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
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, 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. An important subclass of tandem reactions are multicomponent reactions (MCRs). 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. Other MCRs that were discovered long ago, such as the Biginelli and Ugi reactions, saw a true renaissance during the past years becoming the cornerstones of combinatorial chemistry, where the synthesis of focused libraries is 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, 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. 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. General use of these species was stimulated by Khorana’s pioneering investigations of their action in peptide and nucleotide synthesis. 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 possess 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”
Carbodiimide-mediated multi-component reactions

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 central 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 \( O \rightarrow N \) 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 possess 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 \( \alpha,\beta \)-unsaturated carboxylic acids 1 were reacted with carbodiimides 2 in absence of a nucleophile, a one-pot domino condensation/aza-Michael addition/\( O \rightarrow N \) acyl migration process occurred, leading to

![Scheme 1. Pathways for reaction of carbodiimides with E-Nu.](image-url)
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 triphenylophosphine 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 dichloromethane (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

\[
\begin{align*}
\text{R}^1 \text{O} & \xrightarrow{\text{R}^1 \text{N} - \text{C} = \text{N} - \text{R}'} \\
\text{R}^1 \text{N} & \xrightarrow{\text{R}^1 \text{N} - \text{C} = \text{N} - \text{R}'} \\
\text{R}^1 \text{N} & \xrightarrow{\text{R}^1 \text{N} - \text{C} = \text{N} - \text{R}'} \\
\text{R}^1 \text{N} & \xrightarrow{\text{R}^1 \text{N} - \text{C} = \text{N} - \text{R}'}
\end{align*}
\]

Scheme 2. The one-pot domino condensation/aza-Michael addition/O→N acyl migration.
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 $\alpha$-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. 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 $\alpha,\beta$-unsaturated carboxylic acids...
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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$_3$CN at 120 °C in the presence of anhydrous K$_2$CO$_3$ 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 monoethyl esters at rt and in CH$_3$CN as solvent followed by cyclization of the resulting $N$-acylureas, and $C$-alkylation of the resulting 1,3,5-substituted barbiturates by adding K$_2$CO$_3$ 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

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

$i$ NaOH (2N), dioxane, rt; $ii$ an. K$_2$CO$_3$, CH$_3$CN, 120 °C
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 $O\rightarrow N$ 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 monoesters 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 monoesters. However, performing the condensation between DIC and malonic acid monoesters in low polarity solvents, such DCM, and in the presence of an equivalent of a base, e.g., TMP, which facilitated the $O\rightarrow N$ 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$_2$CO$_3$ in CH$_3$CN 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$. 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 noting that $N,N'$-dialkyl barbiturates, independently of the nature of the R$ 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$_2$CO$_3$ in CH$_3$CN, 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 dihydouraciles. 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
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). 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

Scheme 9. MC sequential synthesis of dihydrouraciles 33.
5-aminopentoses provides conjugates with enzymatically stable artificial linkages, also considering the fact that the $-\text{CH}_2\text{NH}_2$ moiety present in this sugars might mimic some elements of the glycine structure.

Accordingly, when azido-galactose or azido-ribofuranoside were reacted with tert-butyli isocyanate, in order to obtain “weakly” asymmetric carbodiimides, or with aryl isocyanates, in order to obtain “strongly” asymmetric carbodiimides, in CH$_3$CN and in the presence of triphenylphosphine, carbodiimides 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 $35a\text{-}h$ 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 regioselectivity 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 $35a\text{-}f$, 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-butyli isocyanate, we developed a MC sequential process to link sugar to hydantoin at the anomeric position, such as in compounds $35g\text{-}h$, 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 $35$. 

$\text{Sugar-N}_9 + \text{R'NCO}$

$\text{PPh}_3$

Organic solvent

rt

TMP

Acid $1 \text{ or } 11$

$\text{Sugar}$

$\text{NaOH}$

$\text{Sugar-N}_9$
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. 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) and in solid phase.

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**Scheme 11.** Mechanism for the MC synthesis of urea-peptide conjugates 38.
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 and marine alkaloids 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(3H)-ones have been synthesized through a MC tandem palladium-catalyzed addition/cyclocarbonylation process starting from 2-idoanilines, N,N'-diarylcarbodiimides and carbon monoxide (Scheme 13).

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 12. Synthesis of 2-aminoimidazolinone derivatives 43.](image-url)

![Scheme 13. MC synthesis of 2-aminoquinazolin-4(3H)-ones 46.](image-url)
works smoothly giving rise to the formation of an array of differently substituted 2-aminoquinazolin-4(3H)-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).

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-naphthol 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(3H)-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(3H)-ones 46.](image-url)
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 iodoaryl 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, carbodiisulfide 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 carbodiisulfide 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 thioaclymigration 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(3H)-ones 46.](image-url)
Carbodiimide-mediated multi-component reactions


Scheme 17. MC synthesis of N,N'-dialkyl-N''-dialkylaminocarbothionyl thioureas 56.
having, respectively, an aryl or a bulky alkyl substituent on the thiouimidic nitrogen.

**Reaction with Carbon Nucleophiles**

Multi-substituted amidines of general formula \( R'N=NC(\text{CR}R')\text{NHR} \) are an important family of heteroatom-containing organic compounds, which possess a wide range of biological and pharmaceutical activities and can serve as building blocks for many biologically relevant compounds. 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).

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 functionalized 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 aliphatic or aromatic \( (61f) \).

Concerning the mechanisms, 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-azoniellenes, \( ^{31} \) 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).

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 \( (R^3 = \text{Ph}, 65c) \) as well as electron-withdrawing \( (R^3 = p-F-\text{Ph}, 65d) \) and electron-donating \( (R^3 = p-\text{MeO-Ph}, 65e) \) para-substituents 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 \( (R^1 = \text{Me}, 65f) \) and electron-withdrawing \( (R^1 = F, 65g) \) substituents. Finally, the authors showed also that the substituent on the alkylnyl 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).
Carbodiimide-mediated multi-component reactions

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 noteworthy 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...
with differently substituted arylaldoximes, thus bearing neutral (R₁ = H, 66a,b), electron-withdrawing (R₁ = F, 66c) or electron-donating (R₁ = 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
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 carbodiimide component and the alkynylbenzaldehydes. \(N,N'\)-Dialkyl, such as DCC (70a) and DIC (70b), and \(N,N'\)-diaryl carbodiimides, bearing either neutral (R3 = Ph, 70c), electron-rich (R3 = p-Me-Ph, 70d), and electron-poor (R3 = 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 tosylhydrazones 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 high yields.
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 copper acetylides but as dipolarophiles.37

In fact, this reaction proceeds 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 ketimmin 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 (\(R_2 = \text{phenyl}, 75a,b\), and \(R_2 = p\text{-MeO-phenyl}, 75d\)), aliphatic (\(R_2 = \text{butyl}, 75e\)), and electron-withdrawing

\[
\begin{align*}
R^1SO_3N_3 &\quad R^2N\equiv C\equiv N\equiv R^3 \quad 2 \\
74 &\quad 75 &\quad \text{CuI, 10%} \quad \text{CH}_{3}\text{CN} \quad \text{rt} \\
60 &\quad 76 &\quad 77 &\quad 78 \quad [2+2] \\
R^1SO_3N_3 &\quad R^2N\equiv C\equiv N\equiv R^3 \quad 2 \\
75a &\quad 75b &\quad 75c &\quad 75d &\quad 75e &\quad 75f &\quad 75g &\quad 75h
\end{align*}
\]

Scheme 24. MC synthesis of 2-(sulfonylimono)-4-(alkylimino)azetidine 75.
(R² = 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-dihydropyrimidinthiones 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 dihydropyrimidinthiones 80a,b in good yields. The process worked well also starting with “strongly”
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 R1 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 pymirindithiones 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 sp3 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 isocyanides3e,6 (eg, Passerini, Ugi) or (2) the combination of β-dicarbonyl compounds, amines, and aldehydes (eg, Hantzsch, Biginelli).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 Ph3PO(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 review3h 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. Contributed 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.

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