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Beyond the Ugi reaction: less conventional interactions between isocyanides and iminium species

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1. Introduction

The history of isocyanide chemistry goes back to the first synthesis of allyl isocyanide by alkylation of silver cyanide reported by Lieke in 1859.[1] These isomers of cyanides remained laboratory curiosities for decades, as their strong repulsive smell prevented most chemists from working with these reactants. The first breakthrough occurred in 1920 with Passerini,[2] who investigated the interactions between isocyanides, carbonyl derivatives, and carboxylic acids; 40 years later, Ugi introduced the most important and widely used reaction with isocyanides by adding amines as a fourth component (Scheme 1).[3] The trapping of the more electrophilic iminium derivatives allows a far more efficient coupling with a wide range of aldehydes and ketones.

At the beginning of the 1990s, the four-component nature of the Ugi reaction, along with the development of combinatorial chemistry in the pharmaceutical industry, set this reaction as the leader

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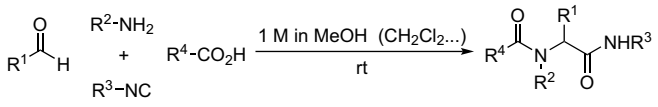
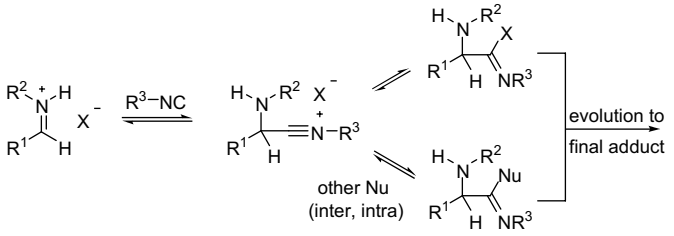


Scheme 1.

of a major trend in organic chemistry. However, over the last fifteen years, it has gradually become apparent that the Ugi reaction could not cover the entire chemical space and fulfill all the expectations of the industry. This extensive use of the Ugi reaction and its related post-condensation transformations has masked many other interesting aspects of the isocyanide reactivity.

In this review, we would like to analyze from a mechanistic point of view the potential of iminium interactions with isocyanides. Imine derivatives, usually not electrophilic enough to interact with the moderately nucleophilic isocyanide, are traditionally activated by the addition of acidic compounds. If the Ugi reaction is mostly known with carboxylic acids, other acidic derivatives have also been used with interesting mechanistic and structural features. Indeed, the fate of iminium interactions with isocyanides is mostly controlled by the following trapping of the nitrilium intermediate. This trapping, either inter or intramolecular, is not always performed by the counteranion of the acidic derivatives (Scheme 2).



Scheme 2.

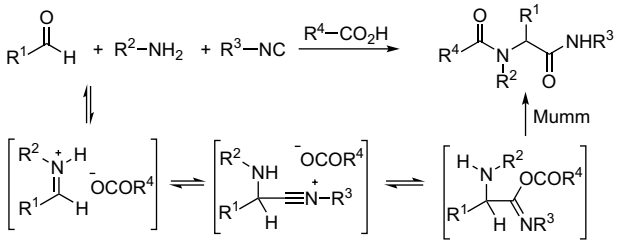
The chemistry of isocyanides and the use of isocyanide-based multicomponent reactions (IMCRs) have been the subject of different reviews.[4] This review, however, concentrates on the role of the acid component or the nucleophile in the Ugi reaction and related processes. It gathers reactions that afford very different structures, but are still mechanistically connected. The literature coverage of this review goes up to April 2008.

In the first part, we shall focus on the reactions between the nitrilium and external nucleophiles: the most obvious are carboxylic acids and their surrogates (thioacids, isocyanic acids, hydrazoic acid, phenols, …), but the use of Lewis acids has further extended the scope of these reactions by allowing less reactive nucleophiles to take part in this process.

An increased choice in the nature of the nucleophiles is offered by intramolecular trappings, which will be developed in the second part. The most thoroughly documented coupling in this set of three-component couplings (3-CCs) is probably the Ugi reaction involving aminoacids. As the behavior of such difunctional carboxylic acid derivatives is extensively described in previous reviews on Ugi-type couplings, these couplings will not be presented here.

2. Reactivity of isocyanides in Ugi-type reactions

Isocyanides are moderate nucleophiles,[5] usually interacting with strong electrophiles to form nitrilium species and α-addition adducts on the carbene. They are considered to be stable in basic conditions and sensitive to the presence of acids. Their lack of reactivity toward simple aldehydes, ketones, or imines is a major advantage for the development of isocyanide-based multicomponent reactions. Indeed, productive couplings of isocyanides with imines require the interaction of a third component to convert the imine into the more reactive iminium derivative. The nitrilium intermediate, formed after addition of the isocyanide onto the iminium, is usually trapped by the counteranion of the acid. This α-adduct is itself not always very stable, since it can revert to the starting material or rearrange into more stable derivatives (Scheme 3).



Scheme 3.

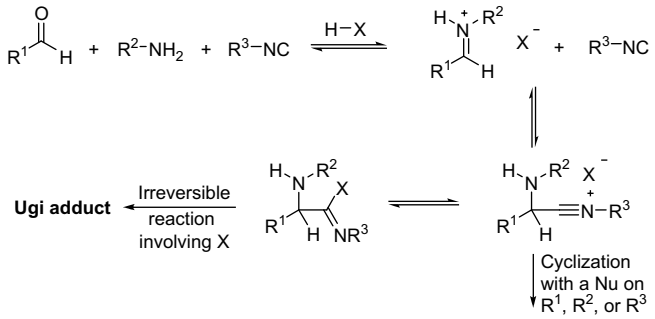
In the classical Ugi reaction with carboxylic acids, after the carboxylate trapping of the nitrilium, a Mumm-type rearrangement is involved:[6] the acyl moiety is transferred from the oxygen onto the nitrogen atom of the starting imine (Scheme 3). This final conversion of an imidate into an amide is irreversible and ensures the efficiency of the coupling. When looking for alternative acidic derivatives, besides the possible interactions between the acidic compound and the imine, two other points must be considered:

- The stability of the isocyanide in the presence of the acidic component.
- Factors that might stabilize the first α-adduct or limit the reversibility of the first steps by allowing a further rearrangement of the adduct (e.g., Mumm rearrangement).

Surprisingly enough, the first point has little influence on the success of the reaction. Indeed, studies on the kinetics and the mechanism of the acid-catalyzed hydrolysis of cyclohexyl isocyanide have shown that the reaction involves a fast pre-equilibrium C-protonation followed by a rate-determining attack of water on the protonated isocyanide.[7] The very low pK_a value of 0.86 found for the cyclohexylnitrilium ion is consistent with the lack of reactivity of isocyanides with moderate acids such as alkyl carboxylic acids:[8] no reaction is usually observed at room temperature and adducts can be isolated only under heating over 100 °C.[9] Furthermore, even with stronger acids, the pH of the medium is usually buffered by the presence of the amino component and its imine adduct with the carbonyl derivative.

The second point of consideration is directly linked to the synthetic power of isocyanide chemistry. Nitriliums are highly electrophilic species that can be trapped by many different nucleophiles. However, those of interest in IMCRs, often associated with the acidic component, are also good leaving groups and therefore lead to a moderate stability of the α-adducts. Efficiency in IMCRs has been reached frequently by an appropriate choice of nucleophile that can further react after the formation of the imidate. These secondary reactions, usually performed intermolecularly, may involve any reactive part of the imidate intermediate (Scheme 4). The different behavior of primary and secondary amines in Ugi 4-CCs can be mainly explained by secondary reactions involving the secondary amine formed from the primary amine. Besides the Ugi reaction involving a Mumm rearrangement with carboxylic acids and primary amines, successful substitutions of the acidic component were observed with:

- Carbonic or thiocarbonic acids with a final Mumm rearrangement.
- Thiocarboxylic acids also engaged in further Mumm-type rearrangement to form thioamides.
- The hydrazoic acid that forms tetrazoles in an irreversible electrocyclization of the imidoyl azide intermediate.
- Isocyanic and isothiocyanic acids that form cyclic adducts with the amine component.
- Phenols and thiophenols triggering Smiles rearrangements.
- Some simple mineral acids as well as Lewis acids.



Scheme 4.

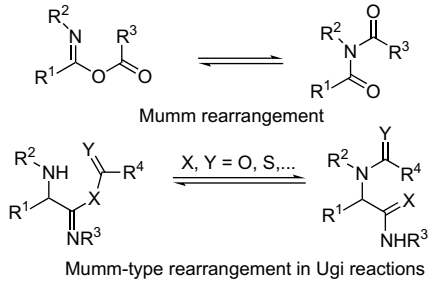
More recently, this Ugi nitrilium manifold has been further enriched by the addition of more complex nucleophiles that are not always involved in the activation of the imine. The most interesting results are obtained by the combination of a Lewis or a Brönsted acid devoid of nucleophilic behavior (such as perchloric acid, …) with the trapping of the transient nitrilium by an intramolecular nucleophile such as in:

- Three-component additions of aminoheterocycles, aldehydes, and isocyanides.
- More general [4+1]-type cycloadditions between a hetero-diene and an isocyanide.
- Oxazole formation from isocyanoacetamides.

3. Ugi-type four-component couplings

3.1. Ugi reactions involving Mumm-type rearrangements

The Mumm rearrangement was disclosed in 1910.[6] It initially stood for the conversion of *O*-acylimidate into *N*-acylamide (Scheme 5). After the discovery of the Ugi reaction, this term was also used to designate the acyl transfer involved in its final step.

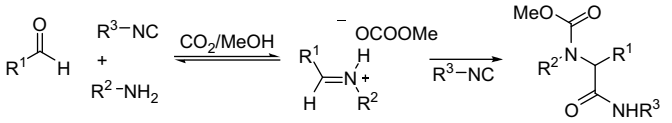


Scheme 5.

Like carboxylic acids, other acids possessing a C=O moiety may be involved in similar reactions: because of their moderate stability, the use of carbonic acid derivatives is of low synthetic interest. Thio analogues of carboxylic acids are much more interesting, as the resulting thioamides can easily be involved in further synthetic transformations.[10]

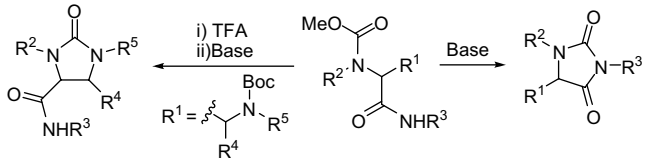
3.1.1. Carbonic acid

Like most other acid surrogates, the first addition of CO_2 in multicomponent reactions with imines and isocyanides was first described by Ugi.[11] When carbon dioxide is added to primary amines and aldehydes in a methanol solution, carbamates can be formed via the intermediate formation of a carbonic acid methyl ester as the activating acid partner (Scheme 6).



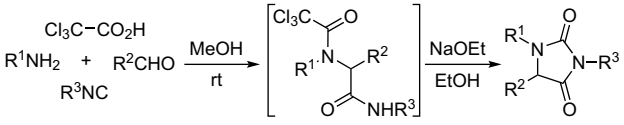
Scheme 6.

There are few reports on the use of this reactive system.[12] Armstrong and Keating obtained efficient couplings only when using low-molecular-weight alcohols as solvents.[12c] Some post-condensations using this system have been described by Hulme et al. Indeed, hydantoins may be formed under basic treatment of the initial adducts. Various urea derivatives have also been prepared by the choice of a suitable *N*-Boc-protected group either on the amino or the aldehyde partner of the Ugi coupling (Scheme 7).[12d]



Scheme 7.

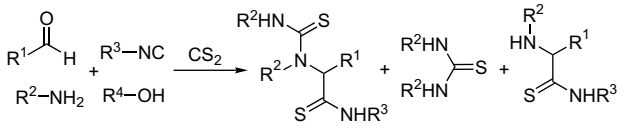
To form such heterocyclic scaffolds with a higher efficiency, Marcaccini et al. proposed alternative post-condensations using trichloroacetic acid in the first Ugi step (Scheme 8).[13]



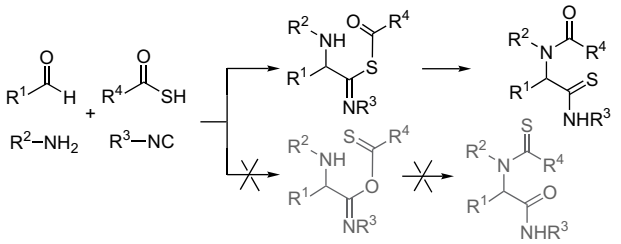
Scheme 8.

3.1.2. Thiocarbonic and thiocarboxylic derivatives

Facing difficulties with the carbon dioxide/alcohol systems, the Armstrong group next examined whether carbon disulfide (CS_2) or carbonyl sulfide (COS) could be used instead of CO_2. These systems turned out to be even less efficient. In both cases, the unavoidable formation of hydrogen sulfide (from the interaction of the amine with CS_2 or COS) is associated with the poor selectivity and inefficient addition of the alcohol component (Scheme 9).



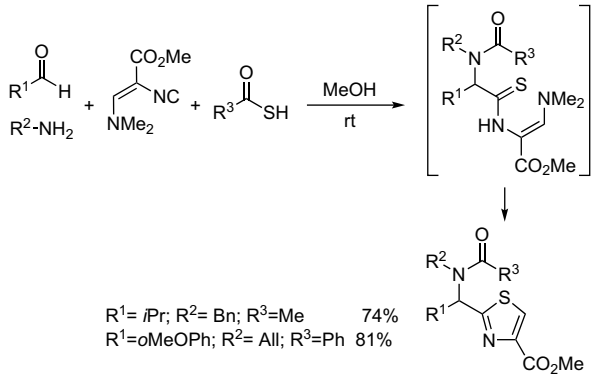
Scheme 9.



Scheme 10.

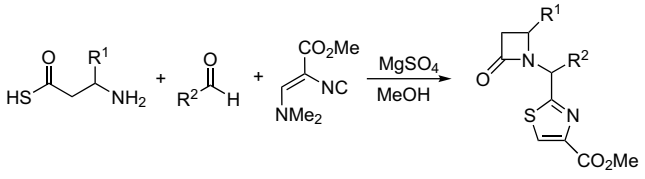
The best results with thiols as acidic derivatives are obtained with thiocarboxylic acids (Scheme 10). Their use in Ugi reactions was first reported by Dömling and Heck.[14] The relative thermodynamic stability of the carbonyl and thiocarbonyl function controls the behavior of the system, giving only one regioisomer where the sulfur atom is located on the carbon of the isocyanide moiety.

Even if thiocarboxylic acids seem to be less efficient than carboxylic derivatives for promoting the coupling of isocyanides with imines, the interest in this reaction lies in the selective and simultaneous formation of an amide and a thioamide. The rich chemistry of the latter can be further exploited in various cascades. The Dömling group has mostly focused on the use of 3-(*N*,*N*-dimethylamino)-2-isocyanoacrylic acid methyl ester, the so-called Schöllkopf isocyanide, as the starting material in this reaction.[15] In this case, the intermediate Ugi adducts are not observed, as they directly cyclize to give the final thiazole (Scheme 11).



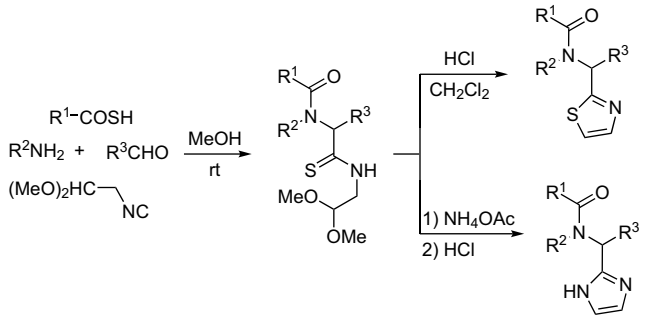
Scheme 11.

This thiazole synthesis has been associated with an elegant β-lactam formation when using a β-aminothiocarboxylic acid as the amine input of the Ugi coupling (Scheme 12).[15a]



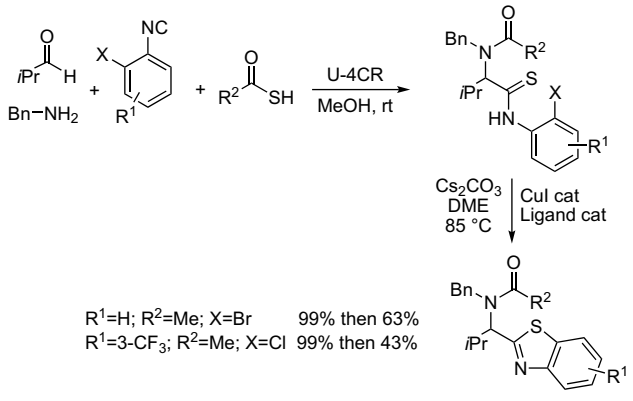
Scheme 12.

More recently, Kazmaier and Ackermann and Nenajdenko et al. worked on related thiazole[16] and imidazole[17] formation from thiocarboxylic acids and 2,2-dimethoxyethyl isocyanide. The heterocycle is, however, formed in a less straightforward manner, as a deprotection step is required after the Ugi coupling for the cyclization to occur (Scheme 13).



Scheme 13.

Regarding the rich chemistry accessible through thioamides, the number of post-condensation transformations reported up to now using thiocarboxylic acids is rather low. Besides the aforementioned thiazole formation, this chemistry has only been exploited in one benzothiazole formation: a two-step sequence involving a Ugi four-component reaction (U-4CR) followed by a cyclization of the resulting thioamides onto an aryl moiety was reported by Spatz et al. (Scheme 14).[18]



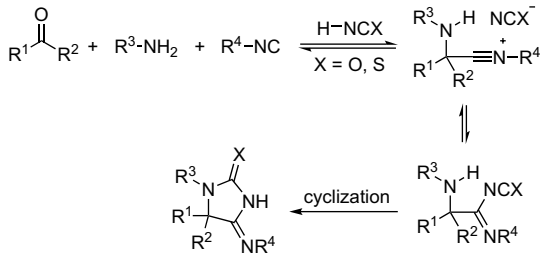
Scheme 14.

These recent studies on thiocarboxylic acids will probably renew interest in the older formation of thioamides reported in the pioneering studies of Ugi on H_2S and $H_2S_2O_3$.[3b]

3.2. Isocyanic acid derivatives

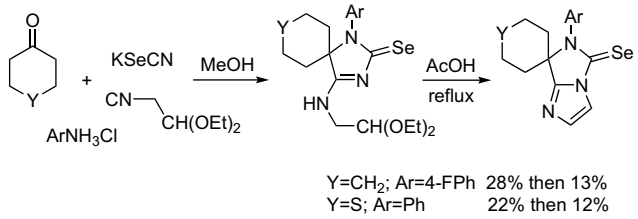
A few months after the first publication of the U-4CR with carboxylic acids, Ugi reported the extension of these couplings to several alternative acids.[19] The mechanisms involved with some of these acids and their final scaffolds are so different that these extensions can also be considered as new reactions. The Ugi reactions with isocyanic acid derivatives belong to this family of new reactions, as their use in conjunction with isocyanides and imines gives a rich entry into the hydantoin family (Scheme 15).[20]

Since isocyanic and isothiocyanic acids are unstable derivatives, these reactions are usually run by mixing together their potassium salts with the amine hydrochloride. Alternatively, in situ generation of cyanic and thiocyanic acids may also be obtained using their salts in combination with pyridinium hydrochloride. There are some striking differences between the reactivity pattern displayed by the isocyanate and the isothiocyanate system. Cyanic acid forms hydantoins in good yields only with aldehydes as the carbonyl derivatives, ketones being hardly reactive.[20b] On the other hand, the formation of thiohydantoins is only observed with a ketone as the starting carbonyl component.[20a] Later on, these reactions were



Scheme 15.

studied to explain some of the side products formed with thiocyanic acid.[21] A solid-supported version of these systems was proposed by immobilizing an isocyanoester onto a Wang resin.[22] More interestingly, when studying the reactivity of 2,2-diethoxyethyl isocyanide in this coupling, Marcaccini et al. introduced potassium selenocyanate to form imidazo–imidazo selenones.[23] The expected intermediate and final selenone are, however, obtained in very low yields, with important amounts of metallic selenium formed in both steps (Scheme 16).

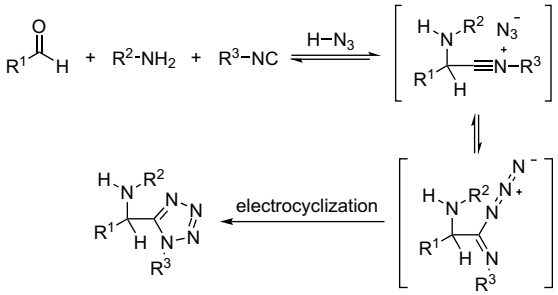


Y=CH_2; Ar=4-FPh 28% then 13%
Y=S; Ar=Ph 22% then 12%

Scheme 16.

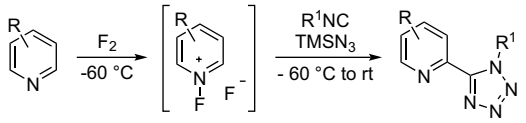
3.3. Hydrazoic acid

Hydrazoic acid was evaluated very early by Ugi. Due to its extreme toxicity and sensitivity to explosion, most studies rely on its in situ generation from a safer source. Although concomitant addition of sodium azide and HCl in a water/acetone mixture was first described, $TMSN_3$ in methanol as the solvent was later preferred for the generation of HN_3. After the first addition of the isocyanide on the iminium, the nitrilium is trapped by the azide, and then a fast 1,5-dipolar electrocyclization occurs to form tetrazoles (Scheme 17).[24] This last step plays the role of the traditional Mumm rearrangement in Ugi coupling with carboxylic acids.



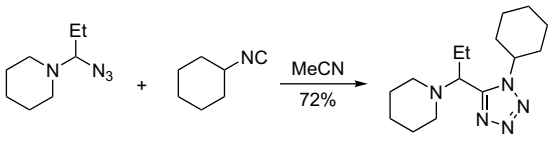
Scheme 17.

Here again, the irreversible nature of this step is linked with the disclosure of a very efficient tetrazole synthesis. This has led chemists to use this reaction as a test for less conventional aldehydes, isocyanides, or amines to couple in an Ugi-type manner. Thus, various hydrazine derivatives have been tested as an alternative amine component.[25] More recently, Kiselyov coupled cyclic iminium derivatives such as *N*-fluoropyridinium fluoride with isocyanide and $TMSN_3$ (Scheme 18).[26]



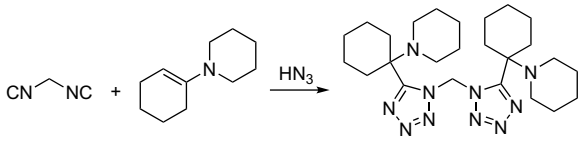
Scheme 18.

Opitz et al. also proposed variants of this reaction by preforming a Mannich adduct between the aldehyde, the amine, and the hydrazoic acid. The final tetrazole is then obtained after insertion of the isocyanide under heating in acetonitrile (Scheme 19).[27]



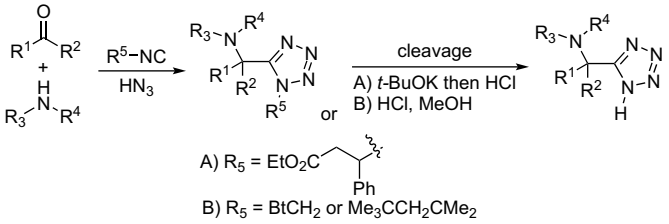
Scheme 19.

Neidlein described another tetrazole synthesis, focused on the isocyanide component.[28] Indeed, the formation of the unstable diisocyanomethane was confirmed by its trapping by an enamine and HN_3 to afford bis-tetrazole derivatives (Scheme 20).



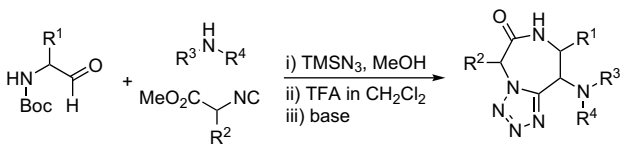
Scheme 20.

In order to synthesize acidic free N–H tetrazoles, several groups chose to introduce cleavable isocyanides, such as 3-isocyanopropionic acid esters,[29] 1-isocyano methylbenzotriazole, or 2,2,4,4-tetramethylbutyl isocyanide[30] (Scheme 21).



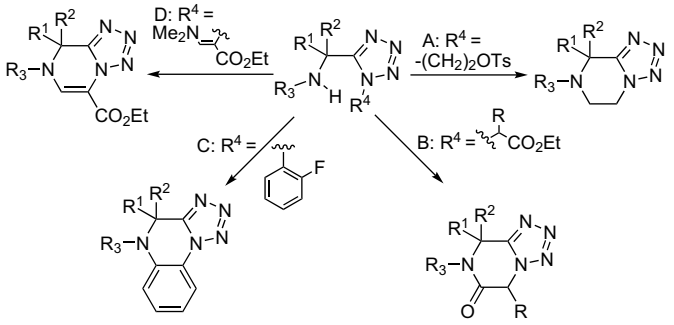
Scheme 21.

The renewed interest in this tetrazole synthesis is partly due to the ability of the tetrazole ring to mimic *cis*-amides in many biologically relevant processes. Their acido-basic properties, associated with the amino residue of Ugi-tetrazole scaffolds, make these amino acid analogues even more interesting for biological assays. Thus, important efforts have been made for the preparation of new Ugi-tetrazole libraries for medicinal chemistry.[31] As the amine input is not involved in the last cyclization step, it is not surprising that secondary amines should behave as efficiently as primary amines in these additions. Hulme's group has used such additions in his UDC (Ugi/de-Boc/cyclize) strategy (Scheme 22).[32]



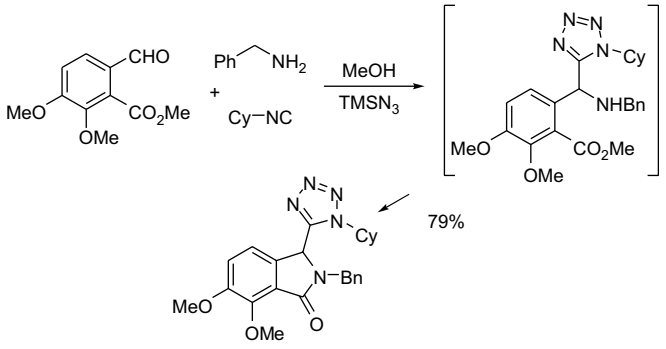
Scheme 22.

However, in the case of primary amines, the diversity offered by this process can be further increased with post-condensations. The resulting secondary amines can be exploited to provide more complex tetrazole derivatives. Most work has focused on intramolecular reactions using an electrophilic moiety on one of the starting materials. For example, when choosing the isocyanide component, fused tetrazolopiperazine derivatives are obtained with tosylate-substituted isocyanides,[33] isocyanoesters,[34] fluoroaryl isocyanides,[35] or Schöllkopf isocyanides[36] (Scheme 23).



Scheme 23.

A similar approach was adopted by Marcaccini et al. in a new isoindolinone synthesis, but, in this case, the intermediate secondary amine cyclizes onto an additional ester tethered to the aldehyde moiety (Scheme 24).[37]

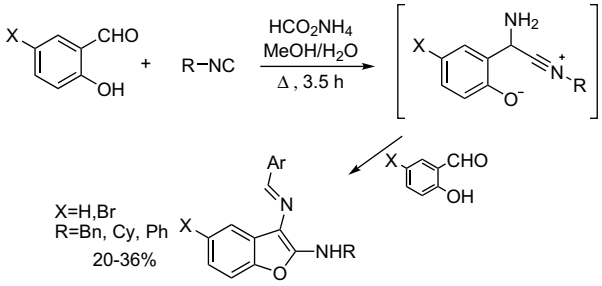


Scheme 24.

3.4. Smiles rearrangement in Ugi-type couplings

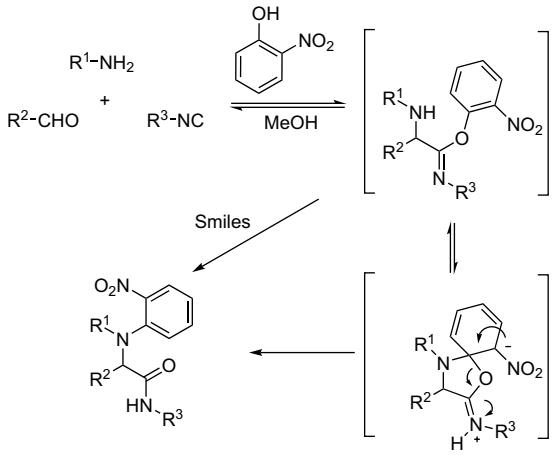
3.4.1. Alcohols and phenols

Alcohols are not acidic enough to trigger any coupling of isocyanides with imines[38] (see Section 3.6 for the activation of these couplings by Lewis acids). Phenols are more acidic and their acidity can be tuned by proper substitution onto the aromatic ring. The first trapping of a nitrilium by a phenol residue after the isocyanide addition onto an imine derivative was observed by Marcaccini et al. with salicylaldehyde.[39] They obtained benzofuran derivatives in moderate yields by reacting ammonium formate with an isocyanide and a two-fold excess of salicylaldehyde (Scheme 25). This example illustrates the synthetic interest of intramolecular trapping of nitrilium intermediates, as plain phenol is unable to promote the coupling of an aldehyde, an isocyanide and an amine.



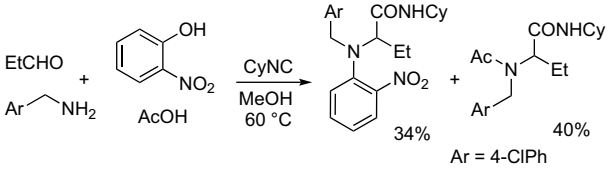
Scheme 25.

The first efficient four-component coupling of phenols with isocyanide and imine derivatives was observed with 2- and 4-substituted nitrophenols. Along with their increased acidity, an interesting feature of these phenols is the ability of the nitro group to trigger S_NAr reactions. This property allows the imidoyl phenolate intermediate to evolve via an intramolecular transfer of the aryl moiety onto the nitrogen of the amine (Scheme 26).[40] This reactive sequence was coined 'Ugi–Smiles coupling' after Smiles studies on a similar aryl transfer via five-membered ring spiro intermediates formed by intramolecular S_NAr reactions.[41]



Scheme 26.

Whereas classical Ugi reactions with carboxylic acids are completed within a few hours at room temperature, Ugi–Smiles couplings are best conducted in refluxing methanol or in toluene at over 60 °C. Competitive experiments between acetic acid and 2-nitrophenol in methanol at 60 °C show a slightly higher reactivity of acetic acid over the phenol in inducing the four-component coupling of cyclohexyl isocyanide, propionaldehyde, and 4-chlorobenzylamine (Scheme 27).[42]



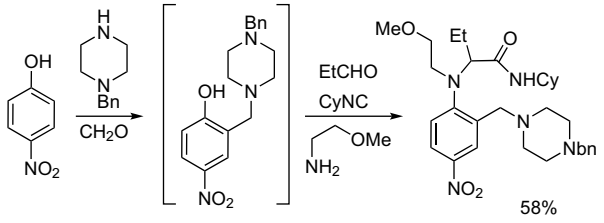
Scheme 27.

Further evidence for this lower efficiency can be found in the lack of reactivity of aromatic amines in Ugi–Smiles couplings. Aliphatic ketones are traditionally much less reactive than aldehydes

in Ugi-type reactions; however, they can still be coupled with nitrophenols in moderate yields when heated for several days.

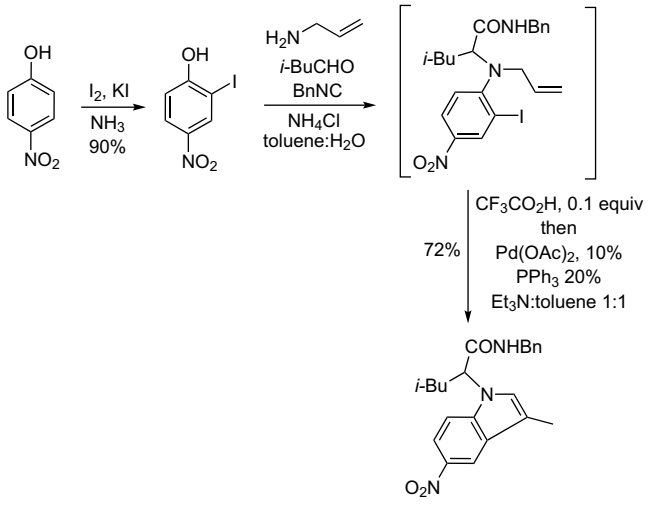
The sequence requires a strong activating group onto the aromatic ring. Indeed, no reaction is observed with the less electron-withdrawing cyano or diethylphosphonate groups at the *ortho* or *para* position relative to the hydroxy group. Esters have a different behavior, according to their *ortho* or *para* substitution pattern. Whereas 4-hydroxybenzoic acid esters are not reactive under these conditions, salicylic acid esters give Ugi–Smiles adducts in good yields. Depending on the amine and aldehyde used, various amounts of hydroxybenzamide can be formed as a side product. Both 2- and 4-hydroxybenzamides are unreactive in Ugi–Smiles couplings. Some of these results can be correlated with the pK_a values of substituted phenols, the more acidic nitrophenol being the most reactive. However, the contrasting results for hydroxybenzoic acid esters (*o*-methyl ester: pK_a 9.8; *p*-methyl ester: pK_a 8.5) show that more complex factors must control the reactivity of these systems.

The rich nucleophilic reactivity displayed by phenols can be advantageously exploited to achieve various sequences involving Ugi–Smiles couplings. Thus, a consecutive Mannich/Ugi–Smiles sequence affords a six-component formation of various α-aryloxy carboxamides (Scheme 28).[42]



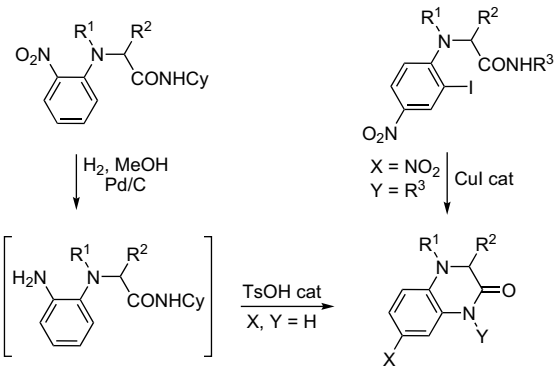
Scheme 28.

More interestingly, the *ortho* halogenation of nitrophenols followed by a Ugi–Smiles reaction forms precursors suitable for palladium-catalyzed cyclizations toward indoles. The Ugi–Smiles reaction and palladium-induced coupling can be performed in the same pot, if the remaining isocyanide is destroyed by introducing some trifluoroacetic acid into the medium prior to catalyst addition (Scheme 29).[43]



Scheme 29.

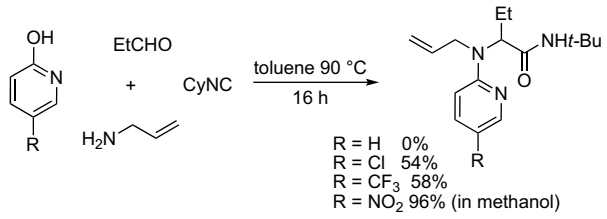
Besides its interest as an activating group for the Ugi–Smiles reaction, the nitro function can be considered as a masked amino group, which can be further used for the preparation of various fused heterocyclic systems. Indeed, the hydrogenation of the Ugi–Smiles adduct of *ortho*-nitrophenol with cyclohexyl isocyanide affords an *o*-phenylenediamine derivative, which can be further cyclized under heating with a catalytic amount of tosic acid (Scheme 30). The loss of the isocyanide residue in the final quinoxaline target can be avoided using *ortho*-iodonitrophenol as the starting Ugi–Smiles phenol. In this case, the quinoxaline is obtained by a copper-catalyzed cyclization of the intermediate Ugi–Smiles adduct (Scheme 30).[44]



Scheme 30.

During these post-condensation studies, an interesting feature concerning the scope of Ugi–Smiles couplings in relation to *ortho* substitution was observed with various 2-substituted 4-nitrophenols. Whereas alkylamino (Scheme 28), iodo (Scheme 29), methoxy, or chloro substituents are tolerated with a wide range of isocyanides, amines, and aldehydes, simple alkyl derivatives such as 2-methyl-4-nitrophenol or 2-allyl-4-nitrophenol cannot be coupled under similar conditions. This surprising *ortho* effect may be associated with the increased reactivity of salicylic acid methyl ester over 4-hydroxybenzoic acid methyl ester.[40b]

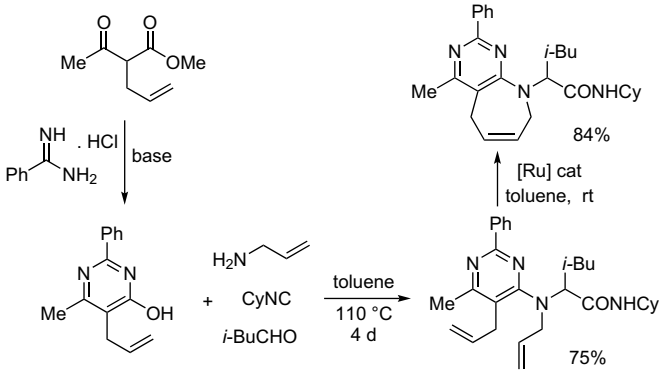
Initially disclosed with nitroaromatic derivatives, the scope of the Smiles rearrangement was later extended to include various nitrogen heteroaromatic derivatives. In the case of six-membered ring systems, the electron lone pair of the nitrogen atom does not belong to the π system and the polarization of the C=N bond decreases the electron density on the aromatic carbon atoms. Thus, for example, pyridines, pyrimidines, and triazines can undergo Smiles rearrangements without needing any further activation of the aromatic system.[45] In agreement with these electronic properties, hydroxypyridines, pyrimidines, and pyrazines were found to be reactive in Ugi–Smiles couplings.[40b,46] Although no reaction can be observed with 2-hydroxypyridine, a chloro substituent at the 4-position is sufficient to induce the coupling (Scheme 31). Except for nitro-substituted pyridines, methanol as solvent gives much lower yields than toluene.



Scheme 31.

As expected, because of their higher electrophilicity, pyrimidines with a hydroxy group at the 2- or 4-position show increased reactivity. The easy synthesis of 4-hydroxypyrimidines from the condensation of amidines and β-ketoesters allows the design of

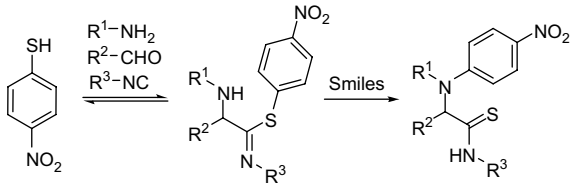
very straightforward multicomponent formation of fused pyrimidine systems. Indeed, allylation of β-ketoesters followed by condensation with amidines affords allylated pyrimidines, which can be engaged in Ugi–Smiles couplings (as mentioned above, the analogous 2-allyl-4-nitrophenol fails to react in Ugi–Smiles couplings). A ring-closing metathesis can be performed easily at room temperature with a second-generation Hoveyda–Grubbs catalyst (Scheme 32).[47]



Scheme 32.

3.4.2. Thiophenols

Their pK_a profiles designate thiophenols as potentially interesting partners in Ugi-type reactions. They are indeed much more acidic than their phenol analogues. With a pK_a value of 5.1, *para*-nitrobenzenethiol is closer in acidity to carboxylic acids than *para*-nitrophenol (pK_a=7.4). Combined with the higher nucleophilicity of mercapto anions, the first Ugi steps should be improved when compared to the reactivity of the phenol derivatives. The following Smiles rearrangement can then give a fast entry to *N*-aryl thiocarboxamides (Scheme 33).[48]

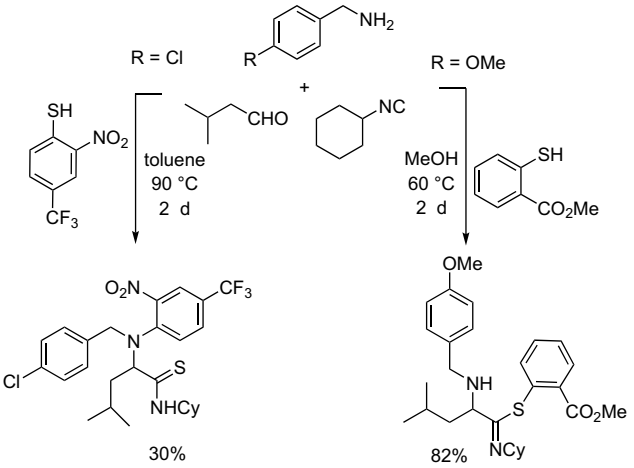


Scheme 33.

However, *para*-nitrothiophenol fails to give adducts with any of the traditionally reactive partners of the Ugi–Smiles reaction. The most obvious reason for this failure probably lies in the lack of efficiency of the Smiles rearrangement. In the case of phenol derivatives, the potential equilibrium involved in the Smiles transformation is fully displaced toward the *N*-aryl carboxamide, due to the higher thermodynamic stability of the amide with respect to the imidate intermediate. With thioamides and thioimidates being much closer in energy, the Smiles step is less prone to displace all the equilibria involved in Ugi processes toward the final adducts.

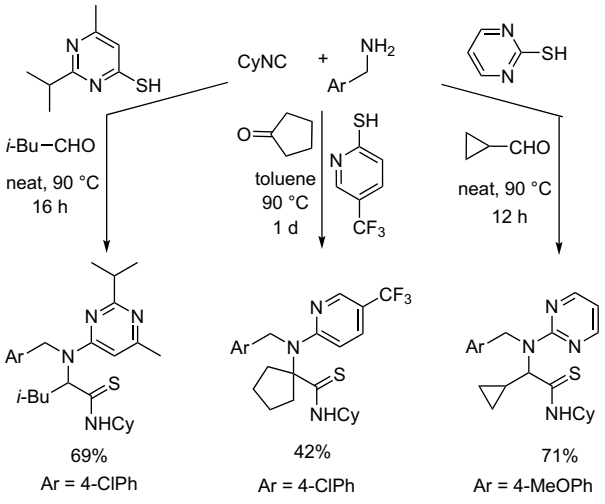
Working with nitrothiophenols, the only Ugi–Smiles adducts that can be isolated in moderate yields are obtained with 2-nitro-4-trifluoromethyl-thiophenol. However, thiosalicylic acid methyl esters give good yields of the corresponding thioimidates (Scheme 34). Further attempts to convert the thioimidate under heating at higher temperature or treatment with a Lewis acid fail to give the expected Smiles-rearranged adduct.

The results obtained with thiosalicylic acid esters stress the importance of the Smiles step in this cascade. Without any aryl transfer, the fate of the reaction is determined by the stability of the thioimidate intermediate. For acidic thiols, an evolution to amides, amidines, and imidates may be expected by the potential addition–elimination processes with the other nucleophiles of the medium (H_2O, amines, alcohols).



Scheme 34.

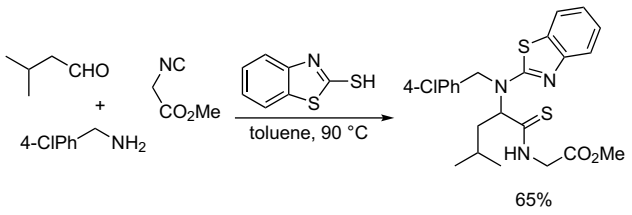
Heteroaromatic thiols give much more interesting results in Ugi–Smiles couplings. 2-Mercaptopyridine does not form any adduct, but, as observed for the hydroxy analogue, the addition of a trifluoromethyl substituent allows the preparation of thioamides in moderate-to-good yields (Scheme 35). In addition, 2- and 4-mercaptopyrimidines are also good partners if solventless conditions are used (Scheme 35). In contrast to their pendant hydroxyl derivatives, pyridines and pyrimidines fail to react with aromatic aldehydes.



Scheme 35.

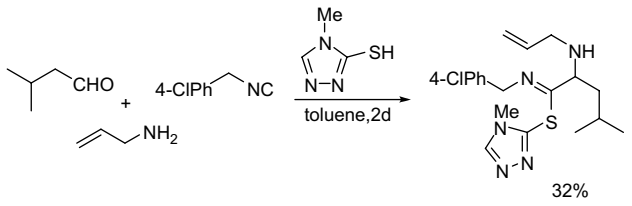
Even if these couplings with six-membered ring heteroaromatic thiols demonstrate the potential of Ugi–Smiles couplings for thioamide formation, their efficiency remains moderate, compared to their hydroxy analogues. Surprisingly, some five-membered ring heteroaromatics show an opposite reactivity trend. When compared to six-membered ring systems, heterocycles such as pyrroles, pyrazoles, and oxazoles are much more electron-rich because of their delocalized heteroatom lone pair. Their hydroxyl-substituted derivatives are thus less acidic and, unless additional withdrawing groups are introduced, Smiles rearrangement should be less efficient. Indeed, all attempts to couple hydroxyl-substituted five-membered-ring heterocycles failed.

The first significant results were obtained with benzothiazoles and benzoxazoles (Scheme 36). The benzofused system stabilizes the negative charge that might develop onto the cyclic nitrogen atom, thus assisting each step of the Ugi–Smiles cascade. Although similar yields are obtained with benzoxazoles and benzothiazoles, the related benzimidazoles, either *N*-alkylated or non-*N*-alkylated, fail to react in this coupling.[48,49]



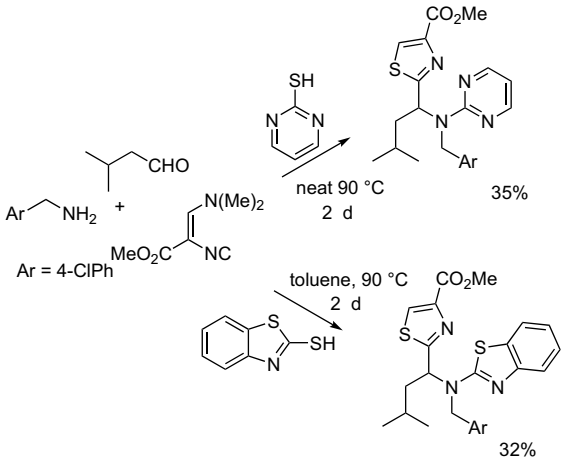
Scheme 36.

Increasing the number of heteroatoms in the cycle does not enhance the Smiles behavior of these systems. With 5-mercaptoisoxazole, variable mixtures of starting materials and amides resulting from hydrolysis of the intermediate thioimidate are obtained. In the case of 3-mercapto-1,2,4-triazole, these intermediates are stable enough to be isolated in moderate yields, as observed with thiosalicylic derivatives (Scheme 37).



Scheme 37.

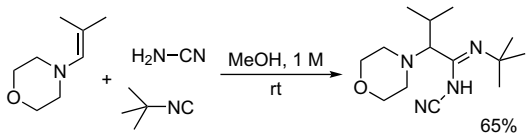
With reactive thiols in Ugi–Smiles couplings, the use of more complex isocyanides such as the Schöllkopf isocyanide can lead to interesting Ugi–Smiles/thiazole formation, as reported by Dömling et al.[15] with thiocarboxylic acids (Scheme 38).



Scheme 38.

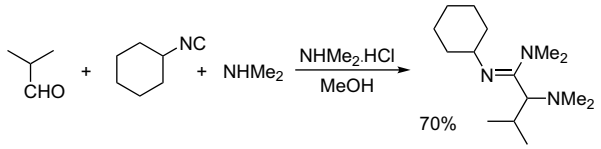
3.5. N–H acidic derivatives

Most of the hydroxy- and mercapto-substituted heterocycles discussed above may exist in a tautomeric amide or thioamide form and, as such, can be considered as N–H acidic derivatives. Apart from these heterocycles, as well as the cyanic derivatives presented in the preceding sections, the usually lower acidity of N–H compounds compared to that of the related O–H or S–H derivatives results in fewer successful Ugi couplings. Nevertheless, the Dömling group has reported the use of cyanamide, with a relatively high pK_a value (17 in DMSO), as an acidic partner in a three-component interaction with enamine and isocyanide (Scheme 39).[50]



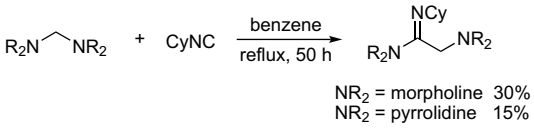
Scheme 39.

Obviously, the more acidic ammonium salts of the amine could be good partners in such a coupling. However, their use raises a competition problem between the two amines introduced into the medium. To overcome this limitation, McFarland used the same amine for the two amino components, allowing an efficient amidine formation (Scheme 40).[51]



Scheme 40.

A related amidine synthesis was reported by Zinner et al. by refluxing various formaldehyde aminals with cyclohexyl isocyanide in benzene for several days (Scheme 41).[52]



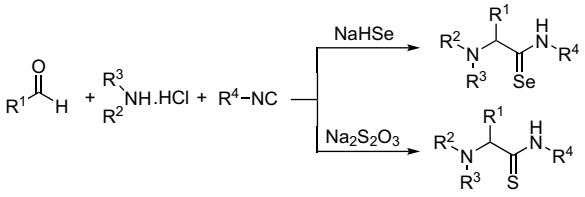
Scheme 41.

Such an insertion of isocyanide without the assistance of any acidic compound seems surprising. However, the low yields and the long reaction times observed may be associated with a partial hydrolysis of the medium followed by the formation of ammonium carbonates which, indeed, might induce the reaction.

3.6. Mineral and Lewis acids

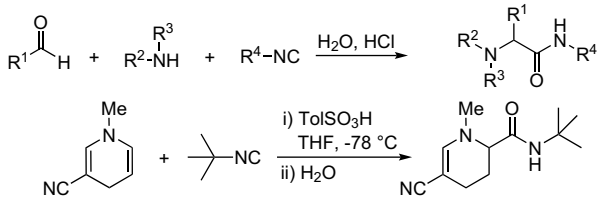
The acidity of water does not permit a proper activation of Ugi couplings. The substitution of oxygen by sulfur and then selenium progressively lowers the pK_a values of the corresponding acids. Indeed, Ugi et al. have shown that hydrogen selenide (pK_a 3.8) could be used as the acidic component, giving an original access to complex selenoamides. A similar formation of a thioamide was best accomplished with thiosulfate instead of hydrogen sulfide (Scheme 42).[3b]

The introduction of amines in the form of their hydrochlorides raises the question of strong mineral acids as activating agents for Ugi-type couplings. The fast degradation of the isocyanide is not observed, as the medium is buffered by the presence of the amine. Furthermore, strong acids with poorly nucleophilic counteranions (HCl, RSO_3H, …) may activate isocyanide couplings with imines and allow external nucleophiles to trap the resulting nitriliums. A good illustration of this behavior may be found in the synthesis of amidines with amine hydrochlorides (see Scheme 40).



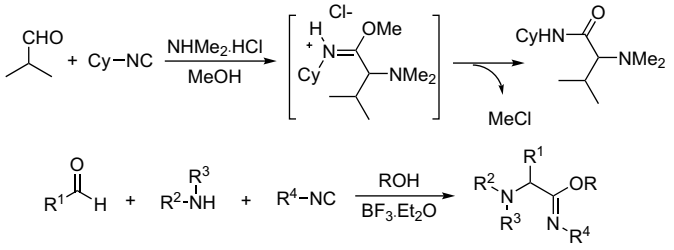
Scheme 42.

Although plain water is unable to promote Ugi couplings, the formation of amides by nucleophilic attack of water on nitrilium intermediates can be observed using aqueous mineral acids[24b] (Scheme 41). More recently, Lavilla et al. used sulfonic acids to trigger the coupling of dihydropyridines with isocyanides in THF at low temperature (Scheme 43).[53]



Scheme 43.

Similar reactions in anhydrous alcohols can give an interesting entry to iminoesters through trapping of nitrilium intermediates by the alcohol. Even if, under these conditions, only amides are mainly formed, due to the instability of the iminoester salts,[51] the replacement of Brönsted acids by Lewis acids such as $BF_3 \cdot Et_2O$ affords the expected iminoesters in good yields (Scheme 44).

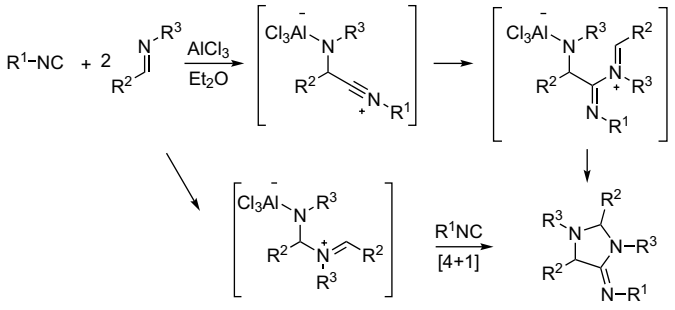


Scheme 44.

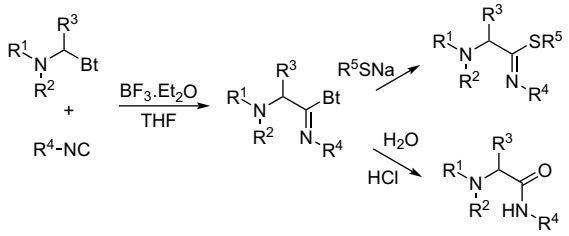
More generally, the use of Lewis acids opens up the way for trapping nitrilium intermediates with more complex nucleophiles. A stoichiometric amount of $AlCl_3$ was used very early on by Saegusa et al. to form imidazolidines (Scheme 45).[54] Although the mechanism might involve the capture of a nitrilium by a second equivalent of imine, an alternative [4+1] cycloaddition may also be proposed. These intramolecular processes will be presented with further details in the following sections.

More recently, Katritzky et al. used benzotriazoles as good nucleophiles toward nitrilium intermediates, with the preformed Mannich base between the benzotriazole and imine as the starting material (Scheme 46).[55] This $BF_3 \cdot Et_2O$-induced reaction represents a formal four-component addition between an amine, an aldehyde, an isocyanide, and a benzotriazole as the acidic partner.

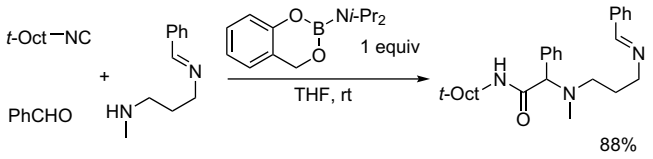
Suginome et al. reported a very efficient Ugi-type reaction with secondary amines with an aminoborane Lewis acid. These conditions allow a selective coupling of a secondary amine in the presence of an imine (Scheme 47).[56]



Scheme 45.

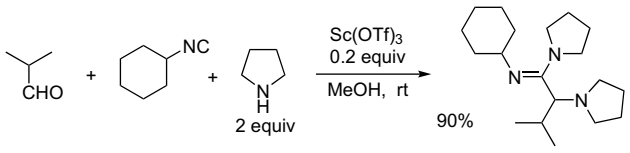


Scheme 46.



Scheme 47.

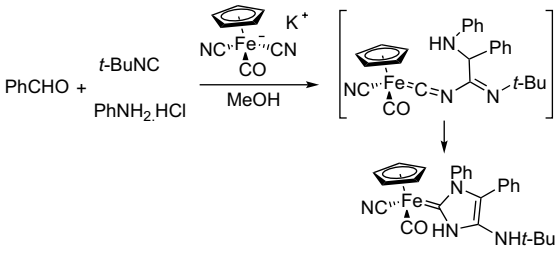
An interesting extension of the McFarland preparation of aminoamidines was described by the Keung group with lanthanum(III) triflates as Lewis acids.[57] Scandium(III) triflate gives the best results with a catalyst loading of 0.2 equiv (Scheme 48).



Scheme 48.

This strategy has permitted the design of very original trappings of nitriliums by various cyano transition-metal complexes. Fehlhammer et al. added isocyanides, aldehydes, and amine hydrochlorides to several cyanometallate complexes ($M(CO)_xCN_yL$, M=Cr, Mo, W, Mn, Fe), and new heterocyclic transition-metal complexes were obtained by a Ugi-type reaction involving the trapping of the nitrilium by the nitrogen atom of the cyano complex (Scheme 49).[58] The final cyclization into a carbenoid imidazoline shares some analogy with the hydantoin formation in Ugi-type reactions with isocyanic derivatives.

In this part, we have listed a number of isocyanide–imine interactions leading to nitrilium trappings with nucleophilic O, S, and N atoms. The scope of these reactions has been increased with the use of Lewis acids. The resulting disconnection between the two steps (the imine activation and the nucleophilic attack onto the nitrilium) should allow the participation of even more complex and less reactive nucleophiles in Ugi-type couplings. However, as shown by the above amidine formation, a competition between less efficient trapping agents and the amine component



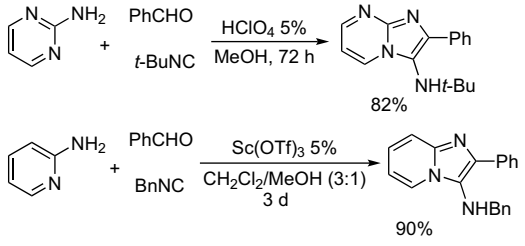
Scheme 49.

will be difficult to avoid. An interesting way to overcome these issues and to have access to the full potential of Lewis acid activation is to limit any competition by focusing on intramolecular trappings of nitrilium. Indeed, as will shortly be demonstrated, this approach has extended the nature of O, S, and N scavengers involved and also allowed the first efficient couplings with nucleophilic carbon atoms.

4. Intramolecular trappings of nitrilium species

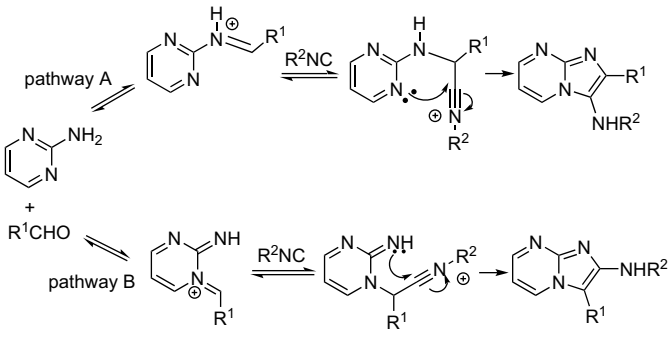
4.1. N-Trapping

In 1998, a new 3-CC involving an isocyanide, an aldehyde and a 2-aminoazine was reported simultaneously by Groebke et al.,[59] Bienaymé and Bouzid,[60] and Blackburn et al.[61] This coupling constitutes a very efficient access to 3-aminoimidazole derivatives (Scheme 50). Such fused imidazoles have attracted much attention, as they have emerged as versatile drug templates in a broad range of therapeutic areas.[62] The preformation of the imine was not necessary, but the reaction requires the use of a Brönsted acid (AcOH,[59] $HClO_4$[60]) or a Lewis acid ($Sc(OTf)_3$).[61]



Scheme 50.

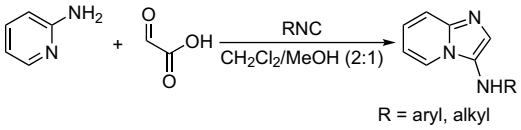
A plausible mechanism involves a non-concerted [4+1] cycloaddition between the iminium species and the isocyanide (Scheme 51, pathway A).



Scheme 51.

A large array of isocyanides has been tested successfully in this coupling. Unsubstituted 3-aminoimidazoles can be synthesized using a cleavable isocyanide such as benzyl isocyanide,[61] 2,2,4,4-tetramethylbutylisocyanide,[63] or trimethylsilyl cyanide[64] as the isocyanide input.

Various aldehydes have additionally been tested. Formaldehyde turns out to be poorly efficient in this reaction. Kercher and Lyon have proposed using glyoxylic acid (or immobilized glyoxalate on macroporous polystyrene carbonate) as a formaldehyde surrogate, to give 2-unsubstituted-3-aminoimidazoles (Scheme 52).[65]



Scheme 52.

More interestingly, a large range of 2-aminoazines can undergo such a versatile coupling: electron-rich as well as electron-poor 2-aminopyridines,[60] aminopyrazines,[60] 2-aminothiazoles,[60] 2-aminothiodiazoles,[60] 2-amino oxazoles,[60] 2-aminotriazoles,[60,66] etc. (Fig. 1).

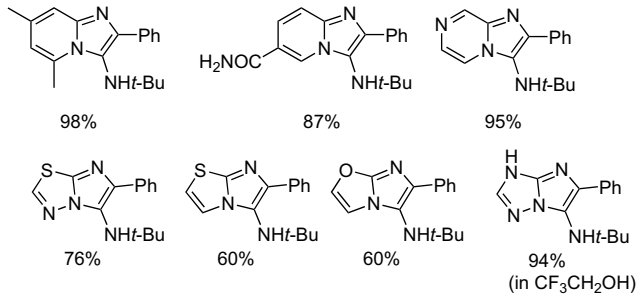
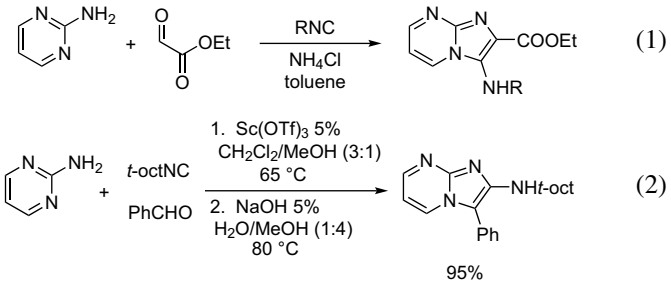


Figure 1.

If 2-aminopyrimidines provide the desired adduct, the concomitant formation of a regioisomer has also been described in these conditions. This probably results from the condensation of a ring nitrogen with the aldehyde, giving an alternative imine, which is then trapped by the isonitrile to give 2-aminoimidazo[1,2-*a*]-pyrimidines in modest yields (Scheme 51, pathway B).[67] This by-product formation can be avoided by using non-polar solvents, such as toluene, and ammonium chloride as an acid promoter (Scheme 53, Eq. 1).[68] However, the synthesis of the regioisomer can be optimized by performing a Dimroth-type rearrangement of the 3-CC resulting mixture (Scheme 53, Eq. 2).[69]



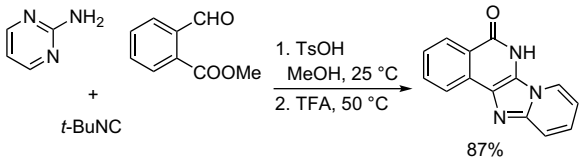
Scheme 53.

The reactions are mostly performed in methanol (or in binary solvent systems involving methanol such as $MeOH/CH_2Cl_2$), but can also be carried out in toluene,[68,70] in water,[71] in ionic liquids,[72] or even neat.[73]

Since the first reports were published, various methods of providing the acidic catalysis have been proposed: ammonium chloride,[62] tosic acid,[74] tosic acid/*N*-hydroxysuccinimide,[75] also some supported acid catalysts such as Montmorillonite K-10,[73] cellulose sulfuric acid,[76] or silica sulfuric acid.[77]

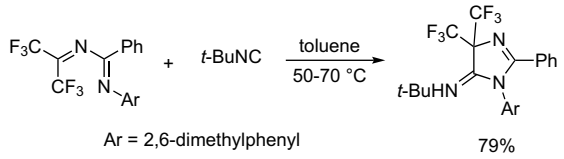
It is possible to reduce the reaction times under microwave irradiation.[73,78] The extraction of the product can be facilitated by using solid-supported inputs,[63,79,80] or fluorous-tagged partners.[81]

Various libraries of biologically relevant scaffolds have been constituted via this reaction.[60,65,66b,74] Combining this 3-CC with post-condensation transformations affords even more complex heterocyclic structures. For instance, the Yang group prepared quinoline-based tetracycles in a very efficient way from a cascade 3-CC-acidic cyclization[74] (Scheme 54).



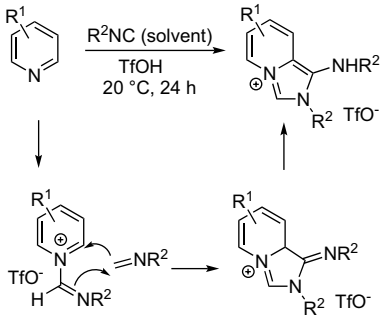
Scheme 54.

Among these cyclizations, some reactions can be considered as [4+1] cycloadditions between an azadiene and an isocyanide. For instance, Burger et al. disclosed interactions of isocyanides with fluorinated 1,3-diazabutadienes in toluene at 50–70 °C to form 5-imino-2-imidazolines (Scheme 55).[82]



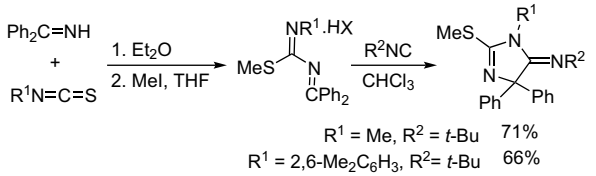
Scheme 55.

The reactivity of various diazabutadienes has been investigated for such a coupling. They can be synthesized and trapped in situ as described by Berthet et al.[83] Pyridinium triflates react with 2 equiv of isocyanide (used as a solvent) to give imidazo[1,5-*a*]pyridinium derivatives in rather good yields (Scheme 56). The 1,3-diazabutadiene resulting from the insertion of a first molecule of isocyanide into the NH-bond of a pyridinium (a nucleophilic attack onto the protonated isocyanide can lead to the same adduct, and both pathways have to be considered) reacts with a second isocyanide molecule to give the fused bicyclic system.



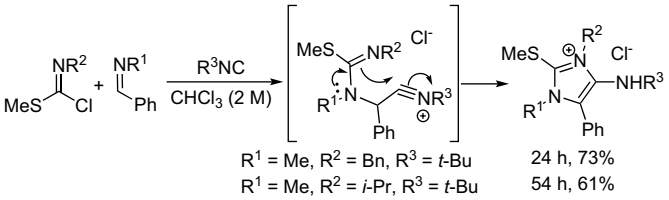
Scheme 56.

The condensation of 2-methylthio-1,3-diazabutadienes with isocyanides provides imidazole derivatives, as reported by Foucaud et al.[84] These heterodienes can be formed by mixing a ketimine with an isothiocyanate followed by methylation of the resulting adduct (Scheme 57).



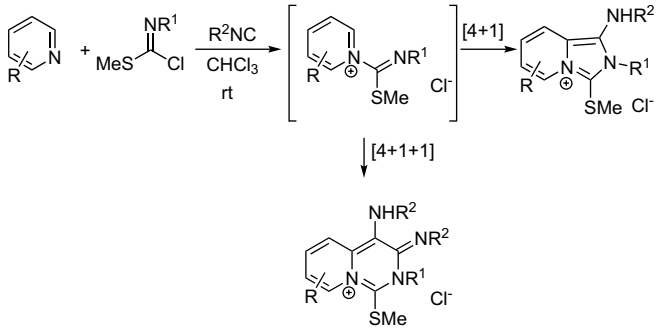
Scheme 57.

As shown by Morel et al., if a benzaldimine is used instead of a ketimine, the reaction affords 4-aminoimidazolium salts in rather good yields (Scheme 58).[85] Highly hygroscopic benzylideniminium salts are prepared in situ and react with a molecule of isocyanide. The intermediate is then attacked by the imidoyl nitrogen atom to give the imidazolium salt, after tautomerism. The reaction is slower with sterically hindered R^1 or R^2 substituents.



Scheme 58.

This coupling has been extended to pyridines and azines as the imine input, affording a convenient access to fused imidazolium or dihydropyrimidinium ions if a [4+1+1] reaction occurs (Scheme 59).[86]

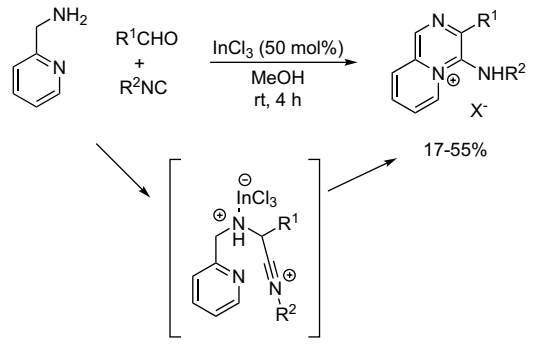


Scheme 59.

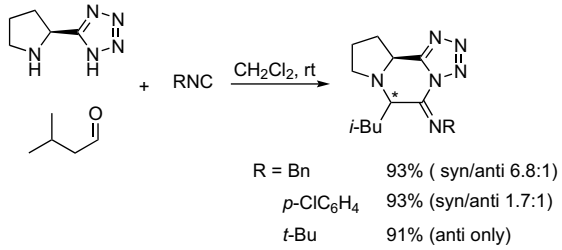
A related nitrogen trapping was developed by Illgen et al., using homologated aminopyridines.[87] The coupling of *o*-picolylamines with an aldehyde and an isocyanide in methanol using a substoichiometric amount of In(III) gives pyrido[1,2-*a*]pyrazines, as proposed by Carballares and Espinosa (Scheme 60).[88]

The mechanism probably involves a nucleophilic attack of the nitrogen atom of the pyridine onto the nitrilium resulting from the condensation of the isocyanide with the iminium, catalyzed by indium salts. Subsequent tautomerization and oxidation afford the pyridopyrazine system (Scheme 60).

Recently, Ley et al. have proposed a new cyclization of a nitrogenated nucleophile onto the nitrilium by coupling a proline tetrazole with an aldehyde and an isocyanide.[89] Whatever the nature of the isocyanide, the reaction allows the formation of tricyclic structures with moderate-to-good diastereoselectivities, but is still limited to aliphatic aldehydes (Scheme 61).



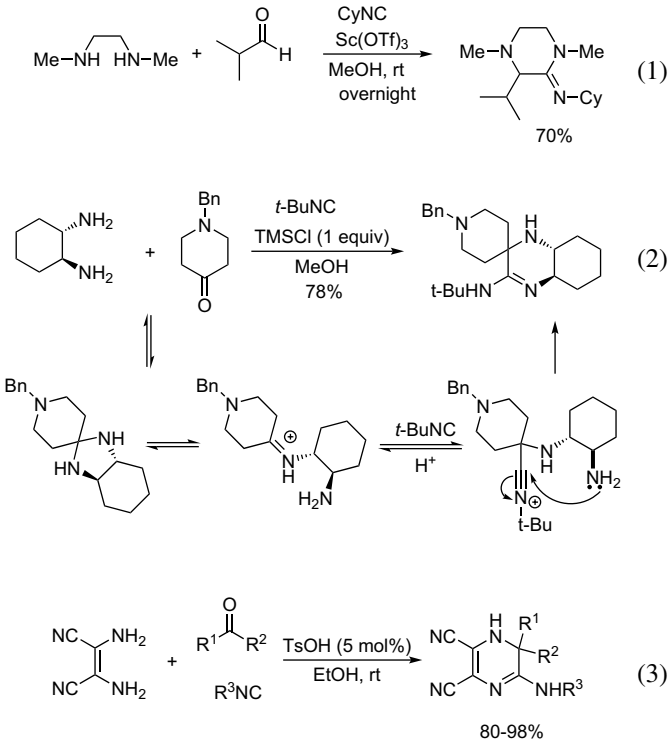
Scheme 60.



Scheme 61.

The insertion of an isocyanide into a cyclic aminal species also involves an intramolecular trapping of the nitrilium by a nitrogen atom. The first example was reported by Keung et al. (Scheme 62, Eq. 1).[57] Recently, this reaction has been studied more thoroughly and independently, by Kysil et al.[90] (Scheme 62, Eq. 2) and Shaabani et al.[91] (Scheme 62, Eq. 3). Krasavin and Parchinsky and Krasavin have extended the reaction to *ortho*-phenylenediamines to form 1,4-dihydroquinoxalines.[92]

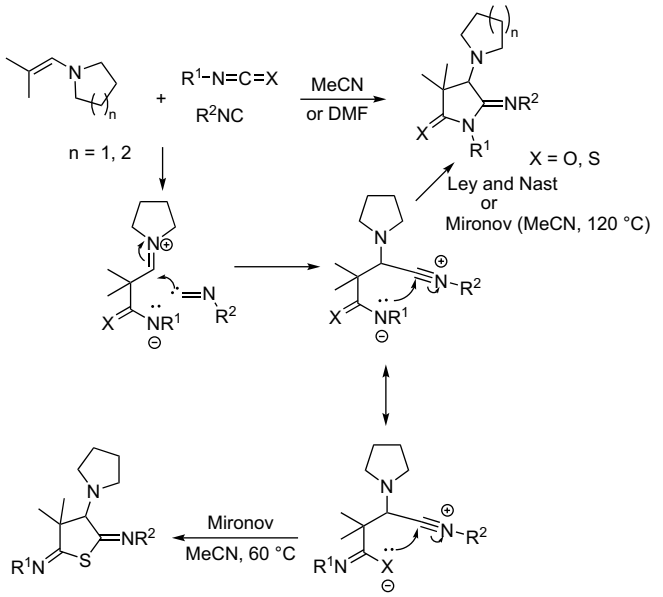
In all cases, the reaction requires an acidic activation; e.g., scandium triflate, trimethylsilyl chloride in methanol or tosic acid.



Scheme 62.

The diamine reacts first with the carbonyl derivative to give the corresponding aminal, probably in equilibrium with the open iminium form. The latter can be captured by the isocyanide, and then the remaining amino group cyclizes onto the nitrilium, giving access to 2-aminopyrazines in good yields (Scheme 62, Eq. 2).

Another variant of an intramolecular nitrilium trapping by a nitrogen atom has been described by Nast et al.[93] α-Aminoalkenes heated in acetonitrile or *N*,*N*-dimethylformamide in the presence of an isocyanide and an isocyanate (or an isothiocyanate) give *N*-substituted 2-imino-5-pyrrolidones (or thiopyrrolidones) in good yields (Scheme 63).



Scheme 63.

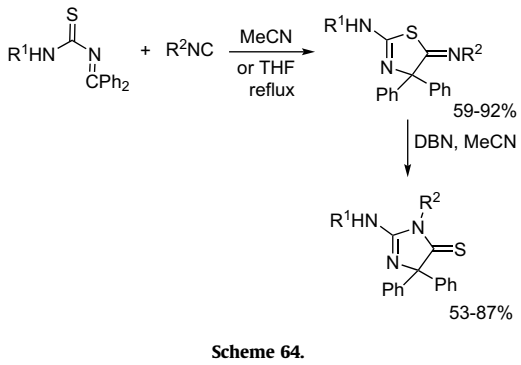
This reaction has been re-investigated recently by Mironov et al.[94] In the case of isothiocyanates, the authors obtain the aforementioned imino-thiopyrrolidones on heating in acetonitrile at 110–120 °C (in 25–92% yields), but, when the temperature is lower (55–60 °C), they isolate dihydrothiophene-2,5-diimines in rather good yields (34–93%). The latter result from the nucleophilic trapping of the nitrilium by the sulfur atom of the thioimidate moiety (Scheme 63).

4.2. S-Trapping

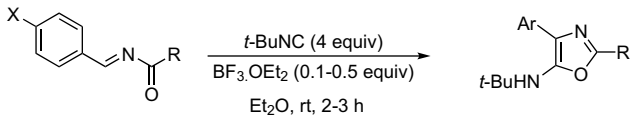
Such a sulfur trapping was previously described via the [4+1] cycloaddition of 3-aza-1-thiabutadienes and isocyanides by Burger et al.[95] Morel et al. have also reported such a coupling.[96] When using 2-amino-3-aza-1-thiabutadienes, dihydrothiazoles are obtained simply by heating in acetonitrile or in tetrahydrofuran at reflux (Scheme 64). These can rearrange under basic conditions to form imidazoline-5-thiones.

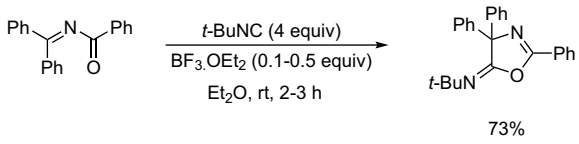
4.3. O-Trapping

Similar [4+1] cycloadditions using *N*-acylimines, with, therefore, an oxygen atom as the nitrilium scavenger, have been developed. Deyrup and Killion[97] first reported the condensation of *N*-acylimines with an excess of *tert*-butyl isocyanide in the presence of a catalytic amount of $BF_3 \cdot OEt_2$. Various 2-aminooxazoles are isolated in good yields (Scheme 65). If acylketimines are used as the input, the corresponding 2-iminooxazolines are obtained. It is noteworthy that sulfonylimines are unreactive under these conditions.



Scheme 64.

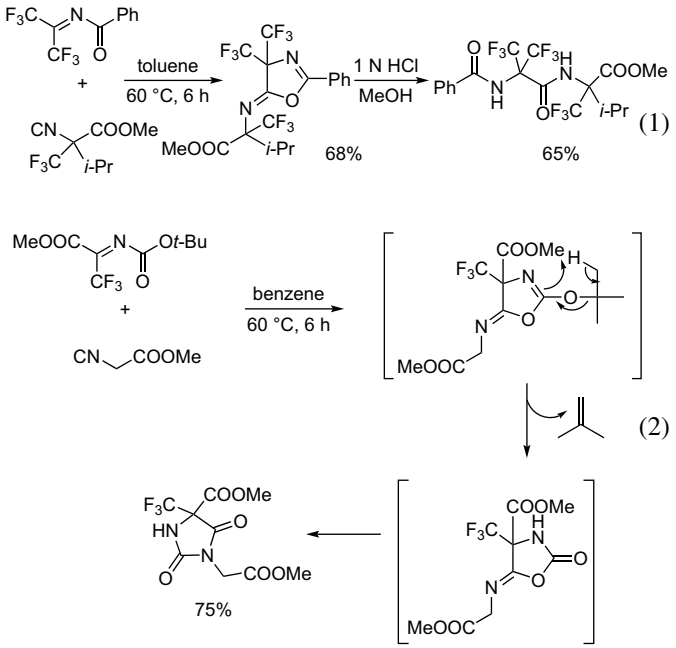




Scheme 65.

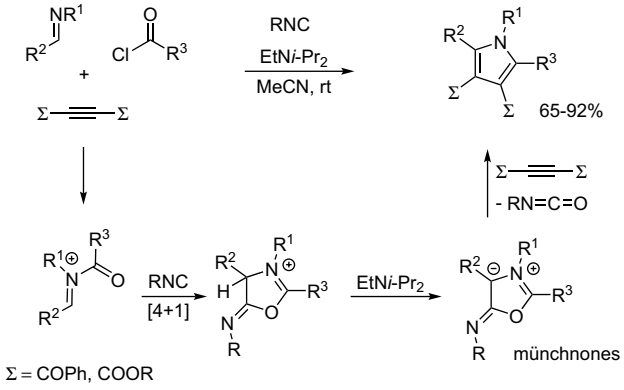
Burger et al. reported that fluoroketone acylimines such as hexafluoroacetone or methyl 3,3,3-trifluoropyruvate also undergo cyclocondensations. The resulting iminooxazolines are easily hydrolyzed under acidic conditions to afford the corresponding trifluoromethylated dipeptide esters (Scheme 66, Eq. 1).[98] When using Boc-protected imines, the corresponding hydantoins are directly obtained in benzene at 60 °C with concomitant elimination of isobutene (Scheme 66, Eq. 2).[99]

Recently, Arndtsen et al. proposed a very efficient access to pyrroles based on such a coupling between acyliminiums and



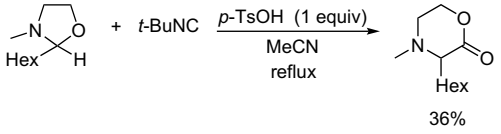
Scheme 66.

isocyanides.[100] Indeed, the basic treatment of the [4+1] cycloadduct constitutes a rapid access to münchnones, which readily undergo 1,3-dipolar cycloadditions with electron-poor alkynes. Subsequent cycloreversion and elimination of an isocyanate afford pyrroles in a powerful manner (Scheme 67). The yields are generally better if a sequential addition is performed.



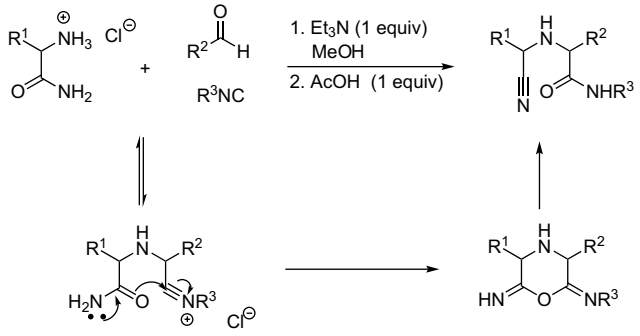
Scheme 67.

Apart from these cycloadditions, various oxygen trappings can be envisaged. For instance, the hydroxy group can be tethered to the iminium moiety, as reported by Motherwell et al.[101] *N*-Alkyloxazolidines, used as iminium precursors, are treated with *tert*-butyl isocyanide in the presence of a stoichiometric amount of tosic acid to give the corresponding lactone, after hydrolysis (Scheme 68).



Scheme 68.

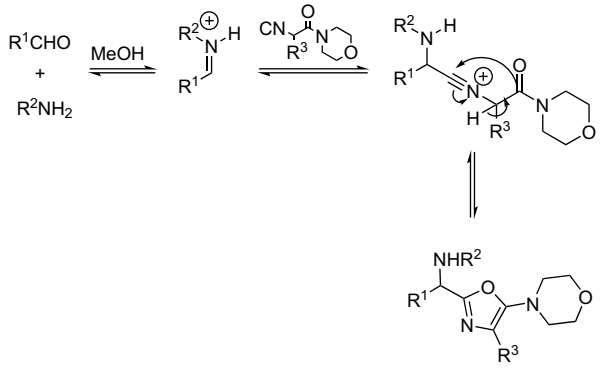
A new intramolecular oxygen trapping was disclosed by Illgen et al. involving an α-amino amide, an aldehyde, and an isocyanide to form 2-(cyanomethylamino) acetamides.[102] In this reaction, the oxygen of the amide moiety cyclizes onto the nitrilium to give an intermediate six-membered ring heterocycle, which rearranges to give the final product (Scheme 69).



Scheme 69.

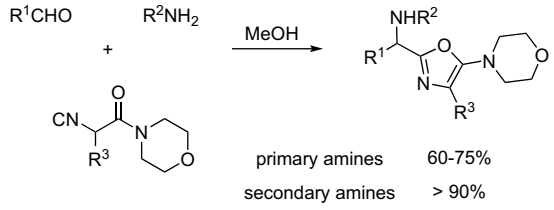
The trapping by an amide moiety tethered to the isocyanide has been extensively studied by Zhu et al. for the past few years. Indeed, they have developed a very efficient three-component access to 5-aminooxazoles via the cyclization of an enolate of an amide onto

the nitrilium. In such couplings, the acidity of the acetamide is enhanced by the presence of the nitrilium neighbor (Scheme 70).



Scheme 70.

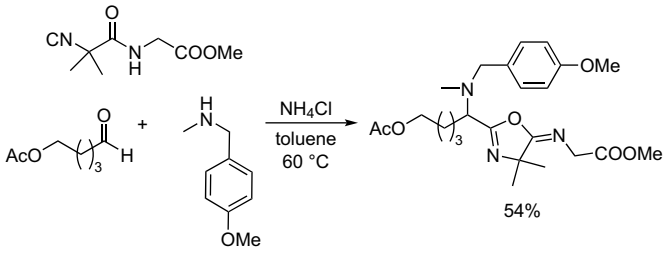
The reaction is performed by heating a methanol solution with stoichiometric amounts of the carbonyl derivative, the amine and the isocyanoacetamide, sometimes using a catalytic amount of camphorsulfonic acid.[103] The yields are good using primary amines and excellent with secondary amines (Scheme 71).[104]



Scheme 71.

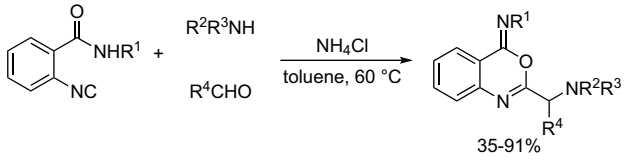
The use of non-polar solvents such as toluene requires additives to obtain similar yields: weak Lewis (lithium chloride)[105] and Brönsted (ammonium chloride)[106] acids have been tested successfully.

α,α′-Disubstituted isocyanoacetamides give access to quite sensitive 5-iminooxazolines (Scheme 72).[107]



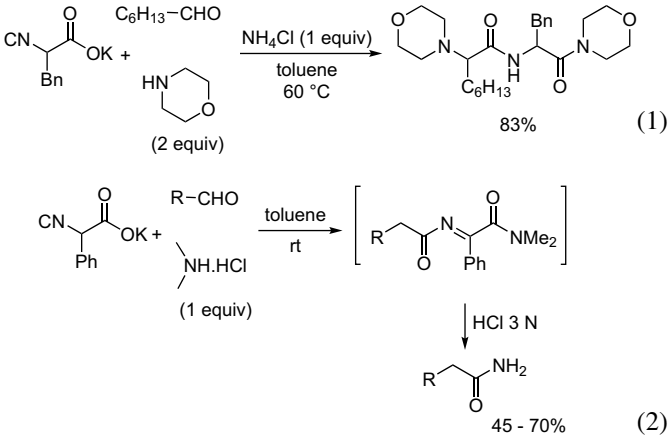
Scheme 72.

Similarly, β-isocyanoacetamides have been coupled successfully with iminium species to give 4-imino-4*H*-3,1-benzoxazines (Scheme 73).[108]



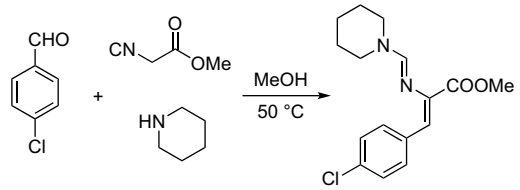
Scheme 73.

When using an α-isocyano carboxylic acid in this coupling, the nitrilium evolves into a 5-hydroxyoxazole. In the presence of a second equivalent of the amine input, it rearranges to give a dipeptide derivative (Scheme 74, Eq. 1).[109] When a sole equivalent of each partner is used, the intermediate forms an α-iminoamide, which is hydrolyzed into a homologated amide (Scheme 74, Eq. 2).[110]



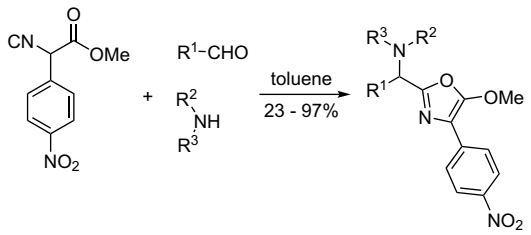
Scheme 74.

Surprisingly, α-isocyanoacetates do not undergo a similar coupling and give, instead, imidazolines or amidines, which is probably due to the lower acidity of the acetate in the nitrilium intermediate (Scheme 75).[111]



Scheme 75.

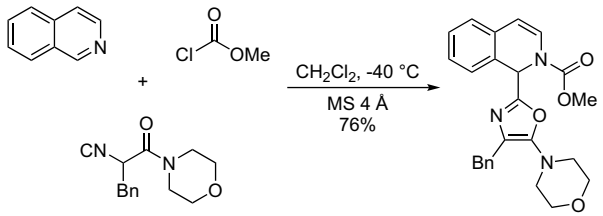
However, introducing an electron-poor aryl moiety onto the α-isocyanoester allows the formation of 5-alkoxyoxazoles, which can also be further transformed (Scheme 76).[112] In this reaction, the presence of an electron-withdrawing group counterbalances the less acidic ester functionality.



Scheme 76.

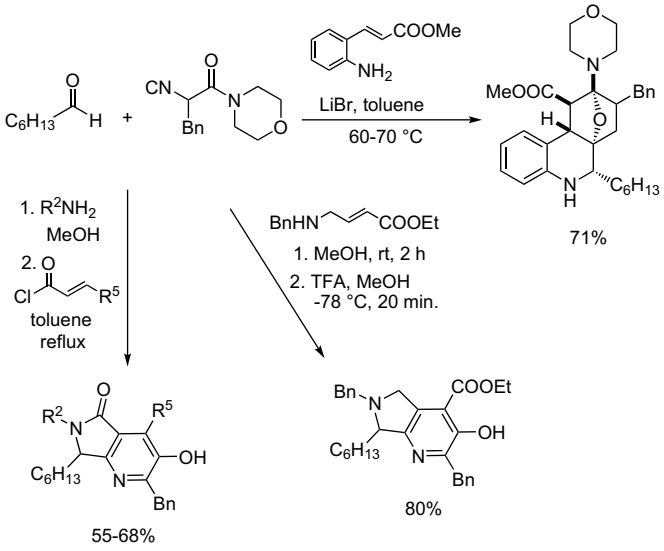
Cyclic imines are valuable partners in this coupling, if activated by a chloroformate. For instance, isoquinolines have been transformed into (1,3-oxazol-2-yl)-1,2-dihydroisoquinolines in good yields (Scheme 77).[113]

These three-component oxazole syntheses are even more interesting, as they offer an impressive structural diversity. Indeed, the resulting oxazoles can be isolated as such, or, more interestingly, they can be engaged in domino processes to give more complex heterocyclic structures. 5-Aminooxazoles have an



Scheme 77.

electron-rich azadiene moiety suitable for a cycloaddition with electron-poor dienophiles. The presence of a secondary amine offers the possibility of easily introducing the olefinic partner via a prior acylation. The 3-CC/Diels–Alder/Michael cycloreversion sequence is performed by heating the oxazole in toluene with an olefin-substituted acylating agent to give the pyrrolopyridine[104,106] (Scheme 78). Similar cascades were described using an allyl or homoallylamine in the 3-CC to synthesize oxa-bridged tetrahydroquinolines (3-CC/DA),[105,114] epoxy-tetrahydronaphthyridines,[115] and pyrrolopyridines[103,116] (3-CC/DA/acidic treatment). An appropriately substituted isocyanide can also react in such cascades to give 6-azaindolines (Scheme 78).[117]



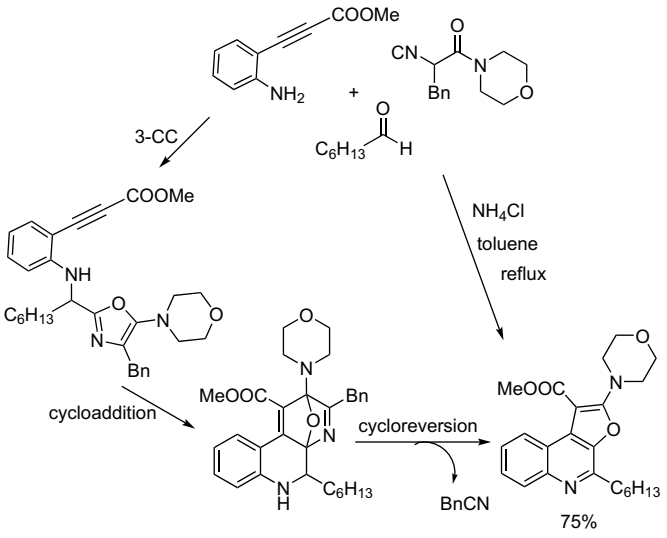
Scheme 78.

The use of an acetylenic partner in the cycloaddition reaction allows a 3-CC/DA/cycloreversion sequence with the loss of a nitrile to give furo-fused derivatives: 4,5,6,7-tetrahydrofuro[2,3-*c*]pyridines[118] (Scheme 79), furo-quinolines,[119] or 5,6-dihydrofuro[2,3-*c*]pyrrol-4-ones.[120]

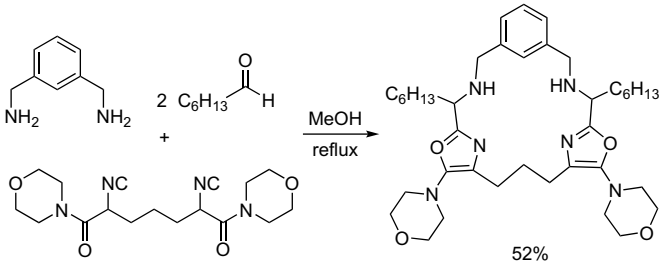
Performing these couplings with difunctional partners constitutes a very convenient access to macrocylic oxazole derivatives.[121] For instance, macrocyclic dioxazoles are obtained with a diamine, a diisocyanide and 2 equiv of aldehyde (Scheme 80).[122] The coupling of an azido-substituted amine with an α-isocyanoacetamide bearing an acetylenic functionality gives macrocyclic structures, according to a 3-CC/click chemistry sequence.[123]

4.4. C-Trapping

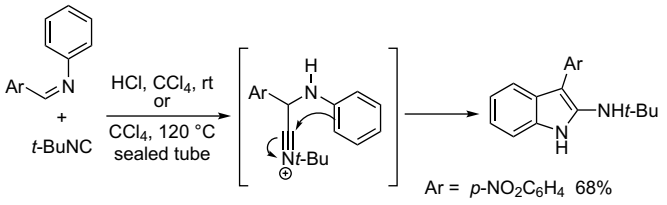
The synthetic potential of intramolecular nitrilium trappings is even more enhanced by the possibility of performing a cyclization involving a nucleophilic carbon atom. For instance, the nitrilium can be attacked by an electron-rich aromatic to form indole derivatives, as described by Deyrup et al. (Scheme 81).[124]



Scheme 79.

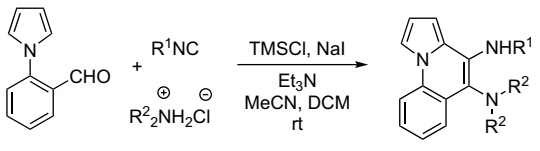


Scheme 80.



Scheme 81.

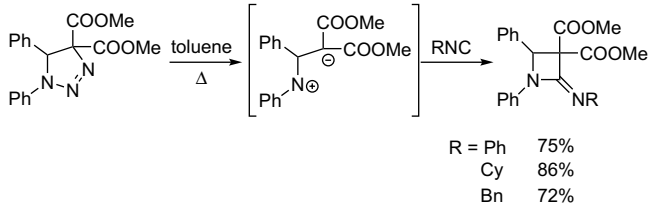
More recently, Kobayashi et al. developed the three-component version of this reaction.[125] The coupling of a suitably functionalized aldehyde with a secondary amine hydrochloride and an isocyanide affords a convenient access to pyrrolo[1,2-*a*]quinolines (Scheme 82).



Scheme 82.

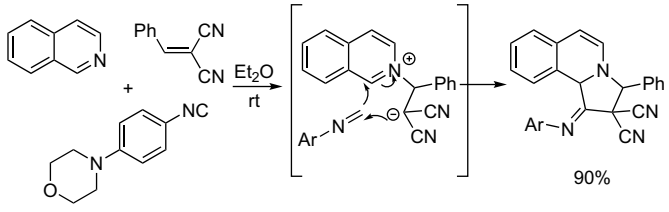
The nitrilium trapping can also be performed by a carbanion. For instance, Burger et al. have developed a [3+1] reaction of an

azomethine ylide, generated in situ by thermolysis of a 1,2,3-triazoline, with an isocyanide, to give azetidine derivatives in excellent yields (Scheme 83).[126]



Scheme 83.

More recently, a highly original 3-CC involving a carbanionic nitrilium trapping was developed by Mironov et al.[127] An isoquinoline reacts with a *gem*-diactivated olefin and an isocyanide in diethyl ether at room temperature to afford fused heterocyclic structures (Scheme 84). In this reaction, the condensation of the isoquinoline with the electron-poor olefin forms an activated iminium, which is attacked by the isocyanide. The resulting intermediate is then trapped by the malonitrile moiety to give the benzofused heterocycle.



Scheme 84.

5. Conclusions

In conclusion, we have presented here an overview of the rich chemistry accessible through isocyanide interactions with iminium derivatives. Two main mechanistic events are associated with these reactions:

- The choice of an acidic derivative to activate the imine toward the isocyanide addition.
- The nature of the nucleophile used as the nitrilium trapping agent.

In the infancy of the Ugi reactions, the choice was rather limited, as the acid and the nucleophile were part of the same component. Efficient couplings were only observed when secondary irreversible rearrangements could occur. With the more recent use of Lewis acids, as well as the development of intramolecular trappings, a wider range of nucleophiles can interact with the nitrilium without requiring any further rearrangement. The extreme structural diversity of the products described in this review illustrates the powerful potential of isocyanides as building blocks for organic synthesis.

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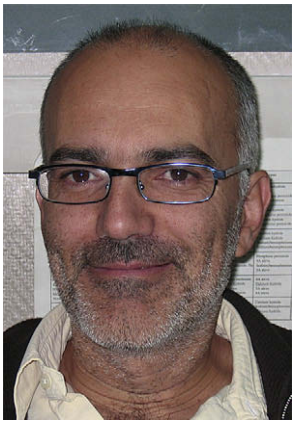
Biographical sketch



Laurent El Kaïm was born in France in 1964. He completed his Ph.D. under the supervision of Professor Samir Zard at the Ecole Polytechnique, where he worked on fluorine and alkyne chemistry. In 1993, he started a research group at the Ecole Nationale Supérieure des Techniques Avancées (ENSTA), in Paris. He got his Habilitation à Diriger des Recherches in 2001, and teaches chemistry at ENSTA and Ecole Polytechnique. He currently works on multicomponent reactions and heterocyclic chemistry involving mainly isocyanides.

Laurence Grimaud was born in France in 1973. She completed her Ph.D. under the supervision of Dr. Jöelle Prunet at the Ecole Polytechnique, where she worked on both the total synthesis of Dolabelide C and the diastereoselective formation of 1,3-diols. In 1999, she joined Dr. Laurent El Kaïm research group at the Ecole Nationale Supérieure des Techniques Avancées (Paris). She got her Habilitation à Diriger des Recherches in 2006. Her research focused on the development of multicomponent reactions and heterocyclic chemistry involving mainly isocyanides.