and deoximation reaction gave a facile access to aryl-α-ketoamide amides, a class of privileged scaffolds in medicinal chemistry and important synthetic intermediates in organic chemistry. A library of eighteen α-keto

amide amides was synthesized in order to demonstrated the generality of this synthetic procedure (Scheme 4).



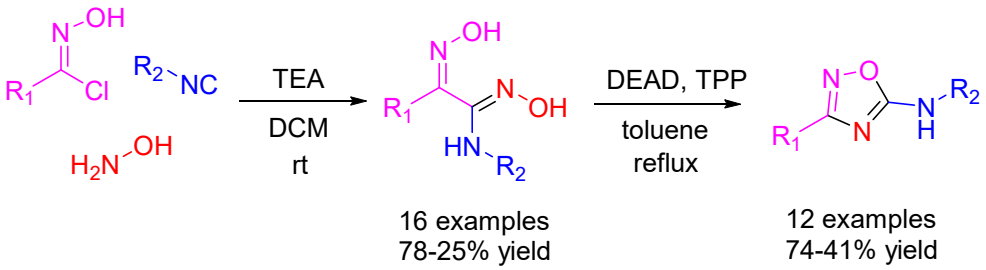
Scheme 4. Synthesis of 1,3-oxazol-2-oxime and subsequently of aryl-α-ketoamide amides.

As a continuation of our studies, we reported the discovery of a novel multicomponent reaction in which electron-deficient phenols were the third component in a reaction with *Z*-chlorooximes and isocyanides. In this case, after the formation of the imidate, the hydroxyl group of the oxime, which was properly positioned, thanks to the stereoselective addition of isocyanide to the nitrile *N*-oxide, triggered a Smiles rearrangement, to form aryloxyiminoamides. To demonstrate the versatility of this novel transformation a solution-phase combinatorial library of 41 aryloxyiminoamides has been produced (Scheme 5).



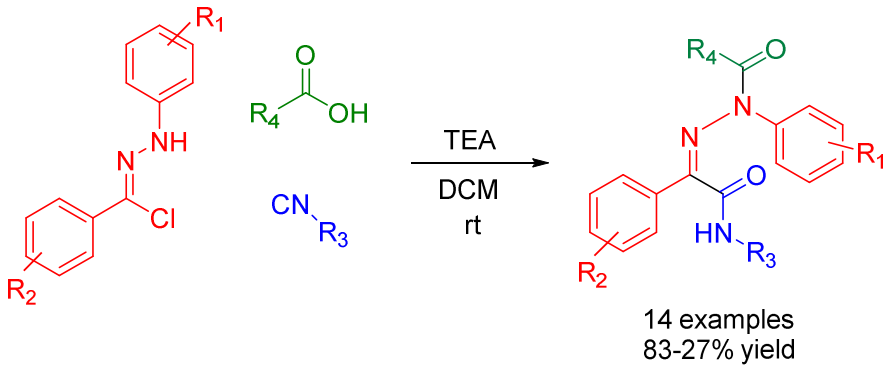
Scheme 5. Three-component synthesis of aryloximinoamides.

We then envisaged a novel multicomponent reaction using a hyper-nucleophile like hydroxylamine as the third component to prepare aminodioximes. Furthermore, the one-pot conversion of aminodioximes to 1,2,3-oxadiazole-5-amines via Mitsunobu-Beckmann rearrangement was reported for the first time (Scheme 6).



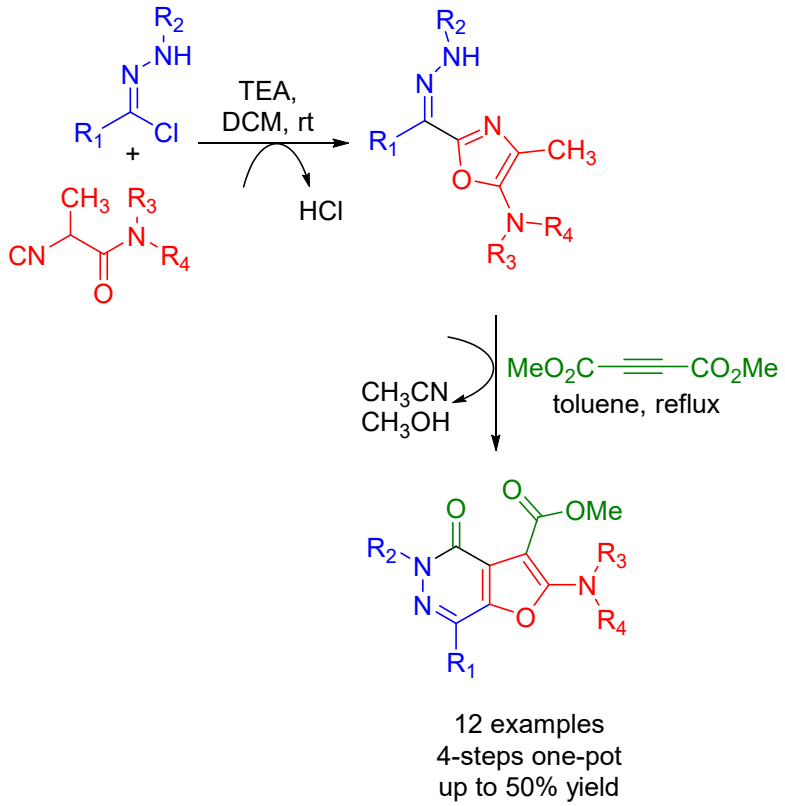
Scheme 6. Three-component synthesis of aminodioximes
aminodioximes and subsequently of 1,2,3-oxadiazole-5-amines.

Subsequently, we used nitrile imines as electrophilic input in a novel three-component reaction from readily available hydrazonoyl chlorides, isocyanides, and carboxylic acids to obtain *α*-aminocarbonyl *N*-acylhydrazones. The strategy exploited the ability of the carboxylic acid as third component to suppress all the competing reactions between nitrile imines and isocyanides (Scheme 7).



Scheme 7. Three-component reaction between hydrazonoyl chloride, isocyanide and carboxylic acid.

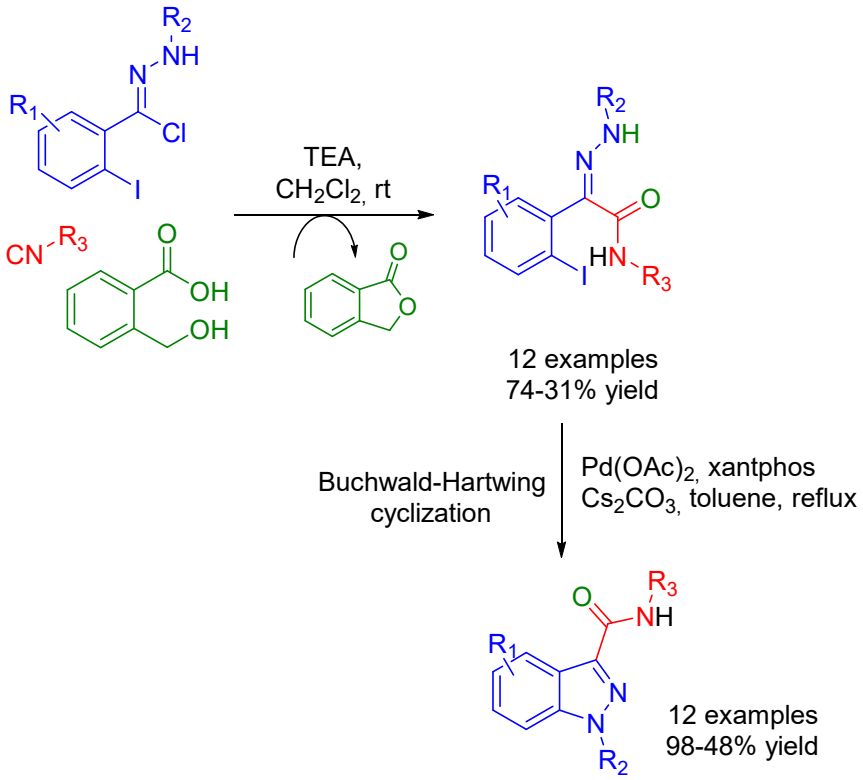
The reactivity of the 1,3-dipolar species nitrilimines was also exploited in combination with *α*-isocyanoacetamides allowing the one-pot synthesis of tetrasubstituted furo[2,3-*d*]pyridazin-4(5*H*)-ones. In brief, hydrazonoyl chlorides react with isocyanoacetamides, in the presence of TEA, to give 1,3-oxazol-2-hydrazones which, without being isolated, can react with dimethylacetylene dicarboxylate to afford furo[2,3-*d*]pyridazin-4(5*H*)-ones with an unprecedented level of complexity in a triple domino Diels-Alder/retro-Diels-Alder/lactamization reaction sequence (Scheme 8).



Scheme 8. Synthesis of furo[2,3-*d*]pyridazin-4(5*H*)-ones.

Continuing our interest for hydrazonoyl chlorides in isocyan

ide-mediated multicomponent reactions, we have disclosed a convergent and efficient two-step synthesis of pharmaceutically relevant 1-arylindazole-3-carboxamides. The process exploited a strategic three-component reaction between isocyanides, 2-iodo-*N*-arylbenzohydrazonoyl chlorides and 2-hydroxymethylbenzoic acid followed by a chemoselective Buchwald-Hartwig intramolecular cyclization (Scheme 9).



Scheme 9. Synthesis of 1-arylindazole-3-carboxamides.

4. Conclusions

In conclusion, we developed seven novel multicomponent reactions between the 1,3-dipolar species nitrile *N*-oxides or nitrile imines, generated from *Z*-chlorooximes or hydrazonoyl chloride respectly, with isocyanides in the presence of a nucleophilic component.

It is important to highlight that the entire sequence of reactions is realized under mild reaction conditions avoiding the use of expensive reagents and using simple and easily available starting materials.

The detailed mechanism of the reaction between nitrile *N*-oxides and isocyanides was also investigated indicating a [3+1] cycloaddition between 1,3-

dipolar species and isocyanides as the most energetically favorable step, thus preventing the direct attack of the third nucleophile to nitrile *N*-oxides.

Curriculum vitae

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8) Giustiniano M., **Mercalli V.**, Novellino E., Tron G.C. An efficient synthesis of 1-arylindazole-3-carboxamides using nitrile imines, isocyanides and 2-hydroxymethylbenzoic acid, followed by a chemoselective Buchwald-Hartwig intramolecular cyclization *RCS Adv.*, **2016**, *6 (41)*, 34913-34920. DOI: 10.1039/C6RA01442A

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5) **Mercalli V.**, Giustiniano M., Del Grosso E., Varese M., Cassese H., Massarotti A., Novellino E., Tron G.C. Solution phase parallel synthesis of aryloxyimino amides via a novel multicomponent reaction among aromatic (*Z*)-chlorooximes, isocyanides and electron deficient phenols *ACS Comb. Sci.*, **2014**, *16 (11)*, 602-605. DOI: 10.1021/co5000882.

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Conferences

XXIV EFMC International Symposium on Medicinal Chemistry – Manchester (UK), 28thAugust -1st September, 2016.
Poster *"Synthesis and characterization of new DGKα inhibitors"* Mercalli V., Gesù A., Massarotti A., Baldanzi G., Graziani A., Tron G.C.

XXXIX "A. Corbella" International Summer School on Organic Synthesis - Gargnano (BS), 15th -19th June 2014.

XXII National Meeting in Medicinal Chemistry, Rome, 10th-13th September 2013.
Poster "*Three component synthesis of C-oximinoamidines: versatile building blocks useful in drug discovery*" Mercalli V., Tron G.C.

VII meeting Nuove Prospettive in Chimica Farmaceutica, Savigliano (TO), 29th-31th May 2013.