Angewandte Highlights

Click Chemistry

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Enamine/Enolate-Mediated Organocatalytic Azide–Carbonyl [3+2] Cycloaddition Reactions for the Synthesis of Densely Functionalized 1,2,3-Triazoles**

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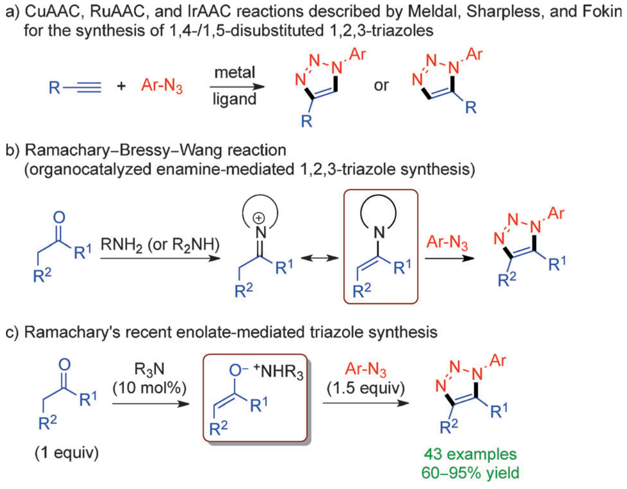
1,2,3-triazoles · azides · click chemistry · enols · organocatalysis

A large number of bioactive molecules feature 1,4/1,5-disubstituted or 1,4,5-trisubstituted 1,2,3-triazole scaffolds.[1] Their applications span from medicinal chemistry to materials science.[2] Straightforward access to this class of compounds is provided by versatile copper-, ruthenium-, and iridium-catalyzed azide–alkyne [3+2] cycloaddition reactions (CuAAC, RuAAC, and IrAAC), thanks to the seminal contributions by the groups of Meldal, Sharpless, Fokin, and others.[3] Alternative strategies, such as the strain-promoted azide–alkyne [3+2] cycloaddition reaction[4] developed by Bertozzi and co-workers and the Ramachary–Bressy–Wang enamine-mediated organocatalytic [3+2] cycloaddition of enolizable carbonyl compounds with azides, have also contributed significantly to the development of this area.[5] Among the existing strategies, organocatalytic methods have certain advantages over the respective metal-mediated versions as they are potentially greener, more sustainable and considered to be non-toxic towards biological systems. Recently developed organocatalytic azide–carbonyl [3+2] cycloadditions will be discussed in this Highlight.

In continuation of their earlier studies on the organocatalytic synthesis of highly functionalized N*H*-1,2,3-triazoles[5a] and benzotriazoles[5g] via the intermediacy of push–pull dienamines, Ramachary and co-workers described an efficient organo-click reaction of enolizable aldehydes that proceeds through the reaction of an in situ generated enolate with aryl azides under DBU catalysis (Scheme 1).[6] Whereas the organo-click reaction of azides with aldehydes and activated methylene compounds via preformed enolates has been extensively studied,[5] the current method constitutes an unprecedented example of an organo-click reaction of enolates that are generated in situ in a catalytic fashion. An attractive feature of this reaction is that it provides an alternative method to access 1,4-disubstituted 1,2,3-triazoles where metal-catalyzed or enamine-mediated click reactions either fail or provide the desired products in low yields. This diversity-oriented approach displays a high degree of flexibility with respect to variations of the aldehyde and azide coupling partners, and the nature of base and solvent was found to be crucial for the effectiveness of the reaction.



Scheme 1. Recently developed methods for triazole synthesis.

Dehaen and co-workers independently described an efficient approach for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles through a metal-free three-component reaction (Scheme 2).[7] Strikingly, the olefin components were accessed in situ through an organocatalytic Knoevenagel condensation between aldehydes and nitroalkanes and subsequently underwent a thermal [3+2] azide–olefin cycloaddition, which was followed by aromatization through the spontaneous loss of HNO_2. A wide range of aliphatic and aromatic aldehydes, azides, and nitroalkanes were suitable substrates for this multicomponent reaction. This method thus provides a rapid entry to diversely functionalized 1,2,3-triazoles. However, the elevated reaction temperatures can be a concern because of the sensitivity of the azides towards high temperatures and might also be a reason for the lower yields that were observed with some substrates. Nevertheless, the generality of Dehaen's highly regioselective, diversity-oriented multicomponent approach was validated by the synthesis of some

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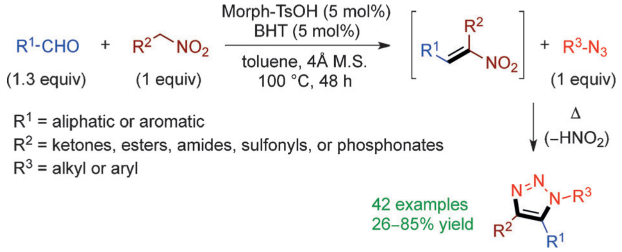
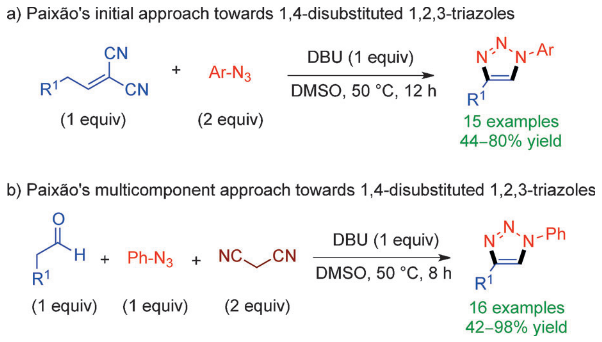


Scheme 2. Dehaen's one-pot organocatalytic Knoevenagel condensation followed by a Huisgen cycloaddition. BHT = 2,6-di-*tert*-butyl-4-methylphenol, Morph-TsOH = morpholinium *para*-toluenesulfonate, M.S. = molecular sieves.

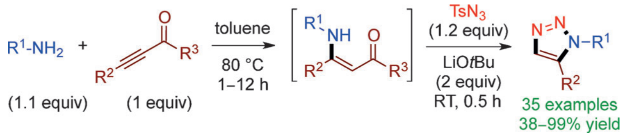
complex molecules, including a novel 1,2,3-triazole fused to a six-membered lactone, a tetraarylporphyrin functionalized with four fully substituted 1,2,3-triazoles, and coumarin-fused triazole derivatives.

Subsequently, Paixão and co-workers described a base-mediated strategy for the synthesis of 1,4-disubstituted 1,2,3-triazoles by an inverse-electron-demand 1,3-dipolar cycloaddition between aryl azides and preformed alkylidene malononitriles. The strategy was eventually modified to a one-pot multicomponent reaction between aldehydes, azides, and malononitrile in the presence of base (Scheme 3).[8] Surprisingly, a catalytic amount of malononitrile drives the reaction, but the question remains whether DBU, especially as it is present in stoichiometric amounts, is capable of catalyzing a background reaction, a process that can be independent of malononitrile, as in Ramachary's DBU-catalyzed enolate-mediated triazole synthesis. The regioselectivity that was observed in this operationally straightforward and efficient one-pot process could be explained by applying the general distortion/interaction theory put forward by Houk and Ess.[9]



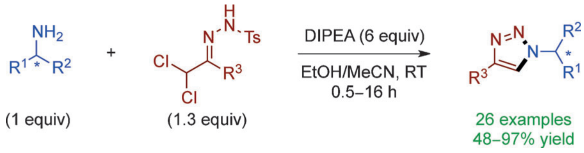
Scheme 3. Paixão's base-mediated one-pot construction of 1,4-disubstituted 1,2,3-triazoles. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

In contrast, Cui and co-workers developed an impressive enol-mediated metal-free regiospecific alternative for the synthesis of 1,5-disubstituted 1,2,3-triazoles by means of a three-component reaction that is based on an unprecedented cascade process that features a Michael addition, deacylative diazo transfer, and a cyclization reaction of primary amines, propynones, and sulfonyl azides (Scheme 4).[10] Although the atom economy is compromised, Cui's method nevertheless represents a novel regiospecific approach for the synthesis of 1,5-disubstituted 1,2,3-triazoles. An obvious advantage of multicomponent strategies is the rapid accumulation of combinatorial compound libraries for subsequent applications. As this protocol provides access to chiral triazoles from unmodified α-chiral amines, which are abundant in biological systems, this method may find applications not only in synthetic chemistry, but also in chemical biology.



Scheme 4. Cui's enolate-mediated multicomponent cascade approach towards 1,5-disubstituted 1,2,3-triazoles. Ts = *para*-toluenesulfonyl.

Towards the development of metal- and azide-free transformations for the highly regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles, Westermann[11] and co-workers revisited Sakai's triazole formation reaction[12] and successfully demonstrated its versatility in the facile generation of pharmaceutically important triazoles. Furthermore, they elegantly applied this strategy for previously unexplored modifications of biologically relevant targets (Scheme 5). A striking feature of Westermann's strategy is that chiral primary amines, which are inherent in biological systems, numerous natural products, and pharmaceuticals, can be modified with functionalized α,α-dichlorotosylhydrazones in a protecting-group-free and racemization-free manner.



Scheme 5. Westermann's metal- and azide-free approach towards 1,4-disubstituted 1,2,3-triazoles. DIPEA = diisopropylethylamine.

In this Highlight, recent advances in the development of organocatalytic and metal-free enamine/enolate-mediated azide–carbonyl [3+2] cycloaddition reactions have been discussed.[13] These approaches not only avoid the necessity of a metal catalyst but also obviate the need for alkyne substrates. Owing to the ready availability of carbonyl compounds, these methods thus offer promising alternatives for the synthesis of 1,2,3-triazoles. Furthermore, these reactions also feature wide substrate scopes, often associated with excellent yields and very high degrees of regioselectivity.

Although the breadth of the recent developments in the metal-free synthesis of 1,2,3-triazoles is impressive, the development of more sustainable variants is still highly warranted as the click reaction has already found important applications in pharmacy and biology. The development of room-temperature reactions with reduced azide loadings could be of immense interest in industry. Azide-free variants will certainly have a significant impact, and greener, atom-economic variants with recoverable/recyclable catalytic systems are still to be developed. As the aforementioned methods provide a rapid entry to 1,4-disubstituted and 1,4,5-trisubstituted 1,2,3-triazoles, we expect that general organocatalytic/metal-free strategies for the synthesis of 1,5-disubstituted 1,2,3-triazoles will be reported in due course.

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