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XXVII Ciclo

NEW STRATEGIES FOR NOVEL ISOCYANIDE MULTICOMPONENT REACTIONS: INNOVATIVE WAYS TO ACCESS TO MEDICINALLY IMPORTANT COMPOUNDS

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Anni accademici 2011-2014

“Le véritable voyage de découverte ne consiste pas à chercher de nouveaux paysages, mais à avoir de nouveaux yeux. ”

“Il vero viaggio di scoperta non consiste nel cercare nuovi paesaggi, ma nell’avere nuovi occhi.”

Marcel Proust

CONTENTS

1. INTRODUCTION

The increasing demand of new chemical entities requires the industry to find new methods for the rapid synthesis of compounds with high therapeutic potential.

Combinatorial chemistry is a great tool for the production of libraries of molecules with different structures. In this field, multicomponent reactions (MCRs), thanks to their ability to create several bonds in one step, are useful means for the construction of structures with high molecular complexity.

In the past century, organic chemistry and synthesis focused mainly on two-component reactions. Much of today's research focuses on improving those reactions (e.g. by improving catalysts, diastereoselectivity and enantioselectivity). New reactions are rarely discovered now, in sharp contrast to the past century, when only minimal research into MCRs

occurred. This field seems to offer a good harvest to those who enter it. A key area of future research efforts, in industry as well as in universities, will cover the applications and discovery of MCRs. In addition, new MCRs offer good protection of intellectual property in the field of drug discovery

Are there any rational ways to find new MCRs?

The rational design and development of new MCRs is regarded as a great intellectual challenge for organic chemists. It is a complex action, requiring imagination, knowledge and creativity.

Working on isocyanides and on the synthesis of heterocycles, our laboratory enter in this dynamics. The discovery of new multicomponent reactions mediated by isocyanides, and original reactions of post-condensation is the key point of our research.

2. ISOCYANIDE MULTICOMPONENT REACTIONS

2.1. MULTICOMPONENT REACTIONS

An ideal synthesis consists in obtaining a desired product using the minimum amount of time and steps, starting from easily available reagents and minimizing the risk for the environment as well as for the manipulator. The usual chemistry, based on sequential reactions in which every intermediate is isolated and purified, is far from this concept. The costs of the solvents used in every purification and the large amount of time spent make this type of chemistry not so efficient, which sometimes can lead to global yield not so high (Figure 1).

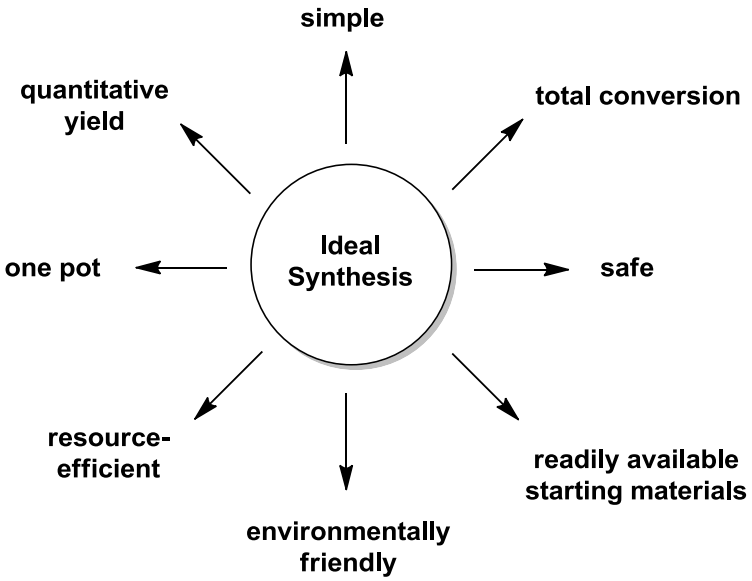


Figure 1. Properties of an ideal synthesis.

Moreover, the increasing demand for new chemical entities, and the develop of combinatorial chemistry require a new type of chemistry. Multicomponent reactions satisfy these requirements.

Multicomponent reactions (MCRs) are processes in which three or more reactants are combined to obtain a product containing all the components, or at least substantial portions of them, in a single step (Figure 2). [1]

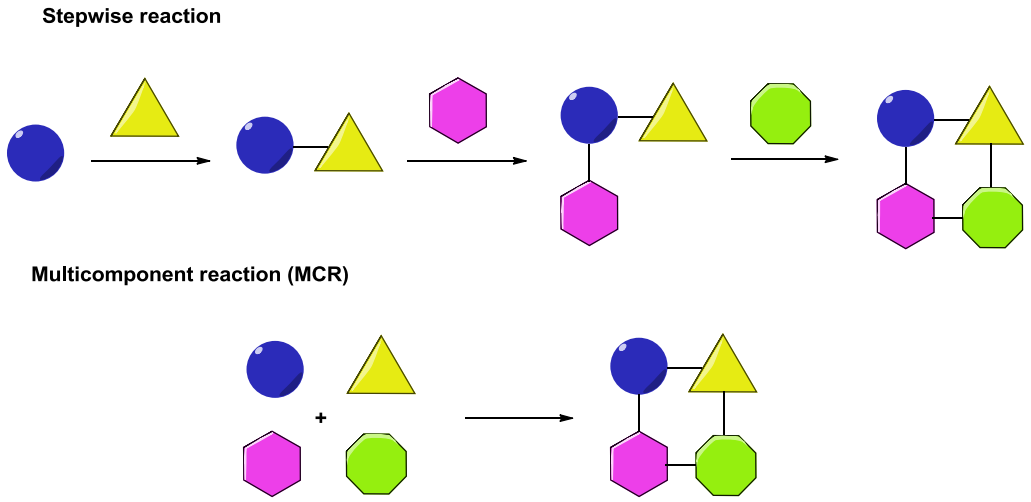
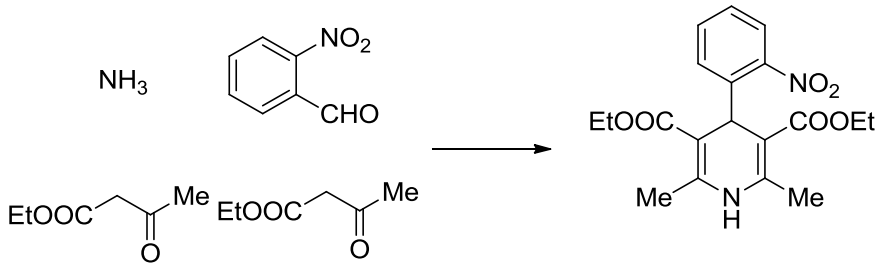


Figure 2. Difference between stepwise reactions and multicomponent reactions.

These reactions consist of several single passages, in which the equilibria can be reversible or not. The formation of the final product depends on these equilibria, as well as the nature of the solvent, presence of catalyst, concentrations and excess of reagents used. Ideally, even a non-expert manipulator could perform an optimized multicomponent reaction. The real difficulty consists in optimize the conditions.

The first multicomponent reaction was reported by Strecker in 1850 for the synthesis of amino acids. [2] After that, several ones followed: the Hantsch dihydropyridine synthesis, [3] the Radziszewski imidazole synthesis (1882), [4] the Biginelli dihydropyrimidine synthesis (1891),[5] and many others.

Besides the application of the MCRs in the drug development, from lead discovery and optimization, their potential can be used also in industrial synthesis: an example is the 132 years old Hantsch reaction, which is utilized still today for the synthesis of the calcium antagonist Nifedipine (Adalat®) (Scheme 1). [6]



Scheme 1. Synthesis of Nifedipine by the Hantsch reaction.

Isocyanide MCRs can be considered as special subclasses of MCRs.

2.2. HISTORY OF ISOCYANIDES

Isocyanides, also called isonitriles or carbylamines, are organic compounds with the functional group -N≡C, which are isomers of the related cyanides (-C≡N). They can be represented as a two-resonance structure: one zwitterionic, in which the nitrogen is positively charged and the carbon negatively charged, and one carbenic. Among the functional groups of organic chemistry the isocyanide group is not only unique because of its formally divalent carbon atom but also because of its unsurpassed versatility in chemical reactivity (Figure 3).

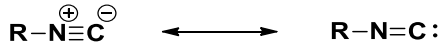


Figure 3. Resonance forms of isocyanides.

In 1859 Lieke, treating allyl iodide with silver cyanide, obtained the first synthesis of allyl isocyanide, [7] and then Hofmann and Gautier [8] extended the

presence of these species synthesizing a greater number of different isocyanides, using the carbylamine reaction (see next paragraph).

Nef, at the end of the 19th century, was interested in the reactivity of these species, which he called "bivalent carbon" compounds. He performed several experiments between isocyanides and different other reactants, exploring their peculiar reactivity. In 1892 he discovered the "Nef isocyanide reaction" (see chapter 3). [9] He also reported the formation of adducts with halogens, hydrogen chloride, phosgene, sulfur, hydrogen sulphide, amines.

In 1921 Mario Passerini discovered the first three component reaction mediated by an isocyanide, and this lead to a renaissance of isocyanide chemistry (Figure 4). [10]

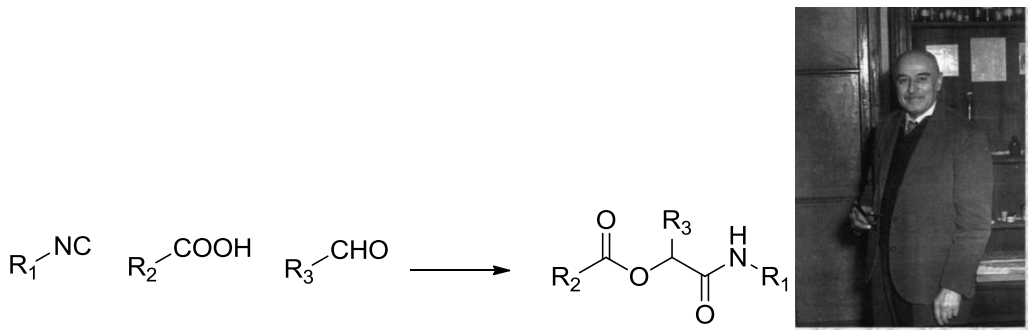


Figure 4. The Passerini reaction, and Mario Passerini (1891-1962).

The reason why isocyanide chemistry did not attract more researchers in its first century was maybe the difficulty in obtaining different isocyanides in an appreciable pure quantity, with the forementioned classical synthesis, and also maybe for their distinctive persistent odour:
"it tainted the air in the room for days and provoked continuing complaints in the neighborhood about the vile odour".[7]

The last step of the synthesis of the antibiotic xanthocillin by Hagedorn in 1956 is the first published synthesis of an isocyanide by dehydration of an *N*-monosubstituted formamide.[11] After a few year Ugi extended this reaction for the preparation of a vaste quantity of isocyanides, and this lead to the discovery of his four component reaction (Figure 5). [12,13]

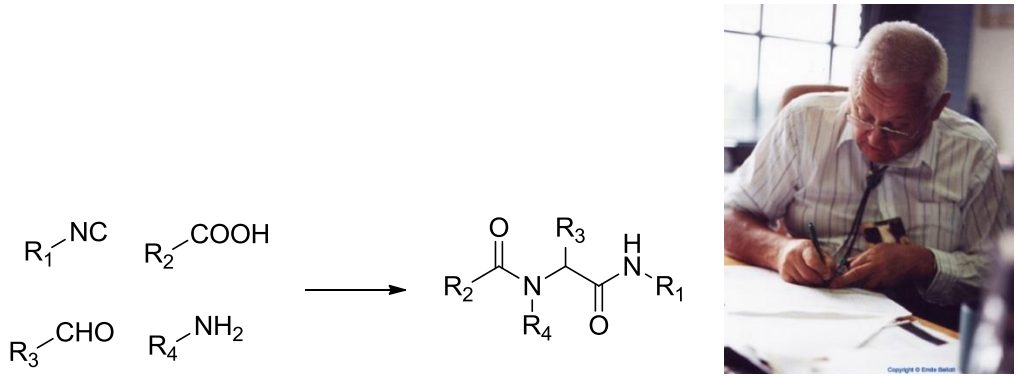


Figure 5. The Ugi reaction, and Ivar Ugi (1930-2005).

Since then, the chemistry of isocyanides began to expand: they are no longer an exotic class of compounds, they are now routinely used as common reagents by organic chemists. The most convenient method for their preparation is based on the dehydration of the formamide, so from any amine the corresponding isocyanide can be obtained in two steps.

Isocyanides are present also in nature: several marine natural products containing an isocyanide group were discovered, together with formamides, isothiocyanates, dichloroimines. Most of them are terpenes isolated from sponges. Interestingly, some of them show also biological activities . It has been demonstrated that in most cases the biosynthesis of the isocyanide occurs from the cyanide ion (Figure 6). [14]

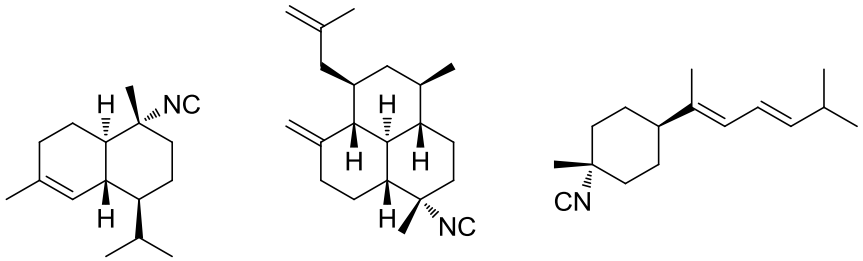
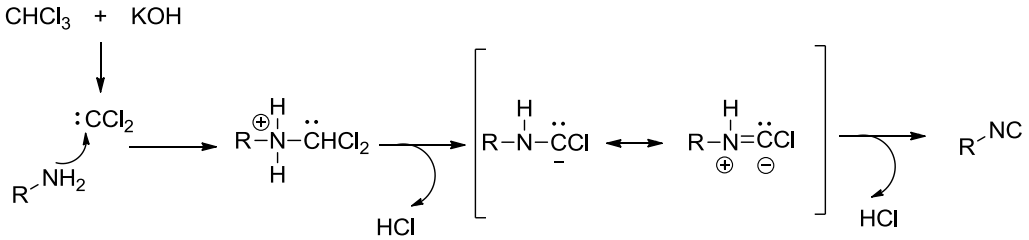


Figure 6. Some natural occurring isocyanides.

2.3. PREPARATION AND REACTIVITY OF ISOCYANIDES

Hofmann, treating a primary amine with chloroform in ethanol, in the presence of a base, like potassium hydroxide, obtained an isocyanide with the "carbylamine method".[15] This synthesis, although better than the synthesis made by Lieke with silver cyanide, is limited to a small number of compounds, and can lead to the formation of side products like dimerization products.

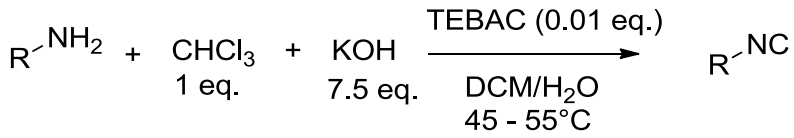
In 1897 Nef proposed a mechanism for this reaction,[16] in which the dichlorocarbene is formed from the reaction between chloroform and the base. This reactive intermediate reacts with the amine and after two eliminations of HCl the desired isocyanide is obtained (Scheme 2).



Scheme 2. Mechanism for the formation of isocyanide with the carbylamine method, proposed by Nef.

Weber, Gokel and Ugi in 1972 proposed a new method for this reaction, [17] using a mixture of water/dichloromethane as solvent and a phase transfert agent (a

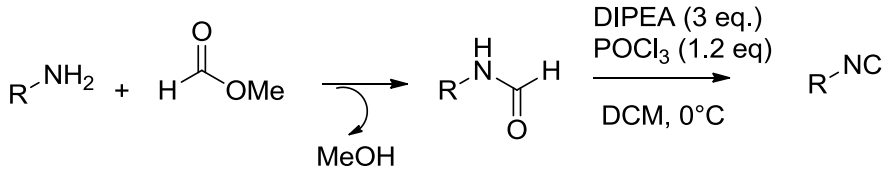
quaternary ammonium salt, TEBAC in this case, scheme 3). This method improves the selectivity of the addition of the dichlorocarbene to the primary amine, and limits the formation of side products. For this reason, it is utilized still today for the preparation of a great number of isocyanides, allowing their access starting from commercial amines in moderate yields in one step.



Scheme 3. Synthesis of isocyanides improved by Ugi.

Another method for the preparation of isocyanides is the dehydration of formamides. This method was developed by Ugi and co-workers[13], although proposed first by Hagedorn in 1956.[11]

The monosubstituted *N*-formamide is easily obtained from the condensation of a primary amine with formic acid or methyl formate. The first dehydrating agent used was phosgene, but due to its toxicity it was soon replaced with other reagents, like phosphorus pentoxide or phosphorus oxychloride, in the presence of a base (trialkylamines, pyridine, sodium hydroxyde, potassium carbonate, DABCO). This method is compatible with a larger number of substrates, so it is the most used (Scheme 4).



Scheme 4. Preparation of isocyanides from dehydration of formamides.

Other synthesis are proposed, but they are less general, like the reduction of isocyanates, isothiocyanates or dichloroketenimines with triethylphosphine, triphenyltin hydride or copper.[18]

The smell of isocyanides is very unpleasant. Volatile isocyanides, like benzyl and methyl isocyanide, present a very persistent odour. For this reason a lot of studies were performed for their use as non-letal weapons. But solid isocyanides, like TOSMIC, or naphtyl isocyanide, do not present a particular smell. Other ones instead, like some isocyanide esters, present pleasant odours like malt, old wood or mild cherry (Figure 7). [19]

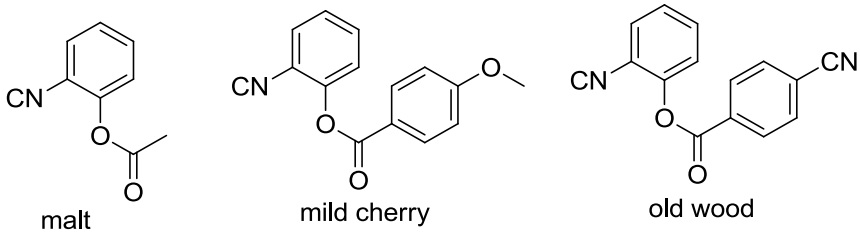


Figure 7. Some "not unpleasant" isocyanides.

In any case, manipulators of isocyanides have to pay more attention when they use these reagents: keep everything under the fume hood, and wash everything which has been in contact with isocyanides with a solution of dilute HCl and methanol, to convert the isocyanide into the formamide.

The main feature of isocyanides is the peculiar reactivity of the terminal carbon atom, which can undergo both nucleophile and electrophile addition (Figure 12). This characteristic is unique in organic chemistry, because the nuceophilic and electrophilic attacks usually occur in two different sites. This peculiarity allows the isocyanide to react with different species through an α-addition: hydrogen

halides, or carboxylic acids, [20] acid chlorides (the Nef isocyanide reaction), organometallics.[21]

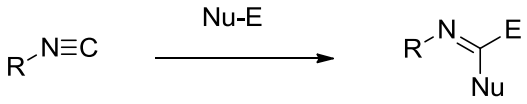
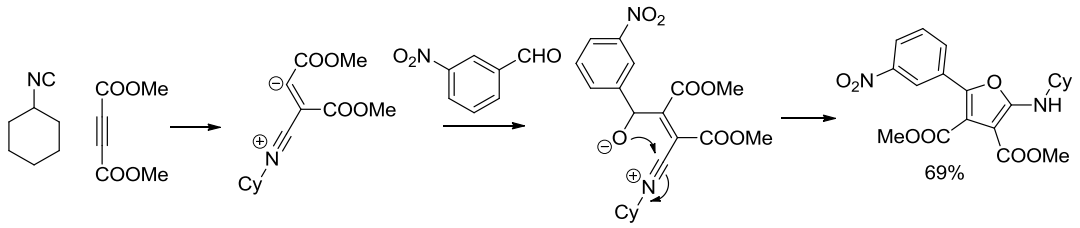


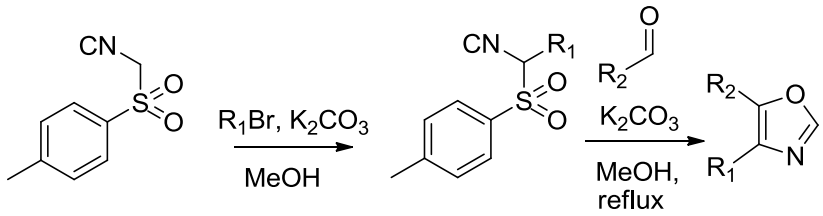
Figure 8. Reactivity of the terminal carbon atom of isocyanides.

Isocyanides are also highly reactive in cycloadditions: Nair has developed the reaction between an isocyanide and DMAD. The isocyanide undergoes addition with the alkyne, forming a zwitterionic specie, trapped by an electrophile. This intermediate can cyclize to form different types of heterocycles. In this case, a furan ring is obtained (Scheme 5). [22]



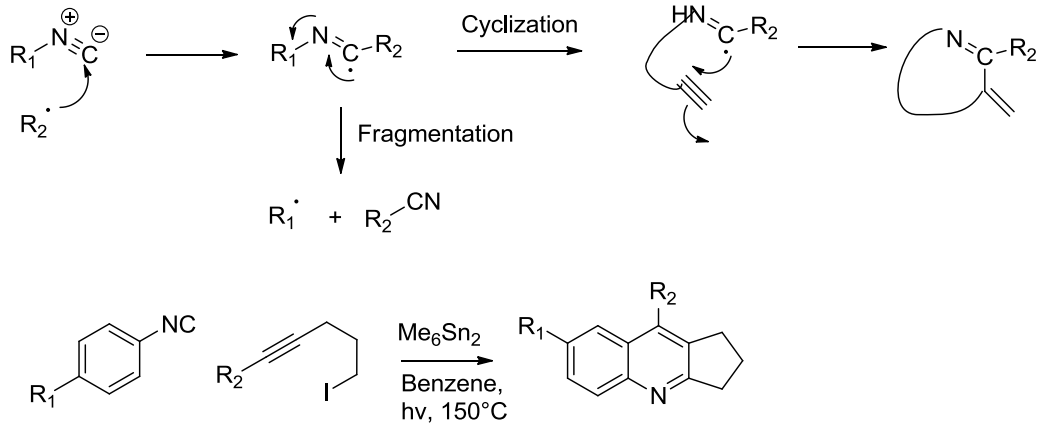
Scheme 5. Nair's synthesis of furanes.

Also the acidity of the proton in α can be exploited. The electron withdrawing effect of the isocyanide group allows the deprotonation of the α proton with a strong base (e.g. *n*-butyllithium, lithium diisopropylamide), which can be replaced with weaker bases if electron-withdrawing groups such as esters, nitriles or sulphonyles are present. The formed carbanion can react with electrophiles, and the intermediate can cyclize on the isocyanide carbon to obtain different heterocycles. Schöllkopf and Van Leusen reactions (Scheme 6) are two main examples.[23,24]



Scheme 6. Van Leusen synthesis of oxazoles.

Also radicals can add to isocyanides: the species formed can fragment into a nitrile and an alkyl radical, or can react to form heterocycles (Scheme 7). [25]



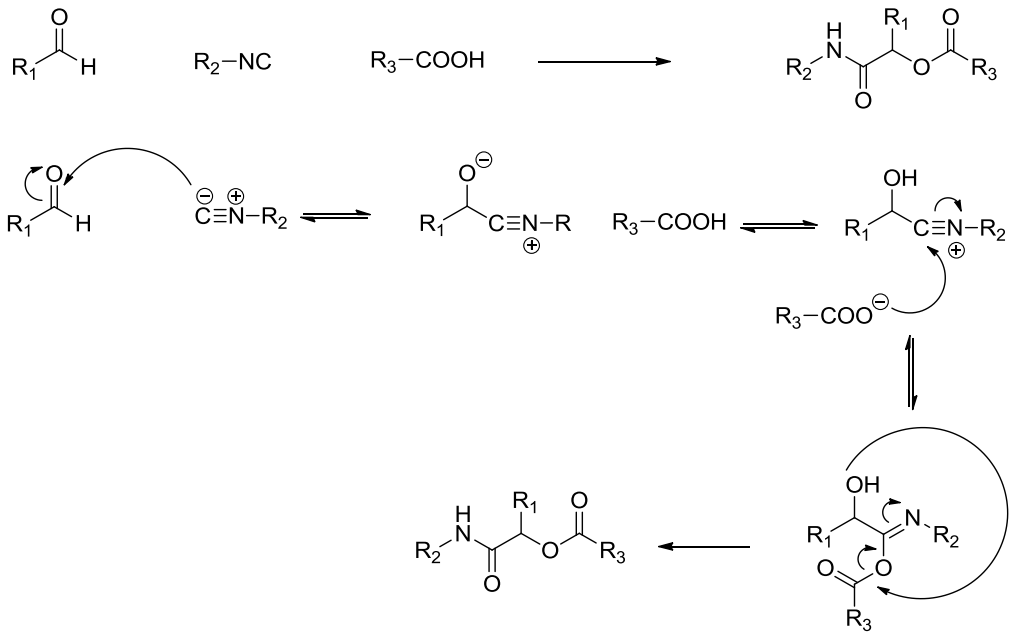
Scheme 7.. Radical reaction on isocyanides, and synthesis of cyclopentaquinoline.

But isocyanides show their maximum versatility and reactivity in multicomponent reactions.

2.4. ISOCYANIDE MULTICOMPONENT REACTIONS

Mario Passerini in 1921 was the first to exploit the reactivity of isocyanides in a multicomponent reaction.[10] The mechanism for the formation of the acyloxycarboxamide was explained by Ugi in 1961:[26] the first step is the formation of the adduct between the carboxylic acid and the carbonyl

compound; the isocyanide then inserts into this intermediate. 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,[27] the intramolecular transfert of the acyl: this is the driving force of the reaction, where an unstable intermediate iminoanhydride converts into a stable double bond C=O (Scheme 8).



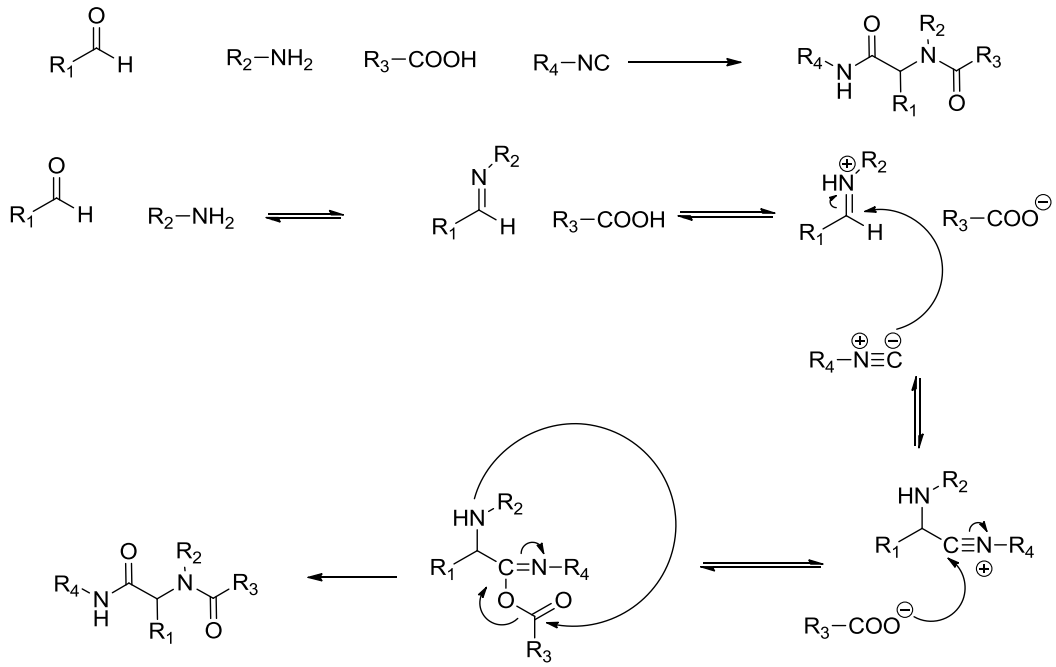
Scheme 8. Mechanism of the Passerini reaction.

This reaction, after its discovery, has been little used because of the difficulty in obtaining isocyanides. But after the 60s, when Ugi improved the accessibility of these species, their use began to expand.

In 1959 Ugi discovered the most famous isocyanide multicomponent reaction.[12] The Ugi reaction is a four component reaction among an amine, a carbonyl compound (ketone or aldehyde), a carboxylic acid and an isocyanide.

After the imine between the ketone and the amine is formed, with loss of water, a proton exchange occurs, that activates the imine towards the attack of the

isocyanide. This activation is very important, as we will see later (Chapter 5) with the use of secondary amines. After this irreversible, rate-determining step, the isocyanide carbon is subjected to nucleophilic attack of the carboxylate to obtain an unstable acyl imidoyl species, or imino anhydride. After the final Mumm type rearrangement, the bis-amide is formed (Scheme 9).



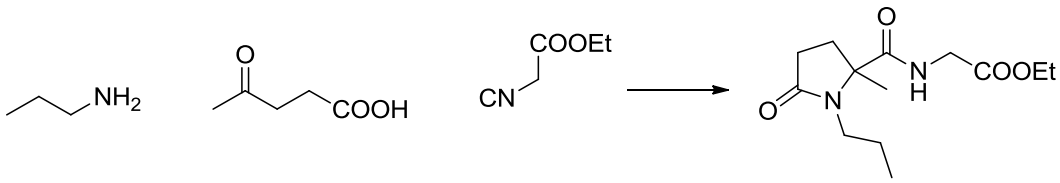
Scheme 9. Mechanism of the Ugi reaction.

The choice of the solvent in these two reactions is fundamental: while in the Passerini reaction the best solvents are aprotic non-polar solvents, in the Ugi reaction the best choices are polar solvents. This explains the ionic mechanism of the Ugi reaction, and suggests that the Passerini reaction proceeds with a non-ionic mechanism, in which hydrogen bonding plays a crucial role. [28,29]

The Ugi reaction has been the most utilized and studied, and a lot of variation of it have been proposed, to give access to a great number of different scaffolds.[30]

A huge number of different IMCRs have been discovered, that can be viewed as variations of the Ugi reaction. They can be categorize from the different approaches utilized:

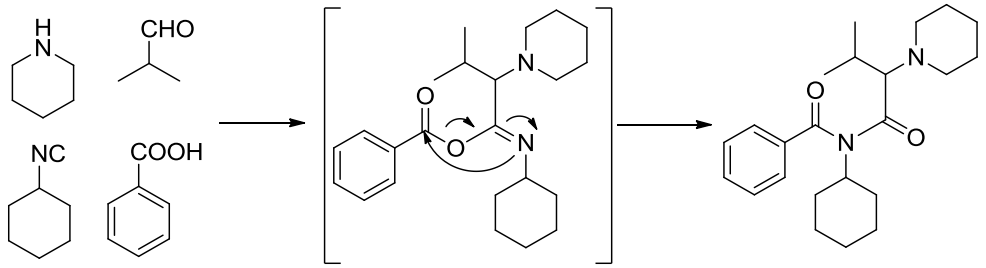
- Using bifunctional reagents, that will lead to the formation of cyclic products. The following is just one example from many others (Scheme 10). [31]



Scheme 10 . Use of bifunctional reagents in Ugi 4-C MCR.

- Changing the nature of one of the reagents:

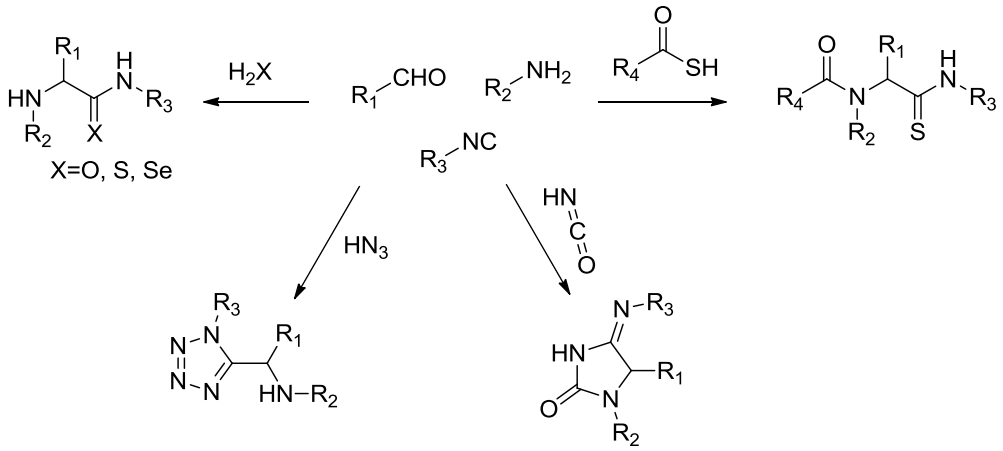
- **Amine.** The main variation of the amine is the use of secondary amines, that will be discussed in detail in chapter 5 (Scheme 11).



Scheme 11. Use of a secondary amine in the Ugi reaction to obtain an imide.

Also surrogates of amines can be used, for example hydrazines, hydrazides, hydroxylamines, oximes, ureas. [32]

- **Acid.** The acid component plays a very important role in the reaction, as it establish the proton exchange of the imine, and acts as nucleophile. Surrogates can be used instead of the carboxylic acid to obtain an Ugi adduct, like water, hydrogen sulphide, hydrazoic acid, isocyanic acid, thiocarboxylic acid. [33] The variation of the acid can be summarized in the following scheme (Scheme 12).

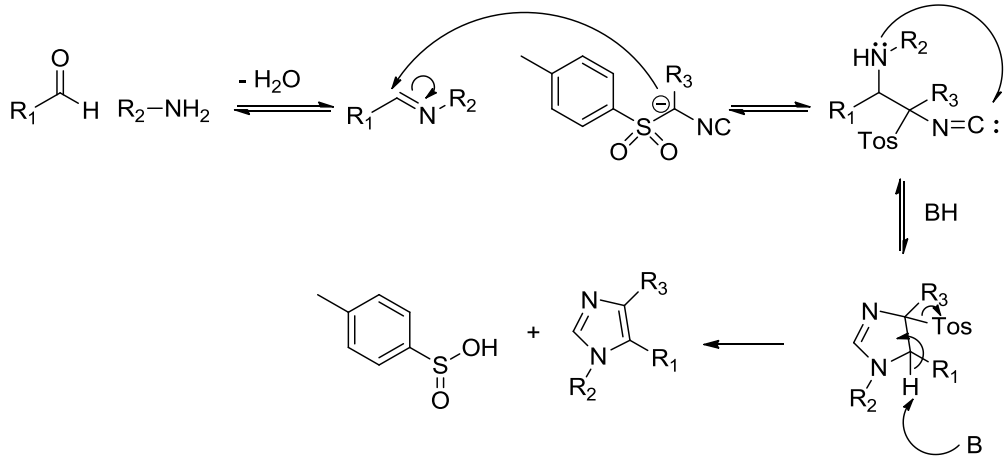


Scheme 12. Variation in the acidic component.

The acidic component can also be removed from the reaction, and in this case an interrupted Ugi reaction would be obtained. This will be discussed in detail in chapter 6.

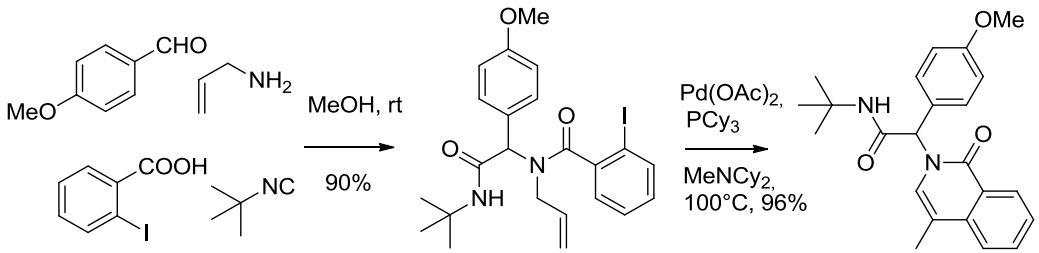
- **Isocyanide**. Among the reactions in which the variation of the isocyanide plays a crucial role is the Van Leusen reaction.[24] The reaction can be performed with the preformed enamine, or in the classic way with the three component. The peculiarity of TosMIC, which contains a reactive isocyanide carbon, an active methylene group and a leaving group, allows under basic conditions a stepwise cycloaddition with the enamine, and after elimination of *p*-toluenesulfinic acid from the

intermediate 4-tosyl-2-imidazoline provides a 1,5-disubstituted imidazole (Scheme 13).



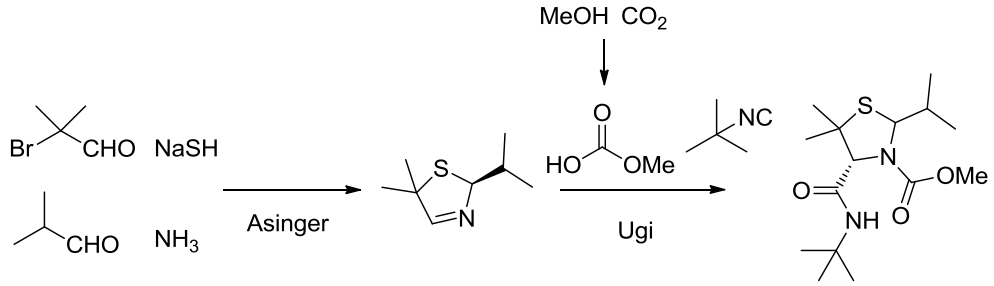
Scheme 13. Van Leusen synthesis of imidazoles.

- Post condensation reactions: of course this approach is the most utilized, because of the many different reactions that can be performed after the Ugi reaction, to obtain different scaffolds. In the last decades different strategies for this approach have been used: Ugi-Knoevenagel sequence,[34] Ugi/Diels-Alder,[35] Ugi-deprotection-cyclisation,[36] Ugi-Pictet Spengler, [37] post-condensations via organometallic coupling, [38] radical post-condensation. [39] There are a lot of examples in literature, and a lot to be still discovered. Here it is just one example, an Ugi reaction followed by an Heck coupling to afford isoquinoline derivatives (Scheme 14). [40]



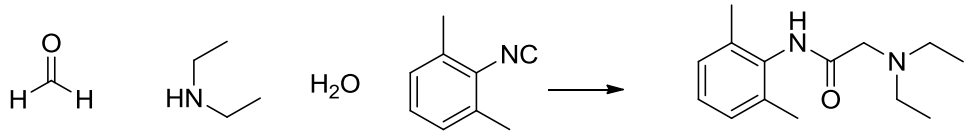
Scheme 14. Ugi reaction followed by Heck coupling.

- The union of two different multicomponent reaction allows the formation of very high molecular diversification, as described by Ugi and with the union of an Ugi reaction with an Asinger reaction[41] (Scheme 15).

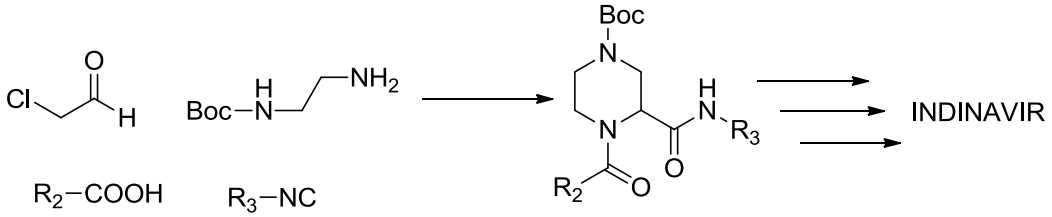


Scheme 15. Ugi-Asinger 7-C reaction.

Isocyanide MCRs, in particular the Ugi reaction, find several applications, both in industrial processes and in drug discovery. Two examples are the synthesis of xylocaine[30] and the synthesis of Indinavir®.[42] The first is a simple Ugi reaction in which the acidic component is substituted by water (Scheme 16), the second is a Ugi reaction with a diamine, in which a post condensation reaction affords the key intermediate for Indinavir® in a very efficient way (Scheme 17).



Scheme 16. Synthesis of the anaesthetic xylocaine.



Scheme 17. Ugi reaction for the access to the important intermediate for the synthesis of Indinavir.

Other applications include peptide coupling, [43] and total synthesis. [44]

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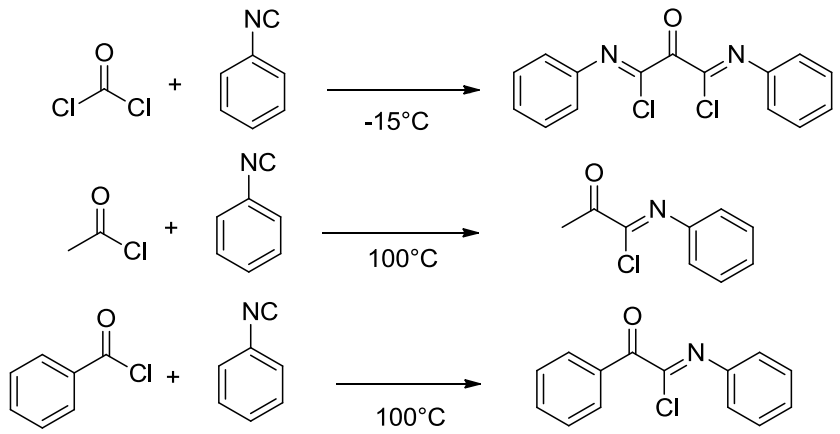
3. THE NEF REACTION OF ISOCYANIDES

3.1. HISTORICAL CONSIDERATIONS

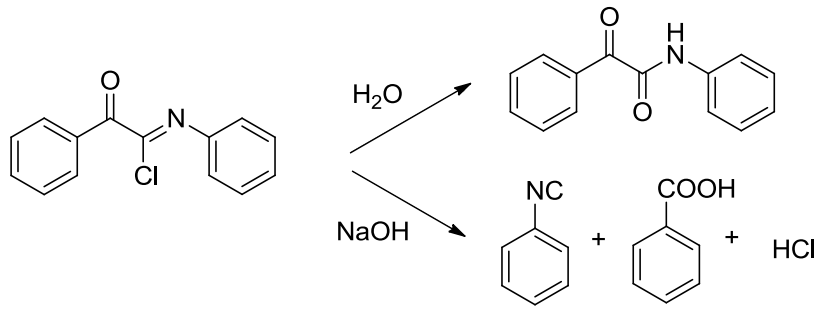
John Ulric Nef was one of the chemists who contributed mainly in the chemistry of isocyanides during the XIX century, disclosing some of the most important early reactions of isocyanides. Among the various new reactions presented in the same publication, one can find the first reference on the addition of acyl chlorides to isocyanides with the formation of α-ketoimidoyl chlorides, known as the Nef isocyanide reaction, together with reaction with chlorine, hydrochloric acid and hydrogen sulfide. This early contribution of Nef remained rather ignored: when chemists speak about Nef reaction, it is common to think about the reaction of primary or secondary nitro-alkanes with inorganic acids to afford the corresponding aldheydes or ketones, or the addition of sodium acetylides to aldehydes and ketones to yield acetylenic carbinols. [1]

In his 1892 report, Nef described the reaction between phenyl isocyanide and acyl chlorides: phosgene, acetyl and benzoyl chloride. While the addition to phosgene is violent and requires low temperature (-15°C to 0°C), the addition of acetyl and benzoyl chloride are carried out heating at 100°C (Scheme 1).



Scheme 1. Reactions carried out by Nef **.**

In a second paper of 1894 [2] he performed the same experiments using methyl and ethyl isocyanide. In both cases, he discovered the formation of the imidoyl chloride adducts, and their low stability. He also noticed the different behaviour in treating these species with water or base (sodium hydroxide). In the first case, the corresponding ketoamides are obtained, in the second case the dissociation to the isocyanide, carboxylic acid and hydrochloric acid takes place (Scheme 2).

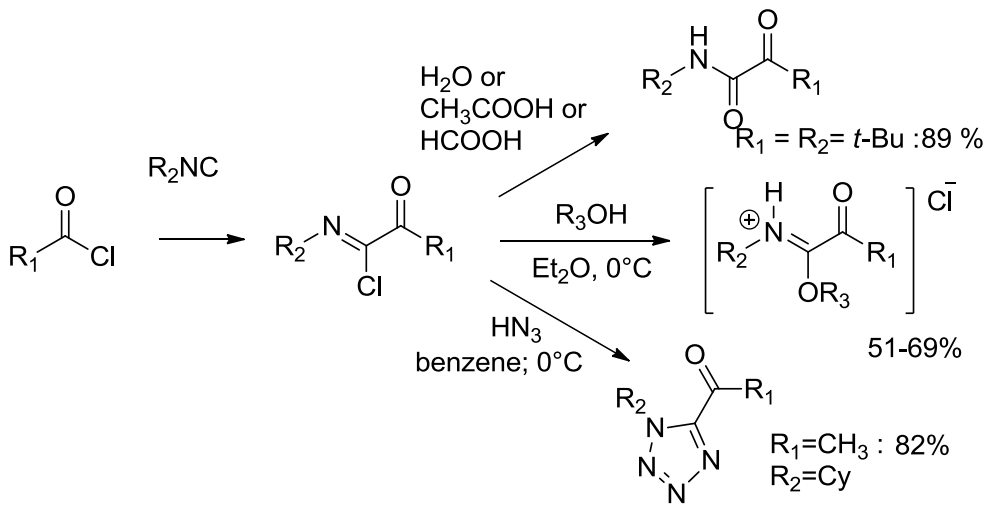


Scheme 2. Behaviour of imidoyl chlorides in water and bases.

It is interesting to say that, as chemists did at the time, Nef used to taste compounds, and he described that the imidoyl chloride obtained from phenyl isocyanide and acetyl chloride was a yellow, hygroscopic oil, with a sweet taste.

This chemistry remained unexplored, because of the difficulty in obtaining isocyanides, until Ugi and Fetzer in 1961 re-discovered the Nef reaction using different isocyanides and acyl chlorides. [3] Different novel α-ketoimidoyl chlorides (yields ranging from 26 to 84 %) were prepared using both aliphatic and aromatic acyl chlorides, while only aliphatic isocyanides were used. IR absorption values for these new compounds were collected, finding that the C=O bond has absorption at 1722-1726 cm^{-1}, the C=N at 1643-1655 cm^{-1}, and the C-Cl bond absorbs at 836-898 cm^{-1}. As already noted by Nef, they could obtain the ketoamides from the α-keto imidoyl chlorides using water, formic acid or acetic acid (Scheme 3). They also reported substitution reactions on the

imidoyl moiety with alcohols (ethanol and cyclohexanol) to give acyl imidates in their salt form, and with hydrazoic acid to form acyl tetrazoles (Scheme 3).



Scheme 3. Ketoamides, acyl imidates and acyl tetrazoles from Nef adduct.

3.2. PREPARATION AND REACTIVITY OF α-KETOIMIDOYL CHLORIDES

The first preparations of α-ketoimidoyl chlorides by Nef were made without solvent. Since the work of Ugi, these reactions are traditionnaly performed in apolar solvents. Most reported solvents are dichloromethane, ether, toluene or benzene, while nitromethane or acetonitrile gave low yields of imidoyl chloride.[4]

The nature of the isocyanide is important in the rate and speed of the reaction. Electron withdrawing groups on the isocyanide (*e.g.* TosMIC and isocyanoesters) make the reaction sluggish and complete only after 48 h at 60 °C.[5] The Nef reaction of aromatic isocyanides is more problematic, relatively

few examples are described in the literature probably due to the high ability of these isocyanides to polymerize under acidic conditions. Indeed, phenyl isocyanide was only used in the Nef report of 1892 together with phosgene, acetyl chloride and benzoyl chloride under solvent free conditions. If the temperature is raised to 80 °C, using toluene as solvent, the reaction of phenyl isocyanide and hexanoyl chloride fails, giving only polymerization products.

Aromatic acyl chlorides require prolonged reaction time (reflux in benzene for 18-24 h), but aliphatic acyl chlorides may be completely converted to α-ketoimidoyl chlorides within 10 minutes under moderate heating. El Kaïm *et al.* showed that the early solvent-free conditions proposed by Nef should be preferred allowing to prepare α-ketoimidoyl chlorides under faster conditions and lower temperature (60 °C, 1 hour for benzoyl chloride, 10 minutes for aliphatic acyl chlorides). Such conditions allow to reduce the decomposition of the Nef adducts and the potential polymerization of the isocyanides. Electrophilic acyl chlorides such as ethyl or methyl oxalyl chlorides react within minutes with isocyanides under neat conditions.[6]

Reaction can be followed by NMR analysis (on primary and secondary isocyanides) of an aliquot following the disappearance of the ^{1}H signal of the C-H group adjacent to the isocyanide and the development of the corresponding signal associated with the α-ketoimidoyl chloride product and/or evaluating the ^{13}C NMR of the imine carbon atom and of the carbon atom α to the nitrogen atom (Figure 1).

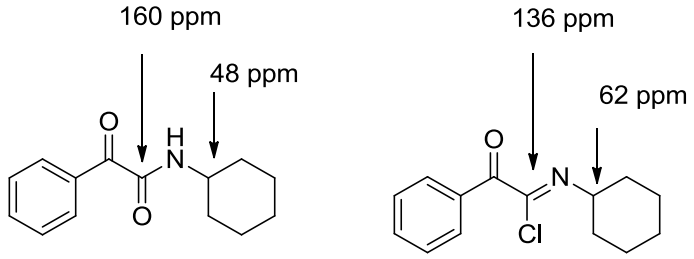
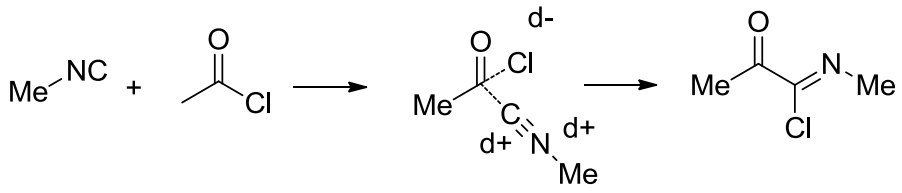


Figure 1 .NMR values for ketoamides and ketoimidoyl chlorides.

With more stable α-ketoimidoyl chlorides the conjugation between the carbonyl and the imine group allows the UV visibility, so in these cases the reaction can be followed by TLC.

A comprehensive study of the Nef reaction was made by Fleurat-Lessard and co-workers in 2011. [7] A single transition state was found, with a concerted mechanism related to S_N2 processes, confirming Ugi's hypothesis based on kinetic data. The choice of aromatic or alkyl substituents on the isocyanides and the acyl chlorides has a low influence on the activation barriers. However highly electrophilic acyl chlorides such as oxalyl chloride monoesters are associated with a low activation barrier (CH_3COCl/MeNC: 21.6 kcal.mol^{-1}, PhCOCl/MeNC 22.5 kcal.mol^{-1},EtOCOCOCl/MeNC 14.7 kcal.mol^{-1}) in agreement with their fast reaction at room temperature (less than 5 min). In contradiction with the traditional uses of apolar solvents in Nef isocyanide reactions, the model indicates that dissociative solvents should be preferred over solvents such as toluene (Scheme 4).

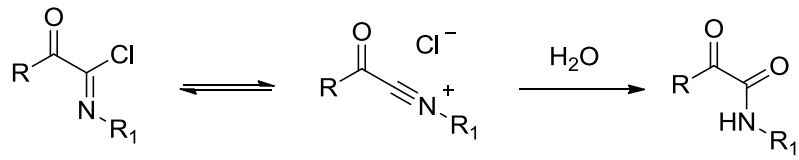


Scheme 4 . Mechanism for the formation of ketoimidoyl chlorides.

In two following reports, [8] the level of modelisation has been refined to examine initial results obtained with highly electrophilic CF_3COCl. Modelisations done with different hybrid density functionals (B3LYP, M06-2X, MP4(SDQ)…) gave either a concerted or a multistep mechanism. Further modelisation with a revised B3LYP functional concluded on a concerted mechanism for all acyl chlorides.

α-ketoimidoyl chlorides are unstable compounds. Even if some have been purified by distillation over 100 °C, at high temperature decomposition is observed, forming back isocyanides and acyl chlorides, and this may lead to products of polymerization of the isocyanide. This reversibility with loss of the isocyanide partner was already observed by Nef for phenylisocyanide, a particularly sensitive isocyanide towards polymerisation. Purification through silica gel column chromatography affords only the ketoamide, because of the acidity of the silica. Also during crystallization the imidoyl chloride is converted into the ketoamide. This leads to the conclusion that the imidoyl chloride can not be purified, but the reaction between acyl chloride and isocyanide gives very high yields, almost quantitative, and no side products, so further reactions can be performed on the formed unpurified adduct.

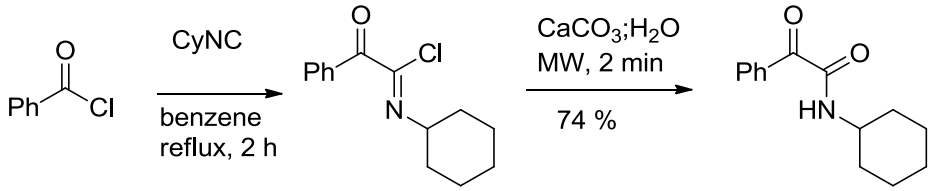
The conversion of α-ketoimidoyl chlorides, obtained from aliphatic acyl chlorides, to the corresponding ketoamides, required 2 h at 0 °C, while stronger conditions were required for derivatives obtained with aromatic acyl chlorides (50 °C; 1 h, acetone/water and calcium carbonate). [3] In a following publication Ugi and co-workers [9] studied in detail the mechanism of this hydrolysis.They performed reactions in water/acetone together with HCl, LiCl or HClO finding that the reaction follows a two stage mechanism, involving a nitrilium-chloride ion pair.



Scheme 5. Mechanism for the formation of ketoamides.

The reaction rate is not much affected by steric hindrance at the α-C position, while a steric acceleration was observed with bulky substituents on the nitrogen atom. But electronic effects are more important. Electron withdrawing groups, linked at the carbon or nitrogen atom, decrease the reactivity while electron donor groups raise the rate of hydrolysis. This observation finds an explanation with a S_N1 mechanism with the formation of a nitrilium intermediate. The difficulties reported in obtaining reliable rate measurements with deviations from first-order can be understood in terms of a large common ion effect between the nitrilium ion, and the chloride ion.

Compared to simple imidoyl chlorides, according to the data obtained by Ugi, it is possible to conclude that α-keto imidoyl chlorides were a little more stable towards hydrolysis. The acyl moiety, through an inductive effect, probably prevents the formation of the nitrilium intermediate. The hydrolysis of the imidoyl chloride can be accelerated and improved under microwave conditions (water:calcium carbonate, MW, 2 minutes) as done recently by Chen[10] (Scheme 6).

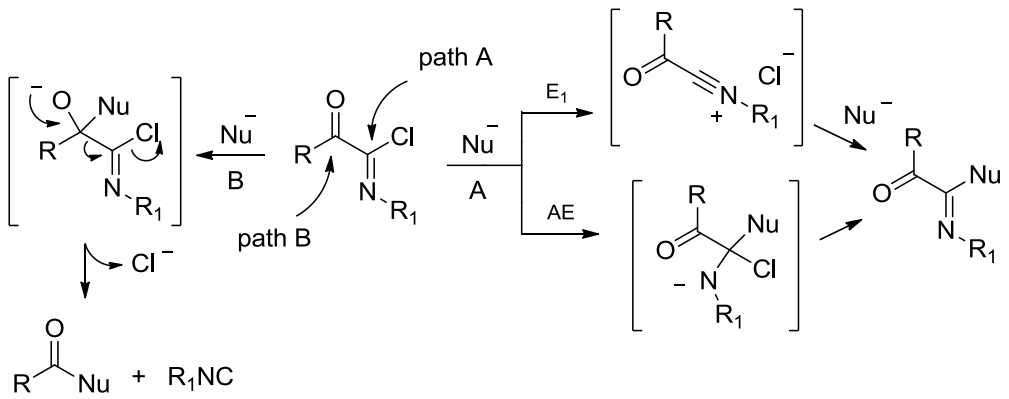


Scheme 6. Synthesis of ketoamides using microwave by Chen**.**

In most previous intramolecular reactions of Nef adducts, the competing addition onto the carbonyl group is not an issue as the chain lenght usually

favors the addition on the imidoyl chloride moiety. According to the results of Nef on the hydrolysis of α-ketoimidoyl chlorides, basic conditions lead to reverse Nef addition either through ketene formation or direct addition onto the carbonyl moiety. Even poorly basic nucleophiles such as anilines lead to the fragmentation of Nef adducts. Ammonia and other primary and secondary amines behave similarly whereas tertiary amines may lead to ketene side-products and polymerisation of the isocyanide.

The Nef adducts can undergo nucleophilic addition following two paths.

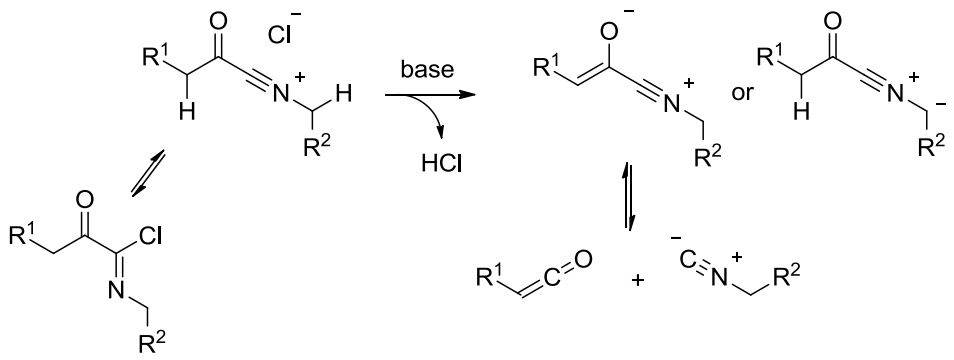


Scheme 7. Reactivity of ketoimidoyl chlorides towards nucleophiles.

Usually they undergo nucleophilic addition onto the imidoyl chloride moiety (Path A, Scheme 7). Indeed, the α-keto group would be expected to enhance its electrophilicity, and this has been explained by a S_N1 type mechanism involving a nitrilium intermediate as observed in many reactions of imidoyl chlorides.[3,9] However, the kinetic data obtained for the hydrolysis of Nef adducts should not discard the potential addition-elimination (AE) pathway leading to tetrahedral intermediates. The nature of the nucleophile, together with the solvent, added salts or acids should have an important effect on the preference for the nitrilium over the AE pathway. This is confirmed by the theoretical study performed on the addition of isocyanides onto Nef adducts. When considering nucleophilic additions onto Nef adduct, the vicinal ketone must not be forgotten. Its

electrophilicity is enhanced by the tethered electron-withdrawing imidoyl group, leading to regioselectivity issues during nucleophilic additions on Nef adducts (Path B). Nef already noticed the different behavior of α-ketoimidoyl chlorides towards water and sodium hydroxide.[1] Upon addition of water, α-ketoamides are observed as previously presented, whereas addition of a sodium hydroxyde solution forms back the isocyanide together with the carboxylate. This may be explained by an attack of the hydroxyde anion following path B leading to a tetrahedral adduct that may fragmentate back to the isocyanide . There is no clear indication in the literature of the rules controlling the selectivity of nucleophilic addition towards imidoyl adducts, however basic conditions should be avoided. This is consistent with the choice of calcium carbonate proposed by Ugi to trap the HCl formed under hydrolysis for less reactive benzoylimidoyl chlorides. The behavior of Nef adducts towards amines was further studied by Nef and then by Ugi. The expected formation of amidines according to path A were not obtained but simple amides were formed through addition following path B. Thus, the latter reactive pathway represents a serious limitation for the synthetic potential of Nef adducts.

If benzylic isocyanides or isocyanoesters are used, two potential acidic positions are present, and this changes the reactivity of the imidoyl chloride under basic conditions. Indeed, a 1,3-dipole is easily formed leading to further potential cyclizations or 1,3-dipolar cycloadditions (Scheme 8). However, an alternative dipole may be obtained through an enolate formation. Such dipole formation has been poorly estimated even though it might represent an alternative to path B in order to explain the instability of some Nef adducts towards basic nucleophiles. Indeed the dipole may easily fragmentate to the isocyanide and the ketene which may be trapped by any nucleophile in the medium.

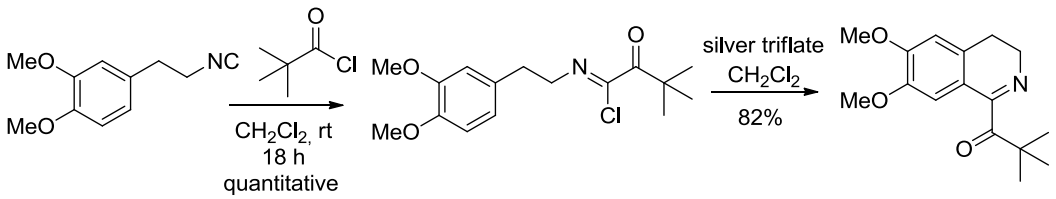


Scheme 8. With α protons the reactivity of ketoimidoyl chlorides is different.

3.3. NEF REACTION OF ISOCYANIDES IN SYNTHESIS

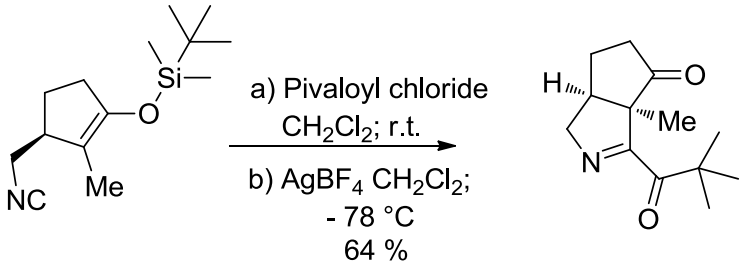
Intramolecular trapping of α-ketoimidoyl chlorides with various nucleophiles has been studied by Livinghouse and his group. In most cases, the α-ketoimidoyl chlorides were activated through formation of nitrilium or iminium species via the addition of various reagents such as silver salts, Lewis acids ($SnCl_4$) or strong Brønsted acids (triflic acid).[11]

The use of silver tetrafluoroborate, from -78 °C to -20 °C in dichloromethane or dichloroethane as solvent, gave the best results for the formation of the nitrilium intermediate. Precipitation of AgCl (in most cases instantaneous) shows the completion of the reaction. In the following example, the imidoyl chloride is obtained from pivaloyl chloride and 2-(3,4-dimethoxyphenyl)ethyl isocyanide. [12] Treatment with silver salts (silver trifluoroborate or silver triflate at -20 °C) forms the dihydroisoquinoline ring (Scheme 9). This reaction can be viewed as a modern revisitation of the Bischler-Napieralski reaction. In opposition with the latter, additions on non-activated aromatic species are possible at low temperature (- 20 °C) as well as with acid sensitive heterocycles such as furans.



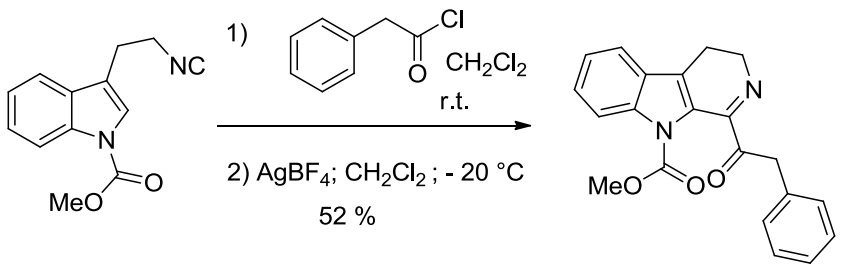
Scheme 9 . Livinghouse's synthesis of dihydroisoquinolines.

Livinghouse exploited this strategy in the synthesis of a lot of different heterocycles, as well in natural product synthesis. Synthesis of 2-acyl pyrrolines has also been reported through intramolecular trapping of the nitrilium ion by a silyl enol ether (Scheme 10).[13]



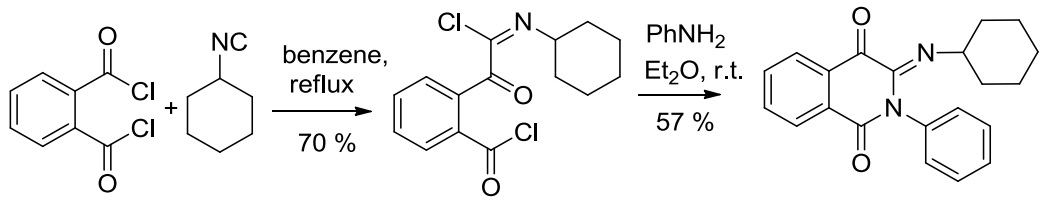
Scheme 10 . Synthesis of 2-acyl pyrrolines.

Five years later the same group reported the total synthesis of Dendrobine using a cyclization of Nef adducts as a key step.[14] The same chemistry has also been used by Cardellina *et al.* in 1989 for the synthesis of antibiotics Eudistomin I and T (Scheme 11).[15]



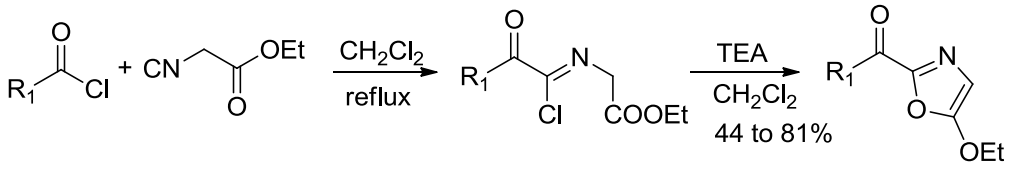
Scheme 11 . Cardellina's synthesis for the preparation of Eudistomin T.

An interesting use of dicarboxylic acid dichlorides in Nef reaction has been proposed by Capuano *et al.* in 1986.[16] The reaction of phthaloyl dichloride with 1 equiv. of cyclohexylisocyanide gives the desired mono keto-imidoyl chloride which reacts further with aniline to form a cyclic amidine (Scheme 12). The same authors used oxalyl chloride and malonyl derivatives in Nef reactions followed by trappings with hydrazine derivatives.



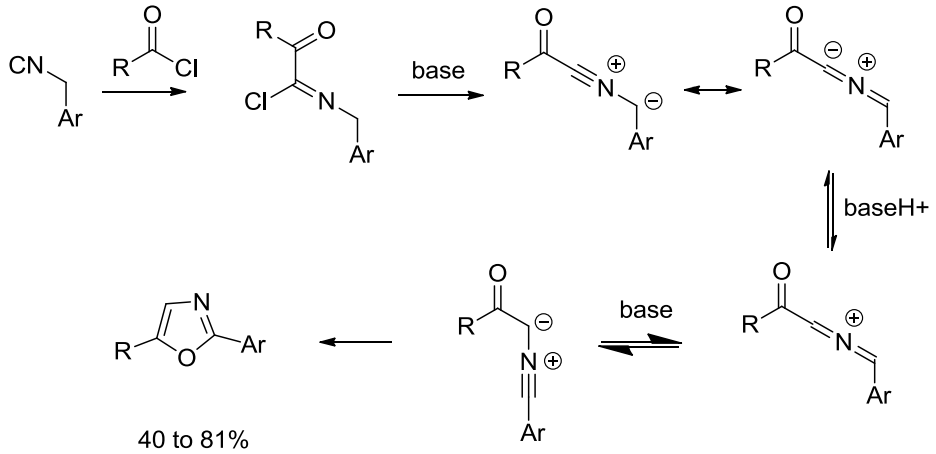
Scheme 12 . Capuano's work using dicarboxylic acid dichlorides.

The formation of 1,3-dipole from α-ketoimidoyl chlorides has been used by Huang for the synthesis of 2-acyl-5-ethoxyoxazoles (Scheme 13).[17]



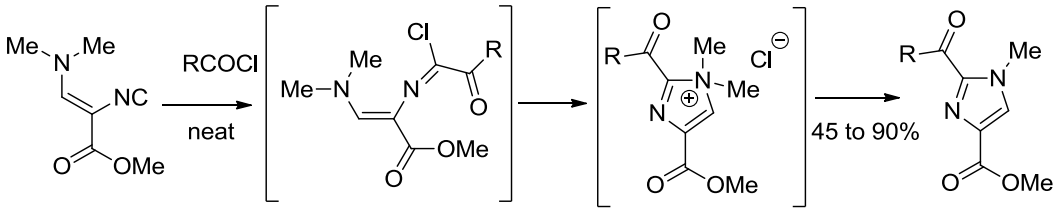
Scheme 13 . Synthesis of 2-acyl-5-ethoxyoxazoles.

El Kaïm and Grimaud reported a novel synthesis of 2,5-disubstituted oxazoles using benzyl isocyanide derivatives. As shown in the scheme, an equilibrium between two nitrile ylides is obtained using 2,6-lutidine as the best base (Scheme 14). This leads to an activation and final cyclization of the benzylic moiety.[18]



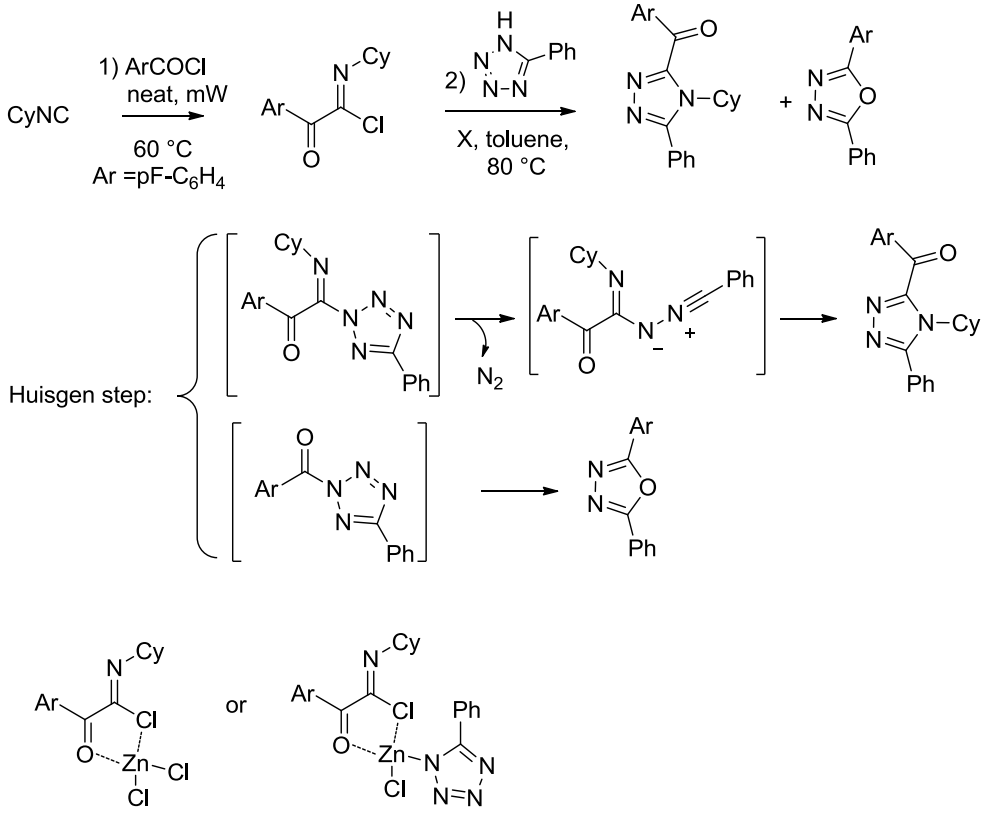
Scheme 14. Proposed mechanism for the synthesis of 2,5-disubstituted oxazoles via α-ketoimidoyl chlorides.

Schöllkopf isocyanide reacts with acyl chlorides (benzoyl, pivaloyl, acetyl, 2 h at 70°C) to give the corresponding α-ketoimidoyl chlorides which cyclize on the dimethylamino moiety with loss of a methyl group and formation of imidazoles in good yields (Scheme 15).[19]



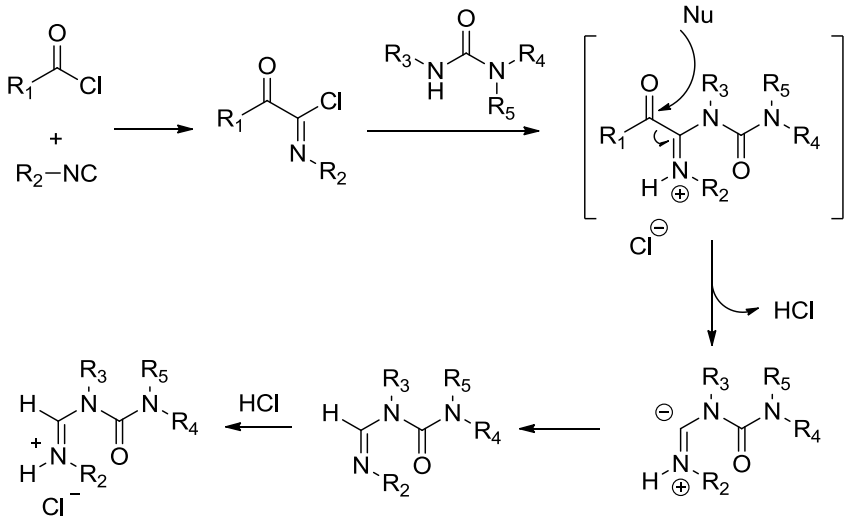
Scheme 15. Reaction between Schöllkopf isocyanide and acyl chloride to give imidazole derivatives.

El Kaïm, Grimaud *et al.* first studied the addition of tetrazoles in an attempt to perfom a Nef/Huisgen fragmentation sequence towards 1,2,4-triazoles.[20] The addition of tetrazoles on Nef adducts in toluene, in the absence of any additive, was sluggish and yielded the expected triazole in a 20% isolated yield from *p*-fluorobenzoyl chloride and cyclohexyl isocyanide. Tetrazoles are rather acidic (pKa around 5) and triethylamine is sufficiently basic to form the more nucleophilic tetrazolyl anion. The reaction was then much faster but the desired triazole was still obtained in a low 39% yield together with 35% of the oxadiazole, coming from a direct Huisgen reaction of N-acyl tetrazole. Here again the deleterious effect of added bases on Nef adduct was observed. Various additives were tested and catalytical amount of $ZnCl_2$ solved the problem enhancing both rates and yields with no more formation of oxadiazole (Scheme 16).



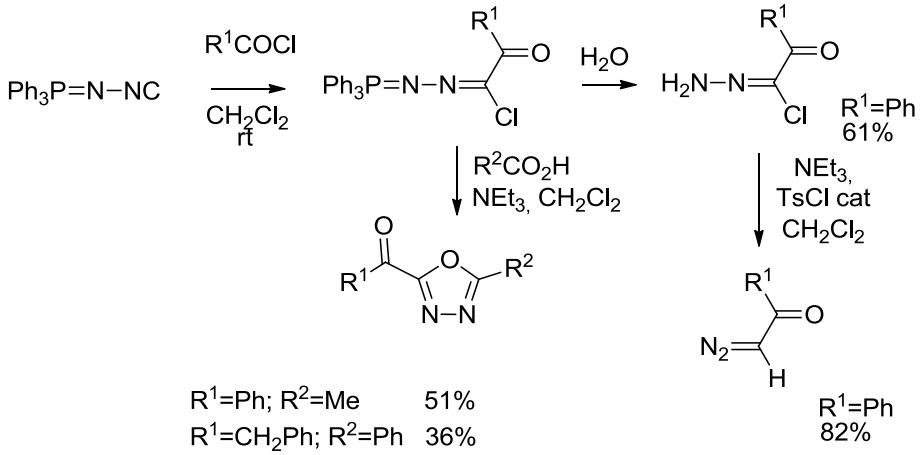
Scheme 16. Three component synthesis of 1,2,4-triazoles.

A synthesis of formamidine ureas involving addition of acyl chlorides and isocyanides to urea derivatives was reported by Finn *et al* and Nef adducts were proposed as intermediates in the mechanism. However a more simple trapping of isocyanides with HCl followed by addition of urea could explain the fate of the reaction and further studies are needed to confirm the mechanism[21] (Scheme 17).



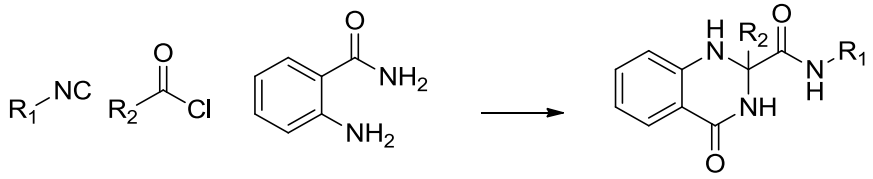
Scheme 17 . Three-component synthesis of formamidine ureas.

The Nef reaction of *N*-isocyanotriphenyl-iminophosphorane has been described by Aller and Molina. [22] The adducts are easily formed at room temperature in dichloromethane. They lead after hydrolysis to hydrazinoyl chlorides, useful synthetic intermediates for the formation of α-diazoketones. Instead of water, carboxylic acids may be added in the presence of triethylamine to form directly oxadiazole derivatives (Scheme 18).



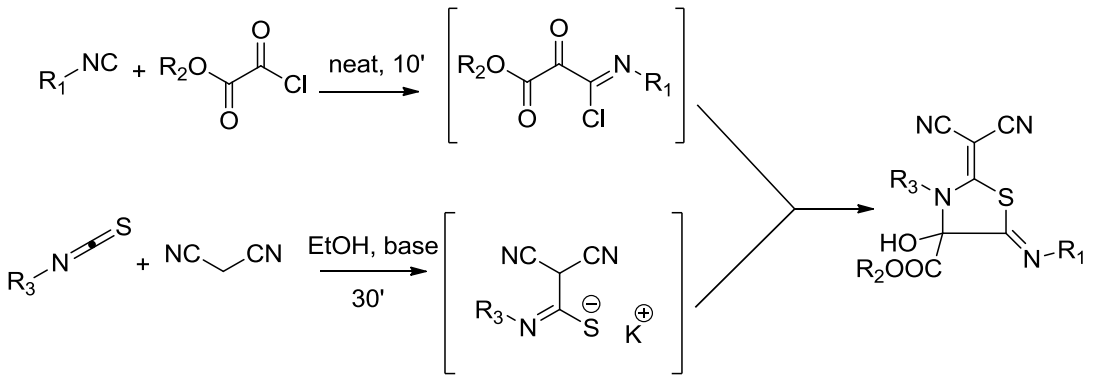
Scheme 18 . Nef reaction of *N*-isocyanotriphenyliminophosphorane.

More recently, in 2013, Shabaani's group described a synthesis of tetrahydroquinazolines via a three component reaction involving a Nef isocyanide reaction and subsequent reaction of an orto-substituted aniline-amide.[23]Although they propose a mechanism in which the imidoyl chloride is the key intermediate for this reaction, we think that the reaction proceeds first with the formation of the α-ketoamide. This is attached by the amine to form an imine, followed by the attack of the amide (Scheme 19).



Scheme 19 . Shaabani's synthesis of tetrahydroquinazolines.

Yavari *et al*. described the use of malononitrile as a potential anionic nucleophile in a reaction involving isothiocyanates and Nef-isocyanide adducts to give highly functionalized 5-iminothiazolidines in very good yields (Scheme 20). [24]



Scheme 20 . 5-iminothiazolidines from Nef adduct and isothiocyanates.

3.4. CONCLUSIONS

The Nef reaction of isocyanides is the first efficient C-C bond formation involving isocyanides. This reaction remained largely ignored for more than a century. After the success encountered by the Ugi and Passerini reactions, it is time to explore its full potential and challenge the problem of the reverse additions triggered by various nucleophilic attacks onto Nef adducts. Some solutions have been brought to achieve three-component couplings using Nef reaction, but the array of nucleophilic partners involved remains scarce and often limited to one or two Nef adducts. One of the strategy that can be adopted is the use of sequential multicomponent reaction, as described in the next chapter.

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4. SYNTHESIS OF ACYL IMIDES, ACYL QUINAZOLINONES AND ACYL INDOLINONES VIA A SEQUENTIAL MULTICOMPONENT REACTION

4.1. RESULTS AND DISCUSSION

As seen in the previous chapter, α-ketoimidoyl chlorides can be considered interesting precursors for further chemical manipulations, [1] but the presence of two different electrophilic sites complicates the situation. Indeed, one electrophilic site is productive (path A) and, allows the disclosure for a series of novel chemical transformations (for example the formation of medicinally important α-ketoamides[2]) while the other one (path B) is unproductive forming an acylated adduct and regenerating the isocyanide [3] (Figure 1).

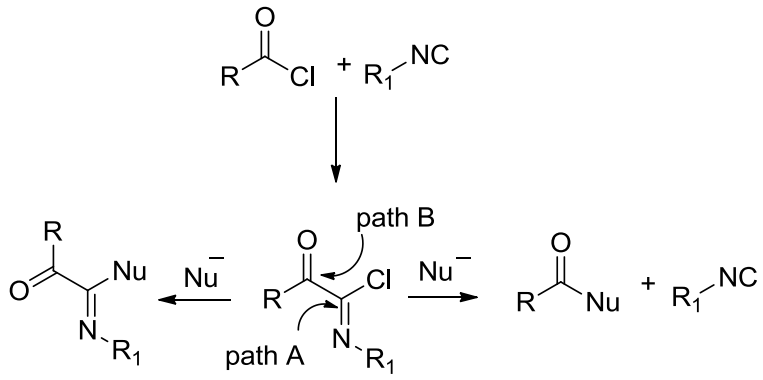
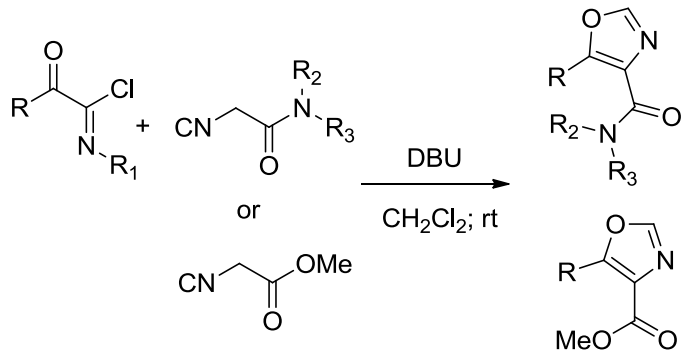


Figure 1. Synthetic paths for the nucleophilic attack to α-ketoimidoyl chlorides.

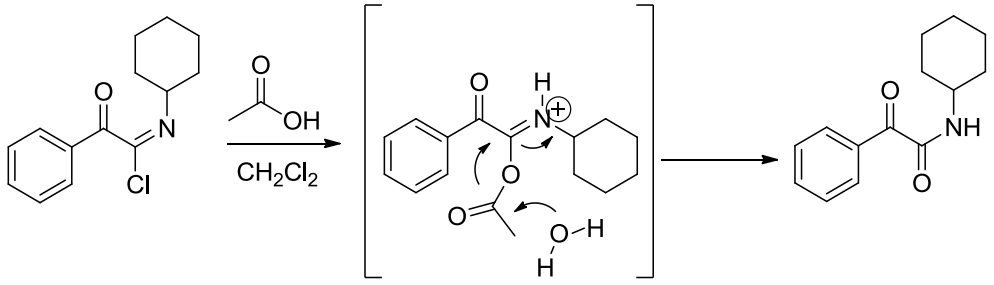
Summarizing, until now, it has been demonstrated that nucleophiles like water, alcohols, hydrazoic acid, tetrazoles,[2] hydrogen sulfide,[3] follow the path A while anilines, primary, secondary and tertiary amines, trialkylphosphites, urea derivatives[4] react according to the path B.

With the aim to discover novel transformations using the α-ketoimidoyl chlorides as key reagents, novel nucleophiles were screened. Using the nucleophilic carbon of isocyanoacetamides or isocyanoesters under base conditions (*e.g.* DBU) gave disappointing results, as only path B was detected, giving 4-acyl-1,3-oxazole derivatives, a class of compounds already described [4] (Scheme 1).



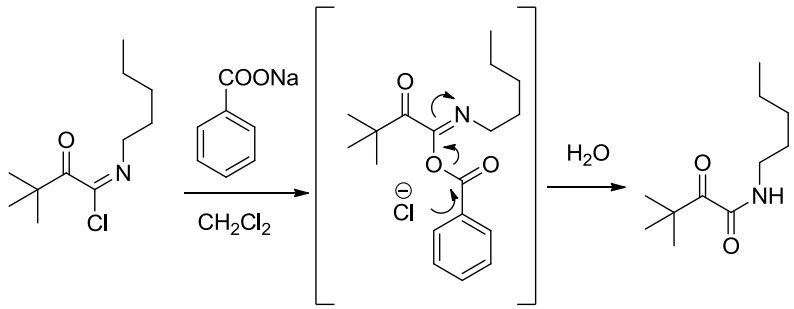
Scheme 1. Isocyanoacetamides and isocyanoesters follow the unproductive path B.

Searching for unreported nucleophiles able to follow the path A, we were intrigued by the hydrolysis of α-ketoimidoyl chlorides to α-ketoamides in presence of acetic acid or formic acid reported by Ugi.[2] This result was again confirmed by us when the imidoylchloride deriving from cyclohexylisocyanide and benzoyl chloride was reacted with acetic acid. We speculated on an active role carried out by the carboxylic acid, acting as nucleophile and not only as proton source, hypothesizing the following scenario: after protonation of the imine nitrogen, the carboxylic anion attacks the imidoyl chloride to give a protonated imino anhydride which is rapidly hydrolyzed to the ketoamide by water (Scheme 2).



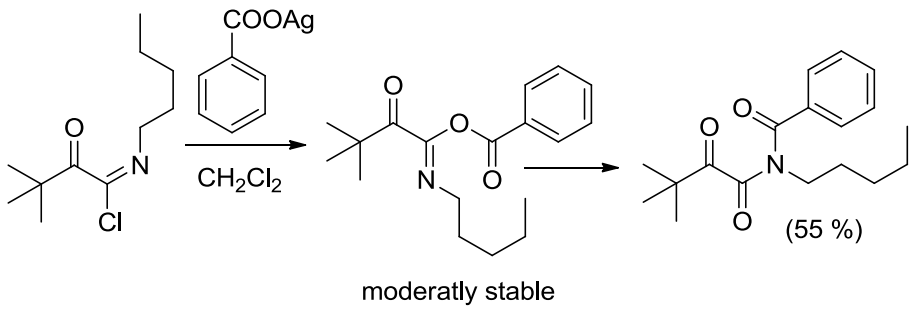
Scheme 2. Proposed reaction mechanism for the formation of ketoamides in the presence of acetic acid.

We, therefore, reasoned that removing the acidity, using a salt of the carboxylic acid, could allow the isocyanide nitrogen atom to participate in a 1,3(*O*,*N*) acyl transfer, also known as Mumm rearrangement,[5] to give an acylimide. Disappointingly, the α-ketoimidoyl chloride deriving from pentylisocyanide and pivaloyl chloride, in the presence of sodium benzoate afforded again the ketoamide . The only plausible reaction mechanism considers the chlorine ion as the culprit of this transformation (Scheme 3).



Scheme 3. Proposed reaction mechanism for the formation of α-ketoamides in the presence of sodium benzoate.

Removing the chlorine ion off the medium, should eventually allow to the Mumm rearrangement to take place. With our delight when silver benzoate was used, we noticed the immediate precipitation of silver chloride and we were able to isolate a novel product different from the α-ketoamide. This compound was enough stable to be purified by column chromatography and for registering proton and carbon NMR spectra, but on standing it converts in a different and more stable compound. Spectroscopic analyses revealed that the first compound was the keto-iminoanhydride, which then converted into the desired α-ketoimide (Scheme 4).



Scheme 4. Silver benzoate reacts in a productive way with imidoylchloride affording the keto-iminoanhydride and then the ketoimide.

It is important to highlight that when benzoic acid was used and a source of silver was added (*e.g.* silver tetrafluoroborate) the only isolated compound was again the α-ketoamide.

A search for the literature revealed us the presence of only few examples where a stable keto-iminoanydride was isolated, in different conditions. [6] The moderate stability of these intermediates with respect those generated with the Ugi reaction both with primary and secondary amines[7] can be explained in the following manner. At first, the carboxylate attacks the nitrilium ion in a stereoselective way, affording the acyl-iminoanhydride with the lone pair and the carboxylate *trans* from each other.[8] In this situation no Mumm rearrangement can occur and the intermediate, in absence of nucleophiles, can be isolated. Its reluctance to undergo a fast isomerization process is due to two factors: a) a lower internal energy compared with the iminoanhydride intermediate which originates from Ugi reaction (Figure 2); b) the neutrality of the medium which requires that the isomerization takes place via nitrogen inversion. As soon as the *E* isomer is formed, it undergoes a fast Mumm rearrangement giving the α-ketoimide (Scheme 5).

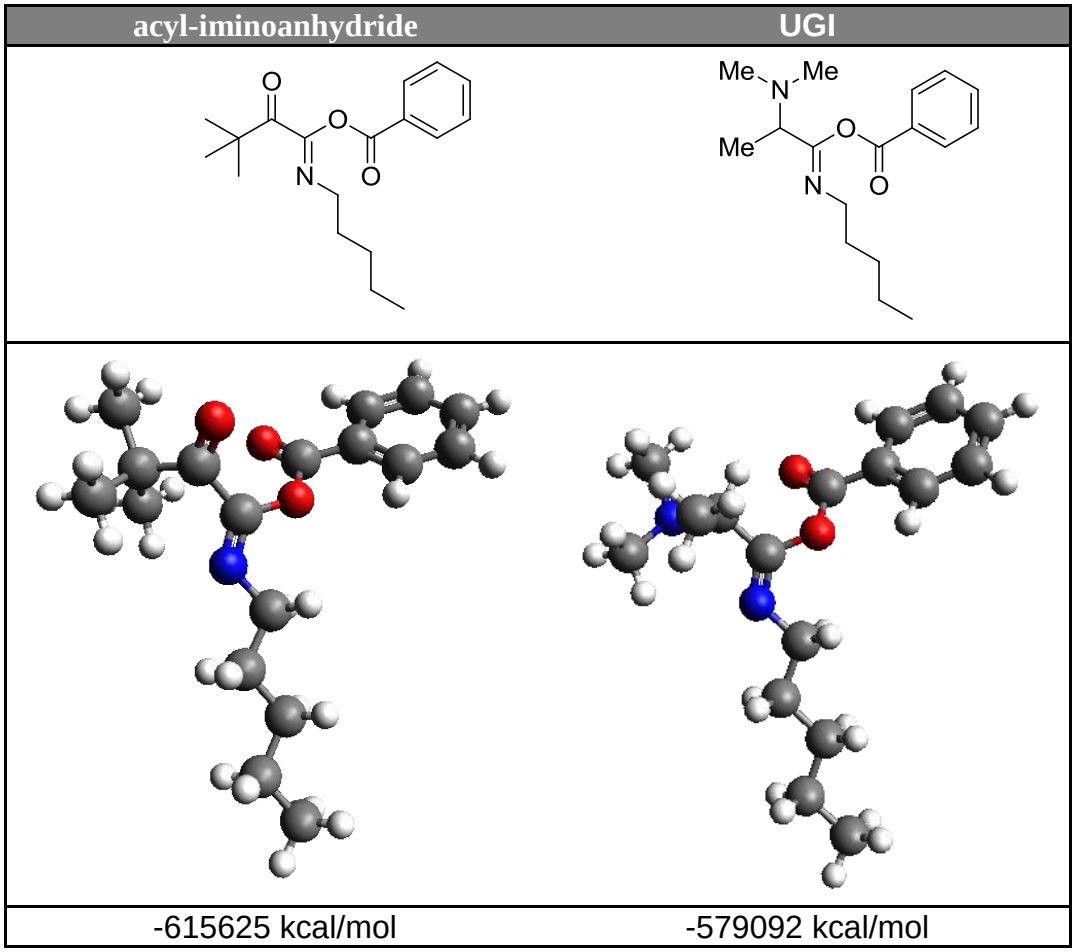
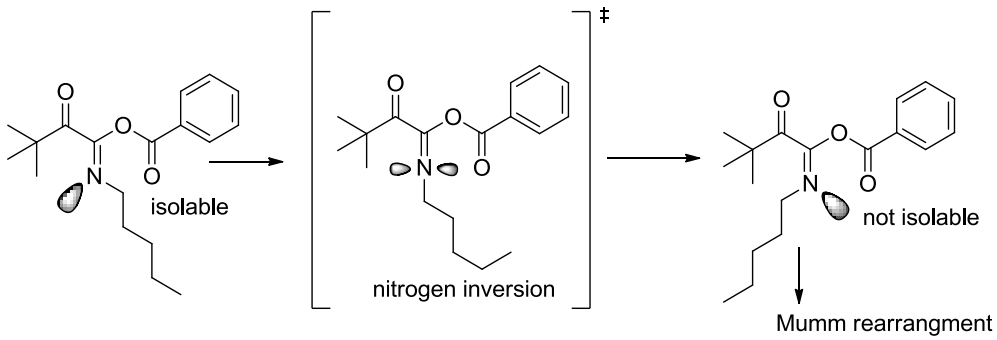


Figure 2. DFT calculation for the acyl-iminoanhydride and its Ugi analogous product.(Dr. Massarotti)



Scheme 5. Proposed mechanism for the Mumm rearrangement.

We next examined the generality of the method by using different acyl chlorides, isocyanides, and silver salts of carboxylic acids, always observing the formation of the acyl-iminoanhydrides followed by the formation of the corresponding α-ketoimides (Figure 3).

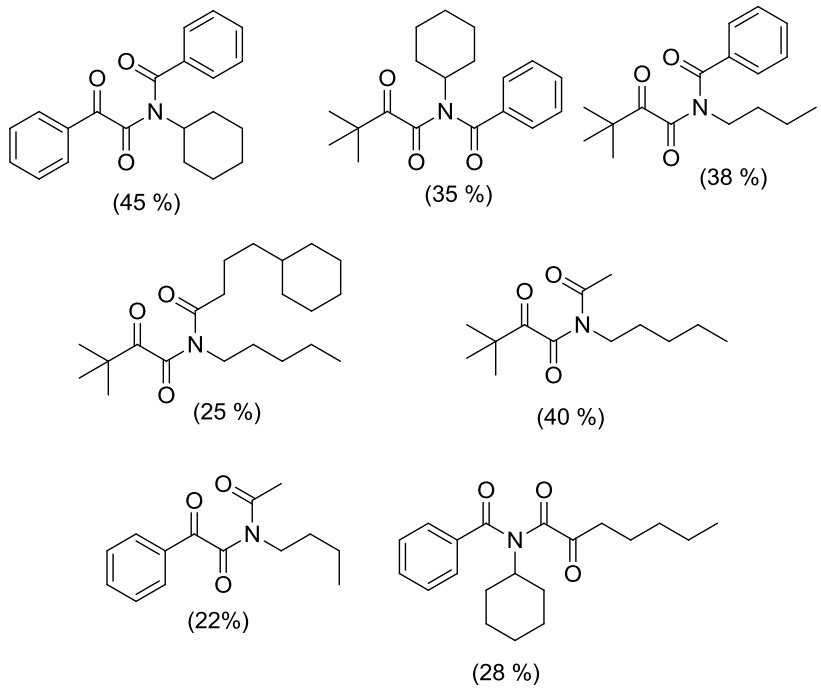
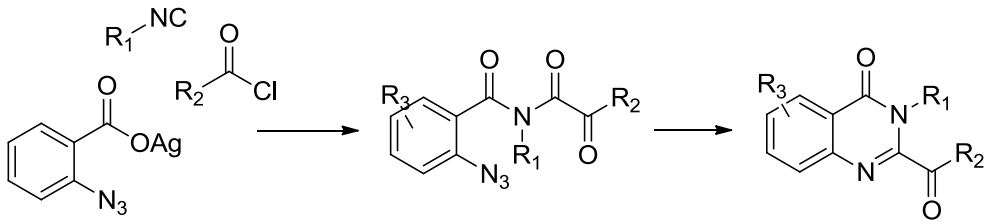


Figure 3. Synthesized α-ketoimides. Yields are referred over two synthetic steps.

There are very few papers on the preparation of α-ketoimides which reflect their difficult preparation most probably due to their reactive nature.[9] This reactive nature has indeed been exploited render them useful intermediates in organic synthesis. Here, we would like to demonstrate, for the first time, the use of an aza-Wittig post-transformation reaction which, exploiting the increased electrophilic nature of the carbonyls of the imide, with respect to a carbonyl of amide, can give access to 2-acyl quinazolinones[10] with yields ranging from 20 to 45 % (Scheme 6).



Scheme 6. α-ketoimide–quinazolinone conversion via an intramolecular aza-Wittig reaction.

As shown, yields are referred over three synthetic steps (an isocyanide Nef reaction, an acylimide formation and an aza-Wittig reaction), indicating an average yield of 60−75% for each synthetic step (Figure 4).

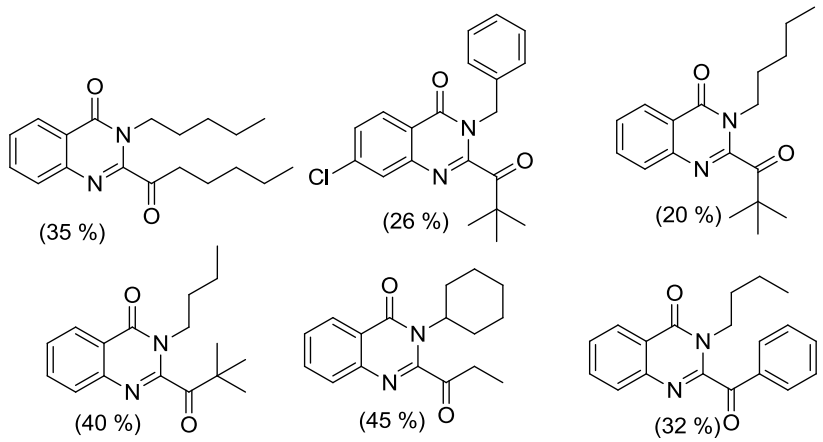
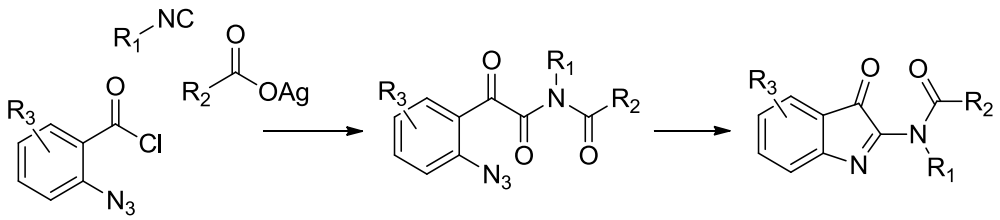


Figure 4. Synthesized 2-acylquinazolinones. Yields are referred over three synthetic steps.

In the same manner, using the same strategy, acyl indolinones could be obtained, using an acyl chloride substituted in ortho with an azido group. After a Nef reaction with an isocyanide, the acyl-iminoanhydride and subsequently the ketoimide could be obtained. The crude product can undergo directly an aza-Wittig reaction to form a new five membered ring (Scheme 7).



Scheme 7. α-ketoimide–indolinone conversion via an intramolecular aza-Wittig reaction.

These structures are not reported in literature, even if some similar analogues without the amide carbonyl are reported (Figure 5). [11] They present a very vivid red colour.

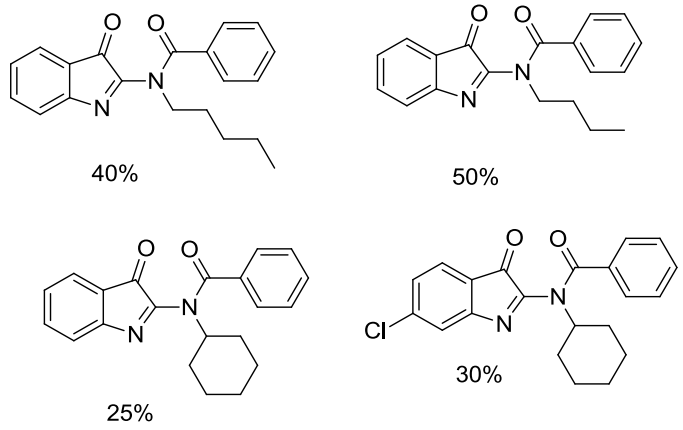
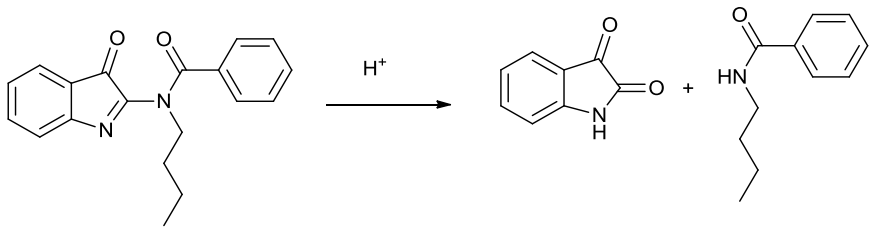


Figure 5. Synthesized indolinones. Yields are referred over three synthetic steps.

But their instability do not rend them good candidates for medicinal chemistry purposes. Indeed, they dissociate very fast in acidic medium to the amide and the indolinone. They do not show neither a good stability in neutral conditions.



Scheme 8. Dissociation of the indolinones in acidic medium.

4.2. CONCLUSIONS

In conclusion, in this chapter, we demonstrated that the silver salt of carboxylic acid attacks in a stereoselective way, the nitrilium ion, gererated by α-ketoimidoyl chlorides, to afford (*Z*)-acyliminoanhydrides. The latter show a weak stability and, after isomerization, undergo a fast Mumm rearrangement to afford α-ketoimides, a class of reactive compounds difficult to synthesize in other ways. Finally, due to their reactive nature, we demonstrated that α-ketoimides can be excellent partners for an intramolecular aza-Wittig reaction to afford 2-acyl quinazolinones and acyl indolinones.

4.3. EXPERIMENTAL SECTION

Materials and methods

Commercially available reagents and solvents were used without further purification and were purchased from Sigma Aldrich and Alfa Aesar.

When needed, the reactions were performed in flame- or oven-dried glassware under a positive pressure of dry N_2 . NMR spectra were recorded with a JEOL ECP 300 MHz spectrometer and the δ values are in part per million. Mass spectra were recorded using a Thermo Finningan LCQ Deca XP-plus equipped with an ESI source and an ion trap detector. Infrared spectra were recorded on a FT-IR Thermo-Nicolet Avatar spectrometer with absorption maxima (ν_{max}) recorded in wavenumbers (cm^{-1}). Column chromatography was performed on silica gel Merck Kieselgel (0.063-0.200 mm; 70-230 mesh ASTM) and Biotage Isolera One (silica gel Merck Kieselgel 0.040-0.063; 230-400 mesh ASTM). 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 F254). When necessary they were developed with $KMnO_4$ or Dragendorff reagent. Elemental analysis (C, H, N) of the 2-acyl quinazolinones are within ± 0.4% of the calculated values.

Due to delicate nature of acyl imides, satisfactory elemental analysis for acyl imides can not be obtained, but HRMS were recorded.

DFT calculation for compound 18 and its Ugi analogous product.

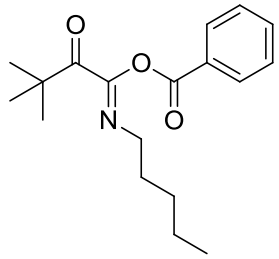
Complete geometry optimization and the atomic charges of the acyl-iminoanhydride and its relative UGI analogous structures was performed *in vacuo* at the hybrid DFT B3LYP level, using the 6-31+G* basis set with the software GAMESS (M. W. Schmidt, K. K. Baldridge, J. A. Boatz, S. T. Elbert, M. S. Gordon, J. H. Jensen, S. Koseki, N. Matsunaga, K. A. Nguyen, S. Su, T. L. Windus, M. Dupuis, J. A. Montgomery, *J. Comp. Chem.* **1993**, *14*, 1347-

1363). 3D pictures were made in Avogadro (Avogadro: an open-source molecular builder and visualization tool. Version 1.0.1. http://avogadro.openmolecules.net/).

General procedure and characterization data for acyl imides

Isocyanide (1 eq.) was dissolved in dry DCM (0.5 M) under nitrogen then 1 eq. of acyl chloride was added. The reaction mixture was refluxed for 2 hours (for aliphatic acyl chlorides) or 24 hours (aromatic acyl chlorides) until completion of the reaction. Then 1.2 eq. of silver carboxylate (silver benzoate, acetate, cyclohexanebutyrrate) were added at -10°C, and an instantaneous precipitation of silver chloride was observed. The reaction was let warm to room temperature, then the suspension was filtered to remove silver chloride, and the solvent was evaporated. The imino-anhydride is let rearrange into the corresponding acyl-imide (24 hours). The product was purified by column chromatography using a gradient of PE/EtOAc from 95:5 to 9:1.

Benzoic-3,3-dimethyl-2-oxo-*N*-pentylbutanimidic anhydride

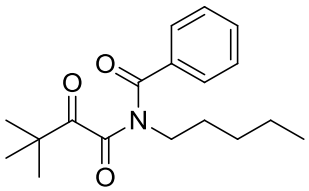


Prepared from pentyl isocyanide (105 µl, 0.83 mmol), pivaloyl chloride (102µl, 0.83 mmol) and silver benzoate (229 mg, 1.00 mmol). Eluant for purification: PE/EtOAc 95:5. Obtained 138 mg as a colourless oil, yield 55%. It converts into the acyl imide in 24 hours, (^{1}H and ^{13}C -NMR spectra already show trace of the rearranged product).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J=7.9 Hz, 2-H), 7.61 (m, 1-H), 7.48 (t, J=7.9 Hz, 2-H), 3.58 (t, J=7.0 Hz, 9-H), 1.68 (m, 2-H), 1.39 (s, 9-H), 1.38-1.33 (m, 4-H), 0.90 (t, J=7 Hz, 3-H); ^{13}C-NMR (75 MHz, $CDCl_3$)

δ 199.0, 163.9, 144.6, 134.1, 130.4, 128.9, 128.2, 48.5, 43.9, 29.7, 29.6, 27.3, 22.4, 14.1.

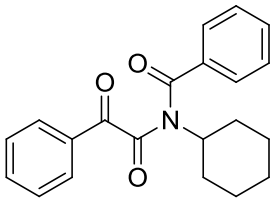
_N_-(3,3-dimethyl-2-oxobutanoyl)-_N_-pentylbenzamide



Obtained quantitatively from benzoic-3,3-dimethyl-2-oxo-_N_-pentylbutanimidic anhydride after rearrangement.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.58-7.46 (m, 5-H), 3.68 (t, J=7.5 Hz, 2-H), 1.54-1.51 (m, 2-H), 1.34 (s, 9-H), 1.19-1.13 (m, 4-H), 0.78 (t, J= 6.5 Hz, 3-H);^{13}C-NMR (75 MHz, $CDCl_3$) δ 204.5, 174.4, 171.2, 133.2, 132.5, 128.9, 128.1, 45.6, 42.3, 28.7, 28.3, 26.8, 22.1, 13.9; IR (liquid film): 2959, 2346, 1679, 1353, 1270, 1065, 698 cm^{-1};MS (ESI) m/z 304 $(M+H)^+$. HRMS (ESI^+) calcd. for $C_{18}H_{26}NO_3$ $[M+H]^+$ 304.1907, found 304.1911.

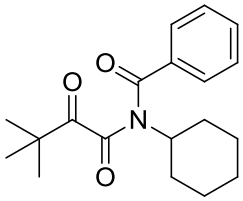
_N_-cyclohexyl-_N_-(2-oxo-2-phenylacetyl)benzamide



Prepared from cyclohexyl isocyanide (113 µl, 0.91 mmol), benzoyl chloride (106µl, 0.91 mmol) and silver benzoate (252 mg, 1.10 mmol). Eluant for purification: PE/EtOAc 95:5. Obtained 159 mg as a white solid, yield 52%.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.81(d, J = 9 Hz, 2-H), 7.58-7.52 (m, 3-H), 7.40-7.35 (m, 3-H), 7.25 (t, J =7 Hz, 2-H), 4.21-4.08 (m, 1-H), 2.39-2.21 (m, 2-H), 1.96-1.79 (m, 4-H), 1.35-1.15 (m, 4-H);^{13}C-NMR (75 MHz, $CDCl_3$) δ 187.7, 174.6, 169.9, 136.2, 134.1, 132.9, 129.9, 129.3, 128.8, 128.5, 59.1, 29.8, 26.4, 25.3; m.p. 92°C; IR (KBr): 2950,2200,1580,1158,768 cm^{-1}; HRMS (ESI^+) calcd. for $C_{21}H_{22}NO_3$ $[M+H]^+$ 336.1594, found 336.1599.

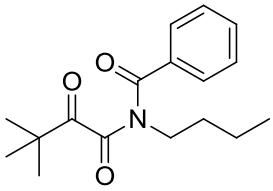
***N*-cyclohexyl-*N*-(3,3-dimethyl-2-oxobutanoyl)benzamide**



Prepared from cyclohexyl isocyanide (113 µl, 0.91 mmol), pivaloyl chloride (112µl, 0.91 mmol) and silver benzoate (252 mg, 1.10 mmol). Eluant for purification: PE/EtOAc 95:5. Obtained 100 mg as a colourless oil, yield 35%.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.65-7.39 (m, 5-H), 3.75-3.62 (m, 1-H), 2.35-2.15 (m, 2-H), 1.84-1.68 (m, 4-H), 1.59-1.35 (m, 2-H), 1.30 (s, 9-H), 1.19-1.00 (m, 2-H);^{13}C-NMR (75.4 MHz, $CDCl_3$) δ 203.9, 175.3,171.0, 133.8, 132.8, 130.4, 128.9, 60.0, 42.3, 29.5, 27.4, 26.2, 25.0; IR (liquid film): 2950, 1710, 1420, 1360, 1220 cm^{-1}; HRMS (ESI^+) calcd. for $C_{19}H_{26}NO_3$ $[M+H]^+$ 316.1907, found 316.1902.

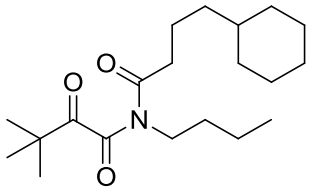
***N*-butyl-*N*-(3,3-dimethyl-2-oxobutanoyl)benzamide**



Prepared from butyl isocyanide (126 µl, 1.20 mmol), pivaloyl chloride (147 µl, 1.20 mmol) and silver benzoate (329 mg, 1.44 mmol). Eluant for purification: PE/EtOAc 95:5. Obtained 132 mg as a colourless oil, yield 38%.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.58-7.44 (m, 5-H), 3.68 (t, J=7.5 Hz, 2-H), 1.51 (q, J=6.5 Hz, 2-H), 1.31 (s, 9-H), 1.23-1.16 (m, 2-H), 0.78 (t, J= 7.2 Hz, 3-H);^{13}C-NMR (75 MHz, $CDCl_3$) δ 204.3, 174.4, 171.2, 133.2, 132.5, 128.9, 128.1, 45.4, 42.3, 30.8, 26.8, 19.8, 13.5; IR (liquid film): 2932, 2847, 1717, 1027 cm^{-1}; HRMS (ESI^+) calcd. for $C_{17}H_{24}NO_3$ $[M+H]^+$ 290.1751, found 290.1763.

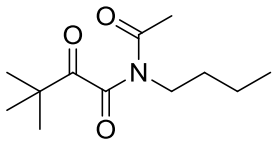
***N*-butyl-*N*-(4-cyclohexylbutanoyl)-3,3-dimethyl-2-oxobutanamide**



Prepared from butyl isocyanide (87 µl, 0.83 mmol), pivaloyl chloride (102 µl, 0.83 mmol) and silver cyclohexanebutyrrate (277 mg, 1.00 mmol). Eluant for purification: PE/EtOAc 9:1. Obtained 70 mg as a colourless oil, yield 25%.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.65 (t, J= 6.5 Hz, 2-H), 2.46 (t, J=7.5 Hz, 2-H), 1.75-1.51 (m, 10-H), 1.44-1.12 (m, 18-H), 0.94 (t, J= 7.5 Hz, 3-H);^{13}C-NMR (75 MHz, $CDCl_3$) δ 204.1, 176.1, 171.1, 42.9, 42.0, 37.6, 36.9, 35.1, 33.3, 31.2, 26.8, 26.7, 26.4, 21.6, 20.2, 13.8; IR (liquid film): 2970,2240,1698,1642, 1005 cm^{-1}; HRMS (ESI^+) calcd. for $C_{20}H_{36}NO_3$ $[M+H]^+$ 338.2690, found 338.2685.

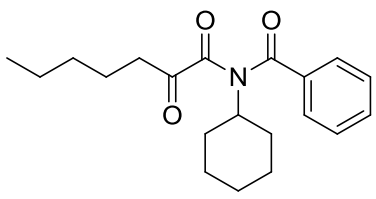
***N*-acetyl-*N*-butyl-3,3-dimethyl-2-oxobutanamide**



Prepared from butyl isocyanide (96 µl, 0.91mmol), pivaloyl chloride (112µl, 0.91mmol) and silver acetate (184mg, 1.10 mmol). Eluant for purification: PE/EtOAc 9:1.Obtained 83 mg as a colourless oil, 40%.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.60 (t, J= 7.5 Hz, 2-H), 2.23 (s, 3-H), 1.62-1.49 (m, 2-H), 1.39-1.25 (m, 2-H), 1.20 (s, 9-H), 0.91 (t, J= 7.5 Hz, 3-H);^{13}C-NMR (75 MHz, $CDCl_3$) δ 203.7, 173.5, 170.7, 60.4, 43.5, 31.0, 26.6, 22.9, 20.1, 13.7; IR (liquid film): 2962,1348,1704,1683,1210 cm^{-1}; HRMS (ESI^+) calcd. for $C_{12}H_{22}NO_3$ $[M+H]^+$ 228.1594, found 228.1597.

***N*-cyclohexyl-*N*-(2-oxoheptanoyl)benzamide**

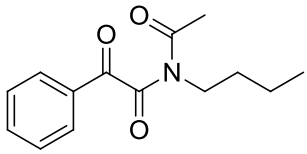


Prepared from cyclohexyl isocyanide (113 µl, 0.91 mmol), hexanoyl chloride (128 µl, 0.91 mmol) and silver benzoate (252 mg, 1.10 mmol). Eluant for purification: PE/EtOAc 95:5.

Obtained 84 mg as a yellow oil, yield 28%.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.70- 7.42 (m,5-H), 4.20-4.05 (m, 1-H), 2.50 (t, J=7.5 Hz, 2-H), 2.33-2.01 (m, 2-H), 1.94-1.56 (m, 6-H), 1.49-1.05 (m, 6-H), 0.83 (t, J= 6.9 Hz, 3-H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) δ 198.9, 174.8, 170.5, 136.4, 133.0, 129.1, 129.0, 58.7, 38.0, 31.0, 29.8, 26.5, 26.3, 25.1, 22.4, 13.9; IR (liquid film): 2931, 2857, 1659, 1450, 711 cm^{-1}; HRMS (ESI^+) calcd. for $C_{20}H_{28}NO_3$ $[M+H]^+$ 330.2064, found 330.2071.

N-acetyl-N-butyl-2-oxo-2-phenylacetamide



Prepared from butyl isocyanide (102 µl, 0.81 mmol), benzoyl chloride (108 µl, 0.81 mmol) and silver acetate (192 mg, 1.00 mmol). Eluant for purification: PE/EtOAc 9:1. Obtained 75 mg as a yellow oil, 22%.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60- 7.35 (m,5-H), 3.52 (t, J= 7.5 Hz, 2-H), 2.35 (s, 3-H), 1.73-1.50 (m, 2-H), 1.24-1.06 (m, 2-H), 0.83 (t, J= 6.9 Hz, 3-H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) δ 192.3, 173.5, 170.1, 136.2, 135.1, 129.1, 129.0, 128.8, 126.4, 61.4, 44.2, 23.2, 20.8, 13.8; IR (liquid film): 2951, 2855, 1709, 1460, 711 cm^{-1}; HRMS (ESI^+) calcd. for $C_{14}H_{17}NO_3$ $[M+H]^+$ 330.2064, found 330.2071.

General procedure and characterization data for acyl quinazolinones.

Procedure for the preparation of benzoate silver salts.

2-azido silver benzoate: 2-azido benzoic acid was dissolved in acetonitrile/water 3:1 (0.2 M) followed by 0,5 eq. of Ag_2O. The suspension was stirred vigorously in the dark at 70°C for 1h, then, after cooling to room temperature, it was filtered through celite and concentrated to dryness to afford

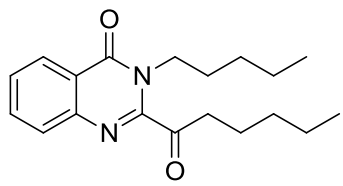
2-azido silver benzoate (65%), which must be protected from light. 2-azido-4-chloro silver benzoate was prepared with the same procedure from 2-azido-4-chloro benzoic acid.

General procedure for the synthesis of acyl quinazolinones .

Isocyanide (1 eq.) was dissolved in dry DCM (0.5 M) under nitrogen, then 1 eq. of acyl chloride was added. The reaction mixture was refluxed for 2 hours (for aliphatic acyl chlorides) or 24 hours (aromatic acyl chlorides) until completion of the reaction. Then 1.2 eq. of silver carboxylate (2-azido silver benzoate or 2-azido-4-chloro silver benzoate) were added at -10°C and an instantaneous precipitation of silver chloride was observed. The reaction was let warm to room temperature, then the suspension was filtered to remove silver chloride, and the solvent was evaporated. The imino-anhydride was let rearrange into the corresponding acyl imide at room temperature. The crude product was then dissolved in dry toluene (0.5 M) and 1.1 eq of PPh_3 were added, and the reaction was refluxed overnight, under nitrogen atmosphere. The product was purified by column chromatography using a gradient of PE/EtOAc (95:5 to 8:2) as eluent.

Characterization data for acyl quinazolinones.

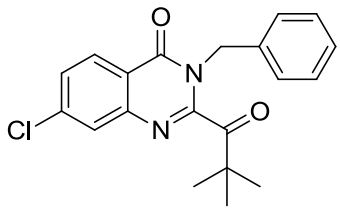
2-hexanoyl-3-pentylquinazolin-4(3*H*)-one



Prepared from pentyl isocyanide (100 µl, 0.79 mmol), hexanoyl chloride (110 µl, 0.79 mmol) and 2-azido silver benzoate (254 mg, 0.95 mmol). The crude imide was then refluxed in toluene overnight with PPh_3 (227 mg, 0.87 mmol). Eluant for purification: PE/EtOAc 95:5. Obtained 87 mg as a pale yellow oil, yield 35%.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.29 (d, J= 6.5 Hz, 1-H), 7.80-7.71 (m, 2-H), 7.60-7.52 (m, 1-H), 4.14 (t, J=7.6 Hz, 2-H), 3.15 (t, J= 7.3 Hz, 2-H), 1.75-1.69 (m, 4-H), 1.40-1.25 (m, 8-H), 0.98-0.85 (m, 6-H); ^{13}C-NMR (75.4 MHz, $CDCl_3$) δ 198.7, 161.7, 150.9, 146.1, 134.4, 128.5, 128.0, 127.1, 122.2, 44.6, 40.8, 31.4, 29.3, 29.1, 23.3, 22.6, 22.4, 14.1, 14.0; IR (liquid film): 2940,2100,1649,1583,842 cm^{-1}; MS (ESI) m/z 316 $(M+H)^+$;$C_{19}H_{26}N_2O_2$: calcd. C, 72.58; H, 8.33; N, 8.91; found C, 72.79; H, 8.39; N, 8.85.

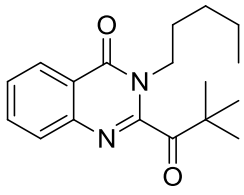
3-benzyl-7-chloro-2-pivaloylquinazolin-4(3*H*)-one



Prepared from benzyl isocyanide (125 µl, 1.02 mmol), pivaloyl chloride (125 µl, 1.02 mmol) and 2-azido-4-chloro silver benzoate (370 mg, 1.22 mmol). The crude imide was then refluxed in toluene overnight with PPh_3 (293 mg, 1.12 mmol). Eluant for purification: PE/EtOAc 95:5. Obtained 94 mg as an orange solid, yield 26%.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J=8.5 Hz, 1-H), 7.69 (s, 1-H), 7.58-7.48 (m, 1-H),7.34-7.23 (m, 3-H), 7.19-7.13 (m, 2-H), 5.40 (s, 2-H), 1.07 (s, 9-H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 204.4, 161.3, 151.7, 146.9, 141.0, 136.1, 128.9, 128.8, 128.5, 128.3, 127.6, 126.9, 120.4, 46.0, 44.6, 27.3; IR (KBr): 2964,1948,1700,1587,688 cm^{-1}; m.p. 111°C; MS (ESI) m/z 355 $(M+H)^+$; $C_{20}H_{19}ClN_2O_2$: calcd. C, 67.70; H, 5.40; N, 7.89; found C, 67.82; H, 5.34; N, 7.81.

3-pentyl-2-pivaloylquinazolin-4(3*H*)-one

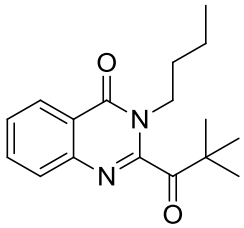


Prepared from pentyl isocyanide (156 µl, 1.23 mmol), pivaloyl chloride (151 µl, 1.23 mmol) and 2-azido silver benzoate (396 mg, 1.48 mmol). The crude imide was then refluxed in toluene overnight with PPh_3 (353 mg, 1.35

mmol). Eluant for purification: PE/EtOAc 8:2. Obtained 74 mg as a colourless oil orange solid, yield 20%.

^{1}H-NMR (300 MHz, $CDCl_3$) δ (8.28, dd, J= 8.0 Hz, 1-H), 7.75-7.62 (m, 3-H), 7.52-7.48 (m, 2-H), 3.80 (t, J=7.8 Hz, 2-H), 1.80-1.60 (m, 2-H), 1.38 (s, 9-H), 1.36-1.29 (m, 2-H), 0.89 (t, J= 7.2 Hz, 3-H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 204.7, 161.4, 151.6, 146.4, 134.3, 127.8, 127.7, 126.8, 121.8, 45.8, 44.6, 29.1, 28.5, 27.4, 22.2, 14.0; IR (liquid film): 2958,1681,1592,1060,770 cm^{-1}; MS (ESI) m/z 301 $(M+H)^+$;$C_{18}H_{24}N_2O_2$: calcd. C, 71.97; H, 8.05; N, 9.33; found C, 72.03; H, 8.01; N, 9.38.

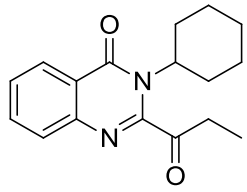
3-butyl-2-pivaloylquinazolin-4(3*H*)-one



Prepared from butyl isocyanide (126 µl, 1.20 mmol), pivaloyl chloride (147 µl, 0.79 mmol) and 2-azido silver benzoate (385 mg, 1.44 mmol). The crude imide was then refluxed in toluene overnight with PPh_3 (345 mg, 1.32 mmol). Eluant for purification: PE/EtOAc 9:1. Obtained 137 mg as a colourless oil, yield 40%.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.26 (d, J= 7.95 Hz, 1-H), 7.73-7.55 (m, 2-H), 7.48 (t, J=7.5 Hz, 1-H), 3.78 (t, J=7.9 Hz, 2-H), 1.76-1.65 (m, 2-H), 1.36 (s, 9-H), 1.30-1.27 (m, 2-H), 0.91 (t, J=7.3 Hz, 3-H);^{13}C-NMR (75 MHz, $CDCl_3$) δ 204.7, 161.4, 151.6, 146.4, 134.4, 128.1, 127.7, 127.0, 121.8, 45.6, 38.8, 30.7, 27.8, 20.2, 13.7; IR (liquid film): 2910,1936,1709,1524,742 cm^{-1}; MS (ESI) m/z 287 $(M+H)^+$; $C_{17}H_{22}N_2O_2$: calcd. C, 71.30; H, 7.74; N, 9.78; found C, 71.48; H, 7.72; N, 9.67.

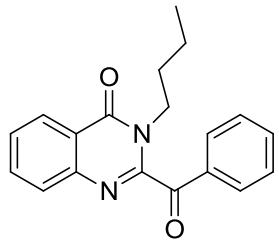
3-cyclohexyl-2-propionylquinazolin-4(3*H*)-one



Prepared from cyclohexyl isocyanide (136 µl, 1.10 mmol), propionyl chloride (95 µl, 1.10 mmol) and 2-azido silver benzoate (353 mg, 1.32 mmol). The crude imide was then refluxed in toluene overnight with PPh_3 (317 mg, 1.21 mmol). Eluant for purification: PE/EtOAc 9:1. Obtained 141 mg as a yellow oil, yield 45%.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.25 (d, J= 7.9 Hz, 1-H), 7.76-7.63 (m,2-H), 7.50 (t, J=7.7 Hz, 1-H),3.90 (m, 1-H), 3.10 (t, J=7.3Hz, 2-H), 2.53 (m, 2-H), 1.92-1.59 (m, 4-H), 1.43-1.18 (m, 7-H);^{13}C-NMR (75.4 MHz, $CDCl_3$) δ 199.6, 162.0, 153.1, 145.9, 134.3, 128.1, 127.5, 126.9, 122.9, 61.7, 34.7, 29.5, 26.5, 25.2, 7.6; IR (liquid film): 2287,1670,1573, 1180, 892 cm^{-1}; MS (ESI) m/z 285 $(M+H)^+$;$C_{17}H_{20}N_2O_2$: calcd. C, 71.81; H, 7.09; N, 9.85; found C, 71.89; H, 7.15; N, 9.78.

2-benzoyl-3-butylquinazolin-4(3*H*)-one



Prepared from butyl isocyanide (126 µl, 1.20 mmol), benzoyl chloride (139 µl, 1.20 mmol) and 2-azido silver benzoate (385 mg, 1.44 mmol). The crude imide was then refluxed in toluene overnight with PPh_3 (345 mg, 1.32 mmol). Eluant for purification: PE/EtOAc 9:1. Obtained 118 mg as a yellow solid, yield 32%.

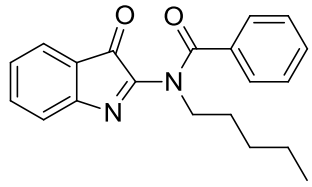
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.35 (d, J= 8.0 Hz, 1-H), 8.01 (d, J= 7.3 Hz, 2-H), 7.80-7.65 (m, 3-H), 7.60-7.45 (m, 3-H),3.98 (t, J=7.9 Hz, 2-H), 1.75-1.65 (m,2-H), 1.35-1.17 (m, 2-H), 0.83 (t, J=7.3 Hz, 3-H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 187.8, 161.4, 151.4, 146.5, 135.1, 134.6, 134.2, 130.6, 129.1, 128.1, 127.9, 127.0, 122.0, 45.0, 31.2, 20.1, 13.6; IR (KBr): 2904,1715,1680,740 cm^{-1};

m.p. 90°C; MS (ESI) m/z 307 $(M+H)^+$; $C_{19}H_{18}N_2O_2$: calcd. C, 74.49; H, 5.92; N, 9.14; found C, 74.43; H, 5.99; N, 9.08.

General procedure and characterization data for indolinones.

Isocyanide (1 eq.) was dissolved in dry DCM (0.5 M) under nitrogen, then 1 eq. of acyl chloride (2-azido benzoyl chloride or 2-azido-4-chloro benzoyl chloride) was added. The reaction mixture was refluxed for 24 hours, until completion of the reaction. Then 1.2 eq. of silver benzoate were added at -10°C and an instantaneous precipitation of silver chloride was observed. The reaction was let warm to room temperature, then the suspension was filtered to remove silver chloride, and the solvent was evaporated. The imino-anhydride was let rearrange into the corresponding acyl imide at room temperature. The crude product was then dissolved in dry toluene (0.5 M) and 1.1 eq of PPh_3 were added, and the reaction was refluxed for 3-5 hours, under nitrogen atmosphere. The product was purified by column chromatography using a gradient of PE/EtOAc (95:5 to 7:3) as eluent.

N-(3-oxo-3H-indol-2-yl)-N-pentylbenzamide

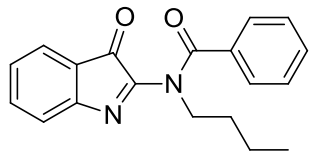


Prepared from pentyl isocyanide (125 µl, 1.02 mmol), 2-azido benzoyl chloride (125 µl, 1.02 mmol) and silver benzoate (370 mg, 1.22 mmol). The crude imide was then refluxed in toluene for 3h with PPh_3 (293 mg, 1.12 mmol). Eluant for purification: PE/EtOAc 8:2. Obtained 90 mg as a red oil, yield 40%.

^{1}H-NMR (300 MHz, CDCl3, 323 K) δ 7.80-7.04 (m, 9-H), 4.09 (t, J=7.35 Hz, 2-H), 1.90-1.75 (m, 2-H), 1.38-1.22 (m, 2-H), 0.90 (t, J=7.35, 3-H);^{13}C-NMR (75.4 MHz, CDCl3, 323 K) δ 185.7, 171.4, 162.9, 159.1, 137.5, 132.0, 128.8,

128.7, 126.9, 126.8, 125.4, 121.4, 121.1, 49.5, 29.5, 29.3, 22.5, 14.1; IR (liquid film): 2970, 2343, 1708, 1681, 1560, 709; MS (ESI) m/z 321 (100%) $(M+H)^+$;$C_{20}H_{20}N_2O_2$: calcd. C, 74.98; H, 6.29; N, 8.74; O, 9.99; found C, 75.22; H, 6.43; N, 8.65; O, 9.67.

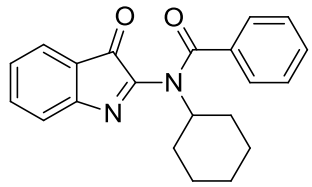
N-butyl-N-(3-oxo-3H-indol-2-yl)benzamide



Prepared from butyl isocyanide (115 µl, 1.10 mmol), 2-azido benzoyl chloride (128 µl, 1.10 mmol) and silver benzoate (380 mg, 1.32 mmol). The crude imide was then refluxed in toluene for 5h with PPh_3 (303 mg, 1.18 mmol). Eluant for purification: PE/EtOAc 8:2. Obtained 112 mg as a red oil, yield 50%.

^{1}H-NMR (300 MHz, CDCl3, 323 K) δ 7.63 (dd, J= 7.45 Hz, J=1.5 Hz, 2-H), 7.50-7.20 (m, 6-H), 7.07 (t, J= 7.5 Hz, 1-H), 4.10 (t, J=7.30 Hz, 2-H), 1.85-1.75 (m, 2-H), 0.95 (t, J=7.05 Hz, 2-H);^{13}C-NMR (75.4 MHz, CDCl3, 323 K) δ 185.7, 170.9, 162.8, 159.1, 137.6, 137.5, 132.0, 128.9, 128.8, 126.9, 125.4, 121.4, 121.1, 49.3, 30.7, 20.3, 13.9;IR (liquid film): 2958, 2348, 1737, 1678, 1560, 717;MS (ESI) m/z 307 (100%) $(M+H)^+$;$C_{19}H_{18}N_2O_2$: calcd. C, 74.49; H, 5.92; N, 9.14; O, 10.44; found C, 74.55; H, 5.88; N, 9.25; O, 10.52

N-cyclohexyl-N-(3-oxo-3H-indol-2-yl)benzamide

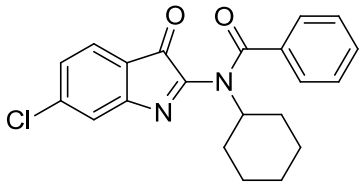


Prepared from cyclohexyl isocyanide (100 µl, 0.92 mmol), 2-azido benzoyl chloride (125 µl, 0.92 mmol) and silver benzoate (278 mg, 1.00 mmol). The crude imide was then refluxed in toluene for 4h with PPh_3 (253 mg, 0.98 mmol). Eluant for purification: PE/EtOAc 7:3. Obtained 75 mg as a red oil, yield 25%.

^{1}H-NMR (300 MHz, CDCl3, 323 K) δ 7.73-7.05 (m, 9-H), 4.7-4.55 (m, 1-H), 2.30-2.05 (m, 2-H), 1.92-1.55 (m, 4-H), 1.45-1.22 (m, 6-H); ^{13}C-NMR (75.4 MHz, CDCl3, 323 K) δ 186.6, 171.4, 161.3, 159.2, 138.2, 137.4, 131.8, 128.9,

128.8, 126.9, 125.3, 121.3, 121.1, 60.1, 30.7, 26.4, 25.3; IR (liquid film): 2930, 2855, 1737, 1560, 721; MS (ESI) m/z 333 (100%) $(M+H)^+$; $C_{21}H_{20}N_2O_2$: calcd. C, 75.88; H, 6.06; N, 8.43; found C, 75.65; H, 6.21; N, 8.22.

N-(6-chloro-3-oxo-3H-indol-2-yl)-N-cyclohexylbenzamide



Prepared from cyclohexyl isocyanide (100 µl, 0.92 mmol), 2-azido-4-chloro benzoyl chloride (115 µl, 0.92 mmol) and silver benzoate (278 mg, 1.00 mmol). The crude imide was then refluxed in toluene for 3h with PPh_3 (253 mg, 0.98 mmol). Eluant for purification: PE/EtOAc 9:1. Obtained 91 mg as a red oil, yield 30%.

^{1}H-NMR (300 MHz, CDCl3, 323 K) δ 7.63 (dd, J= 7.45 Hz, J=1.5 Hz, 2-H), 7.50-7.20 (m, 6-H), 7.07 (t, J= 7.5 Hz, 1-H), 4.10 (t, J=7.30 Hz, 2-H), 1.85-1.75 (m, 2-H), 0.95 (t, J=7.05 Hz, 2-H); ^{13}C-NMR (75.4 MHz, CDCl3, 323 K) δ 185.6, 171.5, 163.2, 160.9, 143.7, 138.1, 132.2, 129.1, 128.9, 126.6, 126.0, 121.9, 119.3, 60.5, 30.4, 26.2, 25.3; IR (liquid film): 2930, 2855, 1742, 1556, 1233, 698; MS (ESI) m/z 367 (100%) $(M+H)^+$; $C_{21}H_{19}ClN_2O_2$: calcd. C, 68.76; H, 5.22; N, 7.64; found C, 68.86; H, 5.40; N, 7.45.

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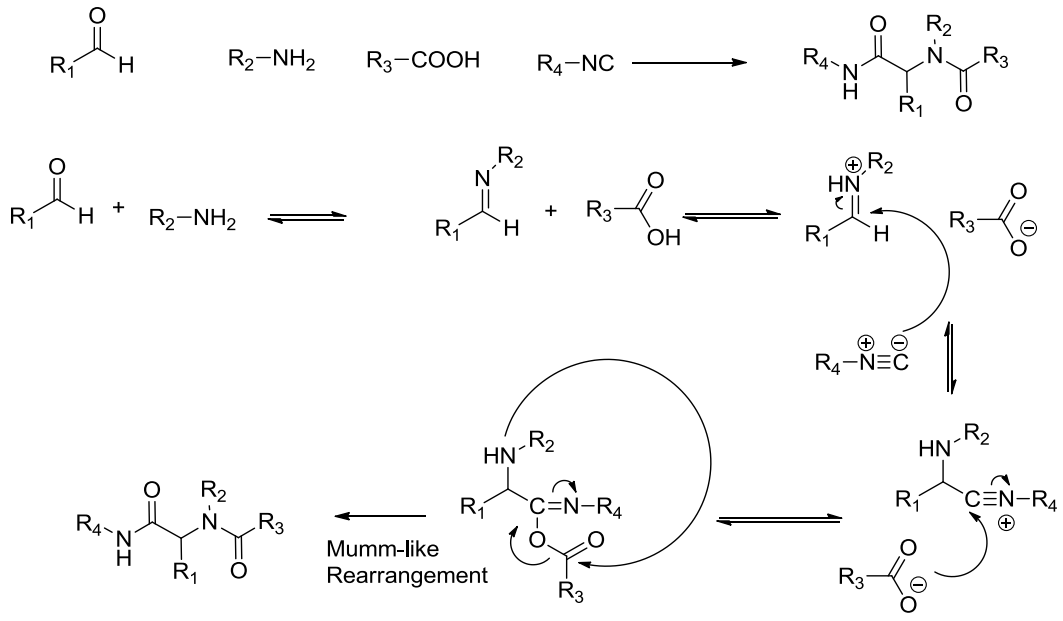
5. THE USE OF SECONDARY AMINES IN THE UGI REACTION

After its discovery in 1959, [1] the Ugi reaction allowed to many scientists, and Ugi himself, the discovery of many variations of it. Indeed, the Ugi reaction should not be considered only as a multicomponent reaction among aldehydes or ketones, carboxylic acids, amines and isocyanides, but a class of reactions. Every reaction in which there is an α-addition of a nucleophile and a Schiff base onto an isocyanide carbon, and a subsequent rearrangement, can be considered an Ugi-like reaction. This opens the way to a plethora of different reactions, who can be considered Ugi reactions.[2]

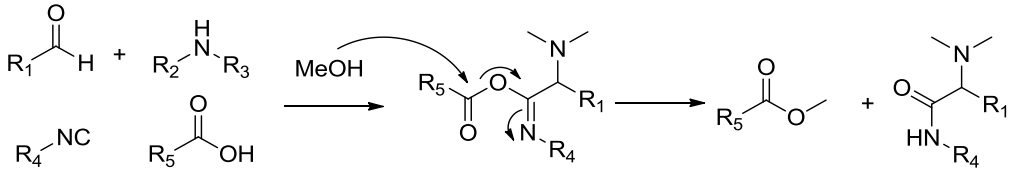
In the classical Ugi reaction, the mechanism proceeds through an interaction between the amine and the aldehyde to give the corresponding imine. The imine, which is a softer electrophile than the starting aldehyde, reacts in an acid–base reaction with the carboxylic acid to afford a very reactive iminium ion, which is then trapped by the isocyanide to give a nitrilium ion. This reacts with the carboxylate ion, generated in the imine activation step, to give an imino-anhydride, an unstable species that undergoes a Mumm-like rearrangement (Scheme 1).



Scheme 1. Mechanism of the Ugi reaction.

This happens if an acylable -NH group is present. As the Mumm rearrangement has a low energy barrier, the imino-anhydride intermediate can undergo different fates.[3]

Indeed, using secondary amines changes the scenario of the reaction: the nitrogen atom of the amine can no longer be acylated, because it becomes tertiary, so the classical Mumm type rearrangement can not occur. It was Ugi who reported first the use of secondary amines in his reaction, discovering that in presence of methanol, this latter reacts with the imino-anhydride to afford an α-aminoamide and a methyl ester (Scheme 2). [4]



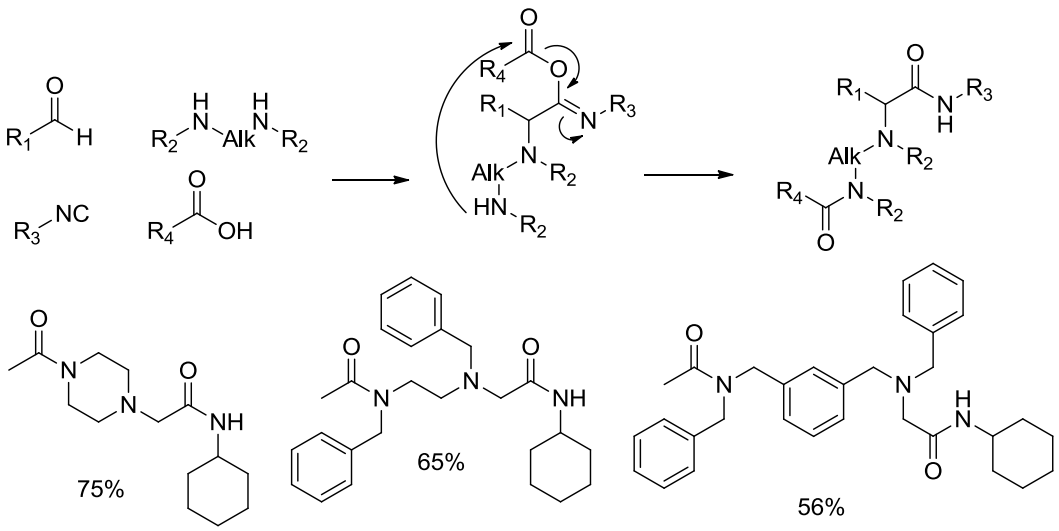
Scheme 2. Methanol can intercept the imidate intermediate.

In 2006 Tron *et al.* reported a new multicomponent reaction in which the primary amine was replaced with a symmetrical secondary diamine, with the idea to form the imino-anhydride intermediate, that thanks to the poor nucleophilicity of the methanol, could be intercepted by the second secondary amine to give a remote Mumm rearrangement. In this way a new molecular scaffold could be obtained, in which the classical Ugi backbone (NCCNC) was split (from this the name "Split-Ugi" reaction) and in which one nitrogen atom was acylated and the other alkylated (Scheme 3). [5] This reaction allows a lot of advantages, for example:

i) A symmetrical diamine can be acylated in one nitrogen atom and alkylated in the other, enabling the desymmetrization in one step.

ii) The generation of a new molecular scaffold through the Ugi reaction without use of protection and deprotection steps.

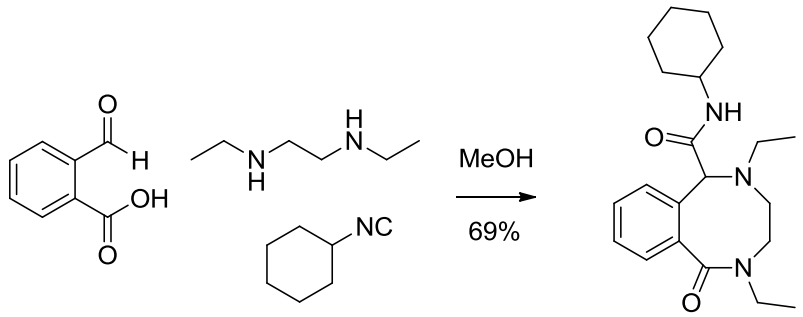
iii) The possibility to use different symmetrical secondary amine to build very different molecular scaffolds.



Scheme 3. The Split Ugi reaction.

If the Ugi reaction allows many strategies to enlarge the molecular diversity of the scaffolds, the same strategies can be adopted for the Split Ugi reaction.[6] The

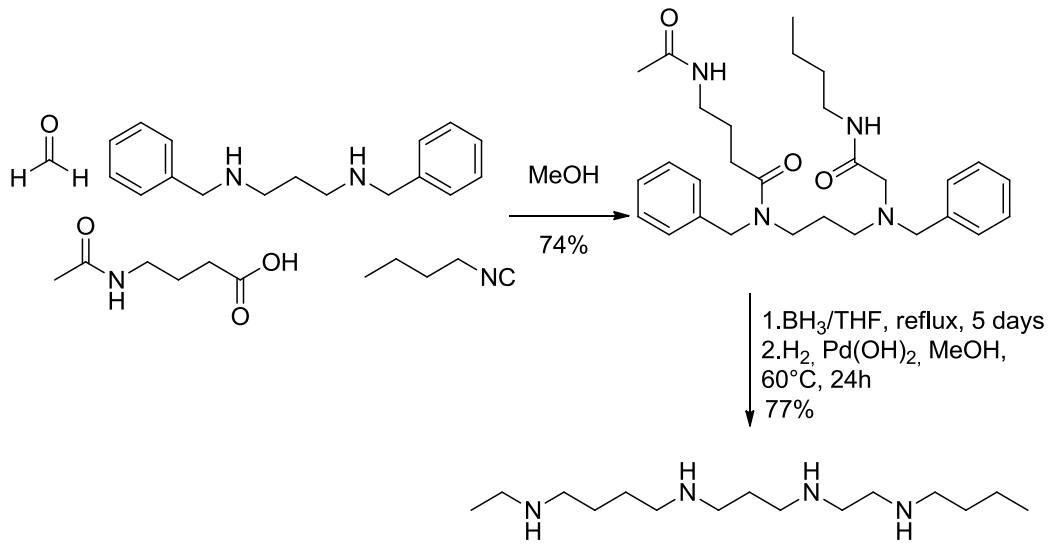
use of difunctionalized substrate, for example, a cyclic product can be obtained, like these bicyclic lactams with different ring sizes, according to the nature of the amine component used (Scheme 4). [7]



Scheme 4. Split-Ugi reaction with a bifunctionalized substrate.

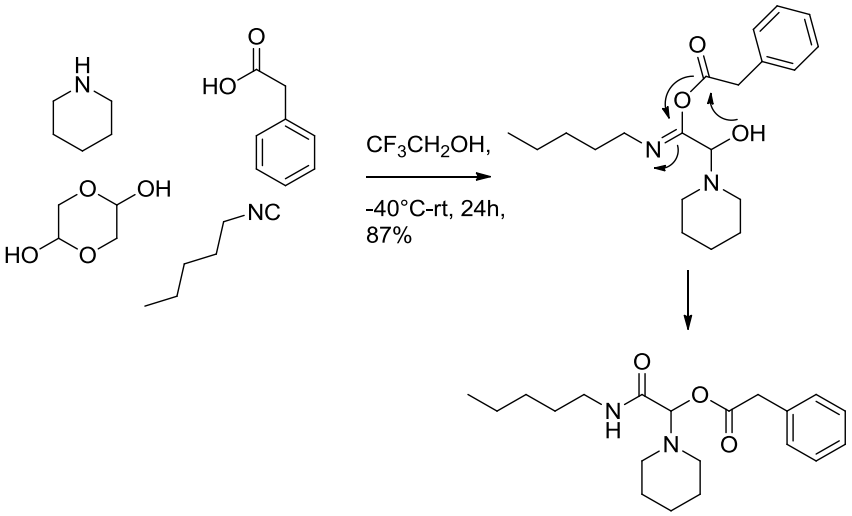
The post-transformation strategy can also be adopted, to produce new molecular entities.

By this approach, in 2008 Tron's group reported a new synthetic strategy for the synthesis of unsymmetrical polyamines, which are are of interest in several branches of chemistry and require very complicated syntheses. In this case, the split Ugi reaction is followed by reduction and hydrogenolysis (Scheme 5). [8]



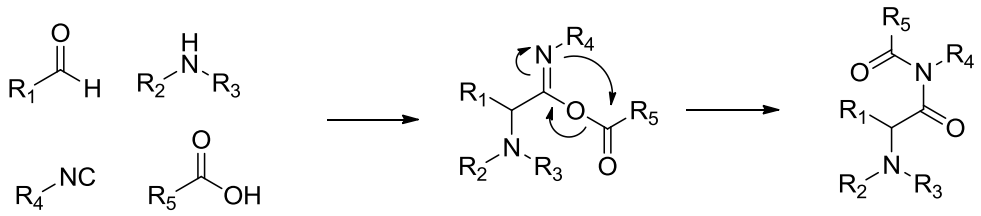
Scheme 5. Synthesis of polyamines via Split Ugi reaction.

Not only nitrogen atoms can intramolecularly intercept the imino-anhydride intermediate generated from a secondary amine, and this opens the possibility for the use of other nucleophiles. For example using glycolaldehyde dimer as the carbonyl reagent allows the access to α-amino-amido esters in a single chemical transformations. In this case the methanol competes with the hydroxy group of the glycolaldehyde , so trifluoroethanol has to be used as solvent (Scheme 6). [9]



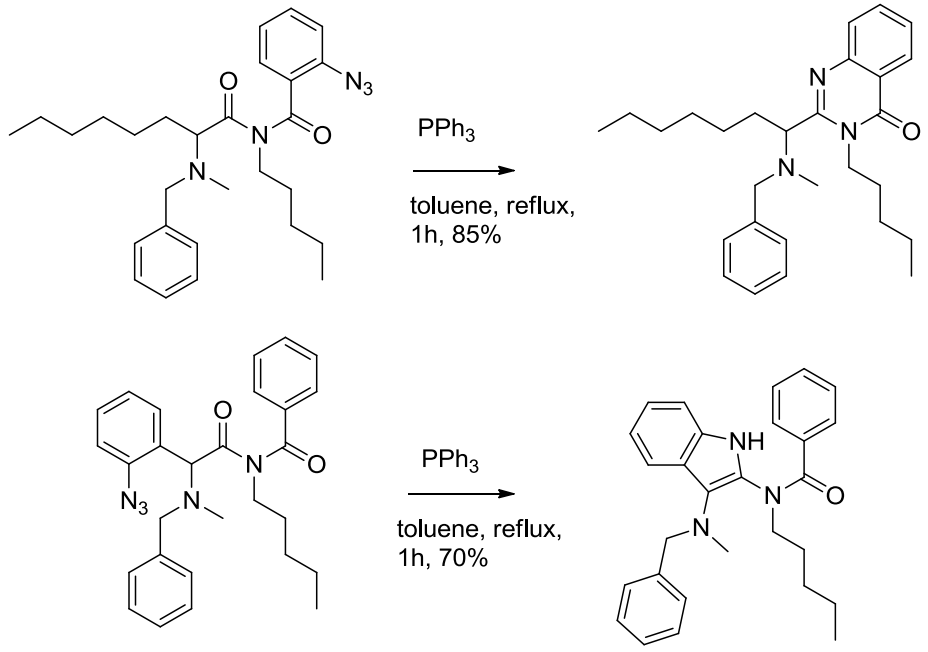
Scheme 6. Synthesis of α-amino-amido esters.

Also the nitrogen atom of the isocyanide can intercept the transient imidate, when no other nucleophilic groups are present. In 1961 Ugi reported the formation of imides from a reaction among an isocyanide, a carboxylic acid and a preformed enamine, to avoid the amine to intercept the imino-anhydride.[10] But in 2011 Tron described how these imides can be obtained without the necessity to preform the enamine. The four components are mixed together in dichloromethane in the presence of 4 A˚ molecular sieves.[11] In this case no Passerini products have been detected, even in the presence of an apolar solvent, and the amine did not interfere by trapping the imino-anhydride intermediate (Sheme 7). The imides generated have acylating properties and can react with various nucleophiles, and the reactivity of the carbonyl group can be exploited for aza-Wittig reactions. [12]



Scheme 7. Formation of the Ugi imide.

For example, with this strategy, after the formation of the imide, quinazolinones and 2,3-diaminoindoles can be obtained, in only two synthetic steps. In the first case 2-azido benzoic acid is used, in the second case 2-azido benzaldheyde (Scheme 8). [11]



Scheme 8. Two-steps syntheses of quinazolinones and 2,3-diaminoindoles via Ugi's imides.

Even if Ugi reaction is 56 years old, it can be considered still a reaction with a great potential, and, as shown in the next chapter, the use of the secondary amine can be exploited for the easy access to a new molecular scaffold.

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6. AN EFFICIENT SYNTHESIS OF SYMMETRIC AND UNSYMMETRIC BIS-(β-AMINOAMIDES) VIA UGI MULTICOMPONENT REACTION

6.1. RESULTS AND DISCUSSION

The use of symmetrical diamines can give the opportunity to exploit the Ugi reaction for the construction of very different molecular scaffolds and medicinally important compounds. For example the piperazine ring is considered a privileged structure in medicinal chemistry, with at least 73 drug entries for piperazine-related drugs deposited in the Drug Bank.[1] Furthermore, symmetrical compounds have played an important role in several branches of chemistry including medicinal chemistry. For example the symmetry of the binding site of HIV protease has brought a plethora of symmetrical protease inhibitors with low nanomolar activity, which paved the way for the non-symmetrical protease inhibitors currently on the market.[2] For this reason the ability to synthesize symmetrical compounds in a simple manner and in a one pot operation is a surplus value for the medicinal chemists involved in drug discovery and it is worth being continually investigated.

For one of our medicinal chemistry programs we needed to synthesize a library of symmetrical and unsymmetrical bis-(β-aminoamides) (Figure 1).

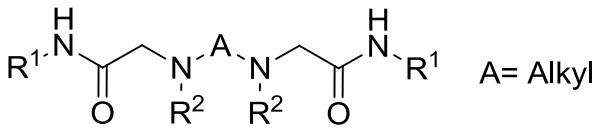
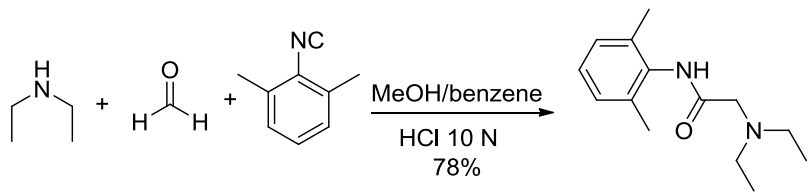


Figure 1. The bis-(β-aminoamide) scaffold.

A first strategy that could be adopted was a four component bis-Ugi like reaction, using water as acid component, as already reported by Ugi.[3]

Anyway, a survey in the literature showed us the lack of a general and valid one-pot procedure using water as acid component in the Ugi reaction. A main reason can explain the lack of such a reaction: the poor nucleophilicity of water in attacking the nitrilium ion. Indeed, even if the attack of water to the nitrilium ion is considered possible and it is reported both in books and papers, there is a paucity of such examples in the literature and the reaction did not appear of general use.[4] To a deeper insight, this reaction always requires the presence of a Lewis or BrØnsted acid pointing out a different mechanism of action. The most puzzling situation is in the first example of an Ugi reaction in which a carboxylic acid has been replaced with water, reported by Ugi himself, in order to obtain the local anesthetic xylocaine in an one pot process. To accomplish this reaction a strong excess of hydrochloric acid was used (Scheme 1). [3]

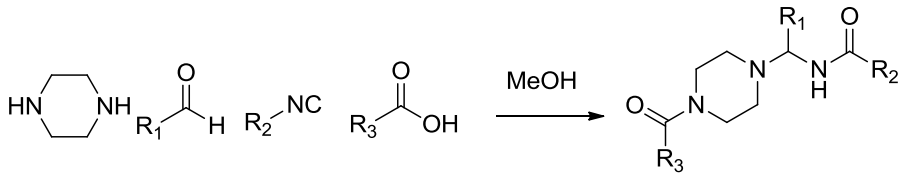


Scheme 1. Ugi's synthesis of xylocaine.

A plausible mechanism of the reaction can be proposed: the more nucleophilic chloride ion attacks the nitrilium ion instead of water. At this point the unstable chloroimidate is then converted into the desired amide by reaction with water. The presence of a secondary amine gives directly an iminium ion, ruling out the use of the acid to activate the imine.[5]

Other works in which water was the fourth component of the Ugi reaction have been and are continuously reported but in all cases Lewis or BrØnsted acids are always used. Very recently Japanese chemists, in order to by-pass the problem of the lack of reactivity of water in the Ugi reaction, reported the use of an aminoborane to give the desired α-aminoamides using secondary amines. [6]

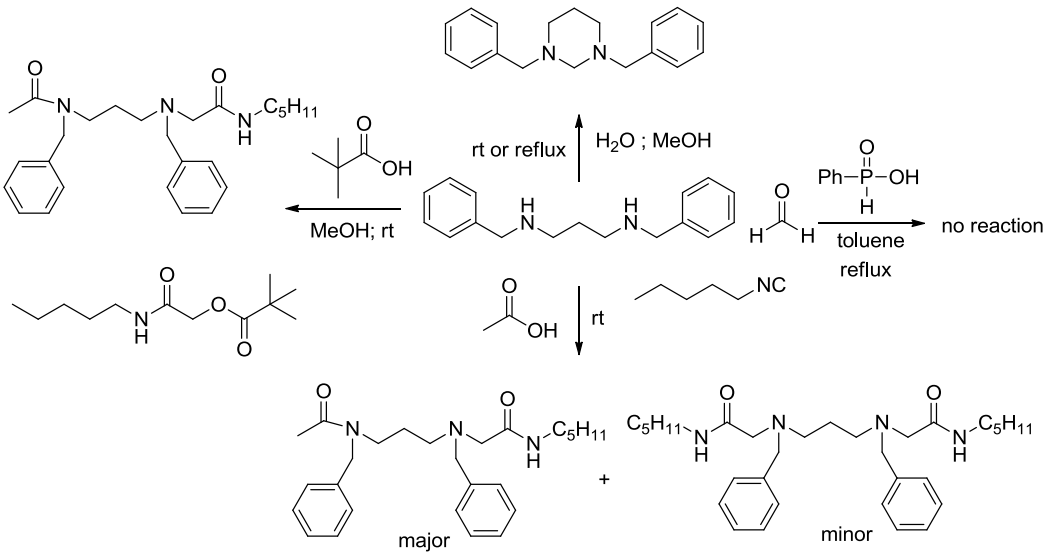
Another way to overcome this problem was the use of an acid such as trifluoroacetic acid. The corresponding amide can then be easily hydrolized under basic condition. Anyway, when symmetrical secondary diamines react with a carbonyl compound, an isocyanide and a carboxylic acid, the split Ugi reaction[7] (see previous chapter) occurs (Scheme 2). In this case the second secondary amine intercepts the imino-anhydride intermediate. Even in the presence of two equivalents of acid, carbonyl group and isocyanide and one equivalent of the diamine the intramolecular split-Ugi reaction still *competes* and *wins* over the classical Ugi reaction being the major component of the mixture.



Scheme 2. The split Ugi reaction.

Because of the limitations cited above, in this chapter we wish to present a novel strategy to synthesize in an easy and straightforward manner symmetrical and unsymmetrical bis-(β-aminoamides) suppressing the competing split-Ugi reaction, and without using excess of mineral or Lewis acids and aminoboranes. In order to demonstrate, once more, the poor nucleophilicity of water, at the beginning, we carried out a reaction between a symmetrical secondary diamine, paraformaldehyde, water and pentyl isocyanide in methanol both at room temperature and at reflux. In both cases we were able to recover only the aminal. The use of the diamine as di-chloridrate did not change the result of the reaction as well as the use of phenylphosphonic acid as catalyst.[8] These results confirm once again the poor nucleophilicity of water and its low propensity to attack the nitrilium ion opening up to other reaction pathways. It is therefore necessary the presence of a carboxylic acid both to hydrolize the aminal and to give the iminoanhydride intermediate. In this particular situation the imidate should be

attacked by the nucleophilic solvent of the reaction (methanol) to release the desired compound. Unfortunately, when two equilvalents of acetic acid, pentyl isocyanide and praraformaldeyde were used, the product of the split-Ugi reaction was always the major component compared to the symmetrical bis-(β-aminoamide) (Scheme 3).

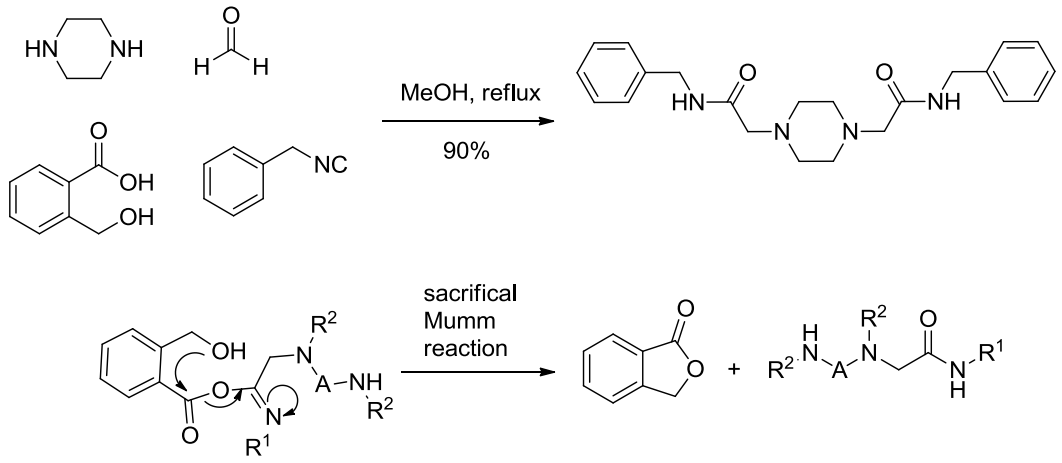


Scheme 3. Results obtained using different acids.

Even with the sterically hindered pivalic acid only the split-Ugi adduct along with the Passerini reaction product could be recovered. At this point, given the importance of the presence of a carboxylic acid to attack the nitrilium intermediate, we thought to use a functionalized carboxylic acid with a nucleophilic arm. This moiety should be able to compete with the other amine component for the reaction with the imino-anhydride intermediate to give a *sacrifical* Mumm rearrangement. To accomplish our task, we thought that 2-hydroxymethyl benzoic acid could be the right choice.

With our satisfaction, when piperazine was reacted with two equivalents of acid, benzyl isocyanide and paraformaldehyde in methanol at reflux, we obtained the

desired product in 90 % yield. It is important to highlight that 2-hydroxymethyl benzoic acid behaves like a pseudo water molecule by first trapping the nitrilium ion as in a normal Ugi reaction. This acid then undergoes an intramolecular cyclization to deliver only one oxygen atom to the product, as water would, producing the aromatic lactone phtalide (Scheme 4). This latter can be easily recovered by column cromatography due to its lipophilic nature and it can be reconverted into the acid.



Scheme 4. Formation of the symmetrical bis-(βaminoamide), and mechanism of the sacrifical Mumm rearrangement.

The generality of the reaction was demonstrated using different isocyanides and bis-amines, so a library of symmetrical bis-(β-aminoamides) was synthesized (Figure 2).

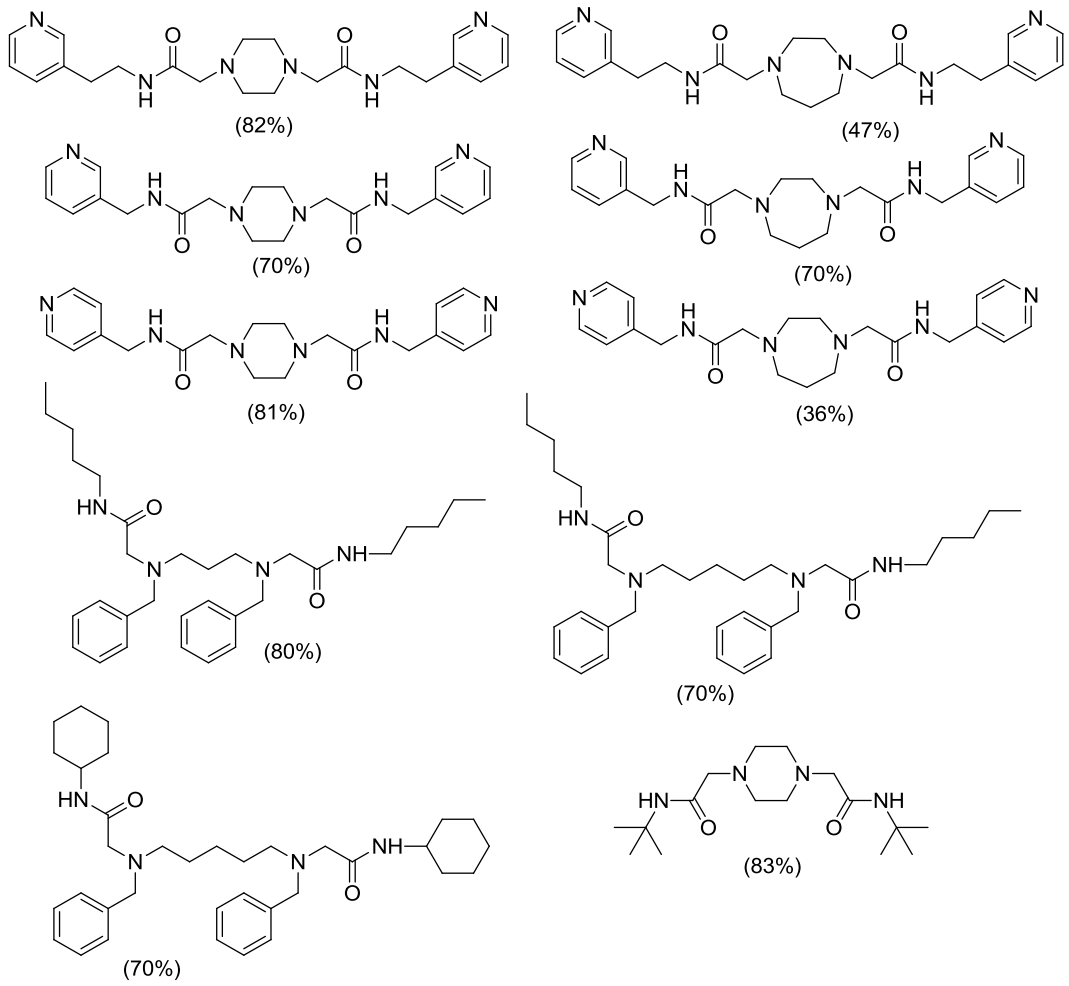
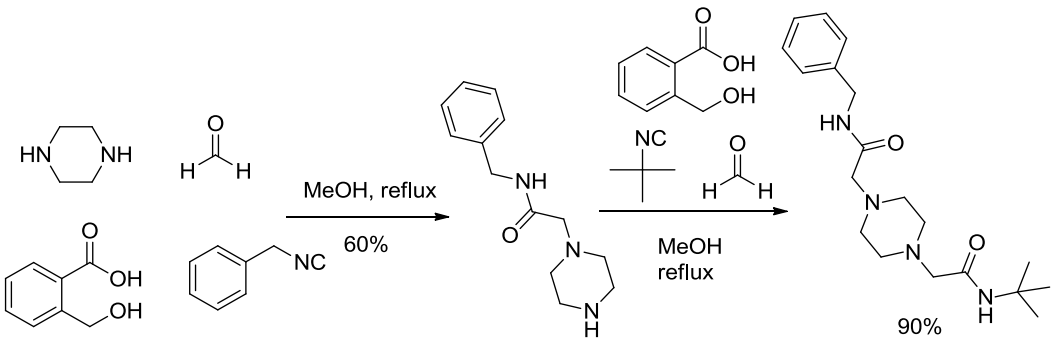


Figure 2. Symmetrical bis-(β-aminoamides) synthesized.

Then, we wondered whether using only one equivalent of 2-hydroxymethyl benzoic acid, aldehyde and isocyanide, the sacrifical Mumm rearrangement could still win over the competing split-Ugi reaction. With our satisfaction reaction among piperazine, paraformaldehyde, benzylisocyanide and 2-hydroxymethyl benzoic acid gave the desired mono-substituted Ugi product in 60 % yield along with the symmetrical bis-(β-aminoamide) in 10 % yield. After chromatographic purification, the compound can undergo a similar reaction using a different isocyanide to give in 90 % yield the desired unsymmetrical bis-(β-aminoamide) (Scheme 5).



Scheme 5. Formation of the unsymmetrical bis-(βaminoamide).

Even in this case a library of unsymmetrical bis-(β-aminoamides) has been prepared (Figure 3).

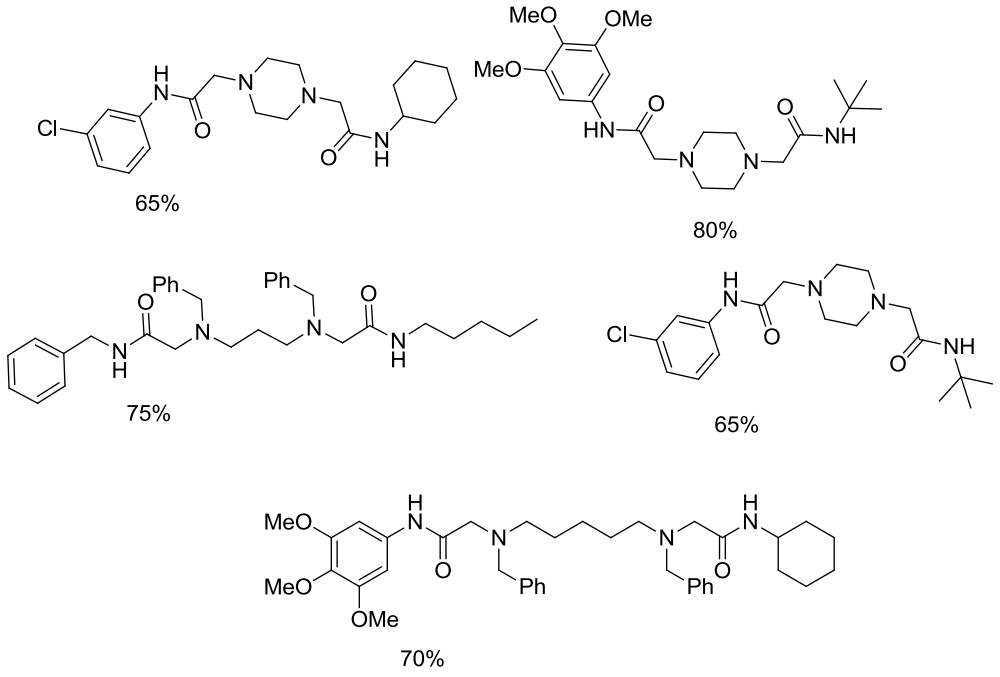
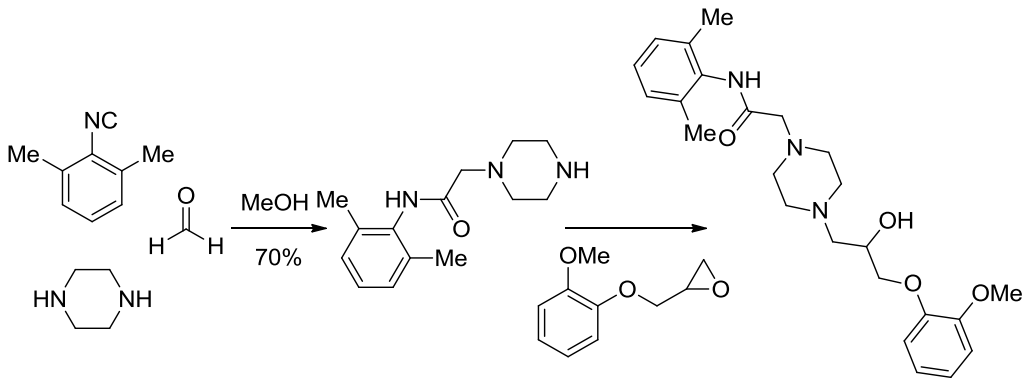


Figure 3. Unsymmetrical bis-(β-aminoamides) synthesized.

6.2. APPLICATIONS

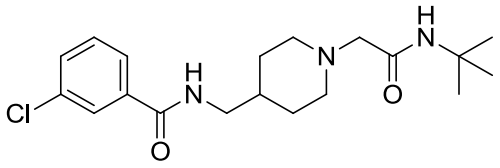
This reaction can find different applications.

The antianginal agent ranolazine contains a piperazine ring, and a β-aminoamide scaffold. With this chemistry the advance intermediate can be prepared in 70 % yield under optimized conditions, and can then be coupled with the epoxy derivative as already shown (Scheme 6). [9]



Scheme 6. Formal synthesis of ranolazine.

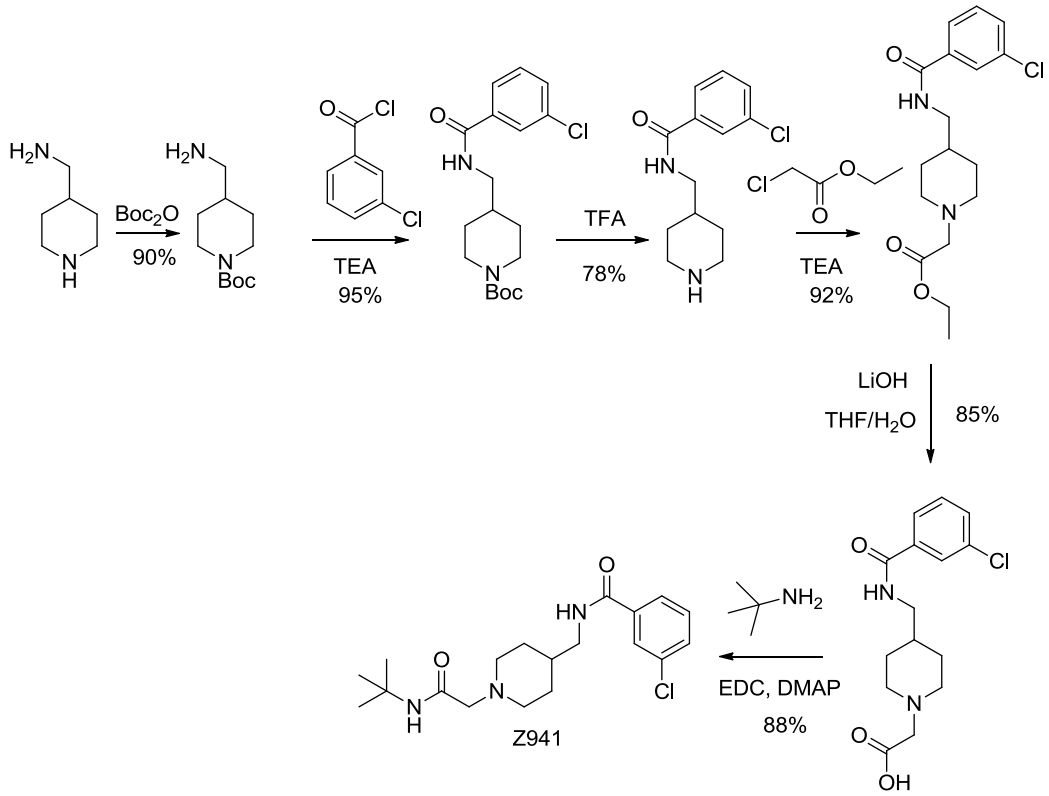
Z941 (Figure 4) is a T-type calcium channel blocker, identified by rational design, in order to discover new antiepileptic drugs, in particular for the treatment of absence seizures.[10]



Z941

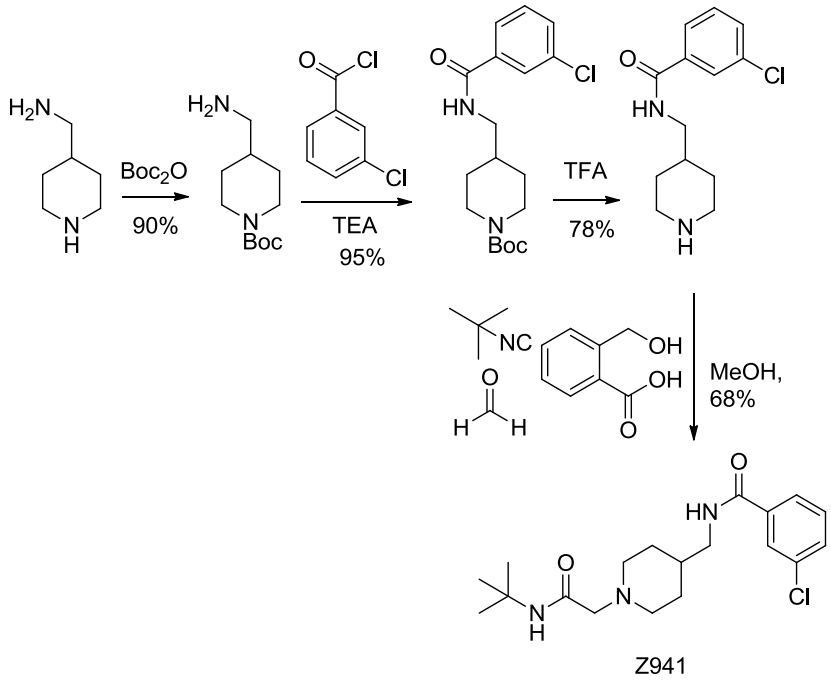
Figure 4. T-type calcium channel blocker Z941.

Even in this case, the molecule contains a β-aminoamide scaffold, but a piperidine ring instead of a piperazine ring. Its synthesis is reported in scheme 7.[11]



Scheme 7. Synthesis of Z941**.**

With our reaction, we can obtain the desired compound starting from the same diamine in a shorter way (Scheme 8).



Scheme 8. Synthesis of Z941 using our methodology.

The structural analogy between our compounds and Z941 can also be exploited for the discovery of new calcium channel blockers, as our methodology allows the easy access to different compounds. For example, in figure 5, the isosterism between Z941 and one of the molecule synthesized by us is highlighted. Comparing the two compounds, an inversed amide and an isosterism N-CH are present.

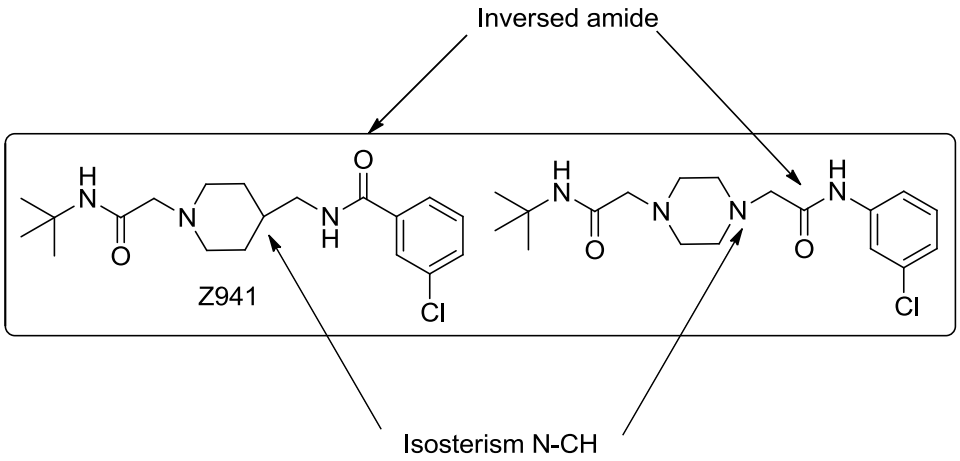


Figure 5. Isosterism between Z941 and one of the molecules synthesized by us.

For this reason the library of symmetrical and unsymmetrical bis-(β-aminoamides) synthesized has been sent to the laboratory of Prof. E. Carbone (University of Turin), and their biological activity is being evaluated.

6.3. CONCLUSIONS

In conclusion we developed a novel methodology for the preparation of symmetrical and unsymmetrical bis-(β-aminoamides) using available starting materials and avoiding the use of protective groups. The use of 2-hydroxymethyl benzoic acid is mandatory to suppress the competing split-Ugi reaction and escaping from the poor reactivity of water on the nitrilium ion. The use of these compounds as potential calcium channel inhibitors will be evaluated.

6.4. EXPERIMENTAL SECTION

Solvents and Reagents

Commercially available solvents and reagents were used without further purification. When needed, the reactions were performed in oven-dried glassware under a positive pressure of dry nitrogen.

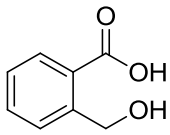
Chromatography

Column chromatography was performed on silica gel (Merck Kieselgel 70-230 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 $KMnO_4$.

Spectra

Infrared spectra were recorded on a FT-IR Thermo-Nicolet Avatar spectrometer with absorption maxima (ν_{max}) 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

Synthesis of 2-hydroxymethyl benzoic acid

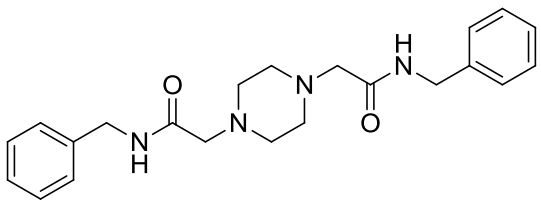


2-(hydroxymethyl)benzoic acid. To a solution of NaOH (4.5 g, 111.9 mmol, 1.5 eq) in H_2O (100 ml), phtalide (10 g, 74.6 mmol, 1eq) was added and the mixture was refluxed for 3 h. The solution was let to reach room tempereture, and then HCl conc. was added. A white precipitate was formed, which was purified by filtration (90 %). White solid. ^{1}H-NMR (300 MHz, MeOD) δ 7.96 (d, *J= 6.6 Hz*, 1H), 7.63 (d, *J=7.98 Hz*, 1H), 7.53 (t, *J=7.71 Hz*, 1H), 7.33 (t, *J= 7.14 Hz*, 1H), 4.92 (s, 2H); ^{13}C-NMR (75 MHz, MeOD) δ 169.5 (C), 143.3 (C), 132.2 (CH), 130.7 (CH), 128.6 (C), 127.6 (CH), 126.8 (CH), 62.6 (CH_2); MS (ESI) *m/z* 153.4 (100%) $(M+H)^+$.

General preparation of symmetric bis- (β-aminoamides)

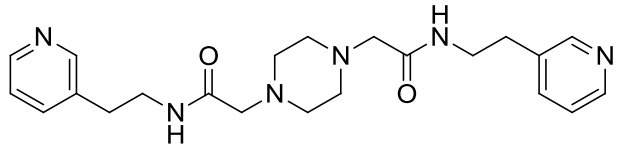
The corresponding diamine (0.5-1.5 mmol, 1 eq) was dissolved in MeOH (5-15 ml), then paraformaldheyde (2 eq), 2-(hydroxymethyl)benzoic acid (2 eq) and the corresponding isocyanide (2eq) were added at room temperature. The reaction mixture was then efluxed until completion (2-5 h). The solvent was removed *in vacuo,* and the product purified by column chromathography (gradient from PE/EtOAc 4:6 to EtOAc/MeOH 8:2).

2,2'-(piperazine-1,4-diyl)bis(N-benzylacetamide)



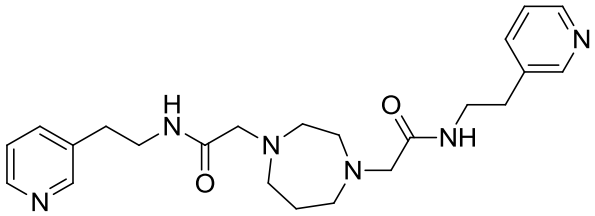
Purified on silica gel using EtOAc/MeOH 9:1 as eluent to afford a white solid (90% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.45-7.2 (m, 10H), 4.46 (d , *J=6.12 Hz*, 4H), 3.05 (s, 4H), 2.52 (s, 8H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.9 (C), 138.4 (C), 128.8 (CH), 127.6 (2x CH), 61.5 (CH_2), 53.6 (CH_2), 43.0 (CH_2) ; MS (ESI) *m/z* 381 (100%) $(M+H)^+$; IR (KBr):1650, 1541, 1172, 694 cm^{-1}; M.p. 162-163 °C. Found: C, 69.64; H, 7.32; N, 14.85; $C_{22}H_{28}N_4O_2$ requires C, 69.45; H, 7.42; N 14.73 %.

2,2'-(piperazine-1,4-diyl)bis(*N*-(2-(pyridin-3-yl)ethyl)acetamide)



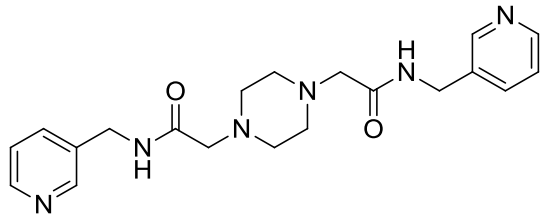
Purified on silica gel using EtOAc/MeOH 8:2 with 1% TEA as eluent to afford an amorphous solid (82% yield). ^{1}H-NMR (300 MHz, MeOD) δ 8.41-8.38 (m, 4H), 7.73 (d, *J=7.68 Hz*, 2H); 7.36 (d.d, *J=7.9 Hz*, *J=4.9 Hz*, 2H), 3.51 (t, *J=7.14 Hz*, 4H), 2.94 (s, 4H), 2.87 (t, *J=6.87 Hz*, 4H), 2.40 (s, 8H); ^{13}C-NMR (75 MHz, MeOD) δ 170.2 (C); 148.1 (CH); 145.8 (CH), 136.3 (CH), 134.5 (C), 122.8 (CH), 59.8 (CH_2), 51.7 (CH_2), 38.3 (CH_2), 31.0 (CH_2); MS (ESI) *m/z* 411 (100%) $(M+H)^+$; IR (liquid film): 1651, 1561, 1451, 1195, 720 cm^{-1}. Found: C, 64.55; H, 7.60; N, 20.10; $C_{22}H_{30}N_6O_2$ requires C, 64.37; H, 7.37; N 20.47 %.

2,2'-(1,4-diazepane-1,4-diyl)bis(*N*-(2-(pyridin-3-yl)ethyl)acetamide)



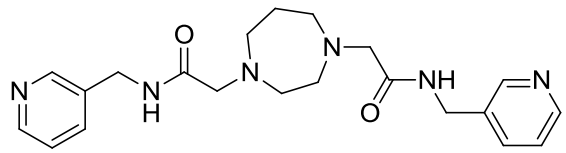
Purified on silica gel using EtOAc/MeOH 8:2 with 1% TEA as eluent to afford a yellow oil (47% yield). ^{1}H-NMR (300 MHz, MeOD) δ 8.50-8.30 (m, 6H), 7.75 (d, *J=7.95 Hz*, 2H), 7.39 (dd, *J=7.95 Hz*, *J=4.9 Hz*, 2H), 3.59-3.49 (m, 4H), 3.42 (s, 4H), 3.34 (s, 4H), 2.98-2.83 (m, 8H), 1.92-1.81 (m, 2H); ^{13}C-NMR (75 MHz, MeOD) δ 168.7 (C); 147.9 (CH), 145.7 (CH), 136.6 (CH), 134.4 (C), 123.1 (CH), 58.9 (CH_2), 53.2 (CH_2), 52.4 (CH_2), 38.6 (CH_2), 30.9 (CH_2), 24.4 (CH_2); MS (ESI) *m/z* 425 (100%) $(M+H)^+$; IR (liquid film):1648, 1529, 1425, 713 cm^{-1}. Found: C, 64.90; H, 7.45; N, 20.15; $C_{23}H_{32}N_6O_2$ requires C, 65.07; H, 7.60; N 19.80 %.

2,2'-(piperazine-1,4-diyl)bis(*N*-(pyridin-3-ylmethyl)acetamide)



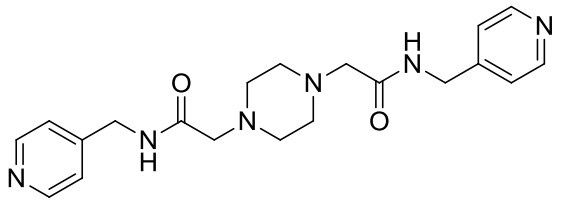
Purified on silica gel using EtOAc/MeOH 8:2 with 1% TEA as eluent to afford a white solid (70% yield). ^{1}H-NMR (300 MHz, MeOD) δ 8.49 (d, *J=1.92 Hz*, 2H), 8.41 (dd, *J=4.95 Hz, 1.92 Hz*, 2H) 7.75 (dt, *J=7.71 Hz, 1.92 Hz*, 2H), 7.38 (dd, *J=7.71 Hz*, *J= 4.95 Hz*, 2H), 4.44 (s, 4H), 3.07 (s, 4H), 2.57 (s, 8H); ^{13}C-NMR (75 MHz, MeOD) δ 170.6 (C), 146.9 (CH), 146.4 (CH), 135.2 (CH), 134.4 (C), 122.8 (CH), 59.8 (CH_2), 51.8 (CH_2), 38.8 (CH_2); MS (ESI) *m/z* 383 (100%) $(M+H)^+$; IR (liquid film): 1658, 1509, 1457,1352, 1301, 1183, 836, 715, 640 cm^{-1}; MP 207-209 °C. Found: C, 63.10; H, 7.00; N, 21.54; $C_{20}H_{26}N_6O_2$ requires C, 62.81; H, 6.85; N 21.97 %.

2,2'-(1,4-diazepane-1,4-diyl)bis(*N*-(pyridin-3-ylmethyl)acetamide)



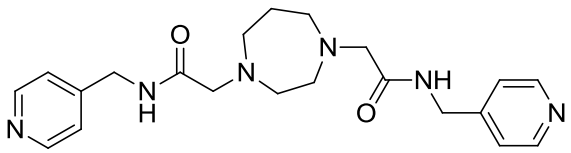
Purified on silica gel using EtOAc/MeOH 8:2 with 1% TEA as eluent to afford an amorphous solid (70% yield). ^{1}H NMR (300 MHz, MeOD): δ 8.50 (d, *J=1.65 Hz*, 2H), 8.42 (dd, *J=4.95 Hz*, *1.65 Hz*, 2H), 7.76 (dt, *J=7.98 Hz*, *1.65 Hz*, 2H), 7.37 (dd, *J=7.98 Hz*, *4.95 Hz*, 2H), 4.92 (s, 4H), 4.45 (s, 4H); δ 3.23 (s, 4H); δ 2.76 (t, *J=7.41 Hz*, 4H), 1.86-1.73 (m, 2H); ^{13}C NMR (75 MHz, MeOD) δ: 171.1 (C), 147.1 (CH), 146.5 (CH), 135.1 (CH), 134.4 (C), 122.8 (CH), 60.2 (CH_2), 54.2 (CH_2), 53.6 (CH_2), 38.9 (CH_2); 26.5 (CH_2); MS (ESI) *m/z* 397 (100%) $(M+H)^+$; IR (liquid film): 1650, 1524, 1427, 711 cm^{-1}. Found: C, 63.60; H, 7.20; N, 21.00; $C_{21}H_{28}N_6O_2$ requires C, 63.62; H, 7.12; N 21.20 %.

2,2'-(piperazine-1,4-diyl)bis(*N*-(pyridin-3-ylmethyl)acetamide)



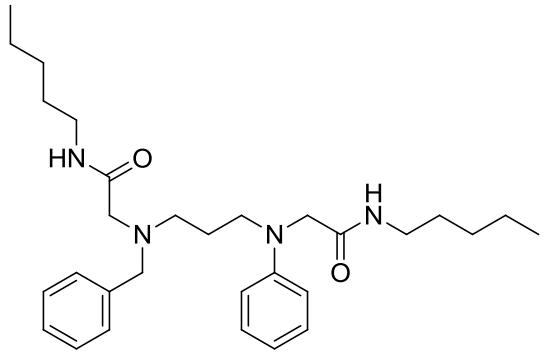
Purified on silica gel using EtOAc/MeOH 8:2 with 1% TEA as eluent to afford an amorphous solid (81% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.47 (d, *J=4.41 Hz*, 4H), 7.55 (brs, 2H), 7.11 (d, *J=4.41 Hz*, 4H), 4.41 (s, 4H), 3.03 (s, 4H), 2.53 (s, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.0 (C), 147.7 (CH), 145.2 (C), 119.9 (CH), 59.0 (CH_2), 51.3 (CH_2), 39.4 (CH_2); MS (ESI) *m/z* 383 (100%) $(M+H)^+$; IR (liquid film): 1651, 1602, 1510, 1420, 1307, 866, 835 cm^{-1}. Found: C, 63.10; H, 7.15; N, 21.67; $C_{20}H_{26}N_6O_2$ requires C, 62.81; H, 6.85; N 21.97 %.

2,2'-(1,4-diazepane-1,4-diyl)bis(*N*-(pyridin-4-ylmethyl)acetamide)



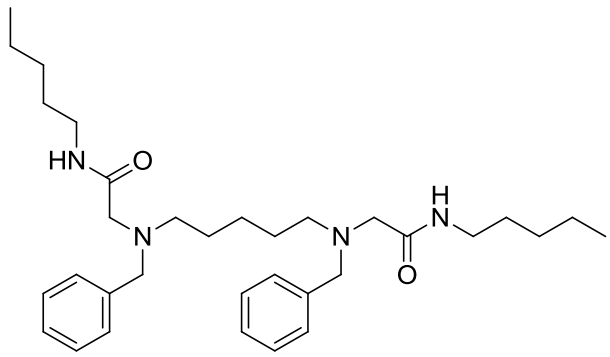
Purified on silica gel using EtOAc/MeOH 8:2 with 1% TEA as eluent to afford an amorphous solid (36% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (dd, *J=4.68 Hz,1.35 Hz*, 4H), 7.57 (t, *J=6.33 Hz*, 2H), 7.14 (dd, *J=4.68 Hz, 1.35 Hz*, 4H) 4.45 (d, *J=6.33 Hz*, 4H) 3.20 (s, 4H), 2.88-2.68 (m, 8H), 1.76 (quint, *J=5.79 Hz*, 2H); ^{13}C NMR (75 MHz, CDCl3) δ: 168.7 (C), 147.8 (CH), 145.2 (C), 120.0 (CH), 59.4 (CH_2), 54.0 (CH_2), 52.9 (CH_2), 39.6 (CH_2); 25.4 (CH_2); MS (ESI) *m/z* 397 (100%) $(M+H)^+$; IR (liquid film): 1659, 1561, 1417, 829 cm^{-1}. Found: C, 63.72; H, 7.22; N, 21.20; $C_{21}H_{28}N_6O_2$ requires C, 63.62; H, 7.12; N 21.20 %.

2,2'-(propane-1,3-diylbis(benzylazanediyl))bis(*N*-pentylacetamide)



Purified on silica gel using EtOAc/MeOH 8:2 as eluent to afford a yellow oil (80% yield).[1]H-NMR (300 MHz, $CDCl_3$) δ 7.34-7.15 (m, 10H), 7.03 (t, *J=11.64 Hz*, 2H), 3.54(s, 4H), 3.15 (q, *J=6.72 Hz*, 4H), 3.02 (s, 4H), 2.45 (t, *J=7.35 Hz*, 4H), 1.66 (quint, *J=7.35 Hz*, 2H), 1.40 (quint, *J=7.05 Hz*, 4H), 1.31-1.17 (m, 8H), 0.84 (t, *J=7.05 Hz*, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.9 (C), 137.9 (C), 128.8 (CH), 128.7 (CH), 127.7 (CH), 59.7 (CH_2), 58.1 (CH_2), 53.1 (CH_2), 38.9 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 25.0 (CH_2), 22.4 (CH_2), 14.1 (CH_3); MS (ESI) *m/z* 509 (100%) $(M+H)^+$; IR (liquid film): 3350, 2930, 1655, 1522, 730 cm^{-1}. Found: C, 73.50; H, 9.90; N, 10.85; $C_{31}H_{48}N_4O_2$ requires C, 73.19; H, 9.51; N 11.01 %.

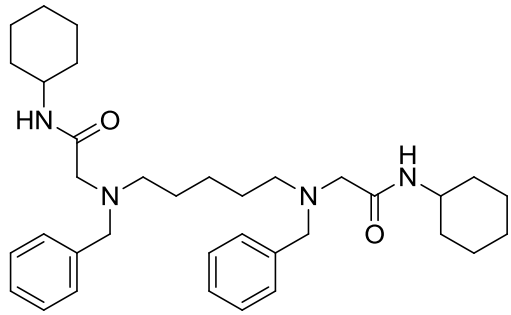
2,2'-(pentane-1,5-diylbis(benzylazanediyl))bis(*N*-pentylacetamide)



Purified on silica gel using EtOAc/MeOH 9:1 as eluent to afford an amorphous solid (70% yield). [1]H-NMR (300 MHz, $CDCl_3$) δ 7.39-7.06 (m, 10H), 3.55 (s, 4H), 3.19 (quart, *J=6.42 Hz*, 4H), 3.02 (s, 4H), 2.42 (t, *J=7.35 Hz*, 4H), 1.53-1.35 (m, 8H), 1.34-1.05 (m, 10H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.2 (C), 138.3 (C), 128.8 (CH), 128.6 (CH), 127.5 (CH), 59.7 (CH_2), 58.1 (CH_2), 55.2 (CH_2), 38.9 (CH_2), 29.4 (CH_2), 29.1 (CH_2), 27.3 (CH_2), 25.2 (CH_2), 22.4 (CH_2), 14.2 (CH_3); MS (ESI) *m/z* 537 (100%) $(M+H)^+$; IR

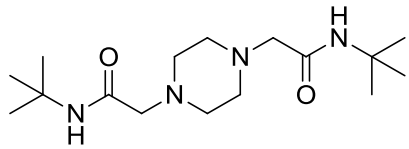
(liquid film): 2930, 2858, 1662, 1522, 730, 699 cm^{-1}. Found: C, 74.10; H, 9.93; N, 10.12; $C_{33}H_{52}N_4O_2$ requires C, 73.84; H, 9.76; N 10.44 %.

2,2'-(pentane-1,5-diylbis(benzylazanediyl))bis(*N*-cyclohexylacetamide)



Purified on silica gel using EtOAc/MeOH 9:1 as eluent to afford an amorphous solid (70% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35-7.05 (m, 10H), 3.67 (quint, *J=4.41 Hz*, 2H), 3.52 (s, 4H), 2.97 (s, 4H), 2.39 (t, *J=7.44 Hz*, 4H), 1.88-1.60 (m, 4H), 1.59-1.47 (m, 6H), 1.46-0.97 (m, 16H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.2 (C), 138.3 (C), 128.8 (CH), 128.6 (CH), 127.5 (CH), 59.8 (CH_2), 58.2 (CH_2), 55.2 (CH_2), 47.3 (CH), 33.1 (CH_2), 27.3 (CH_2), 25.6 (CH_2), 25.2 (CH_2), 24.7 (CH_2); MS (ESI) *m/z* 561 (100%) $(M+H)^+$; IR (liquid film): 2929, 2853, 1659, 1514, 729, 699 cm^{-1}. Found: C, 75.05; H, 9.42; N, 10.20; $C_{35}H_{52}N_4O_2$ requires C, 74.96; H, 9.35; N 9.99 %.

2,2'-(piperazine-1,4-diyl)bis(*N*-tert-butylacetamide)



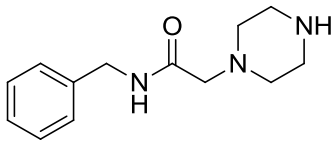
Purified on silica gel using EtOAc/MeOH 9:1 as eluent to afford a yellow oil (83% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 2H), 2.77 (s, 4H), 2.42 (s, 8H), 1.22 (s, 18H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.9 (C), 62.1 (CH_2), 53.5 (CH_2), 50.4 (C), 28.8 (CH_3); MS (ESI) *m/z* 313 (100%) $(M+H)^+$; IR (liquid film): 3351, 2963, 2809, 1670, 1523 cm^{-1}. Found: C, 61.45; H, 10.30; N, 18.10; $C_{16}H_{32}N_4O_2$ requires C, 61.50; H, 10.32; N 17.93 %.

General preparation of monosubstituted β-aminoamides

The corresponding diamine (0.5-1.5 mmol, 1.2 eq) was dissolved in MeOH (5-15 ml), then paraformaldheyde (1 eq), 2-(hydroxymethyl)benzoic acid (1 eq) and the corresponding isocyanide (1eq) were added at room temperature.

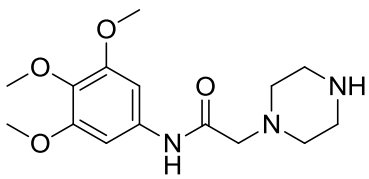
The reaction mixture was refluxed until completion (2-6 h), then the solvent was removed *in vacuo,* and the product purified by column chromathography (gradient from EtOAc/MeOH 9:1 to acetonitrile/NH_3 85:15).

_N_-benzyl-2-(piperazin-1-yl)acetamide



Purified on silica gel using CH_3CN/NH_3 9:1 as eluent to afford an amorphous solid (41% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.28 (s, 1H), 7.31-7.17 (m, 5H), 4.42 (d, *J=6.03 MHz*, 2H), 2.98 (s, 2H), 2.79 (t, *J=4.65 MHz*, 4H), 2.42 (t, *J=4.65 MHz*, 4H), 2.16 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.3 (C), 138.5 (C) , 128.7 (CH), 127.5(2xCH), 62.3 (CH_2), 54.8 (CH_2), 46.1 (CH_2), 43.0 (CH_2); MS (ESI) *m/z* 234 (100%) $(M+H)^+$; IR (liquid film): 3244, 2943, 2820, 1654, 1526, 847, 700 cm^{-1}. Found: C, 67.10; H, 8.45; N, 18.34; $C_{13}H_{19}N_3O$ requires C, 66.92; H, 8.21; N 18.01 %.

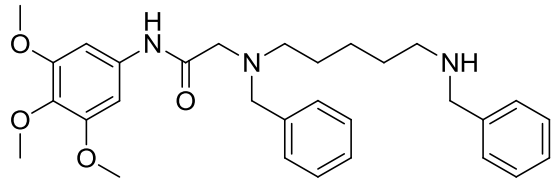
2-(piperazin-1-yl)-_N_-(3,4,5-trimethoxyphenyl)acetamide



Purified on silica gel using CH_3CN/NH_3 9:1 as eluent to afford an amorphous solid (50% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.97 (s, 1H), 6.80 (s, 2H), 3.78 (s, 6H), 3.73 (s, 3H), 3.02 (s, 2H), 2.87 (t, *J=4.92 Hz*, 4H), 2.49 (t, *J=4.92 Hz*, 4H), 2.15 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.4 (C), 153.4 (C), 133.8 (C), 124.69 (C), 97.2 (CH), 62.7 (CH), 61.0 (CH_3), 56.2 (CH_3), 54.7 (CH_2), 46.2 (CH_2); MS (ESI) *m/z* 310

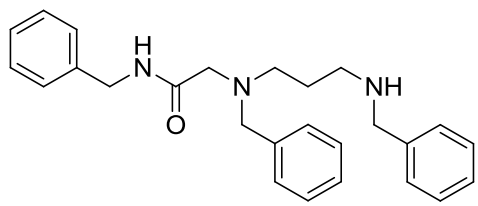
(100%) $(M+H)^+$; IR (liquid film): 2940, 1601, 1506, 1124, 728 cm^{-1}. Found: C, 57.95; H, 7.83; N, 13.10; $C_{15}H_{23}N_3O_4$ requires C, 58.24; H, 7.49; N 13.58 %.

2-(benzyl(5-(benzylamino)pentyl)amino)-*N*-(3,4,5-trimethoxyphenyl)acetamide



Purified on silica gel using CH_3CN/NH_3 85:15 as eluent to afford an amorphous solid (40% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.09 (s, 1H), 7.42-7.21 (m, 10H), 6.78 (s, 2H), 3.83 (s, 6H), 3.79 (s, 3H), 3.75 (s, 2H), 3.67 (s, 2H), 3.18 (s, 2H), 2.62-2.53 (m, 4H), 1.80 (s, 1H), 1.62-1.31 (m, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.5 (C), 153.4 (C), 137.9 (C), 133.8 (C), 129.0 (CH), 128.7 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 127.0 (CH), 97.1 (CH), 61.0 (CH_3), 59.7 (CH_2), 58.7 (CH_2), 56.2 (CH_3), 55.4 (CH_2), 54.1 (CH_2), 49.2 (CH_2), 29.9 (CH_2), 27.2 (CH_2), 25.2 (CH_2); MS (ESI) *m/z* 506 (100%) $(M+H)^+$; IR (liquid film): 3320, 2969, 1738,1127,698 cm^{-1}. Found: C, 71.35; H, 7.80; N, 8.30; $C_{30}H_{39}N_3O_4$ requires C, 71.26; H, 7.77; N 8.31 %.

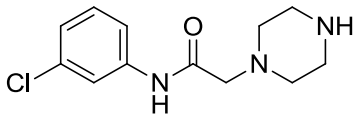
***N*-benzyl-2-(benzyl(3-(benzylamino)propyl)amino)acetamide**



Purified on silica gel using CH_3CN/NH_3 9:1 as eluent to afford an amorphous solid (35% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.4-7.12 (m, 15H), 4.39 (d, *J=5.82 Hz*,2H), 3.66 (s, 2H), 3.57 (s, 2H), 3.13 (s, 2H), 2.58 (q, *J=6.75 Hz*, 4H), 1.69 (q, *J=6.75 Hz*, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.4 (C), 139.7 (C), 138.6 (C), 138.1 (C), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 59.1 (CH_2), 58.1 (CH_2), 53.8 (CH_2), 48.1 (CH_2), 47.2 (CH_2), 43.0 (CH_2), 27.1 (CH_2); MS (ESI) *m/z* 402 (100%) $(M+H)^+$; IR (liquid film):

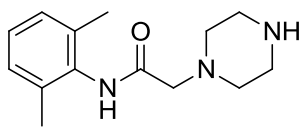
3027, 2816, 2361, 1663, 1452, 696 cm^{-1}. Found: C, 78.06; H, 7.93; N, 10.25; $C_{26}H_{31}N_3O$ requires C, 77.77; H, 7.78; N 10.46 %.

_N_-(3-chlorophenyl)-2-(piperazin-1-yl)acetamide



Purified on silica gel using CH_3CN/NH_3 95:5 as eluent to afford a yellow oil (50% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.62 (t, *J=2.13 Hz*, 1H), 7.35 (dt, *J=7.95 Hz*, *J=0.93 Hz*, 1H), 7.17 (t, *J=7.95 Hz*, 1H), 7.00 (dt, *J=7.95 Hz, 0.93 Hz*, 1H), 3.03 (s, 2H), 2.89 (t, *J=4.59 Hz*, 4H), 2-60-2.46 (m, 4H), 2.25 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.6 (C), 138.8 (C), 134.6 (C), 130.1 (CH), 124.2 (CH), 119.5 (CH), 117.5 (CH), 62.6 (CH_2), 54.6 (CH_2), 46.2 (CH_2); MS (ESI) *m/z* 254 (100%) $(M+H)^+$; IR (liquid film): 3278, 2822, 1681, 1594, 1516, 728 cm^{-1}. Found: C, 56.86; H, 6.35; N, 16.48; $C_{12}H_{16}ClN_3O$ requires C, 56.80; H, 6.36; N 16.56 %.

_N_-(2,6-dimethylphenyl)-2-(piperazin-1-yl)acetamide



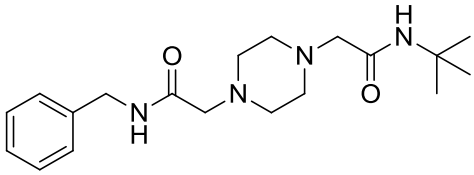
Purified on silica gel using CH_3CN/NH_3 9:1 as eluent to afford an amorphous solid (70% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.67 (brs, 1H), 7.10-7.01 (m, 3H), 3.14 (s, 2H), 2.91 (t, *J=4.60 Hz*, 4H), 2.62 (t, *J= 4.60 Hz*, 4H), 2.19 (s, 6H), 2.13 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.6 (C), 130.1 (C), 133.7 (C), 128.3 (CH), 127.2 (CH), 62.4 (CH_2), 55.0 (CH_2), 46.2 (CH_2), 18.7 (CH_3); MS (ESI) *m/z* 248.34 (100%) $(M+H)^+$; IR (liquid film): 3240, 2869, 1694,1210 ,720 cm^{-1}. Found: C, 68.10; H, 8.72; N, 17.12; $C_{14}H_{21}N_3O$ requires C, 67.98; H, 8.56; N 16.99 %.

General procedure for the preparation of unsymmetric bis-(β-aminoamides)

The corresponding synthesized amine (0.5-1.2 mmol, 1eq) was dissolved in MeOH (5-15 ml), then paraformaldheyde (1 eq), 2-(hydroxymethyl)benzoic acid (1 eq) and the corresponding isocyanide (1eq) were added at room temperature.

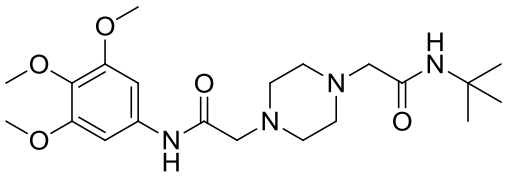
The reaction mixture was refluxed until completion (2-4 h), then the solvent was removed *in vacuo*, and the product purified by column chromathography (gradient from PE/EtOAc 4:6 to EtOAc/MeOH 8:2).

***N*-benzyl-2-(4-(2-(tert-butylamino)-2-oxoethyl)piperazin-1-yl)acetamide**



Purified on silica gel using EtOAc/MeOH 9:1 as eluent to afford an amorphous solid (70% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.28-7.10 (m, 5H), 6.89 (s, 1H), 4.39 (d, J=6.03 MHz, 2H), 3.00 (s, 2H), 2.80 (s, 2H), 2.46 (d, J=7.68 MHz, 8H), 1.27 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.0 (C), 169.0 (C), 138.4 (C), 128.7 (CH), 127.5(2x CH), 62.0 (CH_2), 61.4 (C), 53.6 (CH_2), 53.3 (CH_2), 50.6 (CH_2), 43.0 (CH_2), 28.8 (CH_3); MS (ESI) *m/z* 347 (100%) $(M+H)^+$; IR (liquid film): 2980, 2860, 1720, 1648, 1132, 728 cm^{-1}. Found: C, 64.95; H, 8.70; N, 16.10; $C_{19}H_{30}N_4O_2$ requires C, 65.87; H, 8.73; N 16.17 %.

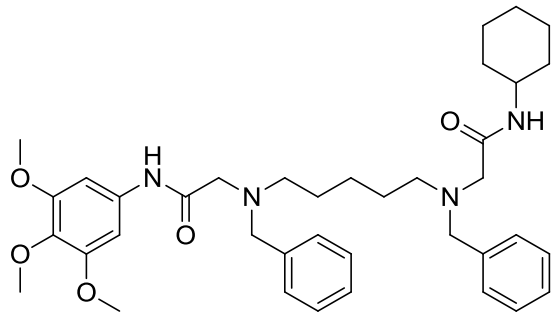
***N*-tert-butyl-2-(4-(2-oxo-2-(3,4,5-trimethoxyphenylamino)ethyl)piperazin-1-yl)acetamide**



Purified on silica gel using EtOAc/MeOH 9:1 as eluent to afford a brown solid (80% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.86 (s, 1H), 6.89

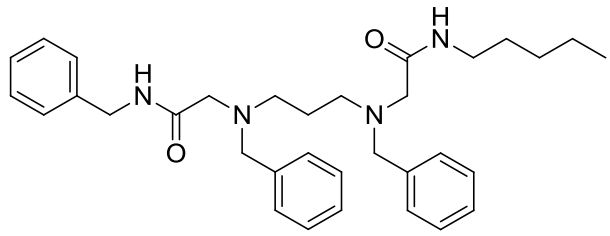
(s, 1H), 6.80 (s, 2H), 3.81 (s, 6H), 3.75 (s, 3H), 3.09 (s, 2H), 2.89 (s, 2H), 2.68-2.52 (m, 8H), 1.31 (s, 9H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.9 (C), 168.0 (C), 153.4 (C), 133.7(C), 123.2 (C), 97.3 (CH), 62.2 (CH), 62.0 (CH_2), 61.0 (CH_3), 56.2 (CH_3), 53.7 (CH_2), 53.5 (CH_2), 50.6 (C), 28.8 (CH_3); MS (ESI) *m/z* 423 (100%) $(M+H)^+$; IR (KBr): 3307, 2964, 1765, 1664, 1134, 836 cm^{-1}; MP: 100-102 °C. Found: C, 59.85; H, 8.30; N, 13.43; $C_{21}H_{34}N_4O_5$ requires C, 59.70; H, 8.11; N 13.26 %.

2-(benzyl(5-(benzyl(2-(cyclohexylamino)-2-oxoethyl)amino)pentyl)amino)-*N*-(3,4,5-trimethoxyphenyl)acetamide



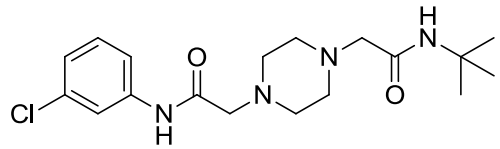
Purified on silica gel using EtOAc/MeOH 9:1 as eluent to afford a dark yellow oil (70% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.35-7.15 (m, 10H), 7.1 (d, *J= 8.55 Hz*, 1H), 6.75 (s, 2H), 3.79 (s, 6H), 3.75 (s, 3H), 3.74-3.65 (m, 1H), 3.64 (s, 2H), 3.52 (s, 2H), 3.15 (s, 2H), 2.98 (s, 2H), 2.53 (t, *J=7.35 Hz*, 2H), 2.41 (t, *J=7.35 Hz*, 2H), 1.82-1.00 (m, 16H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.1 (C), 169.3 (C), 153.5 (C), 138.1 (C), 137.9 (C), 134.9 (C), 133.8 (C), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.7 (CH), 127.5 (CH), 97.1 (CH), 60.9 (CH_3), 59.8 (CH_2), 58.8 (CH_2), 58.1 (CH_2), 56.2 (CH_3), 55.3 (CH_2), 55.2 (CH_2), 47.3 (CH), 33.1 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 25.6 (CH_2), 25.2 (CH_2), 24.7 (CH_2); MS (ESI) *m/z* 645.39 (100%) $(M+H)^+$; IR (liquid film): 3315, 2931, 2360, 1507, 1129, 727 cm^{-1}. Found: C, 70.93; H, 8.42; N, 8.25; $C_{38}H_{52}N_4O_5$ requires C, 70.78; H, 8.13; N 8.69 %.

***N*-benzyl-2-(benzyl(3-(benzyl(2- oxo(pentylamino)ethyl)amino) propyl)amino)acetamide**



Purified on silica gel using EtOAc/MeOH 9:1 as eluent to afford an amorphous solid (75% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.42-7.05 (m, 15H), 7.00 (brs, 1H), 4.38 (d, *J=6.12 Hz*, 2H), 3.54 (s, 2H), 3.49 (s, 2H), 3.27 (quart, *J=6.75 Hz*, 2H), 3.10 (s, 2H), 2.99 (s, 2H), 2.46 (t, *J=7.05 Hz*, 2H), 2.38 (t, J=7.35 Hz, 2H), 1.72-1.59 (m, 2H), 1.58-1.15 (m, 6H), 0.88 (t, *J=7.05 Hz*, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.0 (2xC), 138.1 (C), 137.7 (C), 137.5 (C), 129.0 (2xCH), 128.9(2xCH), 128.8(2x CH), 128.7 (CH), 127.7 (CH), 127.6 (CH), 65.0 (CH_2), 59.6 (CH_2), 59.5 (CH_2), 57.9 (CH_2), 53.1 (CH_2), 53.0 (CH_2), 43.1 (CH_2), 39.0 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 24.9 (CH_2), 22.4 (CH_2), 14.0 (CH_3); MS (ESI) *m/z* 529.13 (100%) $(M+H)^+$; IR (liquid film): 3307, 2955, 1655, 1521, 698 cm^{-1}. Found: C, 75.10; H, 8..67; N, 10.74; $C_{33}H_{44}N_4O_2$ requires C, 74.96; H, 8.39; N 10.60 %.

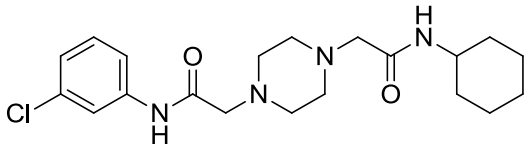
***N*-tert-butyl-2-(4-(2-(3-chlorophenylamino)-2-oxoethyl)piperazin-1-yl)acetamide**



Purified on silica gel using EtOAc/MeOH 8:2 as eluent to afford a red oil (65% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.06 (s, 1H), 7.62 (t, *J=1.83 MHz*, 1H), 7.33 (d, *J=8.28 Hz*, 1H), 7.17 (t, *J=7.95 Hz*, 1H), 7.00 (d, *J=8.28 Hz*, 1H), 6.92 (s, 1H), 3.09 (s, 2H), 2.89 (s, 2H), 2.75-2.49 (m, 8H), 1.29 (s, 9H) ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.9 (C), 168.2 (C), 138.7 (C), 134.6 (C), 130.1 (CH), 124.3 (CH), 119.6 (CH), 117.5 (CH), 65.5 (C), 62.0 (CH_2), 61.8 (CH_2), 53.5 (CH_2), 53.3 (CH_2), 28.8(CH_3); MS (ESI) *m/z* 367 (100%) $(M+H)^+$; IR (liquid film):3307, 2969,

1669, 1516, 728 cm^{-1}. Found: C, 59.20; H, 7.64; N, 15.10; $C_{18}H_{27}ClN_4O_2$ requires C, 58.93; H, 7.42; N 15.27 %

_N_-(3-chlorophenyl)-2-(4-(2-(cyclohexylamino)-2-oxoethyl)piperazin-1-yl)acetamide



Purified on silica gel using EtOAc/MeOH 8:2 as eluent to afford a white solid (65% yield). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.62 (t, *J=2.13 Hz*, 1H), 7.35 (dt, *J=8.08 Hz*, *0.93 Hz*, 1H), 7.18 (*t*, *J=7.98 Hz*, *1H*), 7.02 (dt, *J=0.93 Hz*, *J=8.08 Hz*, 1H), 6.92 (d, *J=8.25 Hz*, 1H), 3.82-3.65 (m, 1H), 3.09 (s, 2H), 2.97 (s, 2H), 2.71-2.48 (m, 8H), 1.9-1.75 (m, 2H), 1.70-1.48 (m, 3H), 1.42-1.05 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.6 (C), 168.2 (C), 138.7 (C), 134.7 (C), 130.1 (CH), 124.3 (CH), 119.5 (CH), 117.5 (CH), 61.9 (CH_2), 61.5 (CH_2), 53.6 (CH_2), 53.5 (CH_2), 47.4 (CH), 33.1 (CH_2), 25.5 (CH_2), 24.7 (CH_2); IR (KBr): 3220, 2928, 1672, 1541, 1173 cm^{-1}; MS (ESI) *m/z* 394 (100%) $(M+H)^+$; Mp 133-135 °C. Found: C, 61.15; H, 7.52; N, 14.10; $C_{20}H_{29}ClN_4O_2$ requires C, 61.14; H, 7.44; N 14.26 %.

References

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7. INTERRUPTED UGI REACTIONS

As we have seen in the previous chapters, the Ugi reaction can be exploited through many different variations in order to obtain different scaffolds. The presence of four components allows the variation of any of them, and along with the possible post transformations the disclosure of new multicomponent reaction is achievable.

But it is also possible to avoid the use of one of the component.

If we see in detail the mechanism of the reaction[1], after the imine is formed, and the isocyanide attacks this latter, a nitrilium ion is generated. This, normally, is intercepted by the carboxylate, which acts as nucleophile. But the nascent nitrilium ion, in theory, could be intercepted intramolecularly by another nucleophile, which is not the carboxylic acid or a surrogate of it. In this case the Ugi reaction is interrupted, because the formation of the iminoanhydride, and the subsequent rearrangement, are avoided (Figure 1).

To date this strategy, usually referred as Ugi-interrupted reaction, has very little been adopted.

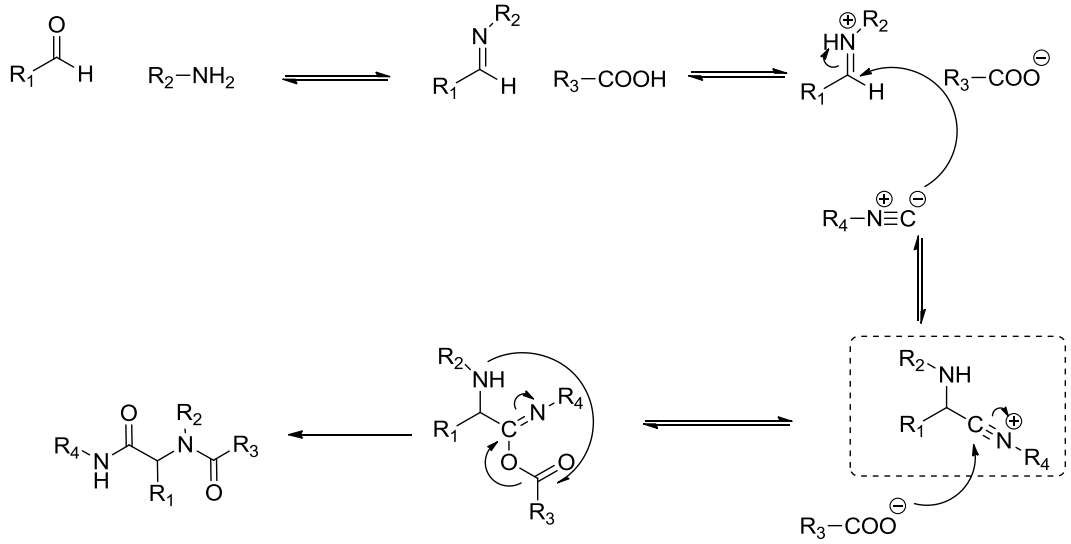


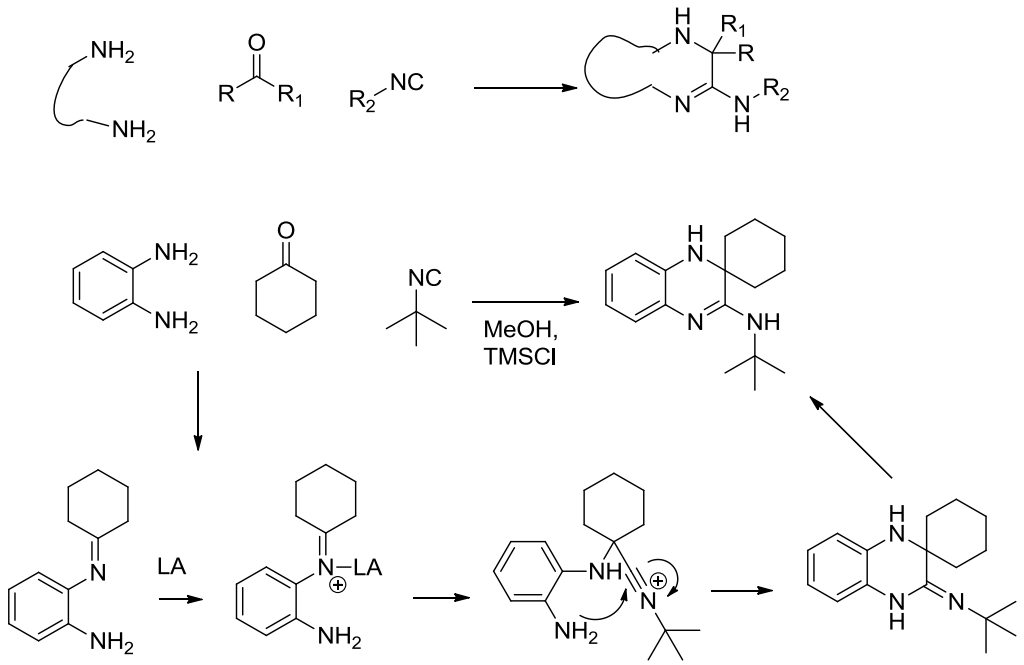
Figure 1. Mechanism of the Ugi reaction. The highlighted nitrilium ion can be intercepted by other nucleophiles.

Reactions with isocyanoacetamides, isocyanoesters, diamine, electron-rich anilines, 2-aminophenols, 2-aminopyridines and related heterocycles, represent the state of the art for the Ugi interrupted reactions.

In 1998, three different groups discovered at the same time the same reaction, which was published in three different journals. It is the three-component reaction known as "Groebke- Blackburn-Bienaymè reaction" (Scheme 1). [2]
This is a reaction among 2-aminopyridine (or pyrimidine), an aldehyde and an isocyanide that affords aminoimidazo[1,2-a]pyridines and pyrazines.
In this reaction, the nascent nitrilium ion is intercepted by the pyridine or pyrazine nitrogen atom. After a proton transfer the related aminoimidazopyridine or pyrazine is obtained.
The reaction is carried in methanol at room temperature. It is important to highlight that, in absence of the carboxylic acid, the proton exchange that activates the imine, forming the more reactive iminium ion, can not take place, so an acid catalyst has to be added. In this reaction perchloric acid or scandium triflate are used.

Scheme 1. Groebke- Blackburn-Bienaymè reaction.

Kysil in 2009 used primary diamines as substrates for a new multicomponent reaction, along with isocyanides and carbonyl compounds (aldheydes or ketones).[3] In this way the nascent nitrilium ion can be intercepted by the second amine, affording different 2-Amino-1,4-diazaheterocycles, depending on the nature of the diamine (Scheme 2). Also in this case an acid catalyst is necessary for the activation of the imine (trimethylsylil chloride).

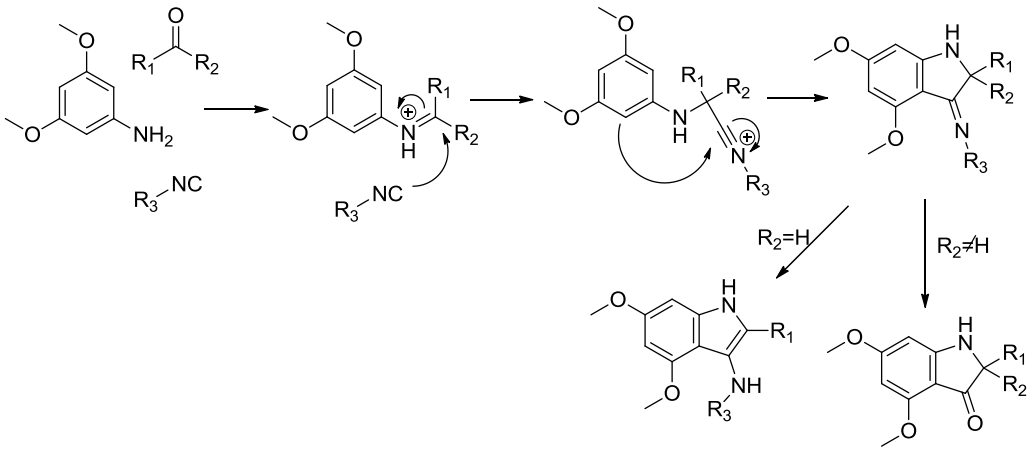


Scheme 2. Kysil's synthesis of 2-Amino-1,4-diazaheterocycles.

In a similar way, Sorensen in 2009 developed an interrupted Ugi reaction among an aldehyde, an isocyanide and electron-rich anilines to obtain substituted aminoindoles (Scheme 3). [4]

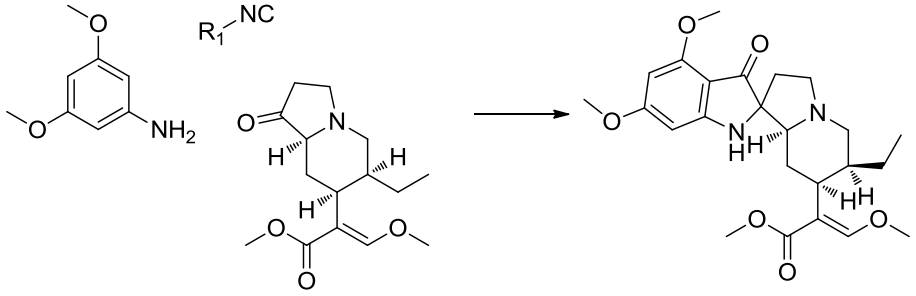
In this case triflyl phosphoramide acid is used to activate the imine, which has been preformed. After that the nitrilium ion is intercepted by the electron rich ring, an imine intermediate is formed.

If an aldehyde is used to form the imine, this intermediate undergoes a proton transfer to obtain aminoindoles. If a ketone is used instead, the intermediate is hydrolyzed to indoxyl, with the loss of the isocyanide part.



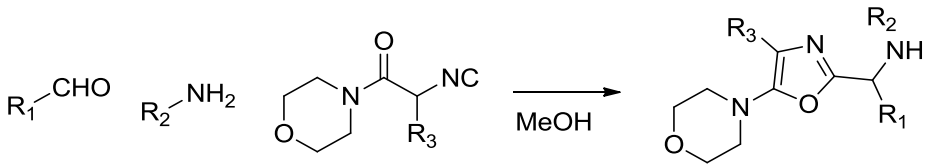
Scheme 3. Sorensen's synthesis of aminoindoles and indoxyls.

This reaction has been exploited by the same group for the synthesis of the opioid agonist 11-methoxy mitragynine pseudoindoxyl (Scheme 4). [5]



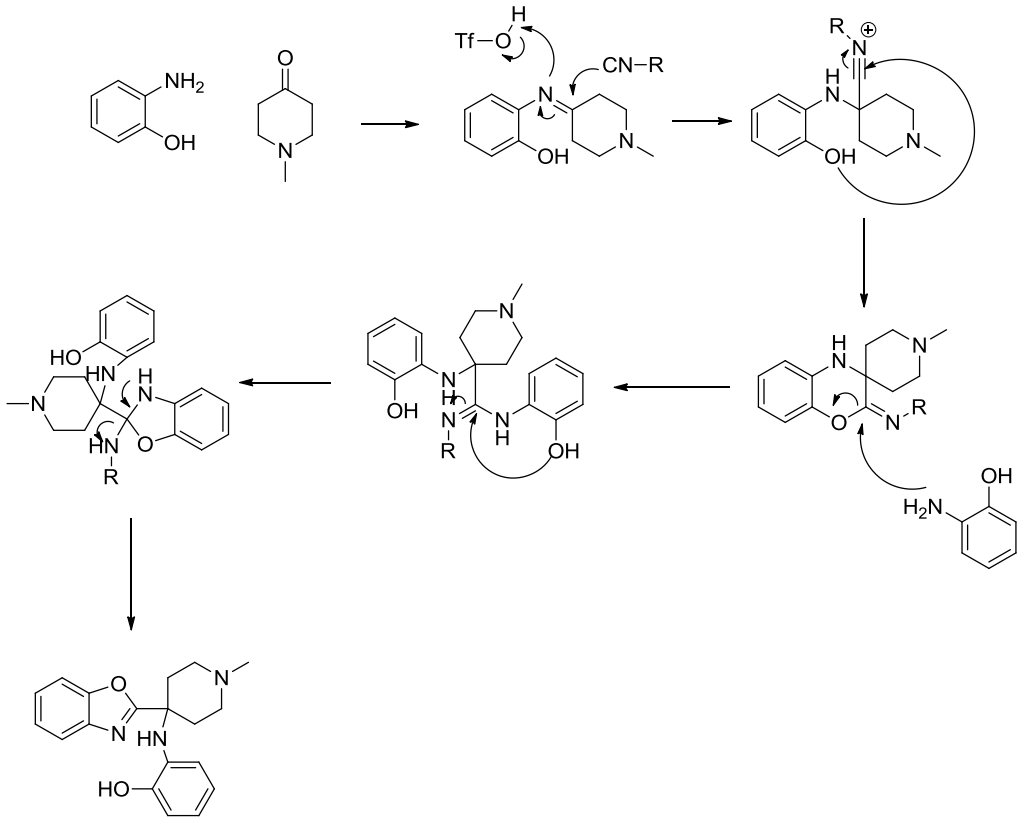
Scheme 4. Synthesis of methoxy mitragynine pseudoindoxyl using Sorensen three component reaction.

In 2001 Zhu proposed a new three component reaction among aldheydes, amines and isocyanoacetamides for the formation of 5-aminooxazoles. In this case the nitrilium ion is trapped by the oxygen atom of the isocyanoacetamide (Scheme 5). [6]



Scheme 5. 5-aminooxazoles from isocyanoacetamides, aldheydes and amines.

Finally, Varadi reported very recently a novel MCR between a ketone, 2-aminophenol, and an isocyanide that leads to the synthesis of benzoxazoles and other heterocycles.[7] The postulated reaction route proceeds via a benzoxazine intermediate. The formation of benzoxazine occurs by intramolecular trapping of the reactive nitrilium ion by the adjacent phenolic hydroxyl of 2-aminophenol (Scheme 6). Owing to its reactivity, the oxazine ring of the trapped nitrilium intermediate can be opened up by a second molecule of aminophenol or other bis-nucleophiles (including 1,2-diaminobenzene, 2-aminothiophenol, and cysteamine) leading to the elimination of an isocyanide-derived amine, finally yielding benzoxazoles or other heterocyclic scaffolds (benzimidazole, benzothiazole, and dihydrothiazole derivatives).



Scheme 6. Mechanism for the formation of benzoxazoles proposed by Varadi.

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8. SYNTHESIS OF HETEROARYLOGOUS 1*H*-INDOLE-3-CARBOXAMIDINES THROUGH A THREE-COMPONENT REACTION

8.1. RESULTS AND DISCUSSION

The intramolecular interception of the nascent nitrilium ion by a nucleophile, avoiding the use of the carboxylic acid, is usually referred as interrupted Ugi reaction. A series of transformations which followed this strategy have been disclosed: to date reactions with isocyanoacetamides, isocyanoesters, diamines, electron-rich anilines, 2-aminophenols, 2-aminopyridines and related heterocycles, represent the state of the art for the Ugi interrupted reactions (see previous chapter) (Figure 1).

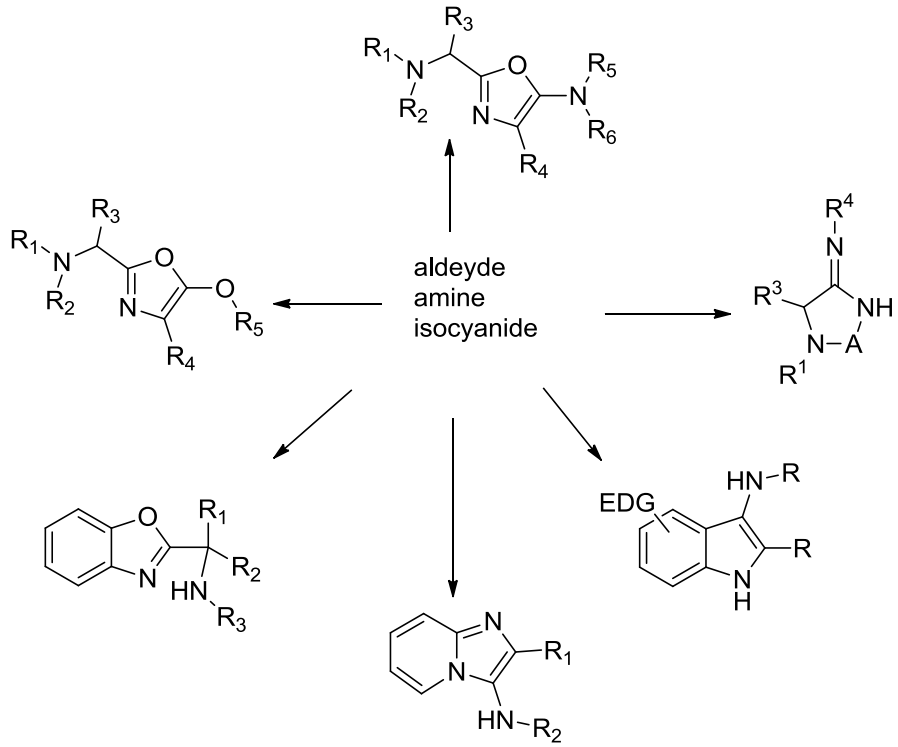
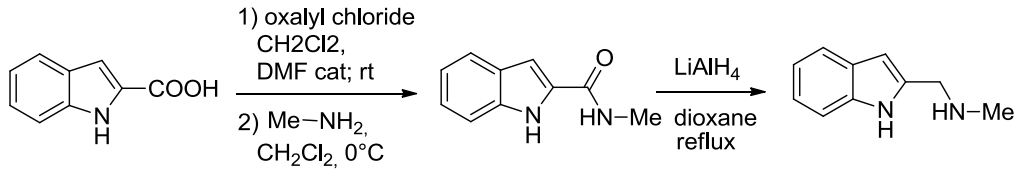


Figure 1. Examples of interrupted Ugi reactions.

As shown in Figure 1, it appears evident that despite most of the above transformations are carried out using methanol as solvent, signs of a successful formation of the imidate by reaction between methanol and the nitrilium ion has never been reported. This result indicates that either the reversibility of the

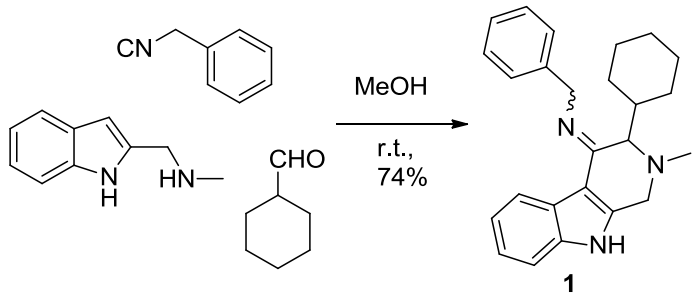
process or the inability of methanol to attack the nitrilium ion. In the same way, the direct attack of the amine nitrogen to the nitrilium ion to afford an aziridin-2-imine has never been described.

Stimulated by these results and aware that this strategy has not fully exploited yet, we started imagining which nucleophile, able to trap in a productive manner the ephemeral nitrilium ion, could be used. Firstly, we focused our attention on the indole ring. Indeed, it is well-known its electron-rich nature which makes the electrophilic aromatic substitution (S_EAr) at the C3 position extremely facile. To our surprise, a preliminary search on literature revealed us that this strategy has not been taken into consideration yet despite the undeniable importance of the indole nucleus in several branches of chemistry. As proof of principle, we therefore synthesized the 1-(1H-indol-2-yl)-N-methylmethanamine, which is easily obtainable starting from the commercially available indole-2-carboxylic acid through an amidation and a reduction reaction (Scheme 1).



Scheme 1. Synthesis of 1-(1H-indol-2-yl)-N-methylmethanamine.

This indole was then reacted with cyclohexylcarboxyaldeyde and benzylisocyanide in methanol at room temperature. With our delight, after 1 h, we observed the formation of a novel product which incorporated all the three starting materials (Scheme 2). ^{1}H and ^{13}C NMR analyses revealed the structure **1**, a novel scaffold never reported in the literature, obtained in 74 % yield, which can be considered as a sort of arylogous carboxamidine. [1]



Scheme 2. Three component reaction.

In order to unequivocally confirm the molecular structure and, at the same time, to establish the spatial distribution of the functional groups, the new synthesized compound was selected for X-ray analysis. Single crystals were obtained from an ethanol solution, and the molecular structure with the arbitrary atom-numbering scheme is represented in Figure 2. Its overall conformation is determined by the tetrahydro-β-carboline-based tricyclic framework, having the side chain in *Z* configuration and the cyclohexane axially oriented. The 1*H*-indole ring system is essentially planar and forms a dihedral angle of 77(1)° with the imine phenyl ring attached to the tetrahydropyridine fragment. The six-membered heterocyclic ring lies between the half- chair and sofa conformations, as shown by the asymmetry parameters[2] QT=0.593(1) Å, ϕ2=-59(2)°, θ=69(1)°, while the cyclohexane adopts an almost perfect chair conformation characterized by the puckering coordinates[3] QT= 0.571(2) Å, ϕ2 = -168(1)°, θ=179(2)°. All bond lengths and angles are within normal ranges. Of note, the extended conformation of the imine skeleton, characterized by the torsion angles C13-N3-C9-C8 of 174(1)° and N3-C9-C8-C7 of 160(1)°, indicates the nearly coplanarity of the indole ring with the imine moiety. This allows a certain degree of electron delocalization, beginning at the imine moiety and extending through the double bond, as shown by the shortening of the bond lengths C8-C9 of 1.459(2)Å and C7-C11 of 1.489(2)Å (Figure 2).

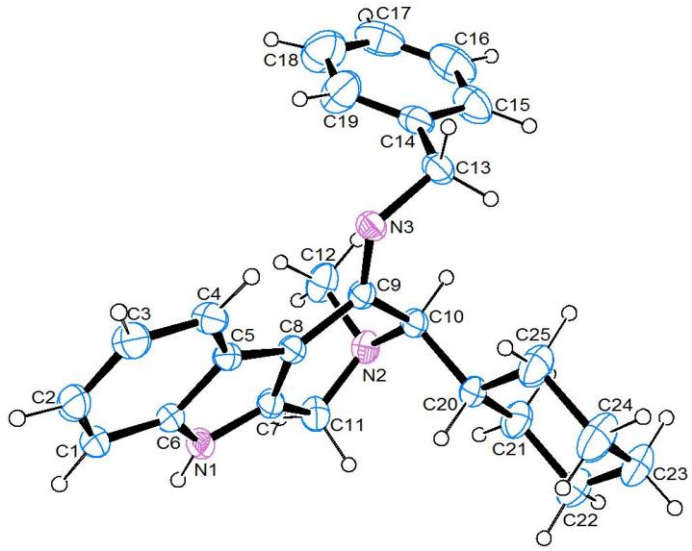
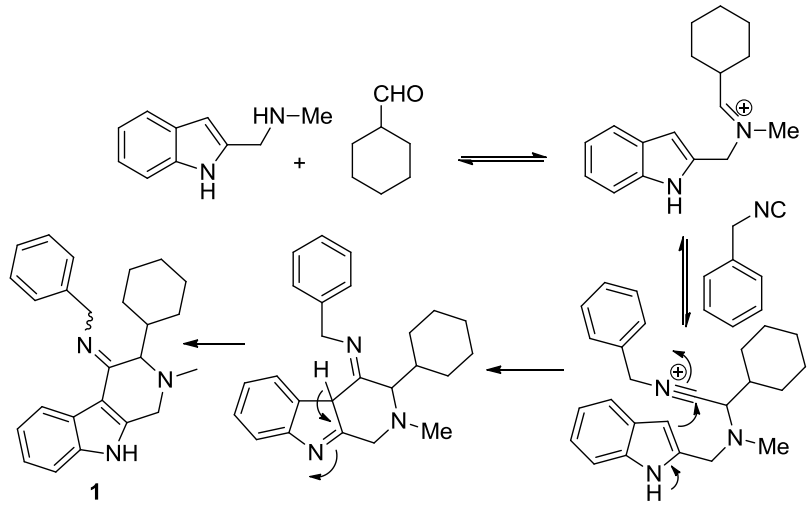


Figure 2. ORTEP view of **1** and the relative atom-numbering scheme (thermal ellipsoids at 40% probability) (Dr. Meneghetti, Unimi).

It is important to highlight that the decision to use a secondary amine in order to obtain the iminium ion under neutral conditions was fundamental for the success of this transformation. Indeed, when the same reaction was carried out with the *nor* analogue of the *N*-methylmethanamine, and a Lewis or Brønsted acid was used as catalyst to form the iminium ion, no product could be detected.

Our proposed plausible mechanism for this novel MCR is described in Scheme 3. The indole reacts with the cyclohexylcarboxyaldehyde to generate an iminium ion. The iminium ion cannot participate in a Pictet-Splenger reaction with the indole nucleus as the closure is a 5-endo trig, disfavoreud by the Baldwin ring closure rules. This intermediate is however electrophilic enough to interact with the isocyanide to form an electrophilic nitrilium ion. The latter is then intramolecularly intercepted by the C3 of the indole nucleus.[4] After a prototropic rearrangement the final product is obtained. The attack of the C3 to the nitrilium ion should presumably happen in a stereoselective way, yielding the *E* isomer.[5] However, we think that reversible protonation on the nitrogen sp^2 could occurs, allowing the isomerization of the double bond.



Scheme 3. Proposed mechanism for the formation of **1**.

In order to verify the generality of this novel transformation, we used different indoles, isocyanides and aldehydes (Figure 3).

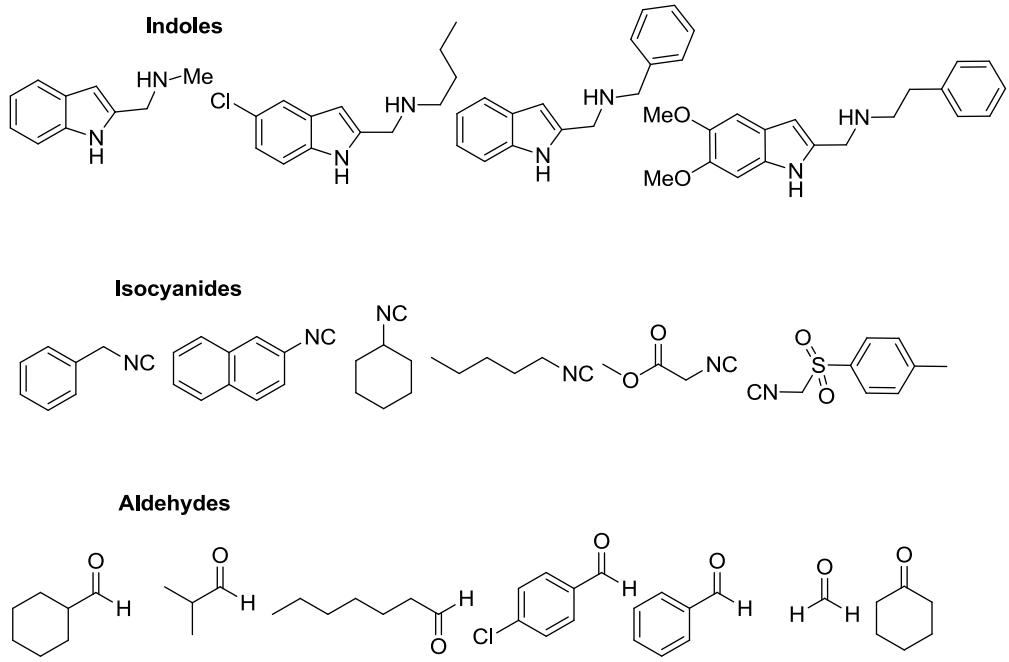


Figure 3. Building blocks used.

In figure 4 the final compounds obtained are shown. The reaction appears to be tolerant toward all type of isocyanides, aliphatic and aromatic as well as the less reactive isocyanides such as isocyanoacetoester and TosMic. Formaldehyde, aliphatic and aromatic aldehydes, the latter requiring higher reaction time, are able to participate in this multicomponent transformation. Remarkably, even cyclohexanone was able to react to produce a spiro compound albeit in modest yield. Finally, both indoles bearing electron-donating and electron-withdrawing groups, maintain the ability to intercept the nitrilium ion via the nucleophilic C3.

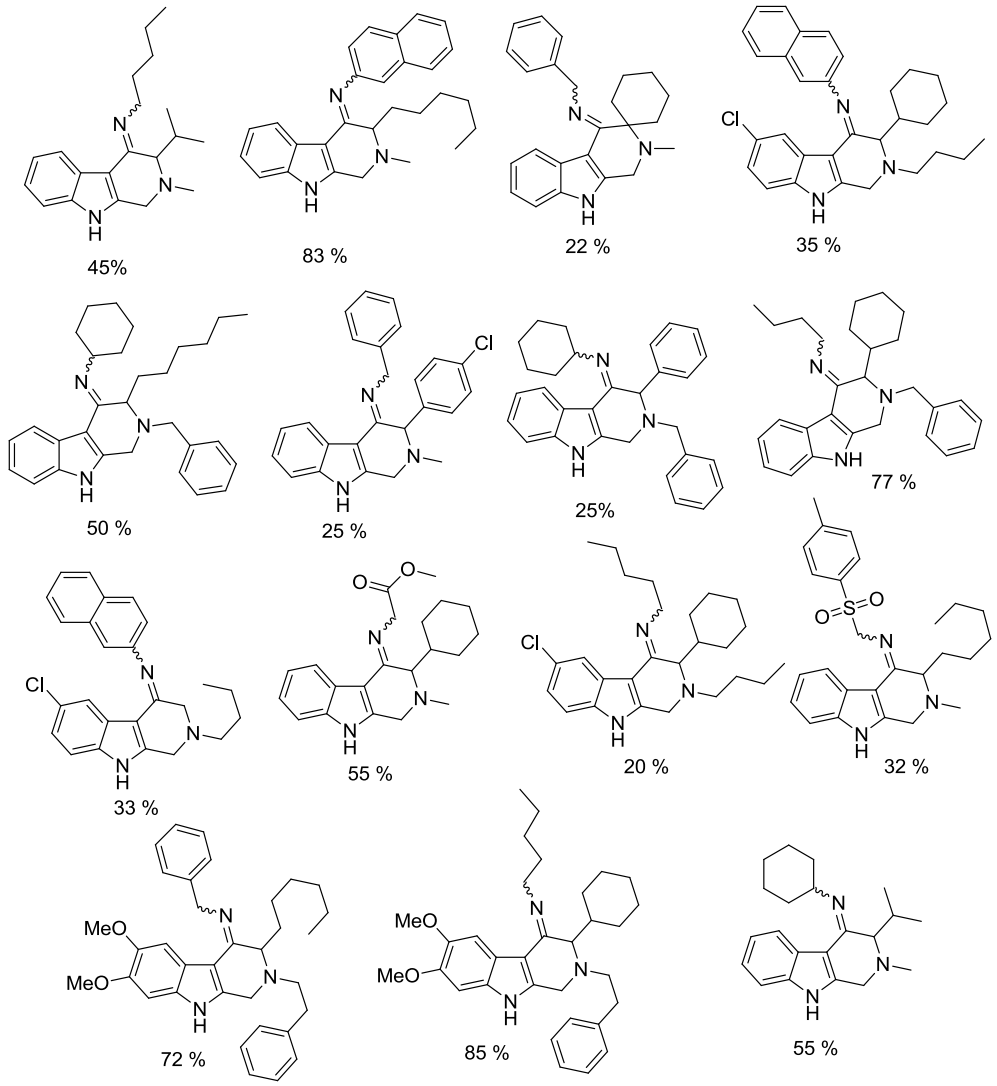
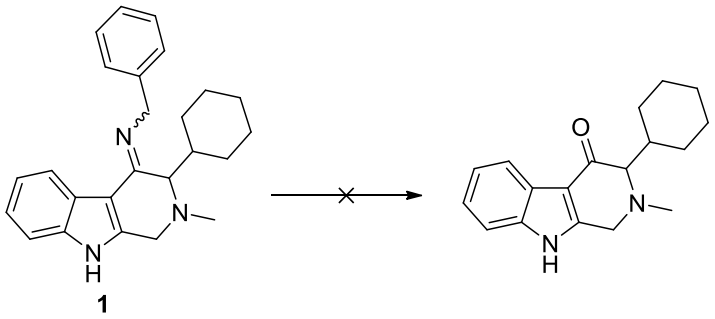


Figure 4. Heteroarylogous *1H*-Indole-3-Carboxamidines synthesized.

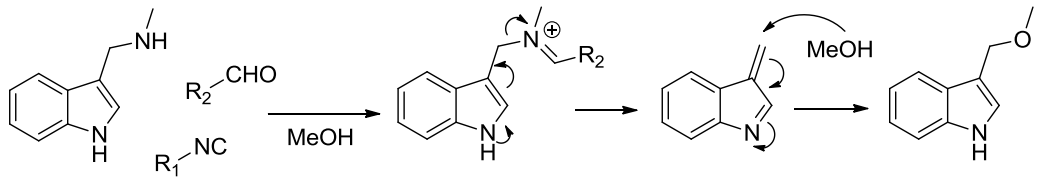
In order to verify the amidine nature of these compounds, we tested the hydrolytic stability of the imino moiety of one of the compound, both in acidic (HCl 6N at reflux) and basic conditions (NaOH 6N, dioxane at reflux). In both cases no sign of hydrolyzed products could be detected (Scheme 4).



Scheme 4. Stability of the amidine moiety.

When we performed the same reaction in the presence or a carboxylic acid (*e.g.* phenyl acetic acid), we obtained again the Ugi interrupted product in low yield (28 %) along with the Passerini adduct (16 %). No trace of the Ugi adduct could be detected.

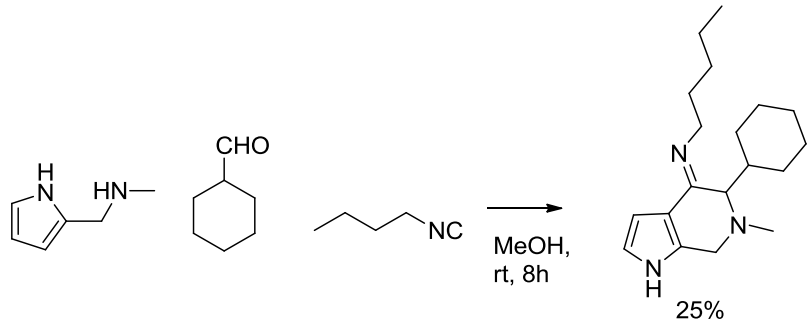
Then, we tried the reaction using 1-(1H-indol-3-yl)-N-methylmethanamine , in order to see if the less reactive C2 could be able to react in the same way. But in this case we recovered only 3-(methoxymethyl)-1H-indole. This can be explained with the following mechanism: after the iminium ion is formed, an Hofmann elimination occurs, to give the reactive intermediate 3-methylene-3H-indole. This is then attached by methanol to afford the final product (Scheme 5).



Scheme 5. 1-(1H-indol-3-yl)-N-methylmethanamine shows a different reactivity.

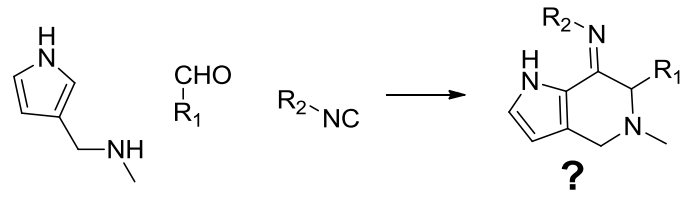
But this reaction could be performed also with other electron rich rings. Some examples are reported in the literature where furan , tiophene[6], pyrrole[7], and also electron rich arenes[6] intercept the nitrilium ion formed.

When, as preliminary tests, we reacted the *N*-methyl-1-(1*H*-pyrrol-2-yl)methanamine we obtained the carboxamidine product, although in low yields (Scheme 6).



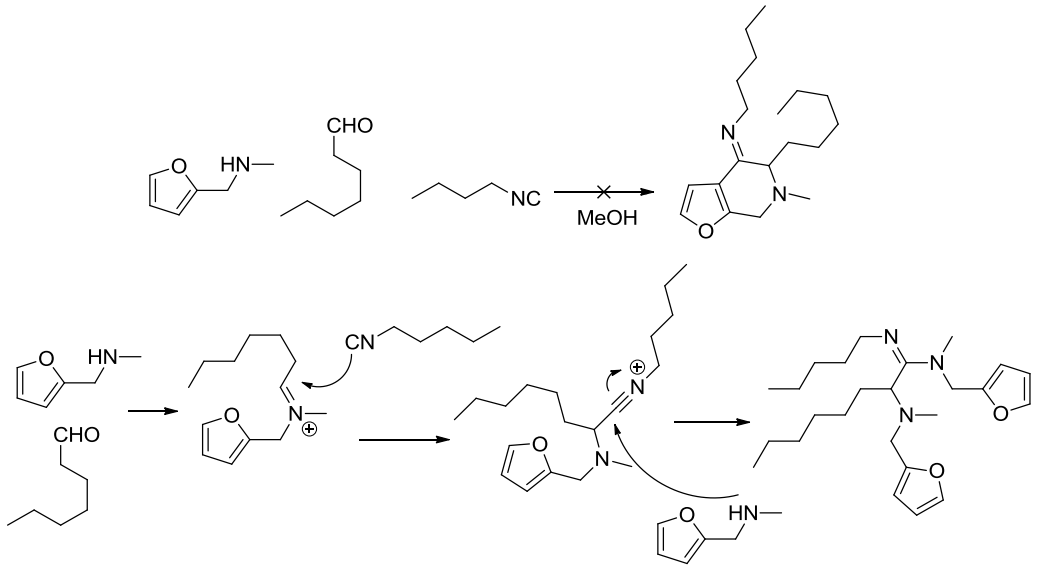
Scheme 6 . Also pyrrole ring shows a similar reactivity**.**

This reaction has to be optimized. Anyway, the pyrrole ring is more reactive in the C2 position: this suggests us a reaction with the analogue substituted in position 3 (Scheme 7).



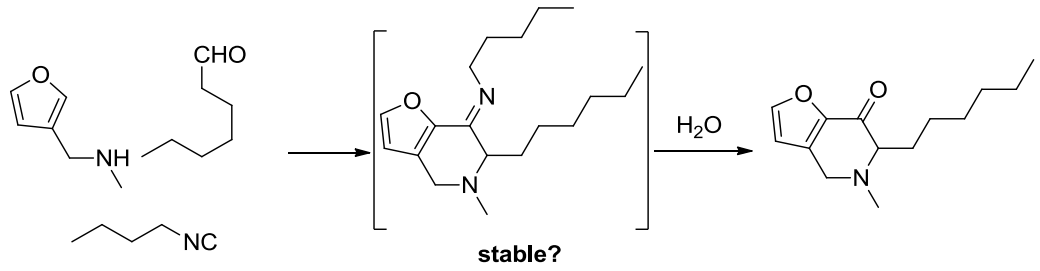
Scheme 7. Proposed synthesis of 5,6-dihydro-1*H*-pyrrolo[3,2-c]pyridin-7(4H)-ylidene amines.

Reactivity of the furan ring also has been investigated. A first experiment with 2-furyl-*N*-methylmethanamine gave un unexpected product, in which the nitrilium ion is intercepted by a second molecule of amine. Also in this case the furan ring should be substituted in position 3 with the amine, because the C2 is the most reactive, as already shown (Scheme 8). [6]



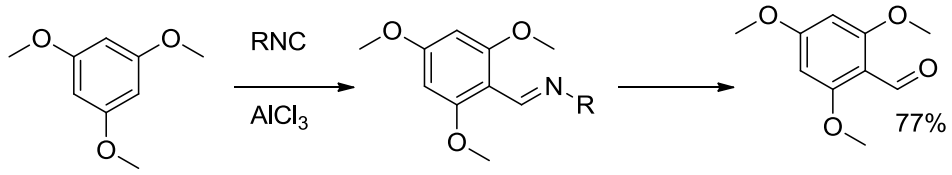
Scheme 8. 2-furyl-*N*-methylmethanamine reacts in an unexpected way.

In this way the more reactive C2 of the furan ring could intercept the nascent nitrilium ion intermediate, to give, after hydrolysis, the 5,6-dihydrofuro[3,2-c]pyridin-7(4H)-one (Scheme 9).



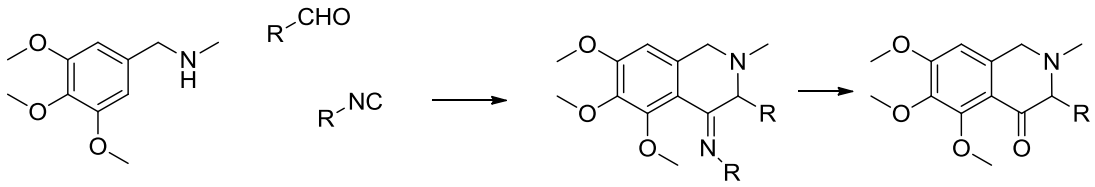
Scheme 9. The furan ring should be substituted in position 3 to give the expected product.

An electron-rich arene can serve as a good nucleophile in this kind of reaction, as reported by Sorensen [8] and other groups. For example Chatani used trimethoxy benzene, in the presence of aluminium trichloride, to attach the isocyanide [6] (Scheme 10) .The imine intermediate is rapidly hydrolyzed to afford the aldehyde.



Scheme 9. Trimethoxybenzene is nucleophile enough to intercept the nitrilium ion.

We think that the substituted benzene ring could be able to trap the nascent nitrilium ion to afford various heterocycles. For example using (3,4,5-trimethoxyphenyl)methanamine in a three component reaction together with an aldehyde and an isocyanide could afford a dihydroisoquinolinone ring.



Scheme 10. Proposed access to dihydroisoquinolinones.

These and other experiments will be carried out in another thesis project, demonstrating that this strategy can be fully exploited for the synthesis of different heterocycles.

8.2. CONCLUSIONS

In conclusion, heteroarylogous 1*H*-indole-3-carboxamidines, a new class of indole derivatives with four point of diversity, were efficiently synthesized through a facile three-component reaction. With this novel MCR, a new carbon-nitrogen bond, two carbon-carbon bonds, a carbon-nitrogen double bond and a six membered ring are produced one-pot with a single operation. The reaction proceeds under mild conditions without requiring catalysts. As the indole ring can be fully considered a privileged structure in agrochemicals and drugs, these compounds may represent novel molecular scaffolds of importance. Furthermore, being completely new and never reported there are no intellectual property associated with them, rendering their exploitation valuable from an industrial point of view.

8.3. EXPERIMENTAL SECTION

Commercially available reagents and solvents were used without further purification and were purchased from Sigma Aldrich and Alfa Aesar. Liquid aldheydes were distilled with Glass Oven B-585 Kugelrohr before being used.

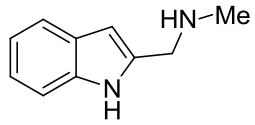
When needed, the reactions were performed in flame- or oven-dried glassware under a positive pressure of dry N2. NMR spectra were recorded with a JEOL ECP 300 MHz spectrometer and the δ values are in part per million. Mass spectra were recorded using a Thermo Finningan LCQ Deca XP-plus equipped with an ESI source and an ion trap detector. Infrared spectra were recorded on a FT-IR Thermo-Nicolet Avatar spectrometer with absorption maxima (νmax) recorded in wavenumbers (cm-1). Column chromatography was performed on silica gel Merck Kieselgel (0.063-0.200 mm; 70-230 mesh ASTM). 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 F254). When necessary they were developed with KMnO4 or Dragendorff reagent. Elemental analysis (C, H, N) are within ± 0.4% of the calculated values.

General procedure for the preparation of amines.

The corresponding carboxylic acid (1eq) was dissolved in DCM (0.3 M), and 1.6 eq of oxalyl chloride and catalytic DMF (0.1 eq) were added. The resulting suspension was stirred for 12 h at room temperature, then the solvent was evaporated *in vacuo*. The acyl chloride was then dissolved in DCM (0.2 M) and 1.2 equivalents of the corresponding primary amine were slowly added at 0°C. The reaction was stirred overnight at room temperature, then washed with NaOH 2M, HCl 2M, brine, then dried over

sodium sulphate. The crude amide was directly used for the next step without further purification: 3 eq. of $LiAlH_4$ were dissolved in dry dioxane, then the amide was added at 0°C. The reaction was refluxed overnight, then it was quenched with a saturated aqueous solution of sodium sulphate at 0°C and then filtrated. The filtrate was basified with NaOH 2M until pH 10, then it was extracted three times with EtOAc. The combined organic phases were washed with brine, then dried over sodium sulphate, and evaporated to dryness.

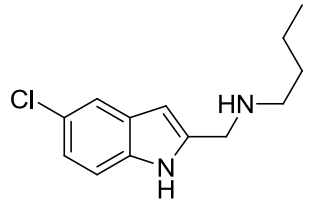
1-(1*H*-indol-2-yl)-*N*-methylmethanamine



Prepared from 3 g of Indole-2-carboxylic acid. Obtained 1.04 g as a brown solid, yield 35%.

Spectroscopic analysis are in agreement with those reported in literature.[9]

***N*-((5-chloro-1*H*-indol-2-yl)methyl)butan-1-amine**



Prepared from 2 g of 5-chloroindole-2-carboxylic acid. Obtained 774 mg as a brown oil, yield 32%.

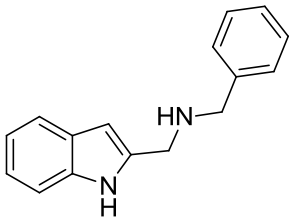
FT-IR (liquid film): 3735, 2240, 1598, 643 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.05 (bs, 1-H), 7.57 (s, 1-H), 7.23-7.01 (m, 3-H), 6.30 (s, 1-H), 3.85 (s, 2-H) 2.65 (t, J=6.7 Hz, 2-H), 1.65-1.15 (m, 6-H), 0.97 (t, J= 7.3 Hz, 3-H).

MS (ESI) m/z 203 $(M+H)^+$.

Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.43; H, 8.01; N, 13.51.

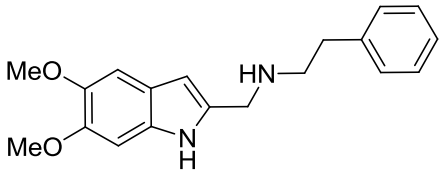
***N*-((1*H*-indol-2-yl)methyl)-1-phenylmethanamine**



Prepared from 2g of Indole-2-carboxylic acid. Obtained 1.34 g as a brown oil, yield 46%.

Spectroscopic analysis are in agreement with those reported in literature.[9]

***N*-((5,6-dimethoxy-1*H*-indol-2-yl)methyl)-2-phenylethanamine**



Prepared from 1g of 5,6-Dimethoxyindole-2-carboxylic acid. Obtained 320 mg as a brown oil, yield 23%.

FT-IR (liquid film): 3726, 2360, 1608, 668 cm^{-1}.

^{1}H-NMR (300 MHz, CDCl3) δ 8.56 (bs, 1-H), 7.35-7.15 (m, 5-H), 6.99 (s, 1-H), 6.80 (s, 1-H), 6.21 (s, 1-H), 3.91 (s, 2-H), 3.90 (s, 3-H), 3.88 (s, 3-H), 2.90 (t, J=6.0 Hz, 2-H), 2.80 (t, J=6.0 Hz, 2-H).

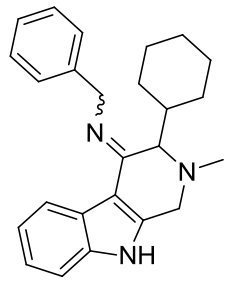
MS (ESI) m/z 311 $(M+H)^{+}$.

Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found C, 73.43; H, 7.01; N, 9.31.

General procedure and characterization data for heteroarylogous 1*H*-indole-3-carboxamidines.

The amine (1 eq) was dissolved in MeOH (0.2 M), then the aldehyde (1 eq) and the isocyanide (1eq) were subsequently added. The reaction was stirred at room temperature until completion (3→24 h). The solvent was evaporated *in vacuo* and the product was purified by column chromatography.

(*Z*)-*N*-(3-cyclohexyl-2-methyl-2,3-dihydro-1*H*-pyrido[3,4-b]indol-4(9*H*)-ylidene)-1-phenylmethanamine



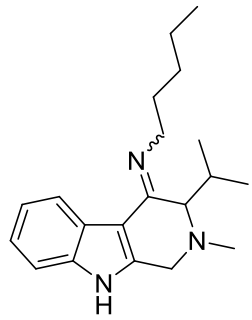
Yellow solid, yield 74%. M.p. 174-175°C. FT-IR (KBr): 2745, 2059, 1480, 978 cm^{-1}.

^{1}H-NMR (300 MHz, CDCl3) δ 8.31 (bs, 1-H), 7.55 (d, J=4.0 Hz, 2-H), 7.38 (t, J=4.0 Hz, 2-H), 7.31-7.21 (m, 3-H), 7.19-7.10 (m, 2-H), 4.85 (s, 2-H), 4.29 (d, J=17.0 Hz, 1-H, AB), 3.62 (d, J=10.0 Hz, 1-H), 3.48 (d, J=17.0 Hz, 1-H, AB), 2.47 (s, 3-H), 2.28-2.15 (m, 1-H), 1.85-1.48 (m, 5-H), 1.30-0.98 (m, 5-H).

^{13}C-NMR (75.4 MHz, CDCl3) δ 164.3, 141.7, 137.1, 133.1, 128.5, 127.8, 126.5, 125.5, 122.4, 121.8, 121.2, 111.2, 109.4, 65.0, 54.5, 45.7, 43.9, 39.0, 32.0, 30.7, 26.6.

MS (ESI) m/z 372 $(M+H)^{+}$. Anal. Calcd for $C_{25}H_{29}N$: C, 80.82; H, 7.87; N, 11.31. Found: C, 80.65; H, 7.65; N, 11.20.

***N*-(3-isopropyl-2-methyl-2,3-dihydro-1*H*-pyrido[3,4-b]indol-4(9*H*)-ylidene)pentan-1-amine**



Yellow solid, yield 45 %.

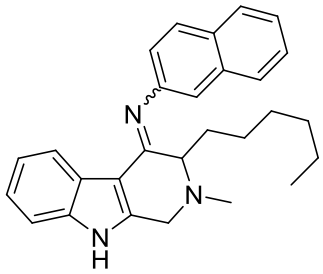
M.p. 125-126 °C.

FT-IR (KBr): 3520, 2780, 1486, 954 cm^{-1}.

^{1}H-NMR (300 MHz, CDCl3) δ 8.13 (bs, 1-H), 7.40-7.30 (m, 1-H), 7.28-7.08 (m, 3-H), 4.28 (d, J=17.0 Hz, 1-H, AB), 3.65-3.35 (m, 4-H), 2.49 (s, 3-H), 1.85-1.70 (m, 3-H), 1.55-1.30 (m, 4-H), 1.15 (d, J= 4.6 Hz, 3-H), 1.00-0.8 (m, 6-H).

^{13}C-NMR (75.4 MHz, DMSO-d6) δ 163.0, 137.9, 137.2, 125.7, 121.7 (2C), 120.3, 111.6, 109.0, 65.1, 50.8, 45.4, 43.9, 31.8, 29.9, 29.3, 22.7, 21.6, 20.3, 14.6; MS (ESI) m/z 312 $(M+H)^{+}$. Anal. Calcd for $C_{20}H_{29}N_3$: C, 77.12; H, 9.38; N, 13.49. Found: C, 77.41; H, 9.12; N, 13.25.

***N*-(3-heptyl-2-methyl-2,3-dihydro-1*H*-pyrido[3,4-b]indol-4(9*H*)-ylidene)naphthalen-2-amine**



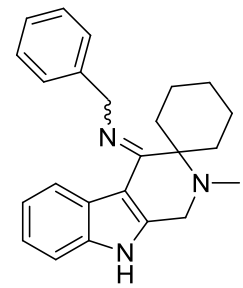
Yellow solid, yield 83%. M.p. 110-111°C. FT-IR (KBr): 3500, 2853, 1060, 967 cm^{-1}.

^{1}H-NMR (300 MHz, CDCl3) δ 8.64 (bs, 1-H), 8.37 (t, J=4.2 Hz, 1-H), 7.82 (d, J=8.2 Hz, 2-H), 7.74 (d, J=8.2 Hz, 1-H), 7.50-7.30 (m, 2-H), 7.30-7.10 (m, 5-H), 4.25 (d, J=17.0 Hz, 1-H, AB), 3.62 (q, J=4.5 Hz, 1-H), 3.51 (d, J=17.0 Hz, 1-H, AB), 2.53 (s, 3-H), 1.78-1.40 (m, 2-H), 1.30-0.95 (m, 6-H), 0.72 (t, J= 7.0 Hz, 3-H).

^{13}C-NMR (75.4 MHz, CDCl3) δ 165.5, 149.2, 139.0, 136.5, 134.4, 130.3, 128.8, 127.8, 127.3, 126.3, 125.0, 124.2, 122.9, 122.1, 121.9, 121.8,121.7, 115.6, 111.2, 109.0, 60.8, 45.6, 43.6, 31.5, 30.6, 28.9, 26.6, 22.5, 14.0.

MS (ESI) m/z 410 $(M+H)^{+}$. Anal. Calcd for $C_{28}H_{31}N_3$: C, 82.11; H, 7.63; N, 10.26. Found: C, 82.40; H, 7.32; N, 10.54.

***N*-(2'-methyl-1',2'-dihydrospiro[cyclohexane-1,3'-pyrido[3,4-b]indol]-4'(9'*H*)-ylidene)-1-phenylmethanamine**



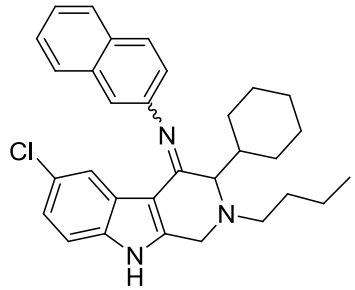
White solid, yield 22 %. M.p.189-190 °C. FT-IR (KBr): 3425, 2363, 1653, 1140, 962 $cm^{-1.}$

^{1}H-NMR (300 MHz, DMSO-d6) δ 11.44 (bs, 1-H), 7.35 (d, J=4.0 Hz, 1-H), 7.43-7.35 (m, 4-H), 7.33-7.27 (m, 1-H), 7.15-6.99 (m, 3-H), 5.02 (s, 2-H), 4.08 (s, 2-H), 2.32 (s, 3-H), 1.80-1.10 (m, 10-H).

^{13}C-NMR (75.4 MHz, DMSO-d6) δ 163.5, 141.4, 138.6, 127.1, 126.5, 126.3, 125.0, 124.3, 119.9, 118.7, 110.5, 104.6, 61.4, 56.1, 47.1, 36.4, 25.2, 20.9.

MS (ESI) m/z 358 $(M+H)^{+}$. Anal. Calcd for $C_{24}H_{27}N_3$: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.87; H, 7.41; N, 11.41.

***N*-(2-butyl-6-chloro-3-cyclohexyl-2,3-dihydro-1*H*-pyrido[3,4-b]indol-4(9*H*)-ylidene)naphthalen-2-amine**

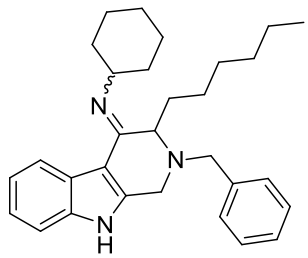


Yellow solid, yield 35%. M.p.187-188 °C. FT-IR (KBr): 3400, 2115, 1022, 946 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d6) δ 11.65 (bs, 1-H), 8.11 (s, 1-H), 7.83 (t, J=7.5 Hz, 2-H), 7.72 (d, J=8.2 Hz, 1-H), 7.55-7.30 (m, 3-H), 7.20-7.00 (m, 3-H), 4.34 (d, J=19.0 Hz, 1-H, AB), 3.80 (d, J=19.0 Hz, 1-H, AB), 3.51 2.80-2.70 (m, 2-H), 1.98-1.90 (m, 1-H), 1.60-0.80 (m, 18-H).

^{13}C-NMR (75.4 MHz, DMSO-d6) δ 164.1, 149.4, 143.1, 135.6, 134.3, 130.1, 128.7, 128.2, 127.4, 126.8, 126.2, 125.7, 124.5, 122.8, 122.2, 120.6, 115.0, 113.6, 108.6, 63.0, 54.9, 44.8, 38.2, 31.7, 30.9, 26.4, 26.2, 20.2, 14.4.

MS (ESI) m/z 485 $(M+H)^{+}$. Anal. Calcd for $C_{31}H_{34}ClN_3$ C, 76.92; H, 7.08; N, 8.68. Found: C, 76.69; H, 6.88; N, 8.87.

***N*-(2-benzyl-3-hexyl-2,3-dihydro-1*H*-pyrido[3,4-b]indol-4(9*H*) ylidene)cyclohexanamine**

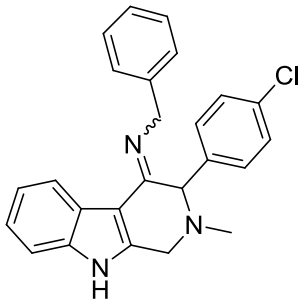


Brown solid, yield 50%. M.p. 96-97°C. FT-IR (KBr): 3509, 2926, 1140, 906 cm^{-1}. ^{1}H-NMR (300 MHz, DMSO-d6) δ 11.16 (bs, 1-H), 8.19 (t, J=7.0 Hz, 1-H), 7.45-6.95 (m, 8-H), 4.26 (d, J=17.0 Hz, 1-H), 3.85-3.60 (m, 4-H), 3.55-3.22 (m, 3-H), 1.90-1.10 (m, 18-H), 0.95-0.85 (m, 3-H).

^{13}C-NMR (75.4 MHz, DMSO-d6) δ 161.5, 139.9, 138.6, 136.8, 129.1, 128.6, 127.5, 125.8, 122.3, 121.8, 120.3, 111.6, 108.8, 59.2, 57.3, 56.6, 43.5, 35.4, 31.8, 31.2, 30.3, 28.7, 26.4, 24.8, 22.7, 14.5.

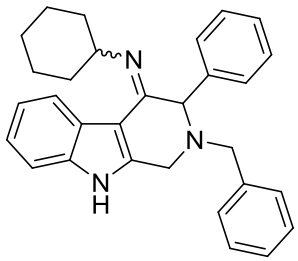
MS (ESI) m/z 442 $(M+H)^+$. Anal. Calcd for $C_{30}H_{39}N_3$: C, 81.59; H, 8.90; N, 9.51. Found: C, 81.75; H, 9.05 N, 9.28.

_N_-(3-(4-chlorophenyl)-2-methyl-2,3-dihydro-1_H_-pyrido[3,4-b]indol-4(9_H_)-ylidene)-1-phenylmethanamine



Yellow solid, yield 25 %. M.p. 104-105 °C.
FT-IR (KBr): 3320, 2831, 1184, 902 cm^{-1}.
^{1}H-NMR (300 MHz, DMSO-d6) δ 11.20 (bs, 1-H), 8.32-8.26 (m, 1-H), 7.80-7.00 (m, 13-H), 5.09 (s, 1-H), 3.97 (d, J=14.0 Hz, 1-H), 3.80-3.20 (m, 4-H), 1.80-0.90 (m, 10-H).
^{13}C-NMR (75.4 MHz, DMSO-d6) δ 158.5, 139.5, 137.5, 136.8, 129.2 (2C), 128.9 (2C), 128.8, 128.0, 127.7, 122.3, 122.1, 120.6, 112.3, 110.1, 61.3, 58.5, 57.6, 43.7, 35.2, 26.2, 24.5.
MS (ESI) m/z 400 $(M+H)^+$. Anal. Calcd for $C_{25}H_{22}ClN_3$: C, 75.08; H, 5.54; N, 10.51. Found: C, 75.30; H, 5.67; N, 10.12.

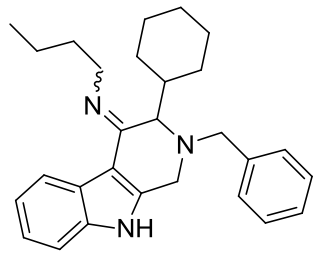
_N_-(2-benzyl-3-phenyl-2,3-dihydro-1_H_-pyrido[3,4-b]indol-4(9_H_)-ylidene)cyclohexanamine



Yellow solid, yield 25 %. M.p. 84-85 °C.
FT-IR (KBr): 3520, 2231, 1114, 902 cm^{-1}.
^{1}H-NMR (300 MHz, DMSO-d6) δ 11.20 (bs, 1-H), 8.32-8.26 (m, 1-H), 7.80-7.00 (m, 13-H), 5.09 (s, 1-H), 3.97 (d, J=14.0 Hz, 1-H), 3.80-3.20 (m, 4-H), 1.80-0.90 (m, 10-H).
^{13}C-NMR (75.4 MHz, DMSO-d6) δ 158.5, 139.5, 137.5, 136.8, 129.2 (2C), 128.9 (2C), 128.8, 128.0, 127.7, 122.3, 122.1, 120.6, 112.3, 110.1, 61.3, 58.5, 57.6, 43.7, 35.2, 26.2, 24.5.

MS (ESI) m/z 434 $(M+H)^+$. Anal. Calcd for $C_{30}H_{31}N_3$: C, 83.10; H, 7.21; N, 9.69. Found C, 83.25; H, 7.45; N, 9.48.

_N_-(2-benzyl-3-cyclohexyl-2,3-dihydro-1_H_-pyrido[3,4-b]indol-4(9_H_)-ylidene)pentan-1-amine



Yellow oil, yield 68 %

FT-IR (liquid film): 3517, 2145, 1090, 942 cm^{-1}.

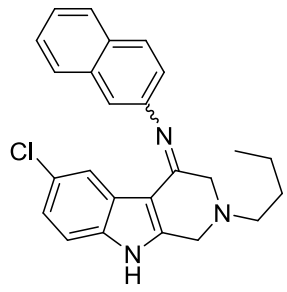
^{1}H-NMR (300 MHz, DMSO-d6) δ 11.07 (bs, 1-H), 8.13 (d, J=7.0 Hz, 1-H), 7.40-6.98 (m, 8-H), 4.31 (d, J=20.0 Hz, 1-H, AB), 3.82-3.60 (m, 3-H), 3.54 (d, J=10.0 Hz, 1-H), 3.38 (s, 2-H), 3.30-3.18 (m, 1-H), 2.35 (d, J= 10.0 Hz, 1-H), 1.80-0.90 (m, 16-H), 0.87(t, J= 7.0 Hz, 3-H).

^{13}C-NMR (75.4 MHz, DMSO-d6) δ 162.5, 140.1, 138.2, 137.0, 129.0, 128.7, 127.8, 127.2, 126.0, 121.9, 120.0, 111.4, 109.1, 61.9, 59.2, 51.0, 41.5 (overlapped DMSO), 38.7, 32.0, 30.5, 30.0, 26.8, 26.5, 22.8, 14.3.

MS (ESI) m/z 428 $(M+H)^+$.

Anal. Calcd for $C_{29}H_{37}N_3$: C, 81.45; H, 8.72; N, 9.83. Found: C, 81.20; H, 8.45; N, 10.08.

_N_-(2-butyl-6-chloro-2,3-dihydro-1_H_-pyrido[3,4-b]indol-4(9_H_)-ylidene)naphthalen-2-amine



Yellow solid, yield 33 %. M.p. 109-110 °C.

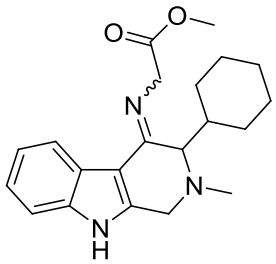
FT-IR (KBr): 3394, 2929, 1651, 1491, 1164 cm^{-1}.

^{1}H-NMR (300 MHz, CDCl3) δ 8.34 (s, 1-H), 7.85-7.78 (m, 2-H), 7.72 (d, J=8.0 Hz, 1-H), 7.49-7.35 (m, 2-H), 7.18 (s, 1-H), 7.15-6.99 (m, 2-H), 7.07 (d, J=2.0 Hz, 1-H), 3.97 (s, 2-H), 3.40 (s, 2-H), 2.41 (t, J=7.0 Hz, 2-H), 1.40-1.20 (m, 4-H), 0.83 (t, J=7.3 Hz, 3-H).

^{13}C-NMR (75.4 MHz, DMSO-d6) δ 160.7, 148.8, 143.8, 134.7, 134.3, 130.5, 128.9, 127.9, 127.5, 127.4, 126.4, 125.8, 124.4, 123.3, 121.8, 121.5, 115.9, 112.1, 110.8, 56.8, 54.2, 49.6, 29.1, 20.5, 14.0.

MS (ESI) m/z 402 $(M+H)^+$. Anal. Calcd for $C_{25}H_{24}ClN_3$: C, 74.71; H, 6.02; N, 10.45. Found C, 75.03; H, 5.77; N, 10.18.

Methyl-2-((3-cyclohexyl-2-methyl-2,3-dihydro-1*H*-pyrido[3,4-b]indol-4(9*H*)-ylidene)amino)acetate



Yellow oil, yield 55 %.

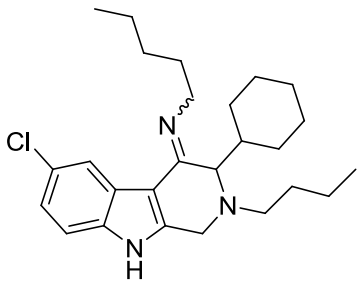
FT-IR (liquid film): 2927, 1740, 1612, 1449, 727 cm^{-1}.

^{1}H-NMR (300 MHz, CDCl3) δ 8.27 (bs, 1-H), 7.30-7.21 (m, 1-H), 7.20-7.05 (m, 3-H), 4.41 (s, 2-H), 4.30 (d, J=17.0 Hz, 1-H, AB), 3.84 (s, 3-H), 3.52 (d, J=17.0 Hz, 1-H, AB), 3.35 (d, J=10.0 Hz, 1-H), 2.46 (s, 3-H), 2.21-2.15 (m, 1-H), 1.85-0.90 (m, 10-H).

^{13}C-NMR (75.4 MHz, CDCl3) δ 172.1, 166.8, 137.2, 136.7, 125.3, 122.4, 121.8, 121.3, 111.0, 109.6, 65.3, 53.3, 52.1, 45.6, 43.9, 38.9, 31.8, 30.5, 26.5.MS (ESI) m/z 354 $(M+H)^+$.

Anal. Calcd for $C_{21}H_{27}N_3O_2$: C, 71.36; H, 7.70; N, 11.89. Found C, 71.45; H, 7.54; N, 11.67.

***N*-(2-butyl-6-chloro-3-cyclohexyl-2,3-dihydro-1*H*-pyrido[3,4-b]indol-4(9*H*)-ylidene)pentan-1-amine**



Yellow solid, yield 20 %. M.p. 147-148 °C.

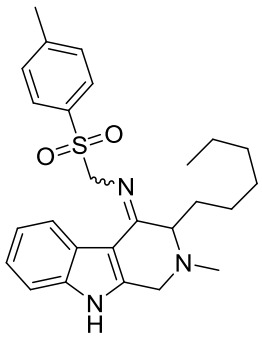
FT-IR (KBr): 3214, 2258, 1100, 896 cm^{-1}.

^{1}H-NMR (300 MHz, DMSO-d6) δ 11.29 (bs, 1-H), 8.03 (s, 1-H), 7.33 (d, J=8.2 Hz, 1-H), 7.07 (d, J=8.2 z, 1-H), 4.23 (d, J=18.0 Hz, 1-

H, AB), 3.70 (d, J=18.0 Hz, 1-H, AB), 3.55-3.50 (m, 1-H), 2.55-2.35 (m, 2-H), 2.17 (d, J=11.0 Hz, 1-H), 1.80-0.80 (m, 28-H).

^{13}C-NMR (75.4 MHz, DMSO-d6) δ 162.6, 144.8, 136.3, 126.7, 125.0, 121.5, 120.7, 113.3, 109.2, 62.0, 54.6, 50.9, 44.5, 31.8, 30.8, 30.5, 30.0, 26.8, 26.6, 22.6, 20.3, 14.6, 14.4. MS (ESI) m/z 428 $(M+H)^+$. Anal. Calcd for $C_{26}H_{38}ClN_3$: C, 72.95; H, 8.95; N, 9.82. Found C, 72.67; H, 8.57; N, 10.04.

_N_-(3-hexyl-2-methyl-2,3-dihydro-1_H_-pyrido[3,4-b]indol-4(9_H_)-ylidene)-1-tosylmethanamine

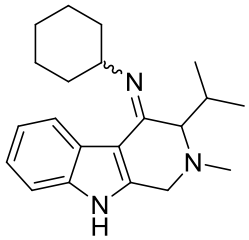


Brown oil, yield 32 %. FT-IR (liquid film): 2910, 1863, 1450, 964, 762 cm^{-1}.

^{1}H-NMR (300 MHz, CDCl3) δ 8.91 (bs, 1-H), 7.93 (t, J=5.5 Hz, 3-H), 7.33-7.25 (m, 3-H), 7.20-7.02 (m, 2-H), 5.03 (q, J=14.0 Hz, 2-H, AB) 4.25 (d, J=17.0 Hz, 1-H, AB), 3.65-3.50 (m, 2-H), 2.41 (s, 3-H), 2.33 (s, 3-H), 1.60-1.15 (m, 10-H), 0.87 (t, J= 6.5 Hz, 3-H).

^{13}C-NMR (75.4 MHz, CDCl3) δ170.8, 144.8, 139.3, 136.5, 135.0, 129.6, 129.5, 125.0, 122.7, 122.1, 121.5, 111.2, 108.8, 73.0, 60.6, 45.1, 43.6, 31.8, 30.2, 29.3, 27.0, 22.7, 21.8, 14.2. MS (ESI) m/z 452 $(M+H)^+$. Anal. Calcd for $C_{26}H_{33}N_3O_2S$: C, 69.15; H, 7.36; N, 9.30. Found C, 69.34; H, 7.21; N, 9.56;

***N*-(3-isopropyl-2-methyl-2,3-dihydro-1*H*-pyrido[3,4-b]indol-4(9*H*)-ylidene)cyclohexanamine**



White solid, yield 55 %. M.p. 210-211 °C.

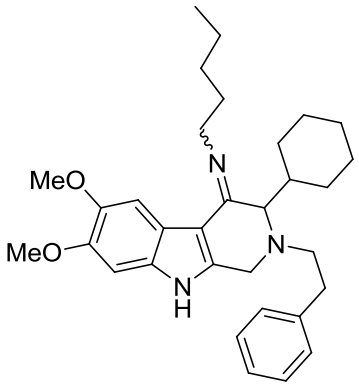
FT-IR (KBr): 3477, 2146, 1147, 945 cm^{-1}.

^{1}H-NMR (300 MHz, DMSO-d6) δ 11.08 (bs, 1-H), 8.05 (d, J=8.2 Hz, 1-H), 7.30 (d, J=7.5 Hz, 1-H), 7.06-7.02 (m, 2-H), 4.28 (d, J=17 Hz, 1-H), 3.65-3.58 (m, 2-H) , 3.45-3.35 (m, 1-H), 2.40 (s, 3-H), 1.90-1.20 (m, 11-H), 1.10 (d, J= 6.5 Hz, 3-H), 0.83 (d, J= 6.5 Hz, 3-H).

^{13}C-NMR (75.4 MHz, DMSO-d6) δ 160.4, 138.0, 137.0, 125.7, 121.9 (2C), 120.3, 111.6, 108.9, 65.2, 57.6, 45.3, 43.9, 35.4, 34.9, 28.7, 26.1, 24.7, 21.5, 20.1.

MS (ESI) m/z 324 $(M+H)^{+}$. Anal. Calcd for $C_{21}H_{29}N_3$: C, 77.97; H, 9.04; N, 12.99. Found C, 78.14; H, 8.86; N, 13.15

***N*-(3-cyclohexyl-6,7-dimethoxy-2-phenethyl-2,3-dihydro-1*H*-pyrido[3,4-b]indol-4(9*H*)-ylidene)pentan-1-amine**



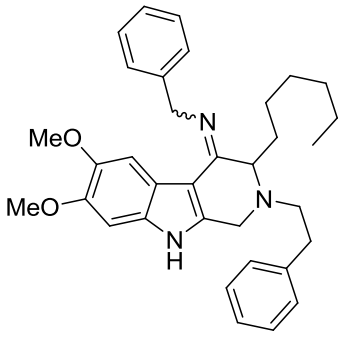
Yellow oil, yield 85 %. FT-IR (liquid film): 3215, 2341, 1652, 1488, 1207, 750 cm^{-1}.

^{1}H-NMR (300 MHz, DMSO-d6) δ 10.78 (bs, 1-H), 7.62 (s, 1-H), 7.30-7.10 (m, 5-H), 6.87 (s, 1-H), 4.22 (d, J= 17.0 Hz, 1-H, AB), 3.75 (s, 3-H), 3.72 (s, 3-H), 3.63 (d, J= 17.0 Hz, 1-H, AB), 3.50-3.23 (m, 3-H), 2.80-2.60 (m, 4-H), 2.13 (d, J=11.6 Hz, 1-H), 1.75-0.93 (m, 16-H), 0.86 (t, J=7.0 Hz, 3-H).

^{13}C-NMR (75.4 MHz, DMSO-d6) δ 162.9, 146.6, 145.3, 140.8, 137.0, 131.5, 129.2, 128.6, 126.3, 118.5, 109.6, 104.7, 96.1, 62.3, 57.3, 56.4, 56.2, 50.7, 44.5, 38.9, 35.4, 32.0, 31.9, 30.6, 30.1, 26.6, 22.8, 14.7.

MS (ESI) m/z 502 $(M+H)^+$. Anal. Calcd for $C_{32}H_{43}N_3O_2$: C, 76.61; H, 8.64; N, 8.38. Found C, 76.45; H, 8.34; N, 8.56.

***N*-(3-hexyl-6,7-dimethoxy-2-phenethyl-2,3-dihydro-1*H*-pyrido[3,4-b]indol-4(9*H*)-ylidene)-1-phenylmethanamine**



Yellow oil, yield 72 %

FT-IR (liquid film): 2929, 2344, 1477, 1300, 733 cm^{-1}.

^{1}H-NMR (300 MHz, CDCl3) δ 7.88 (bs, 1-H), 7.55 (d, J=7.3 Hz, 2-H), 7.36 (t, J=7.6 Hz, 2-H), 7.30-7.10 (m, 5-H), 7.08 (d, J=7.6 Hz, 1-H), 6.77 (s, 1-H), 4.80 (s, 2-H), 4.23 (AB, J= 17.0 Hz, 1-H), 3.98-3.77 (m, 8-H, 2x OMe and 2-H overlapped), 3.63 (AB, J= 17.0 Hz, 1-H), 2.85-2.60 (m, 4-H), 1.70-1.20 (m, 11-H), 0.89 (t, J= 6.4 Hz, 3-H).

^{13}C-NMR (75.4 MHz, DMSO-d6) δ 165.4, 147.0, 145.5, 142.8, 140.7, 137.7, 129.9, 129.0, 128.7, 127.9, 126.5,118.4, 108.8, 104.6, 96.2, 58.0, 57.3, 56.5, 56.2, 52.9, 40.4, 35.2, 32.0, 29.6, 28.9, 26.6, 14.2.

MS (ESI) m/z 524 $(M+H)^+$. Anal. Calcd for $C_{34}H_{41}N_3O_2$: C, 77.98; H, 7.89; N, 8.02. Found C, 78.20; H, 7.58; N, 8.33.

X-ray crystallographic analysis

Crystals of **1** were grown by slow evaporation of an ethanolic solution. Diffraction data have been collected by means of a Bruker-Axs CCD-based three circle diffractometer, working at ambient temperature with graphite-monochromatized Mo-Kα X-radiation (λ = 0.71073 Å).

X-ray diffraction data in the θ range 2-30° (or 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 50 mm, phi angle fixed at four different values (120°, 0°, 60°, 240°) for each of the four different sets.

Omega-rotation frames were processed with the SAINT software [10] for data reduction (including intensity integration, background, Lorentz and polarization corrections) and for determination of accurate unit-cell dimensions, obtained by least-squares refinement of the positions of 4418 independent reflections with $I > 10\sigma(I)$ in the θ range 2-23°. Absorption effects were empirically evaluated by the SADABS software [11] and absorption correction was applied to the data (0.844 and 0.993 min and max transmission factor).

The structure was solved by direct methods [12] and the refinement was carried out with SHELX-97 [13]. All non-H-atoms were refined anisotropically. The positions of hydrogen atoms were detected in the Fourier difference map and refined isotropically. The supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC deposition number: 1003584). These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk.

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SUMMARY

The main research activity during my Ph.D. was focused on the discovery of novel isocyanide-mediated multicomponent reactions (IMCRs), in order to unveil new synthetic strategies for the construction of medicinally important compounds.

After a brief introduction, in chapter 2 multicomponent reactions are described, focusing the attention on isocyanides, their preparation, reactivity and multicomponent reactions in which they are involved.

In chapter 3, the Nef reaction of isocyanides is discussed in detail, in order to introduce the project described in the following chapter. This reaction between an isocyanide and an acyl chloride leads to the formation of an α-ketoimidoyl chloride, an useful intermediate in the synthesis of a plethora of different structures.

Chapter 4 describes the discovery of a new sequential multicomponent reaction in which the Nef reaction of isocyanides is the key step. This approach allows the access to α-ketoimides. This new methodology is exploited then for the synthesis of 2-acyl quinazolinones and acyl indolinones.

Chapter 5 is a description of the use of secondary amines in the Ugi reaction, to introduce the project discussed in chapter 6, concerning the synthesis of of symmetric and unsymmetric bis-(β-aminoamides) via Ugi multicomponent reaction. The mechanism of this reaction, in which a sacrificial Mumm rearrangement is involved, and its diverse applications are described.

Chapter 7 is an overview of the interrupted Ugi reactions, to understand the project discussed in chapter 8, where I describe how this strategy can be exploited for the synthesis of heteroarylogous *1H*-Indole-3-Carboxamidines, where the nascent nitrilium ion is intercepted by the nucleophilic indole ring.

SOMMARIO

L’attività di ricerca durante il dottorato si è concentrata sulla scoperta di nuove reazioni multicomponente con isonitrili (IMCRs), per trovare nuovi approcci sintetici per molecole di interesse farmaceutico.

Dopo una breve introduzione, nel capitolo 2 sono descritte le reazioni multicomponente, concentrando l’attenzione sugli isonitrili, la loro preparazione, reattività, e le reazioni in cui sono utilizzati.

Nel capitolo 3 è discussa in dettaglio la reazione di Nef degli isonitrili, per introdurre il progetto descritto nel capitolo successivo. Questa reazione tra un isonitrile e un cloruro acilico porta alla formazione di α-chetoimidoil cloruri, intermedi interessanti per la sintesi di differenti strutture.

Il capitolo 4 descrive la scoperta di una nuova reazione multicomponente sequenziale, nella quale la reazione di Nef degli isonitrili è il passaggio principale, che permette la formazione di α-chetoimmidi. Questa nuova metodologia è usata per la sintesi di 2-acil chinazolinoni e acil indolinoni.

Il capitolo 5 è una descrizione sull’uso delle ammine secondarie nella reazione di Ugi, per introdurre il progetto discusso nel capitolo 6, riguardante la sintesi di bis-(β-amminoammidi) attraverso una reazione di Ugi. In particolare sono trattati il meccanismo di questa reazione, nella quale è previsto un riarrangiamento di Mumm sacrificale, e le sue diverse applicazioni.

Il capitolo 7 è un riepilogo sulle reazioni di Ugi interrotte, per comprendere il progetto discusso nel capitolo 8, dove descrivo come questa strategia può essere utilizzata per la sintesi di 1*H*-Indol-3-Carbossamidine, dove lo ione nitrilio formato viene intercettato dal C-3 dell’ anello indolico.

CURRICULUM VITAE et STUDIORUM

PERSONAL INFORMATION

Name	**Fabio**
Surname	**La Spisa**
Date of birth	**14/06/1987**
Address	**Via Morbio 10, Novara**
Nationality	**Italian**
Mobile phone	**+39 3403850599**
e- mail	**fabio.laspisa@gmail.com**

WORK EXPERIENCE

- November 2011-october 2014: Ph.D. student at "Dipartimento di Scienze del Farmaco", Università del Piemonte Orientale A. Avogadro, Novara. My research has been focused on the discovery of novel multicomponent reactions for the synthesis of potential new *lead compounds*.
- January 2013-july 2013: internship at "Institut de Chimie des Substances Naturelles", Gif sur Yvette, France. During this period I did research on synthetical derivatives of Vinca alkaloids, for the discovery of potential new antitumoral agents.
- January 2011-august 2011: internship at "Max Planck Institute of Colloids and Interfaces", Berlin, Germany. During the internship I carried out research for my degree thesis, working on the synthesis of GPI (GlycosylPhosphatidylInositol).
- October 2010-january 2011: professional internship at "Farmacia Madonna Pellegrina", L.go Cantelli 8, Novara.
- July 2010-october 2010: professional internship at the Hospital Pharmacy "Ospedale Maggiore", Novara.

EDUCATION AND TRAINING

- 2014: Ph.D. in "Science of Bioactive Substances", Università del Piemonte Orientale A. Avogadro, Novara. Title of the dissertation: "New Strategies for Novel Isocyanide Multicomponent Reactions: Innovative Ways to Access to Medicinally Important Compounds".
- December 2012: Qualification for the profession of Pharmacist, mark 130/150.
- October 2011: Degree in "Chimica e Tecnologia Farmaceutiche", (Pharmaceutical Chemistry and Technologies), Università del Piemonte Orientale A. Avogadro, Novara, mark 101/110.
  Title of the thesis: "Synthesis of GPI fragments: new strategies for the incorporation of unsaturated lipids".
- July 2006: High School Diploma, "Istituto Magistrale Bellini", Novara.
  Main subjects: english, german, french mark: 88/100.

LANGUAGES

- English
- German
- French

COMPUTER SKILLS

- Excellent knowledge of Office (certificate ECDL obtained in 2005).
- Excellent knowledge of Chemdraw and Scifinder.

DRIVING LICENSE

- Driving license type B and car availability.

SCIENTIFIC PUBLICATIONS

- **"**An efficient synthesis of symmetrical and unsymmetrical bis-(βaminoamides) via Ugi multicomponent reaction" La Spisa, F.; Feo, A.; Mossetti, R.; Tron, G.C. *Org. Lett.,* **2012**, *14*, 23, 6044-6047.
- "The Nef reaction of Isocyanides", La Spisa, F.; Tron, G.C.; El Kaïm, L. *Synthesis* **2014**, *46*, 829-841.
- "Sequential Multicomponent Synthesis of α-ketoimides, from Acyl chlorides, Isocyanides and Silver Salt of Carboxylic Acids", La Spisa, F.; Tron G.C., *Tetrahedron Lett*. ASAP.
- "Synthesis of heteroarylogous 1*H*-indole-3-carboxamidines through a three-component interrupted Ugi reaction", La Spisa, F.; Meneghetti, F.; Pozzi, B.; Tron, G.C., *Synthesis*, ASAP.

PARTICIPATIONS IN CONFERENCES AND SEMINARS

- March 2011: "The 5th Glycan forum in Berlin" Berlin, Germany.
- June 2012: " XXVI Summer School on Organic Synthesis", Gargnano, BS, Italy.
- June2013: "13th Symposium ICSN", Gif sur Yvette, France.
- June 2014: 13° National Conference in "Economics of Drugs and Health Technologies", Novara, Italy.
- July 2014: "European School of Medicinal Chemistry", Urbino, PU, Italy.
- September 2014: "XXIII International Symposium on Medicinal Chemistry"**,** Lisbon, Portugal.

RINGRAZIAMENTI

Eccoci alla pagina dei ringraziamenti, che sebbene si trovino all'ultima pagina, sono la vera essenza della tesi: racchiudono tutte le emozioni e le motivazioni, senza le quali non sarebbe stato possibile il raggiungimento di quest'obiettivo.
Non avrei mai immaginato di dover scrivere ancora una pagina di ringraziamenti, dopo quelli della tesi di laurea, eppure eccomi qui, perché non bisogna mai dire mai. Questo perché dopo il conseguimento della laurea non avevo intenzione di svolgere un dottorato, perciò il primo ringraziamento va al Prof. Tron, che mi ha incoraggiato a prendere questa strada, che sebbene a volte dura e impegnativa, è sicuramente valsa la pena percorrere.

Grazie anche al Prof. Panza, il coordinatore del dottorato, per essere stato sempre disponibile, con la sua cordialità e gentilezza.

Grazie a tutte le persone che hanno reso piacevoli questi tre anni di lavoro, anche se non posso nominarle tutte! Grazie agli studenti ed ai tesisti con i quali ho potuto condividere la mia modesta esperienza, perché è solamente trasmettendo gli insegnamenti che si apprende davvero. Grazie anche a tutti i colleghi e amici conosciuti durante il periodo passato in Francia, che mi hanno ospitato e reso veramente piacevole il mio soggiorno all'estero.

Grazie a tutte le persone che mi hanno aiutato e motivato, ma soprattutto grazie a quelle persone che mi hanno ostacolato e cercato di abbattermi, perché ciò mi ha reso più forte e determinato.

Infine, è al di fuori dell'università che va il ringraziamento più grande, agli amici ed alla mia meravigliosa famiglia, che anche senza saperlo, hanno dato il contributo più grande: l'affetto e l'amore.

Penso di aver ringraziato tutti…per te, Annalisa, sarebbe banale un ringraziamento…semplicemente dai un senso a tutto ciò che faccio.