Organic Chemistry Insights

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SHORT REVIEW

Carbodiimides-Mediated Multi Component Synthesis of Biologically Relevant Structures

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Abstract: Multi-component reactions are very popular because they offer a wealth of products, while requiring only a minimum effort combining many elements of an ideal synthesis, such as operational simplicity, atom economy, bond-forming efficiency, and the access to molecular complexity from simple starting materials. As such, multi-component reactions have become the cornerstones of both combinatorial chemistry and diversity-oriented synthesis and thus playing a central role in the development of modern synthetic methodology for pharmaceutical and drug discovery research. In this Insight we will highlight the development of novel multi-component reactions based on the reactivity of carbodiimides, paying particular attention on their mechanistic features. We will address our attention on the process developed by us and others groups, in these last years, for the synthesis of biologically relevant structures such as, for example, heterocycles and glyco-conjugates.

Keywords: Multi-component reactions, domino process, carbodiimides

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Introduction

The complexity of organic target molecules is constantly increasing and novel strategies allowing the efficient formation of new carbon-carbon and carbon-heteroatom bonds between functionalized moieties are needed. Although the past 50 years have witnessed extraordinary progress in the discovery of new reagents, reactions, and synthetic strategies,[1] the tools of synthetic organic chemistry are often inadequate when confronted with the challenge of preparing even modestly elaborate molecules in practical fashion. A seemingly trivial but rather serious limitation in practice is set by the mere number of steps accumulating in linear sequences and by extensive protecting-group strategies used. A more convergent approach is desired that ideally provides the suitable decorated scaffold in a single operation. Procedures that yield molecules by performing multiple reaction steps in which several bonds are formed without isolation of intermediates are commonly referred as tandem reactions.[2] An important subclass of tandem reactions are multicomponent reactions (MCRs).[3] MCRs are convergent transformations, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed compound. Applications of MCRs in all areas of applied chemistry are very popular because they offer a wealth of products, while requiring only a minimum effort combining many elements of an ideal synthesis, such as operational simplicity, atom economy, bond-forming efficiency, and the access to molecular complexity from simple starting materials. The oldest MCR according to current standards is the Strecker reaction of amines, aldehydes and cyanides to give α-aminonitriles.[4] Other MCRs that were discovered long ago, such as the Biginelli[5] and Ugi[6] reactions, saw a true renaissance during the past years becoming the cornerstones of combinatorial chemistry, where the synthesis of focused libraries to be screened for their ability to bind preselected protein targets is the ultimate goal. However, such application of MCRs suffers from the classical pitfall of combinatorial chemistry: the focus on appendage diversity. Modern drug discovery often involves screening small molecules for their ability to modulate a biological pathway in cells or organisms, without regard for any particular target. In this contest, scaffold diversity, rather than appendage diversity, becomes the most important level of diversity to be addressed and reached with the use of a planned synthetic strategy. This is pursue with the concept of diversity-oriented synthesis (DOS) introduced by Schreiber in 2000,[7] which involves short reaction sequences combined with a forward planning strategy (rather than a retrosynthetic analysis). Consequently, the design and discovery of new MCRs is vital to address scaffold diversity in compound collections. Although serendipity has always played an important role in the discovery of novel MCRs, the most straightforward approach to address the issue of limited scaffold diversity is the rational design of novel MCRs.[8] In this "Insight" Article we will highlight the use of carbodiimides as starting materials for the development of novel MCRs for the synthesis of biologically relevant structures such as heterocycles, glyco-conjugates, and others.

Carbodiimides are a unique class of reactive organic compounds having the heterocumulene structure R–N=C=N–R.[9] General use of these species was stimulated by Khorana's pioneering investigations of their action in peptide and nucleotide synthesis.[9a] Other growing points in carbodiimide chemistry include the continued use of synthesis of nucleotides and peptides, heterocycle synthesis, oxidation with dimethylsulfoxide, permease inhibition, biological modification, and cycloaddition reactions. Probably the most important feature of carbodiimides relating to their wide use relies on their relatively low uncatalyzed reactivity which allows easy storage. In fact, carbodiimides fulfill most of the properties of a perfect reagent: it is unreactive until a catalyst is added but provides a powerful driving force for a reaction to proceed. Indeed, carbodiimide molecules have two centers of reactivity, the electrophilic central carbon which reacts with nucleophiles upon activation of one of the two nucleophilic nitrogen atoms with electrophiles like protons, acyl chlorides or metals. It is just this characteristic, namely the presence at the same time of a nucleophilic and an electrophilic reactive center, such as in β-ketoesters used in Biginelli MCR and in isocyanides used in Passerini/Ugi MCRs, which render carbodiimides suitable compounds for the development of new MCRs. Moreover, carbodiimides posses in their own structure two diverse appendage (the two nitrogen substituents) which are suitable for generating molecular diversity in the construction of molecules incorporating such moieties. This "Insight"

Article is intended to highlight our work in the development of new carbodiimide-mediated MCRs for the synthesis of biologically relevant structures incorporating the carbodiimide framework such as heterocycles and glyco-conjugates, paying particular attention on the mechanistic features of these process. Related carbodiimide-mediated MCRs developed by other groups are also included. For the sake of clarity, when asymmetric carbodiimides are involved in the process, we will refer as "strongly asymmetric" those carbodiimides that have two *N*-substituents very different in terms of electronic features, such as an aromatic and an alkyl substituents, and "weakly asymmetric" those carbodiimides that have two alkyl substituents at the nitrogen atoms very different in terms of steric bulkiness. For every multi-component process described herein, only representative results will be reported in this Insight, so for a more exhaustive treatment of the process, the reader should refer to the original manuscript. The "Insight" Article will be organized in two main paragraphs depending on the mechanistic outcome involving the reactivity of the carbodiimide component, namely nucleophilic attack to the activated carbodiimide C=N bond or cycloaddition reaction.

MCRs by Nucleophilic Attack on Carbodiimides

Probably, the most important reaction of carbodiimides involves nucleophilic attack of a reagent E-Nu which may add by stepwise or concerted path (Scheme 1).

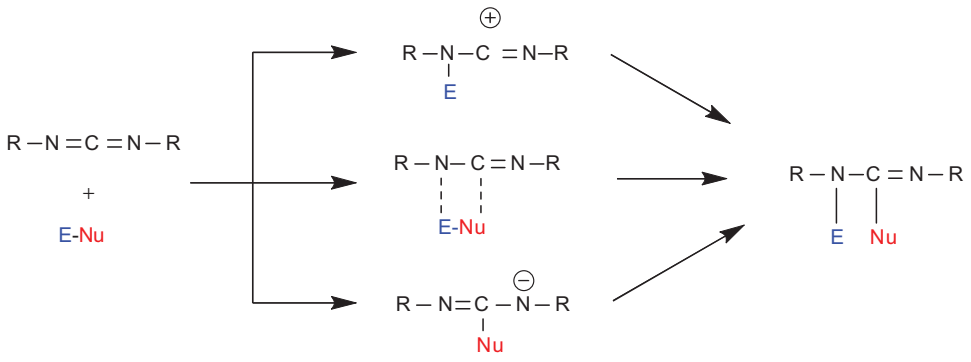
The reaction essentially occurs by interaction of the highest occupied molecular orbital of the reagent and the lowest vacant orbital on the carbodiimide which has large coefficient on the central carbon.[9c] Even if strong nucleophiles, such as carbanion and amines can react with carbodiimides without the need of a previous activation, generally pre-activation with protons, acyl chlorides and/or metals facilitates the nucleophilic attack to the central carbon. This section will be sub-divided in three sections according to the nucleophiles used for the MC process.

Reaction with carboxylic acids

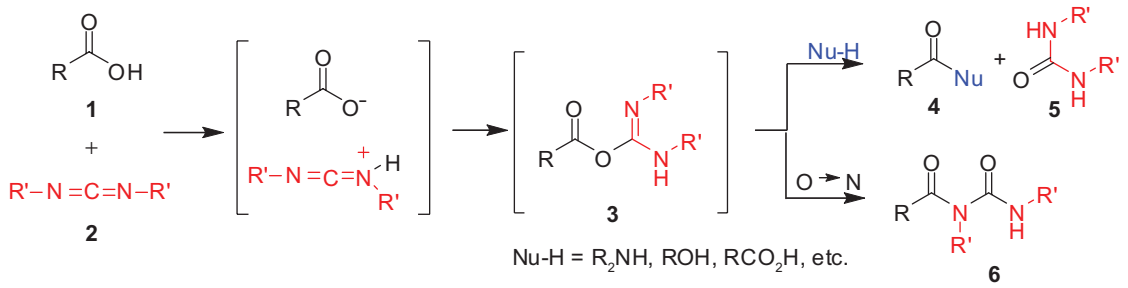
The widest use of carbodiimides relies on the activation of carboxylic acids toward the coupling with nucleophiles such as alcohols and amines (Scheme 2).

The reaction sequence involves a proton transfer from the carboxylic acid **1** to the basic nitrogen of the carbodiimide **2**, followed by addition of the carboxylate to form the *O*-acyl isourea **3**, which is a reactive species and in the presence of a nucleophile affords the coupling product **4**, together with a urea coproduct **5**. However, **3** can undergo a rearrangement, the so-called O→N acyl migration, to give the *N*-acylurea **6**, which is a frequently found by-product in these reactions.[10]

Our work in the development of new carbodiimides-mediated MCRs originates from the observation that *O*-acyl isourea compounds **3** posses a nucleophilic nitrogen that could be involved in an intramolecular nucleophilic substitution when an electrophile is introduced in a suitable position of the skeleton of the carboxylic acid. Indeed, when activated α,β-unsaturated carboxylic acids **1** were reacted with carbodiimides **2** in absence of a nucleophile, a one-pot domino condensation/aza-Michael addition/O→N acyl migration process occurred, leading to



Scheme 1. Pathways for reaction of carbodiimides with E-Nu.

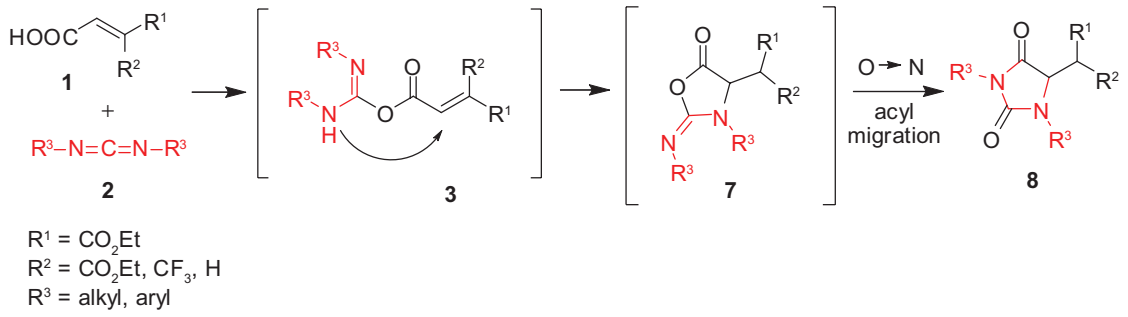


Scheme 2. Mechanism of carbodiimides activation toward coupling with nucleophiles.

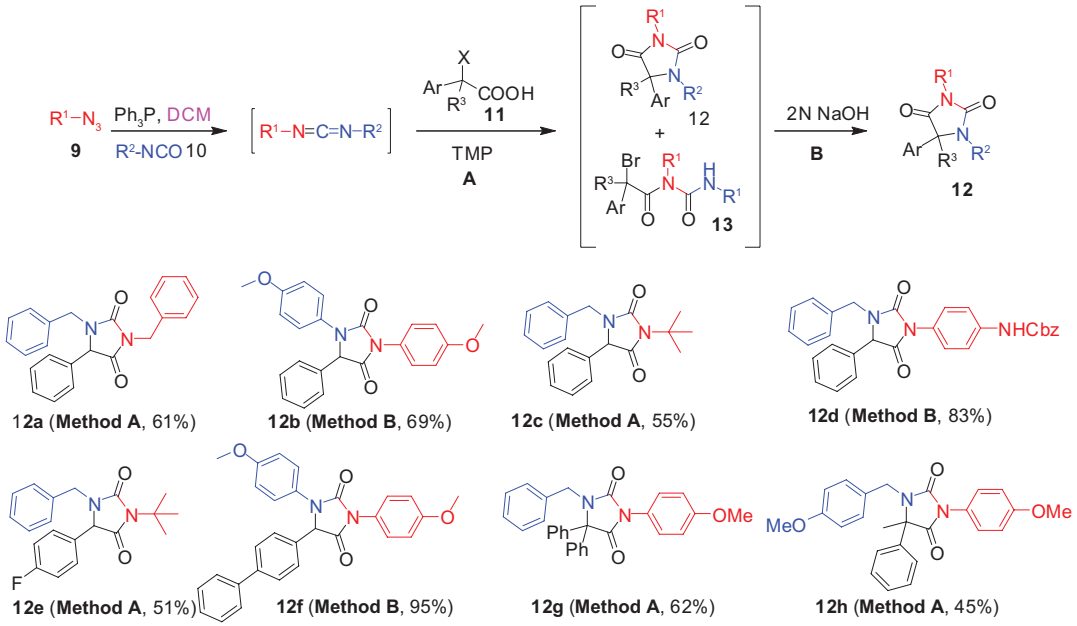
the formation of hydantoin scaffolds **8** in high yield and very mild conditions, *i.e.* room temperature (Scheme 3).[11]

Since carbodiimides could be prepared by Staudinger reaction between easily accessible isocyanates and azides leading to a clean reaction with triphenylphospine oxide as the only by-product, we reasoned out the possibility to exploit this reaction for the development of a one-pot sequential MC process for the synthesis of differently substituted hydantoins. We began our study using α-halo-arylacetic acids as starting carboxylic acids because we found them very attractive due to the presence in their skeleton of a highly reactive electrophilic carbon, namely the benzylic carbon which bears in α position an excellent leaving group (the halogen atom), and another activating moiety such as the carboxy group.[12] Thus, by adding triphenylphosphine to a mixture of azides **9** and isocyanates **10** in dicholoromethane (DCM), we were able to obtain the clean formation of carbodiimides which were directly treated with acids **11** and 2,4,6-trimethylpyridine (TMP), leading to the formation of the corresponding hydantoins **12** as the only products or in a mixture with *N*-acyl ureas **13**. However, *N*-acyl ureas **13** can be convergently transformed into the target hydantoins **12** by in situ treatment with a suitable base (Scheme 4).

Symmetric dialkylcarbodiimides, such as *N,N′*-dibenzylcarbodiimide generated from benzyl azide and benzyl isocyanate, reacted in situ with α-bromophenylacetic acid affording hydantoin **12a** in good yields, while symmetric diarylcarbodiimides, such as *N,N′*-di-*p*-MeO-phenylcarbodiimide, gave a mixture of the corresponding hydantoins and *N*-acyl ureas. However, by treating in situ the mixture of the two products with a 2N NaOH aqueous solution, we obtained hydantoins, such as **12b**, as the only product and in good yields. Moreover, the reaction worked well also with asymmetric carbodiimides, giving rise to completely regioselective process. Indeed, the reaction with both "weakly" and "highly" asymmetric carbodiimides lead to the formation of only one out of the two possible regioisomers, like **12c** and **12d**, even if in the last case, one-pot cyclization triggered by NaOH was required. The reaction appeared to be very general giving rise to the formation of the hydantoin products also starting with either aryl- and alkyl-substituted α-halophenylacetic acids, such as in the case of **12g** and **12h**, respectively. It is worth noting that the yields of the process were higher when there



Scheme 3. The one-pot domino condensation/aza-Michael addition/O→N acyl migration.



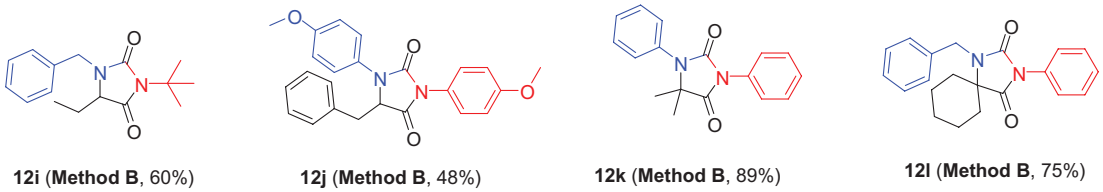
Scheme 4. MC sequential synthesis of fully substituted hydantoins **12.**

is at least one aryl substituent on the carbodiimide component. This is consistent with the fact that the Staudinger reaction works well when aryl azides and/or arylisocyanates are involved.

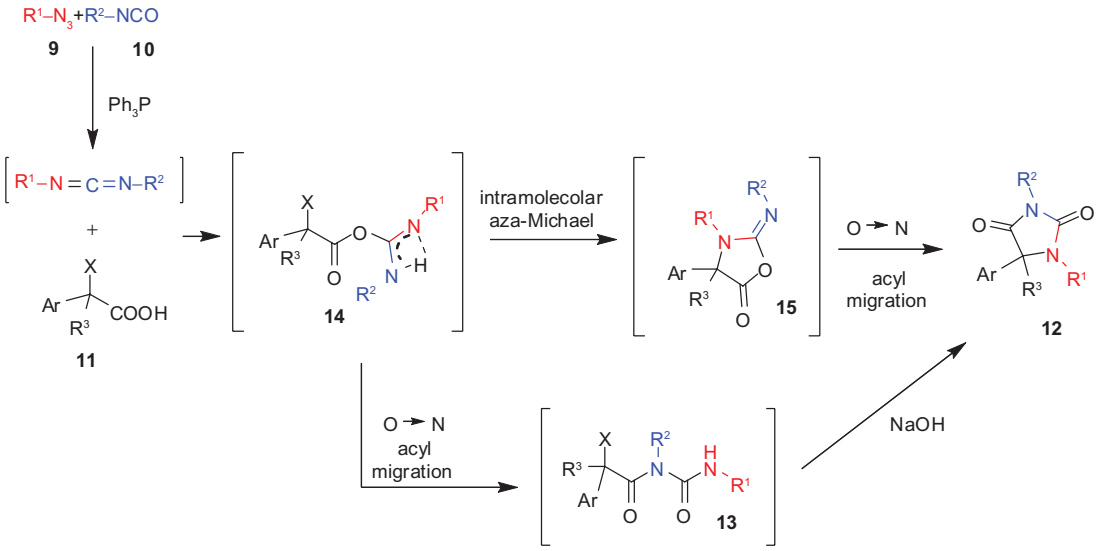
Very recently, we discovered that also less reactive alkyl- and dialkyl-substituted α-halo-acetic acids reacted smoothly with carbodiimides producing the corresponding hydantoins **12i-l** when the solvent is changed with the more polar DMF and upon cyclization triggered in situ with NaOH or potassium *tert*-butoxide.[13] Also in this case, when asymmetric carbodiimides are involved, the reactions were totally regioselective (Scheme 5).

All the experimental results suggested us to propose the mechanism portrayed below (Scheme 6). The reaction sequence involves a first addition of acid **11** to the in situ generated carbodiimide to form the reactive *O*-acyl isourea **14** which readily cyclises to the intermediate **15** through an intramolecular nucleophilic displacement of the halide. When the two carbodiimide *N*-substituents are different ($R^1 \neq R^2$) such reaction is completely regioselective, leading to the formation of the hydantoin regioisomer arising from the intramolecular nucleophilic attack of the more nucleophilic carbodiimide moieties, namely the *N*-alkyl nitrogen in "strongly" substituted carbodiimides or the less sterically hindered *N*-alkyl nitrogen in "weakly" asymmetric carbodiimides. The following O→N acyl migration gives rise to the formation of the hydantoins **12**. In some cases, the O→N acyl migration is competitive with the cyclization, leading to the formation of the *N*-acyl ureas **13** as a byproduct or even as the main product, always with total control of the regiochemistry, which can be convergently transformed into the target hydantoins **12** by in situ treatment with a suitable base.

Once demonstrated that carbodiimides react efficiently with activated α,β-unsaturated carboxylic acids

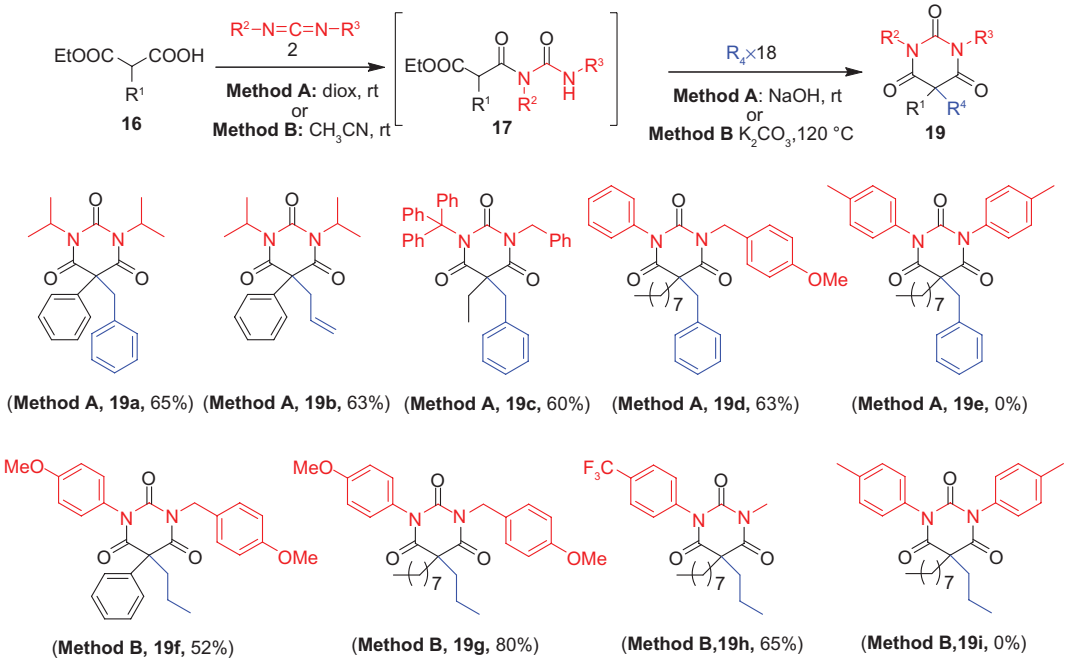


Scheme 5. Synthesis of *C*-alkyl and *C*-dialkyl hydantoins.



Scheme 6. Mechanism of the domino process for the synthesis of fully substituted hydantoins **12.**

and differently substituted α-halo acetic acids producing hydantoins following the proposed mechanisms, we argued that, by choosing suitable starting carboxylic acids, we could be able to synthesize different heterocycles incorporating a *N*-acyl urea moiety which arises from the attack of the carboxylate to the carbodiimide, followed by O→N acyl migration. A class of interesting heterocycles are surely barbituric acids. A retrosynthetic analysis showed us the possibility to synthesize fully substituted barbiturates by reaction between carbodiimides and carboxylic acids having a second carboxy group suitable to undergo the intramolecular nucleophilic attack.[14] Accordingly, the reaction between substituted malonic acid monoesters **16** and carbodiimides **2** afforded *N*-acyl urea products **17** in high yield and very mild conditions (organic solvent, rt), which underwent one-pot cyclization and alkylation in the presence of a base and an alkylating agent **18**

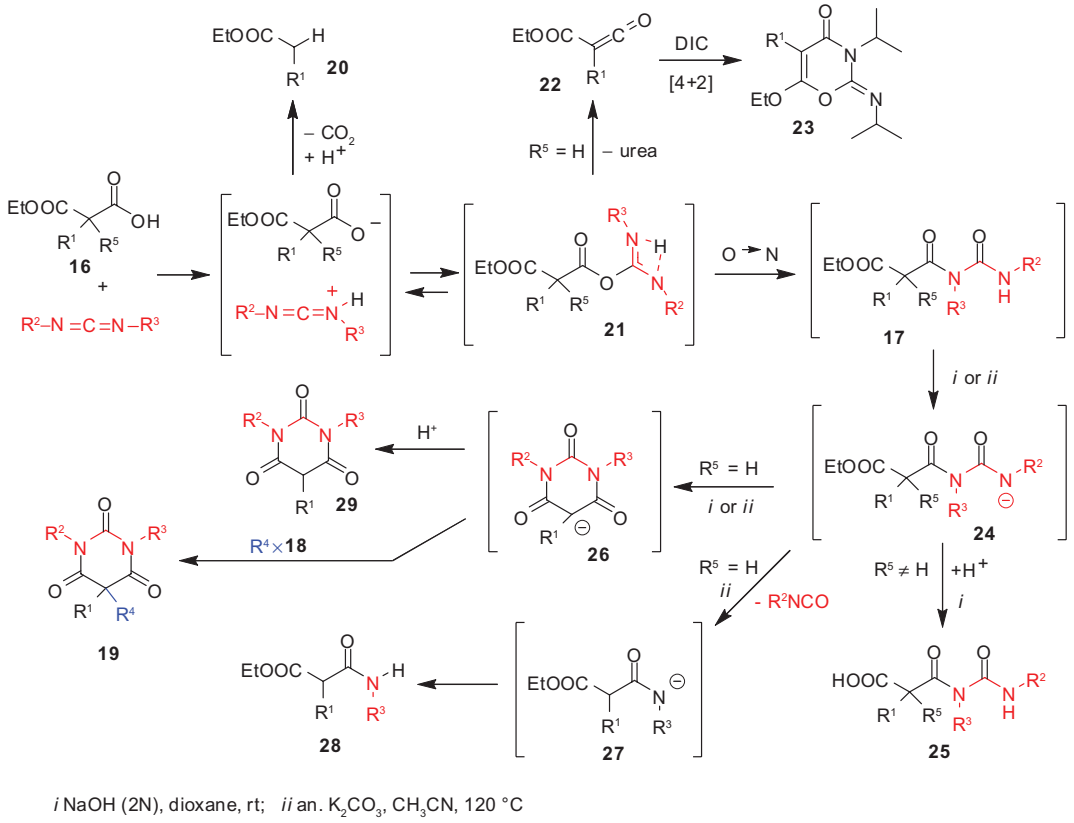


Scheme 7. Synthesis of fully substituted barbiturates **19**.

affording the desired fully substituted barbiturates **19** in high yields (Scheme 7).

For instance, by reacting acids **16** with either *N,N′*-dialkyl, *N*-alkyl, *N′*-aryl or *N,N′*-diaryl carbodiimides in dioxane at rt we obtained the corresponding *N*-acylurea derivatives **17** that could be easily cyclised by adding in situ a 2N aqueous NaOH solution. This process represents a general straightforward one-pot sequential procedure for the synthesis of 1,3,5-trisubstituted barbiturates in mild conditions. Performing the reaction in the presence of an electrophile **18** resulted in the formation of fully substituted (namely 1,3,5,5-tetrasubstituted) barbiturates **19** through a three-component one-pot sequential process. The latter, however, occurred only with highly reactive electrophiles, such as benzyl (compounds **19a**,**c**,**d**) and, in some instances, allyl halides (compound **19b**) and only when at least one carbodiimide *N*-substituent is an alkyl group (compound **19e** was not formed). In order to expand the scope of the process, we sought to develop a general method for the *C*-alkylation of 1,3,5-trisubstituted barbiturates. We found that *C*-alkylation occurred upon treatment of 1,3,5-trisubstituted barbiturates with an alkyl halide in CH_3CN at 120 °C in the presence of anhydrous K_2CO_3 affording the target 1,3,5,5-tetrasubstituted barbiturates in good yields. The MC process was accomplished by combining the three steps in a one-pot sequential fashion, *i.e.* the condensation of carbodiimides with malonic acid monoethylesters at rt and in CH_3CN as solvent followed by cyclization of the resulting *N*-acylureas, and *C*-alkylation of the resulting 1,3,5-substituted barbiturates by adding K_2CO_3 and raising the temperature to 120 °C. The process worked well in almost all cases, with different alkyl halides leading to the formation of a wide variety of barbiturates such as **19f-h**. Only when acids **16** were reacted with *N,N′*-diaryl carbodiimides the reaction did not afford the desired product (see compound **19i**) because the cyclization step did not occur. The full scope and limitations of this MC sequential process for the synthesis of fully substituted barbiturates could be understood by considering the detailed proposed mechanism depicted in Scheme 8.

The sequence involves a first proton transfer from the carboxylic acids **16** to the basic nitrogen of the

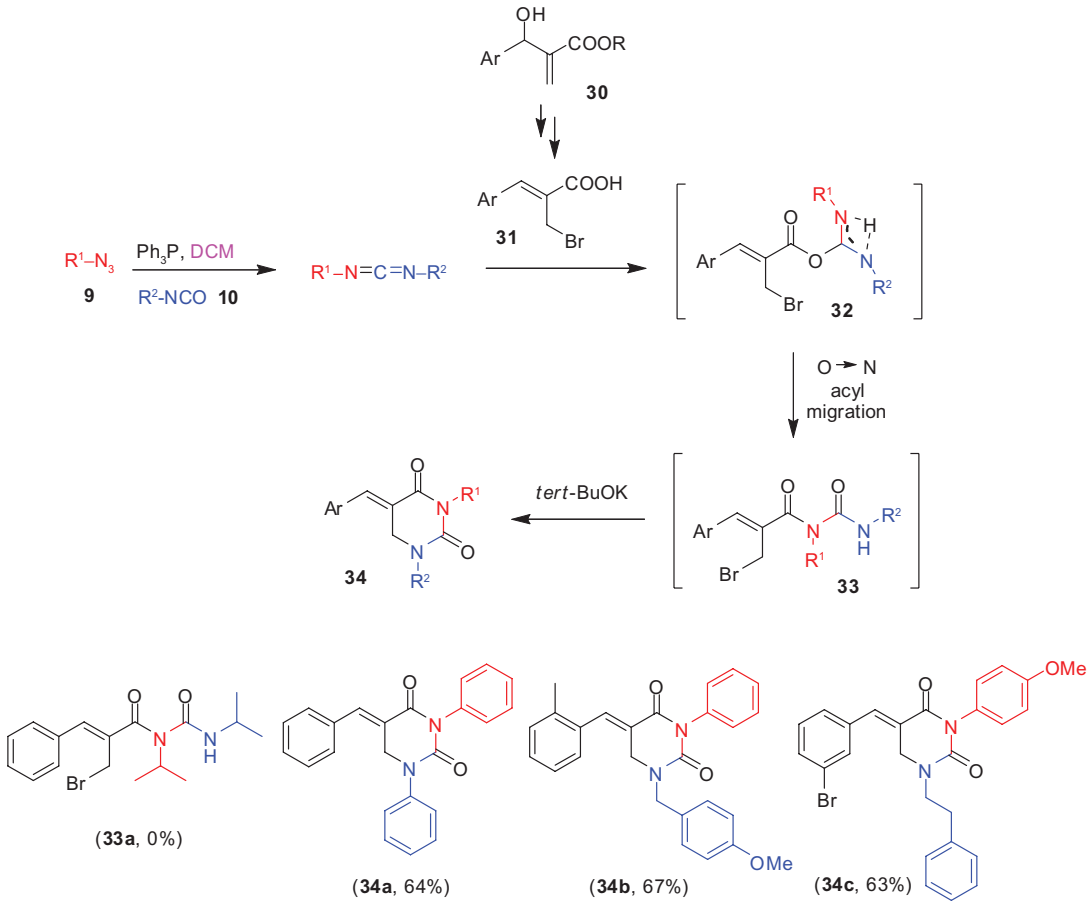


i NaOH (2N), dioxane, rt; *ii* an. K_2CO_3, CH_3CN, 120 °C

Scheme 8. Proposed mechanism for the MC sequential process leading to the formation of barbiturates **19**.

carbodiimide followed by reversible addition of the carboxylate to form the *O*-acyl-isourea intermediate **21**. The latter, in the absence of a nucleophile, can undergo the O→N acyl migration, to give *N*-acylurea derivatives **17**. To obtain compound **17** in good yield one should suppress two side-processes that could arise when malonic acids such as **16** are used. In fact, it is known that, once formed, malonic carboxylates easily undergo decarboxylation. *C*-Alkyl and, even more, *C*-aryl malonic acid monoethylesters are prone to decarboxylation when treated with *N,N′*-dialkyl carbodiimides such as DIC, because these carbodiimides are less electrophilic and the equilibrium leading to **21** is less shifted to the right, thus favouring the loss of CO_2 leading to **20**. In fact, when the reaction was carried out with more electrophilic *N*-alkyl, *N′*-aryl or *N,N′*-diaryl and even *N*-alkyl, *N′*-trityl carbodiimides the corresponding *N*-acylureas **17** were formed in good yields. Moreover, the intermediate *O*-acyl-isourea **21** can undergo elimination of urea leading to the formation of the highly reactive ketene **22** that, in the absence of a nucleophile, could react with a molecule of carbodiimide leading to the formation of a [4+2] cycloadduct **23**. Again, we observed the formation of **23** as a byproduct only when the reaction was carried out with basic DIC and *C*-monoalkyl malonic acid monoethylesters. However, performing the condensation between DIC and malonic acid monoethylesters in low polarity solvents, such DCM, and in the presence of an equivalent of a base, ie, TMP, which facilitated the O→N acyl migration process, we were able to suppress almost entirely the formation of **23**, leading to the formation of the *N*-acylureas **17** in good yields. *N*-acylureas **17** could be cyclized and alkylated upon in situ treatment with a base (that should be compatible with the solvent used for their generation), followed by an electrophile, producing a one-pot three-component sequential process leading to the target substituted barbiturates. Two different protocols were explored, namely a "soft" protocol consisting in the treatment with aqueous 2N NaOH in dioxane at rt and a "hard" protocol consisting in the use of anhydrous K_2CO_3 in CH_3CN at high temperature. The choice of the most appropriate protocol depends on the reactivity of the electrophile and of the resulting carbanion **26,** which is strongly stabilized by the two adjacent carbonyl groups. Moreover, the nucleophilicity of **26** depends on (1) the substituents on the nitrogen atoms and (2) the substituent R^1. When such substituents are electron-withdrawing aromatic rings, the negative charge is further stabilized rendering **26** even less nucleophilic. Thus, barbiturates derived from *N,N′*-dialkyl carbodiimides are more nucleophilic than those derived from *N*-alkyl, *N′*-aryl carbodiimides which, in turn, are more nucleophilic than *N,N′*-diaryl barbiturates. Accordingly, 5-alkyl barbiturate carbanions having at least one *N*-alkyl group were able to react only with highly electrophilic benzyl halides using the "soft" protocol, whereas more stabilized 5-aryl derivatives were unreactive. It is worth nothing that *N,N′*-dialkyl barbiturates, independently of the nature of the R^1 substituent, could be alkylated both with benzyl and allyl bromides following the "soft" protocol. Barbiturates derived from *N,N′*-diaryl carbodiimides could not be alkylated by means of the "soft" protocol. However, all of the barbiturate carbanions, could be *C*-alkylated using the "hard" protocol, regardless of the *N*-substituents, with a wide range of alkyl halides providing a general method for the synthesis of fully substituted barbiturates. Unfortunately, when the one-pot sequential process was carried out according to the "hard" protocol, we discovered that the cyclization step failed with *N,N′*-diaryl substrates. In these cases the anion **24** is likely to be too stable to undergo sufficiently rapid cyclization, therefore elimination of the corresponding isocyanate becomes competitive, leading to the formation of the amide **28**. However, this is not a big limitation because the corresponding *N*-*N′*-diaryl barbiturates could be easily synthesized through a step-wise process, namely the synthesis of the *C*-monosubstituted barbiturate through the "soft" NaOH protocol followed by chromatographic isolation and alkylation using the "hard" protocol (K_2CO_3 in CH_3CN, 120 °C, or DMF at 80 °C for *N,N′*-diaryl-*C*-aryl barbiturates). In all other cases, the three-component one pot sequential process produced the desired fully substituted barbiturates in good yields.

Another class of interesting *N*-acylurea-containing heterocycles are dihydrouraciles. Such heterocycles could be synthesized by reaction between in situ formed carbodiimides and carboxylic acids containing a relatively highly reactive allyl bromide in their scaffold, such as in acids **31**, which could be easily prepared starting from Baylis-Hillman adducts **30** (Scheme 9).[15]



Scheme 9. MC sequential synthesis of dihydrouraciles **33**.

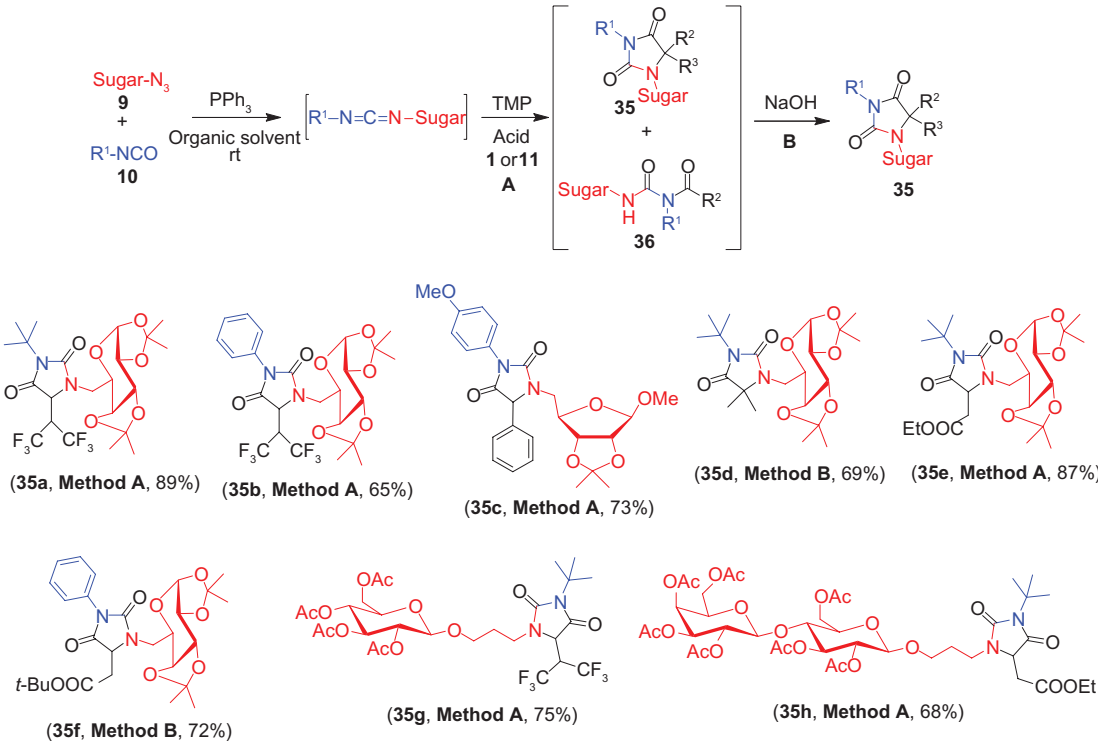
The reaction worked smoothly giving rise to the formation of the corresponding *N*-acylurea derivatives **33** in DCM as solvent *via O*-acylisourea **32**, which underwent a regioselective O→N acyl migration process. Any attempt to obtain the direct formation of the dihydrouraciles **34** by increasing the polarity of the solvent or by adding a Lewis base such as TMP failed. Moreover, starting from more basic *N,N′*-dialkyl carbodiimides, such as DIC, we did not obtain the formation of *N*-acylurea **33a** but we only detected byproducts probably arising from the decarboxylation of the starting acids **31**. By adding a non-nucleophilic base such as potassium *tert*-butoxide, we were able to produce a wide array of dihydrouraciles, such as **34a-c** starting with acids having different aryl substituents and either *N*-alkyl, *N′*-aryl or *N,N′*-diaryl carbodiimides, which were formed in situ starting from the corresponding azides **9** and isocyanates **10**.

Among the biologically relevant structures, we became interested in the synthesis of glyco-conjugates exploiting our MC process with carbodiimides. Indeed, one can think to anchor a glyco moiety to the carbodiimide framework. We envisioned that the transformation of easily accessible sugar-azides and isocyanates to glyco-hydantoin conjugates could be accomplished in a one-pot, MC sequential fashion by forming in situ the reactant carbodiimide through the Staudinger reaction. Since we had already demonstrated that both "weakly" and "strongly" asymmetric carbodiimides lead to highly, often totally, regioselective process when reacted with activated α,β-unsaturated carboxylic acids **1** and substituted α-halo acetic acids **11**, we decided to exploit such reactivity for the synthesis of glyco-hydantoin conjugates in a high regioselective way starting from carbodiimides having a *N*-primary glyco-substituent, such as 6-aminohexoses and 5-aminopentoses, and a *N′*-tertiary or -aryl substituent (Scheme 10).[16] Apart for regiochemical concern, the choice to use *N*-primary glyco-substituents is very intriguing because linking heterocycles or peptides at primary positions of 6-aminohexoses and

5-aminopentoses provides conjugates with enzymatically stable artificial linkages, also considering the fact that the $-CH_2NH_2$ moiety present in this sugars might mimic some elements of the glycine structure.

Accordingly, when azido-galactose or azido-ribofuranoside were reacted with *tert*-butyl isocyanate, in order to obtain "weakly" asymmetric carbodiimides, or with aryl isocyanates, in order to obtain "strongly" asymmetric carbodiimides, in CH_3CN and in the presence of triphenylphosphine, carbodiimmides and triphenylphosphineoxide were cleanly formed after 3 h. By adding to the resulting solution TMP followed by acids **1** or **11** we were able to obtain in high yield the desired diastereoisomeric conjugates **35a-h** with, in almost all cases, a totally regioselective process and with a diastereoisomeric ratio ranking from 3.5 to 1.0 to an equimolecular mixture depending on the carbodiimide substituents and on the acid used. The mechanism of the reaction is clearly the same of that depicted in Scheme 3, and the regioseletivity of the process depends on the more nucleophilic character of the primary *N*-glyco substituents compared to either the tertiary *N*′-*tert*-butyl substituent in "weakly" asymmetric carbodiimides and the *N*′-aryl substituent in "strongly" asymmetric carbodiimides. As evidenced from the structure of compounds **35a-f**, the process resulted to be highly versatile, with the only exception when glyco-azides having the azido group at the anomeric position were used. Probably, in the latter case the corresponding carbodiimides are too low electrophilic to be able to react with weak nucleophiles such as carboxylates. However, since compounds in which a glycosyl residue is linked through the anomeric carbon to another sugar or nonsugar moiety, such as amino acids and heterocyles, are very important in medicinal chemistry and in glycobiology, we decided to synthesize glycosyl-azides in which the anomeric carbons of the sugars are tethered to a simple linker bearing a primary azido group. In this way, using the corresponding "weakly" asymmetric carbodiimides obtained with *tert*-butyl isocyanate, we developed a MC sequential process to link sugar to hydantoin at the anomeric position, such as in compounds **35g,h**, with a totally regioselective reaction.

Considering the mechanism of the process (see Scheme 3), we wondered what could have happened if we performed the reaction in the presence of a nucleophile, such as amines. In theory, two possible pathways could occur leading to



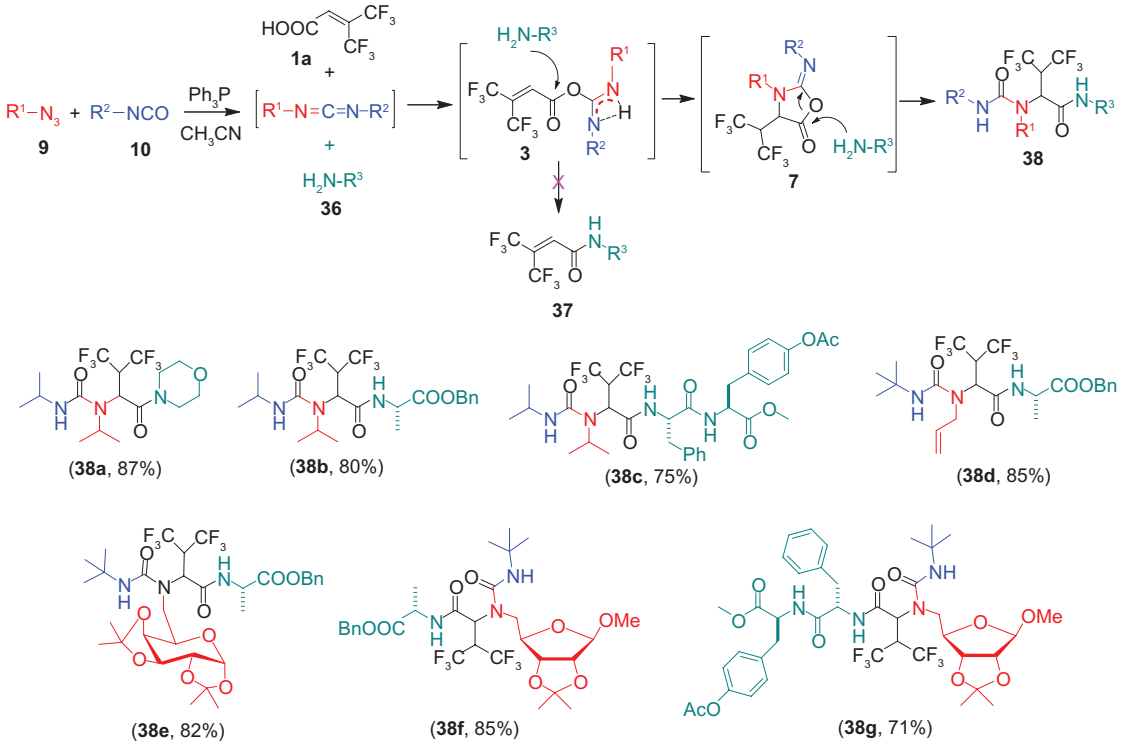
Scheme 10. MC sequential synthesis of glyco-hydantoin conjugates **35**.

the formation of two different products: (1) the amine nucleophile can attack the highly reactive *O*-acylisourea **3** leading to the amide **37** or (2) if the intramolecular nucleophilic aza-Michael process is faster, the amine nucleophile can steps into the reaction mechanism when the imidazolidinone **7** is already formed, leading to the formation of urea-peptide conjugates **38** (Scheme 11).

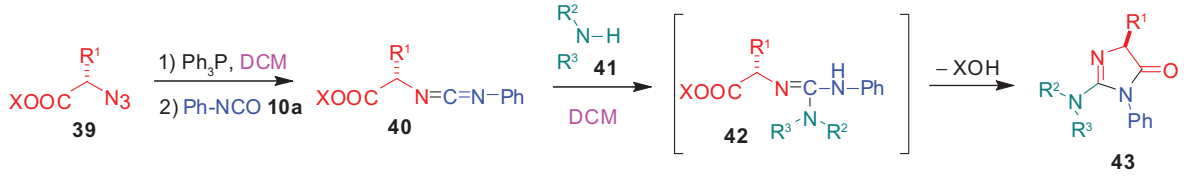
Indeed, by performing the reaction starting with acid **1a** and DIC, in the presence of an amine **36**, such as morpholine, we obtained the urea-amide conjugate **38a** in high yields through the three-component cascade reaction depicted above. The process resulted to be very versatile because worked nicely even with less nucleophilic amino acids and dipeptides, leading to the formation of urea-peptides conjugates incorporating hexafluorovaline such as **38b** and **38c**, respectively. Moreover, starting from "weakly"asymmetric carbodiimide bearing a primary *N*-allyl substituent and a tertiary *N′-tert*-butyl substituent, we obtained, as expected, a completely regioselective process producing compound **38d** in high yields. These results prompted us to use this strategy for the regioselective synthesis of glyco-peptides conjugates such as **38e-g** through a four-component sequential domino process starting from the corresponding glyco-azides **9** and *tert*-butyl isocyanate **10**.

Reaction with amines

Primary aliphatic amines are known to undergo direct guanylation with carbodiimides to yield *N,N′,N″*-trialkylguanidines under rather forcing conditions.[18] Moreover, less nucleophilic aromatic amines or secondary amines hardly react with carbodiimides under the same or harsher conditions. However, when carbodiimides bear an *N*-electron-withdrawing substituent, they can undergo nucleophilic attack by primary or secondary amines in milder conditions. For instance, carbodiimides having two electron-withdrawing substituents, such as *N*-β-ester, *N′*-phenyl carbodiimides **40**, which could be easily synthesized by Staudinger reaction between α-azido esters **39** and phenylisocyanate **10a**, react with secondary amines **41** at room temperature giving rise to guanidines **42** that spontaneously cyclize to the corresponding 2-iminoimidazolidinone derivatives **43** both in solution (Scheme 12)[19] and in solid phase.[20]



Scheme 11. Mechanism for the MC synthesis of urea-peptide conjugates **38**.

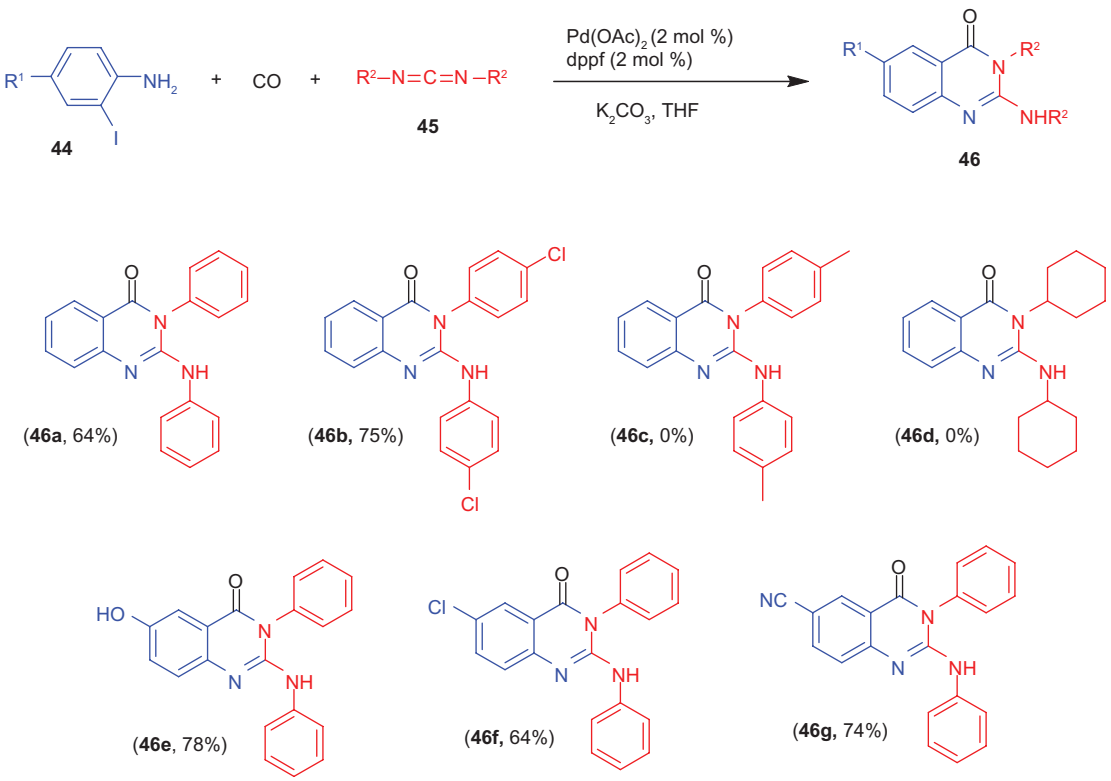


Scheme 12. Synthesis of 2-aminoimidazolinone derivatives **43**.

Since, as described above, the isolation of carbodiimides is not needed when they are prepared through Staudinger reaction, the synthetic pathway depicted in Scheme 12 could be used for the development of a MC sequential process. Indeed, the synthesis of bicyclic guanidines[21] and marine alkaloids[22] has been accomplished by performing such process in a one-pot sequential fashion without isolating the intermediate carbodiimides and using only primary amines as nucleophiles. However, the reactivity of the intermediate carbodiimides has not been studied in details, showing only three examples where the other *N*-substituent is a neutral aryl moiety such as phenyl, naphtyl, and tosyl.

The nucleophilic addition of amines to carbodiimides has been exploited also by the group of Prof. Alper for the preparation of quinazolidinone derivatives. In an earlier report 2-aminoquinazolin-4(3*H*)-ones **46** have been synthesized through a MC tandem palladium-catalyzed addition/cyclocarbonylation process starting from 2-iodoanilines **44**, *N,N′*-diarylcarbodiimides **45** and carbon monoxide (Scheme 13).[23]

The reaction worked well only when the substituents on the carbodiimide aryl moieties were neutral (H, **46a**) or electron-withdrawing (Cl, **46b**) while no reaction occurred with electron-donating substituents (Me, **46c**) or starting with *N,N′*-dialkyl-carbodiimides (**46d**). However, both electron-donating (OH, **46e**) or electron-withdrawing (Cl, **46f** and CN, **46g**) substituents on the iodoaniline reactants were well tolerated. Although the reaction

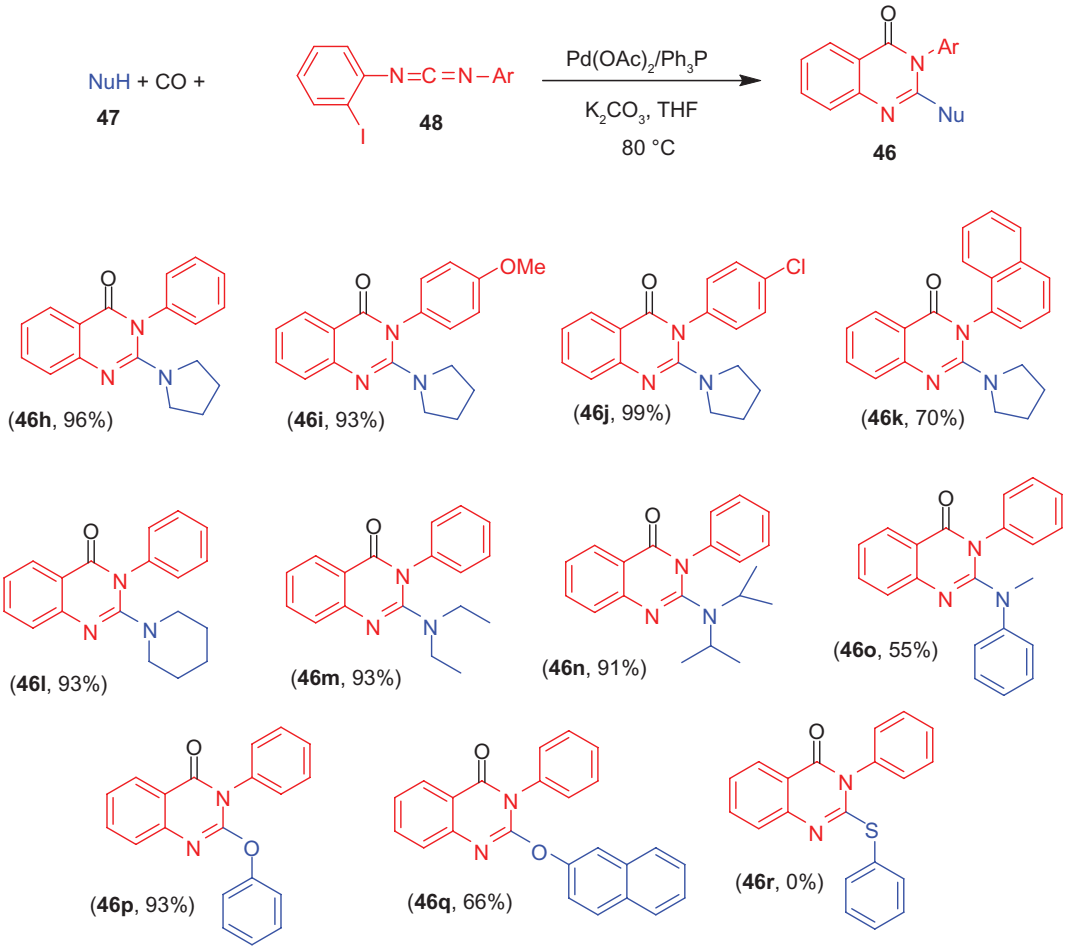


Scheme 13. MC synthesis of 2-aminoquinazolin-4(3*H*)-ones **46.**

works smoothly giving rise to the formation of an array of differently substituted 2-aminoquinazolin-4(3*H*)-ones in good to excellent yields, the authors did not explore the reactivity of "highly" asymmetric carbodiimides that could have done a regioselective process. In fact, the mechanism of the reaction is likely to arise through a first nucleophilic attack of the aniline to the carbodiimide leading to the formation of the corresponding guanidine derivatives which acts as nucleophile in the following palladium catalyzed cyclocarbonylation reaction step (see below). The same kind of products **46** could be obtained by introducing the iodoaniline moiety in the carbodiimide framework and using different secondary amines as nucleophiles (Scheme 14).[24]

The process was highly versatile since neutral (H, **46h**), electron-donating (*p*-MeO, **46i**), and electron-withdrawing (*p*-Cl, **46j**) groups on the other *N*-aromatic substituent of the carbodiimide were tolerated and worked efficiently with different secondary amines such as cyclic (**46h-l**), acyclic (**46m,n**), and aromatic (**46o**). Moreover, when phenol and 2-naphtol were used as nucleophiles, the desired products **46p** and **46q**, respectively, were formed in reasonable yields, while with thiophenol the formation of the corresponding product **46r** was not detected. Also in this case, the authors did not explore the reactivity of "strongly" asymmetric carbodiimides such as *N*-2-iodophenyl, *N*′-alkyl carbodiimides that could afford *N*-alkyl substituted 2-heteroquinazolin-4(3*H*)-ones.

These cyclocarbonylation reactions proceed through in situ generation of isomeric guanidines **49** and **49′** from addition of the amine nucleophiles **47** to carbodiimides **48**, which are prone to act as nucleophile toward the in situ generated palladium(0) species leading to complex **50**, **50′** which undergo carbon monoxide insertion into the aryl carbon-palladium bond. Thus, base-catalyzed intramolecular cyclization of **51**, **51′** gives palladacycle **52**, which



Scheme 14. MC synthesis of 2-aminoquinazolin-4(3*H*)-ones **46.**

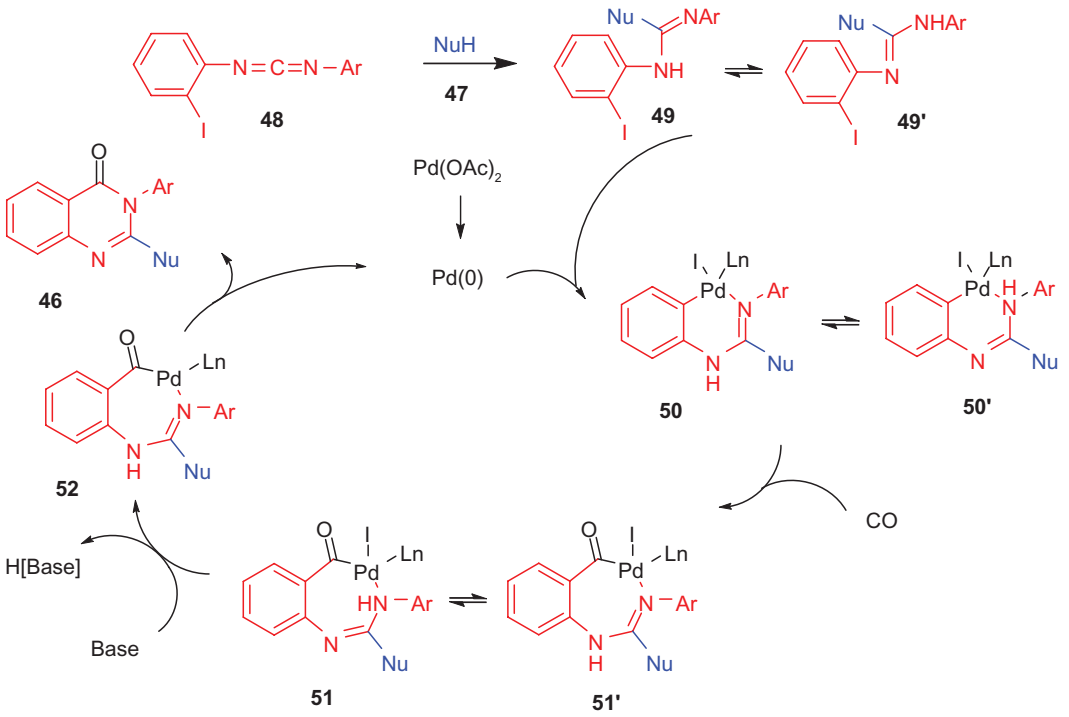
undergoes reductive elimination affording the final heterocycle **46** with regeneration of the palladium(0) species (Scheme 15).

The same authors exploited this reactivity also for the synthesis of ring-fused quinazolinones **54** starting from symmetric *N,N′*-substituted iodophenyl carbodiimides **53** and primary amines (Scheme 16).[25]

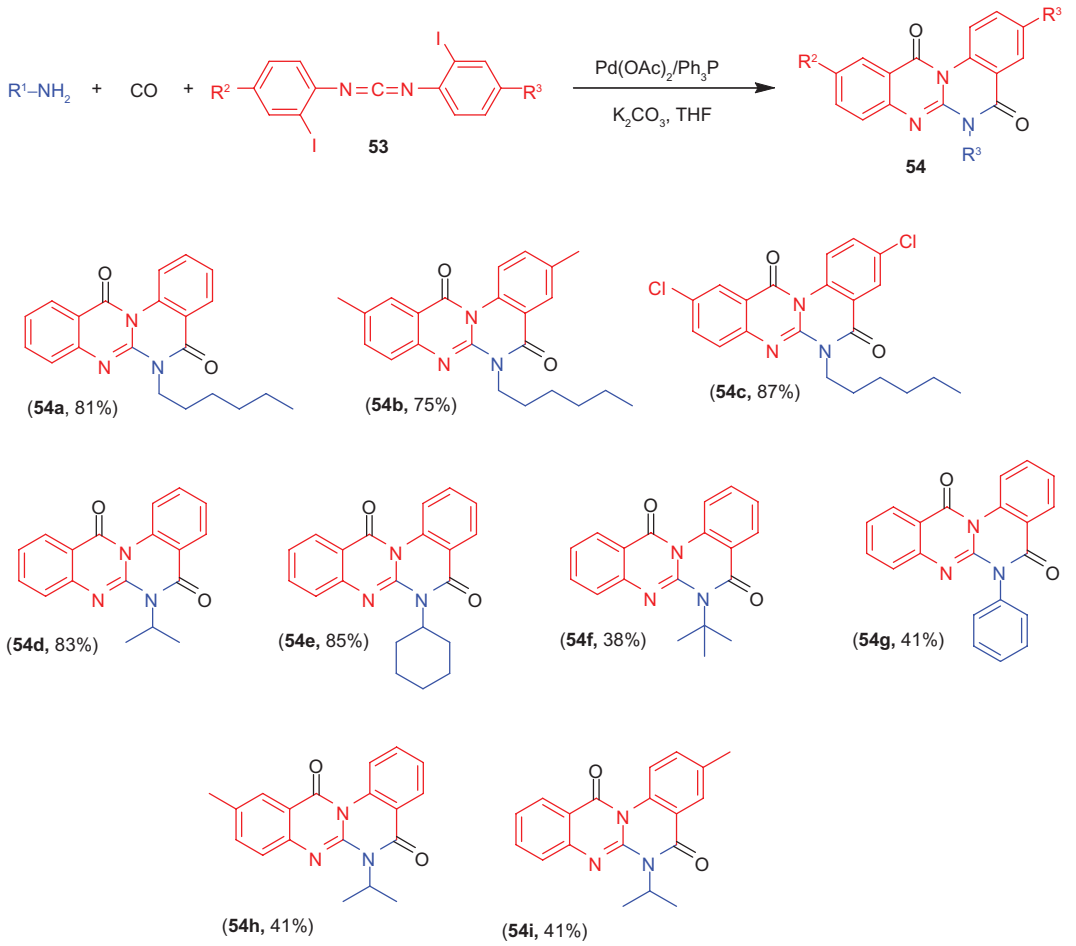
Also this reaction resulted to be highly versatile since tolerated neutral (H, **54a**), electron-donating (*p*-Me, **54b**), and electron-withdrawing (*p*-Cl, **54c**) groups on the *N*-aromatic substituents of the carbodiimides, and different primary amines as nucleophiles bearing primary (**54a-c**), secondary (**54d,e**) and even tertiary (**54f**) substituents, even if in the latter case the yields are lower due to the steric hindrance of the *tert*-butyl group. The process works well also with less nucleophilic aniline (**54g**) leading to the corresponding product although in lower yields. Moreover, the authors tried the reaction with asymmetric carbodiimides obtaining an equimolecular mixture of two regioisomers **54h,i** in high overall yield. The process is likely to occur with a mechanism similar to that depicted in Scheme 15, where the first step consists in the nucleophilic addition of the amines to the carbodiimides.

Amine nucleophiles have been also used in the MC synthesis of *N,N′*-dialkyl-*N″*-dialkylaminocarbothionyl thioureas **56** starting from cyclic secondary amines **55**, carbondisulfide and symmetric *N,N′*dialkyl carbodiimide **2** (Scheme 17).[26]

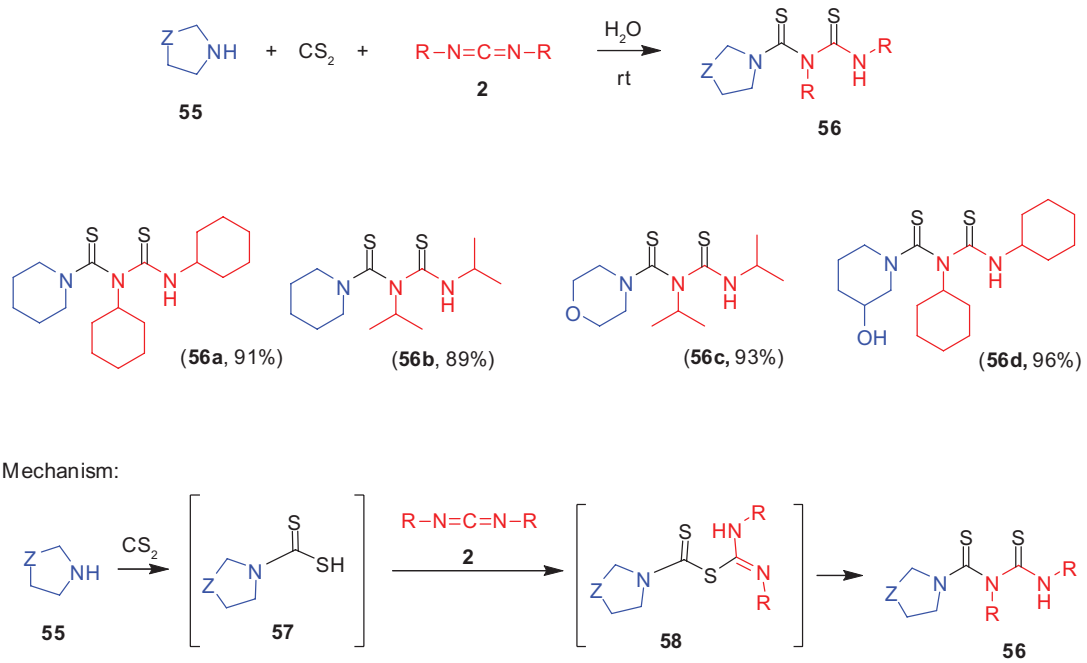
However, in this reaction the amines did not attack directly the carbodiimides, but react with carbondisulfide leading to the formation of dithiocarbamic acids **57** which, in turn, react with carbodiimides leading to the formation of intermediate **58** which evolves in the final compounds **56** through a S→N thioacylmigration mechanism. The authors studied the reactivity of symmetric *N,N′*-dialkyl carbodiimides showing that the process worked well either with DCC (**56a,d**) or DIC (**56b,c**). We strongly believe that, due to the similarity with the reaction between carbodiimides and carboxylic acids depicted in Scheme 2, starting from either "strongly" or "weakly" asymmetric carbodiimides they could have obtained a highly regioselective process leading to the final carbothionyl thioureas



Scheme 15. Mechanism for the MC synthesis of 2-aminoquinazolin-4(3*H*)-ones **46**.



Scheme 16. MC synthesis of quinazolino[3,2-*a*]quinazolinones **54.**



Scheme 17. MC synthesis of *N,N'*-dialkyl-*N''*-dialkylaminocarbothionyl thioureas **56**.

having, respectively, an aryl or a bulky alkyl substituent on the thioimidic nitrogen.

Reaction with Carbon Nucleophiles

Multi-substituted amidines of general formula R′N=C(CR^{1}R^2)NHR′ are an important family of heteroatom-containing organic compounds, which posses a wide range of biological and pharmaceutical activities[27] and can serve as building blocks for many biologically relevant compounds.[28] Such substrates could be easily obtained by nucleophilic addition of metal-organic reagents to carbodiimides. This process has been exploited by the group of Prof. Xu for the MC synthesis of functionalized propiolamidine derivatives **61** (Scheme 18).[29]

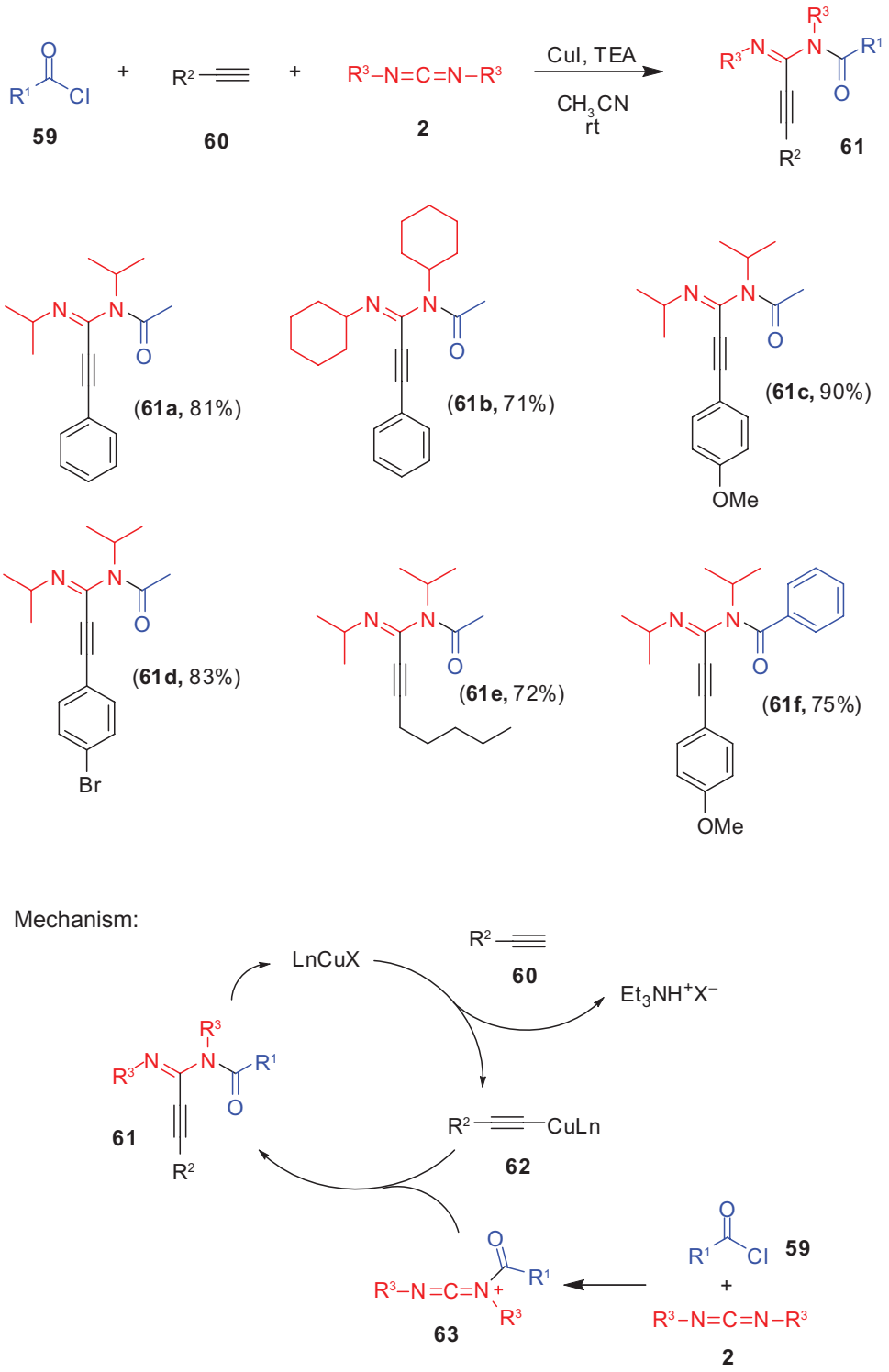
Starting with symmetric *N,N′*-dialkyl carbodiimides **2**, monosubstituted acetylenes **60**, and acyl chlorides **59**, in the presence of catalytic CuI and a base such as TEA, Xu et al obtained the formation of an array of functionalizated propiolamidine **61** in very good yields. The process works efficiently either with DIC (**61a**) or DCC (**61b**) but did not work when mono- and diaryl *N,N′*-substituted carbodiimides were used. On the contrary, the reaction seems very versatile with respect of the acetylenes working efficiently with neutral (**61a,b**), electron-donating (**61c**) and electron- withdrawing (**61d**) aryl substituted acetylenes, with alkyl acetylenes (**61e**), and with respect of the acyl chlorides that could be alkylic or aromatic (**61f**). Concerning the mechanism, carbodiimide **2** reacts with acyl chlorides **59** to form highly electrophilic *N*-acyliminium salts **63** which react with copper acetylide **62** giving rise to the formation of the desired product **61** and liberating the copper catalyst to complete the catalytic cycle. Probably, more electron poor *N*-aryl substituted carbodiimides did not afford the final compounds because are unable to react with the acyl chloride.

MCRs by Cycloaddition on Carbodiimides

Cycloaddition reactions of carbodiimides are now very well documented and may occur to yield 1:1 or 2:1 adducts. Carbodiimides usually act as the two-electron component when reacting with 1,3-dipolar reagents such as 1-aza-[30] and 1,3-diaza-2-azoniallenes,[31] or with nitrile oxides and imines.[32] The 1:1 cycloaddition may be concerted or stepwise, and there is evidence for both pathways (Scheme 19).

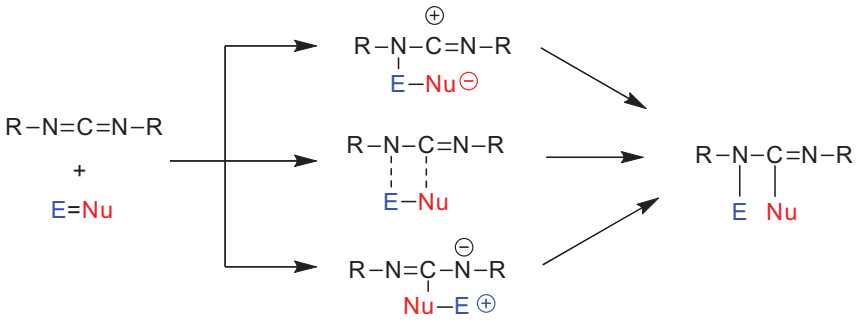
Very recently the group of Prof. Wu demonstrated that carbodiimides could be used for the synthesis of isoquinoline derivatives through [3+2] dipolar reaction with in situ generated isoquinoline *N*-oxides.[33] This reaction has been further exploited by the same group for the MC synthesis of a library of 1-(isoquinolin-1-yl)urea **65** by performing this process in the presence of a base (DABCO) and an electrophile, such as bromine, which triggers the formation of the dipolar isoquinoline *N*-oxides by reaction with 2-alkynylbenzaldoxime **64** (Scheme 20).[34]

This MC process showed a broad substrate scope. Indeed, it worked efficiently with either symmetric *N,N′*-dialkyl carbodiimides, such DCC (**65a**) and DIC (**65b**) and symmetric *N,N′*-diaryl carbodiimides. Moreover, in the latter case, neutral (R^3 = Ph, **65c**) as well as electron-withdrawing (R^3 = *p*-F-Ph, **65d**) and electron-donating (R^3 = *p*- MeO-Ph, **65e**) *para*-substituent are very well tolerated. Again, the authors did not report the reaction with asymmetric carbodiimides which could have done the regioselective synthesis of differently substituted urea moieties. The electronic effect of the substituent on the aromatic ring of the 2-alkynylbenzaldoxime **64** was also invisible, since the yield remained very high starting with either neutral (R^1 = H, **65a**) compound or with benzaldoxime bearing electron-donating (R^1 = Me, **65f**) and electron-withdrawing (R^1 = F, **65g**) substituents. Finally, the authors showed also that the substituent on the alkynyl chain did not affect the yield of the process, leading to the formation of the final 1-(4-haloisoquinolin-1-yl) ureas bearing either an aromatic (**65a-g**) or an aliphatic chain (**65h-j**) in 3-position. Very interestingly, in another work,[35] the same authors showed that the process run without the base, namely in a mixture of DCM/dioxane, gave rise to the formation of substituted 1-aminoisoquinoline derivatives **66** (Scheme 21), thus loosing a urea moiety framework that originated from the carbodiimide **2** (see below).



Scheme 18. MC synthesis of functionalized propiolamidine derivatives **61**.

This process worked nicely with *N,N′*-dialkyl carbodiimides, such as DCC (**66a**) and DIC (**66b**), while there are no reports on the reactivity of the corresponding diaryl carbodiimides. It is note worthy that in this case the reaction of asymmetric carbodiimides do not have sense since one of the two carbodiimide *N*-substituents is lost during the process. Concerning the other substituents, the reaction works well starting

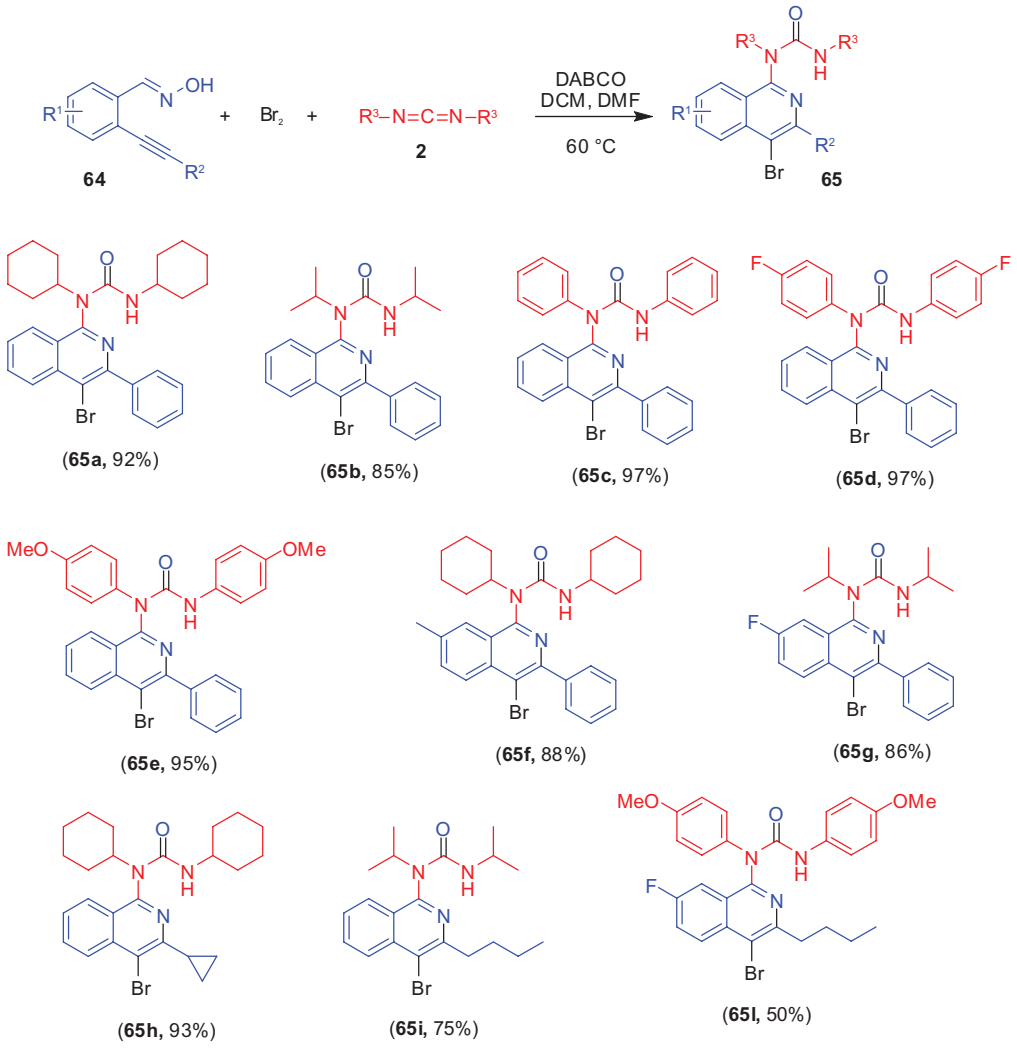


Scheme 19. Pathways for cycloaddition reactions with carbodiimides.

with differently substituted arylaldoximes, thus bearing neutral (R^1 = H, **66a,b**), electron-withdrawing (R^1 = F, **66c**) or electron-donating (R^1 = OMe, **66d**) substituents on the aromatic ring, and starting with either aryl (**66a-d**) or alkyl (**66e,f**) substituted carbon-carbon triple bonds.

The mechanism proposed by the authors for these two processes is reported in Scheme 22.

The initial reaction between 2-alkynylbenzaldoxime **64** and bromine produced the reactive 4-bromoisoquinoline-*N*-oxide **67** *via* 6-*endo* cyclization. Then, [3+2] cycloaddition between **67** and carbodiimide **2**



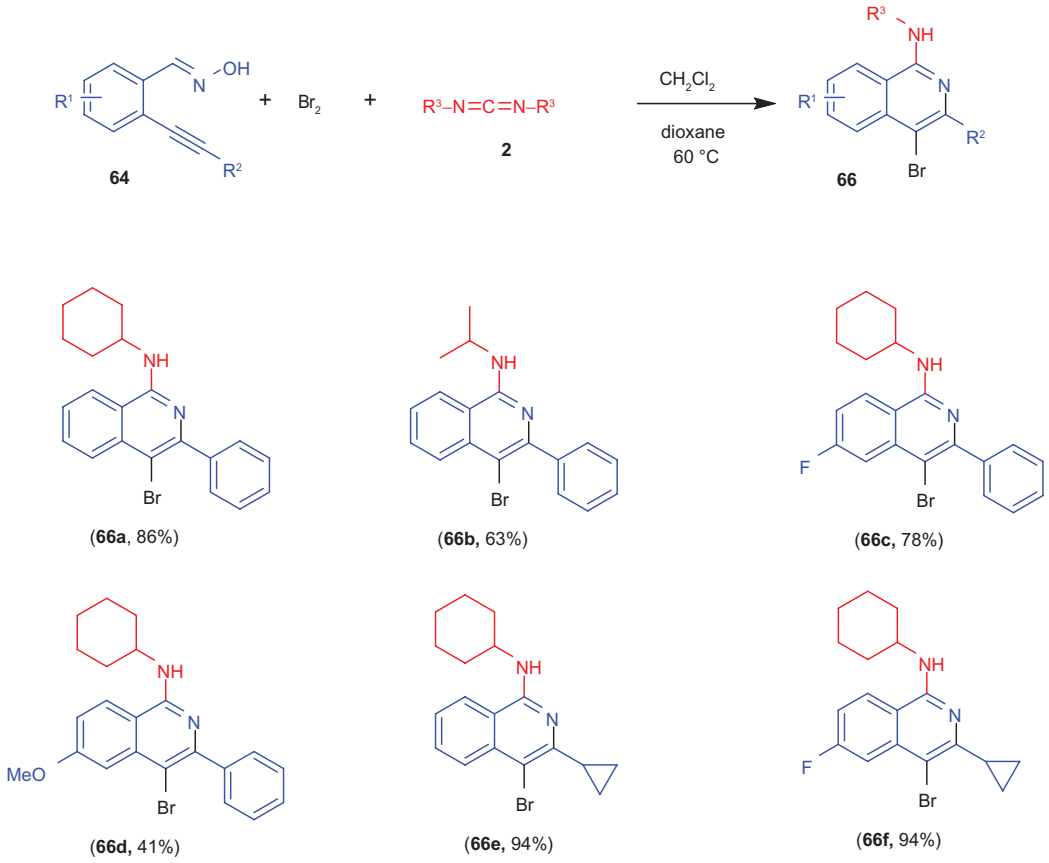
Scheme 20. MC synthesis of 1-(4-haloisoquinolin-1-yl)ureas **65**.

occurs giving rise to the formation of intermediate **68** which undergoes an intramolecular rearrangement to afford 4-bromo-1-(isoquinolin-1-yl)urea **65**. The latter is the product of the reaction carried out in the presence of a base which serves as scavenging agent of the HBr produced during the process. In absence of such scavenging agent, the HBr produced triggers the hydrolysis of the urea moiety leading to the formation of the final 1-aminoisoquinolines **66**.

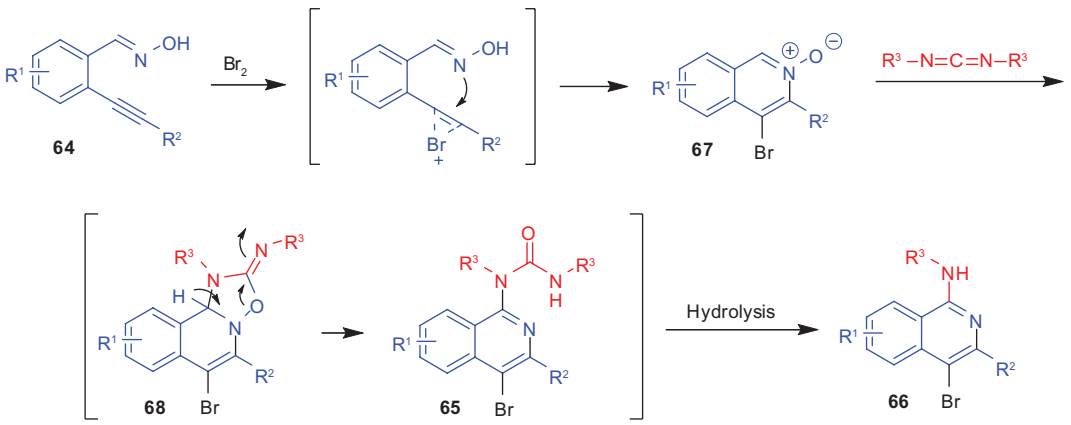
Since the key feature of the previous process is the in situ generation of the dipolar reagent, one can think to develop different MC processes generating other dipolar reagents. Indeed, always the same authors developed a MC domino process for the synthesis of 1-(isoquinolin-1-yl)guanidines **70** starting from 2-alkynylbenzaldehydes **69**, tosylhydrazine, and carbodiimides **2**. The mechanism of the process is related to that described above: in this case the dipolar reactant is formed by silver catalyzed 6-*endo*-cyclization of **71** which in turn is formed in situ by reaction between **70** and tosylhydrazine (Scheme 23).[36]

Also in this case the process was very versatile both concerning the carabodiimide component and the alkynylbenzaldehydes. *N,N′*-Dialkyl, such as DCC (**70a**) and DIC (**70b**), and *N,N′*-diaryl carbodiimides, bearing either neutral (R^3 = Ph, **70c**), electron-rich (R^3 = *p*-Me-Ph, **70d**), and electron-poor (R^3 = *p*-Cl-Ph, **70e**) aromatic rings, worked efficiently producing the corresponding 1-(isoquinolin-1-yl)guanidines in good yields. Moreover, various substitutions attached on the triple bond or in the aromatic ring of 2-alkynylbenzaldehydes **69** do not affect the final outcome. Also in this case, the authors did not report on the reactivity of asymmetric carbodiimides that could have produced guanidine moieties with different substituents in a regioselective way. Moreover, another drawback of this process relies on the use of tosylhydrazone as a component which does not bring about diversity in the final library.

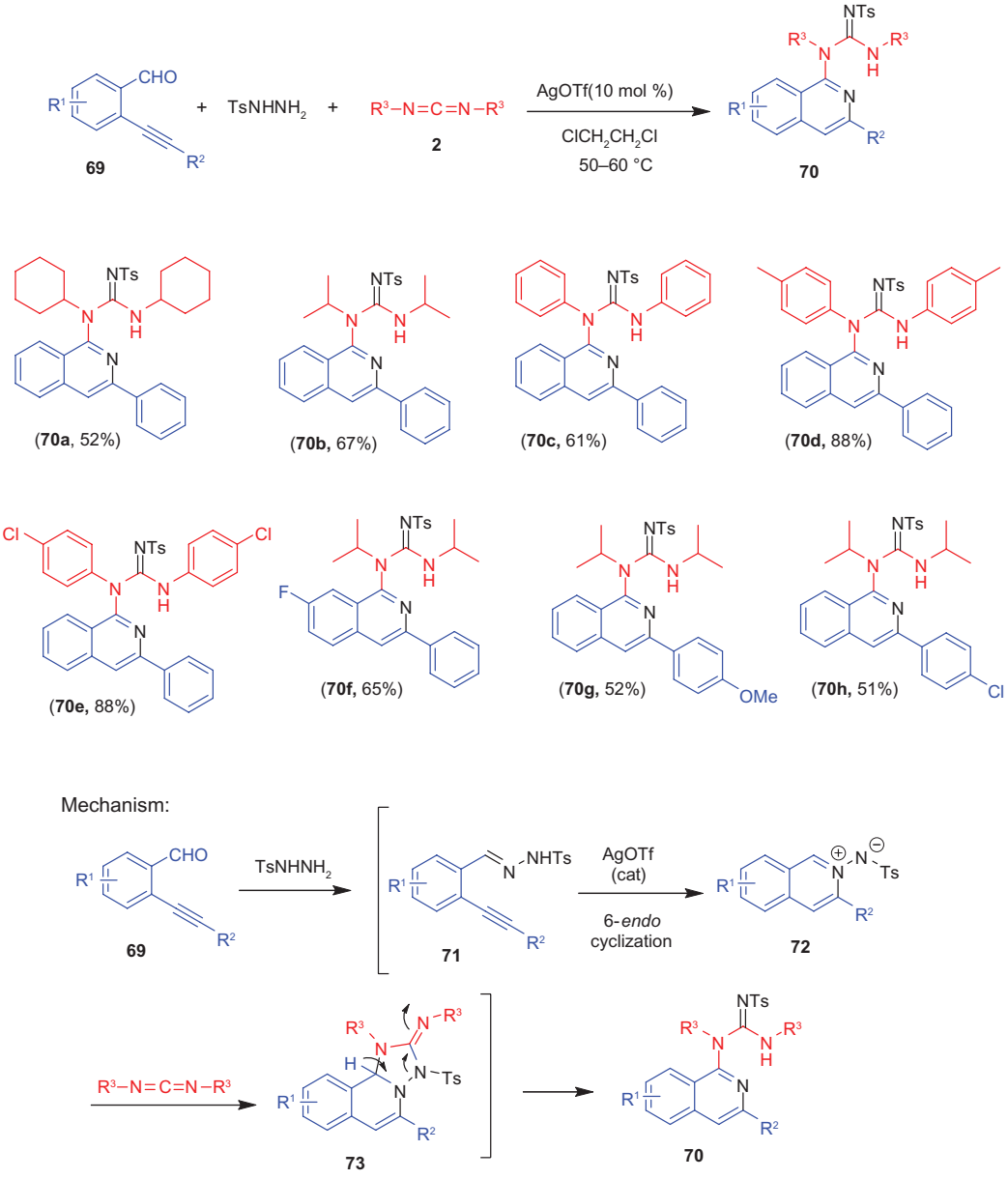
When terminal alkynes **60** were reacted with carbodiimides **2** in the presence of sulfonyl azides **74** and cupper catalyst, 2-(sulfonylimono)-4-(alkylimino)azetidine **75** could be obtained in very



Scheme 21. MC synthesis of 1-aminoisoquinoline **66**.



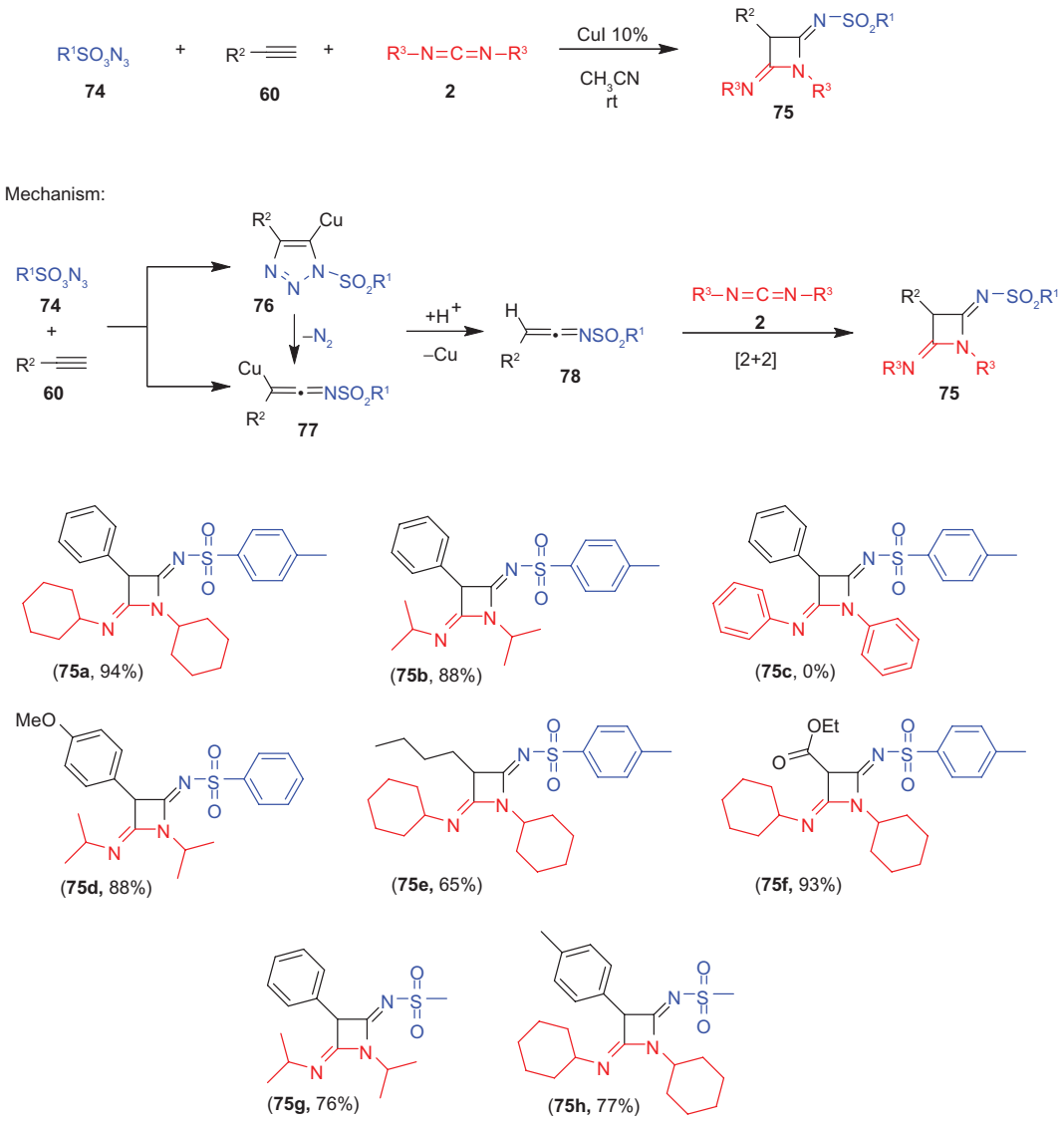
Scheme 22. Mechanism for the MC synthesis of 1-(4-haloisoquinolin-1-yl)ureas **65** and 1-aminoisoquinoline **66.**



Scheme 23. MC synthesis of 1-(isoquinolin-1-yl)guanidines **70.**

mild conditions through a MC process (Scheme 24) where carbodiimides did not act as electrophiles with cupper acetylides but as dipolarophiles.[37]

In fact, this reaction proceed through a first addition of the alkyne **60** to sulfonyl azide **74**, rather than to carbodiimide **2**, producing, through two possible pathways ketimmine species **77**, where carbodiimide **2** likely acts as a weak base. Protonation of **77** regenerates the copper catalyst and gives rise to the highly reactive ketimmine **78**, which reacts with carbodiimide **2** through a [2+2] cycloaddition to afford the desired product **75**. The process worked very well with basic symmetric *N,N′*-dialkyl carbodiimides such as DCC and DIC affording the corresponding 2-(sulfonylimono)-4-(alkylimino)azetidine **75a,b** in very high yield. However, starting with *N,N′*-diaryl carbodiimides such as *N,N′*-diphenyl carbodiimide, the desired product was not obtained, probably because aromatic carbodiimides are not basic enough. The authors did not report on the reaction with asymmetric carbodiimides. We believe that "strongly" asymmetric carbodiimides could be basic enough to be used efficiently in this process leading to the formation of a regioselective process. The same could be said for "weakly" asymmetric carbodiimides whom basicity is very similar to that of DCC or DIC. Concerning the other points of diversity, different substituents are tolerated on the alkyne **60**. Indeed, aromatic (R^2 = phenyl, **75a,b**, and R^2 = *p*-MeO-pheyl, **75d**), aliphatic (R^2 = butyl, **75e**), and electron-withdrawing

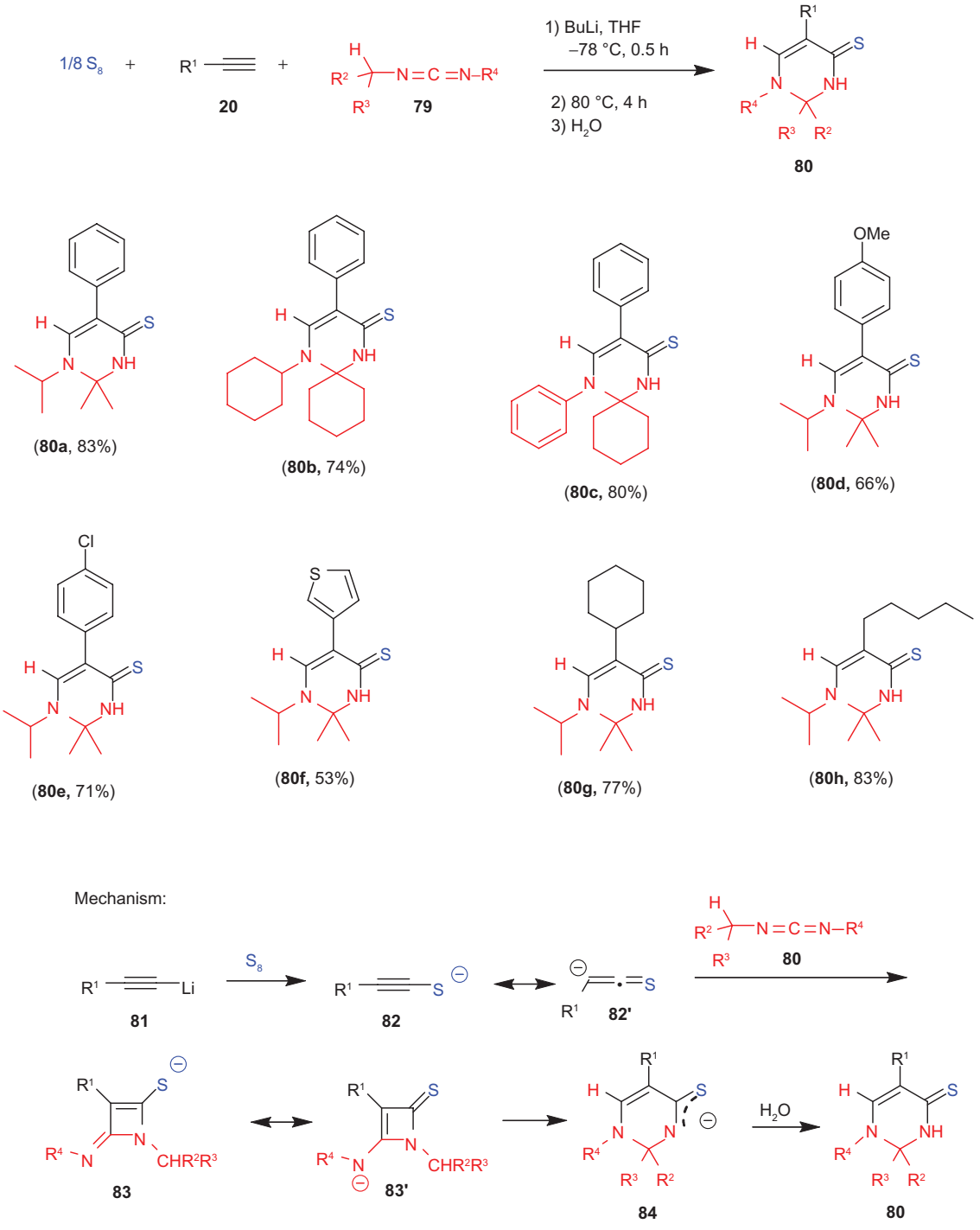


Scheme 24. MC synthesis of 2-(sulfonylimono)-4-(alkylimino)azetidine **75**.

(R^2 = COOEt, **75f**) substituents produced the corresponding final targets in very good yields. Also the substituent of the sulfonyl azide **74** could be indifferently aromatic (**75a-f**) or aliphatic (**75g,h**).

Terminal alkynes **60** have been also used for an organolithium-promoted MC sequential synthesis of 2,3-dihydropymiridinthiones **80** involving elemental sulphur and carbodiimides **79** bearing at least one hydrogen on the carbon directly attached to one of the two nitrogen atoms (Scheme 25).[38]

Both DCC and DIC posses such hydrogen and worked nicely in this process producing the corresponding dihydropymiridinthiones **80a,b** in good yields. The process worked well also starting with "strongly"



Scheme 25. MC synthesis of 2,3-dihydropyrimidinthiones **80**.

asymmetric carbodiimides, such as *N*-cyclohexyl, *N′*-phenyl-carbodiimide leading to the formation of **80c** as single regioisomer. The other point of diversity, namely the R^1 substituent on the terminal alkynes **60**, could be changed widely. In fact, when such substituent is an aromatic ring, neutral (phenyl, **80a-c**), electron-rich (*p*-MeO-phenyl, **80d**), electron-poor (*p*-Cl-phenyl, **80e**) phenyls, and heterocycles (thiophene, **80f**) are tolerated. Moreover, starting with alkyl-substituted terminal alkynes **60** the corresponding final pymiridinthiones **80g,h** have been obtained in good yields. The most interesting novelty on this work is that for the first time the authors demonstrated that carbodiimide can undergo interesting and useful C=N double bond cleavage and an sp^3 C-H bond functionalization, which can be used for the planning of novel process involving carbodiimides. In fact, the proposed mechanism for this process involve the reaction between lithium acetylide **81** and elemental sulphur leading to the formation of lithium alkynethiolate **82** and **82′** which react through a stepwise dipolar cycloaddition with carbodiimide **2** producing four-membered-ring intermediates **83** and **83′**. At the moment, it is not clear how the final lithium specie **84** is formed from the four-membered-ring intermediates **83** or **83′**.

Conclusions

Many classical MCRs involve (1) the unique reactivity of isocyanides[3e,6] (eg, Passerini, Ugi) or (2) the combination of β-dicarbonyl compounds, amines, and aldheydes (eg, Hantzsch, Biginelli).[5,39] Variation of these themes could led to the discovery of many interesting MCRs. If we consider the reactivity of isocyanides, β-dicarbonyl compounds, or imines, they have a common character that is beneficial for their involvement in MC process: they posses in their skeleton a nucleophilic and an electrophilic moiety. This character enables them to react at the same time with an electrophile and a nucleophile which is a favourable factor for the development of MC process. If we consider the structure of carbodiimides, which posses two iminic moieties, it becomes suddenly clear that they can be involved in related MC process. Indeed, such strategy has been exploited for the MC synthesis of biological interesting compounds such as propyolamidine derivatives and many heterocycles. Moreover, carbodiimides could be synthesized, in many organic solvent and in high yields, by Staudinger reaction between easily accessible azides and iso(thio)cyanates leading to the formation of $Ph_3PO(S)$ as the only byproduct. This characteristic feature could be exploited for the development of new MC sequential process by reacting the in situ formed carbodiimides with a third component. As reported in the first part of this Insight, we have used such reactivity for the regioselective MC synthesis of heterocycles and glyco-conjugates. Since the reagents can not all be added simultaneously, these kind of sequential process have not always be considered true MCRs. However, we strongly agree with what reported in a recent review[3h] where it is stated that it is more practical to consider what we wish to achieve with a MCR, that is, a practical, atom-economic, one-pot procedure that delivers complex molecules with high variability, without involving intermediate work-up or solvent change. For this reason, new MC sequential reactions involving carbodiimides for the straightforward synthesis of biological interesting compounds are still under active investigation in our laboratories.

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Author Contributions

Conceived wrote the first draft of the manuscript: AV. Contribued to writing of the manuscript: MCB. Agree with the manuscript results and conclusions: MCB, AV. Jointly developed the structure and arguments for the paper: MCB, AV. Made critical revisions and approved final version: AV.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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