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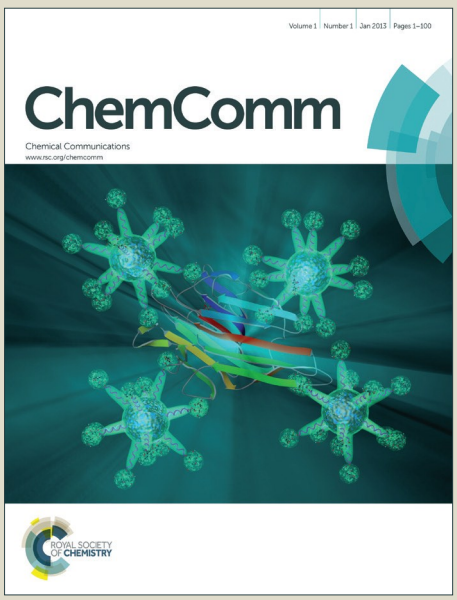

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A General Metal-Free Route Towards the Synthesis of 1,2,3-Triazoles From Readily Available Primary Amines and Ketones

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An unprecedented approach that enables the direct and selective preparation of 1,5-disubstituted 1,2,3-triazoles from abundantly available building blocks such as primary amines, enolizable ketones and 4-nitrophenyl azide as a renewable source of dinitrogen *via* an organocascade process has been developed. Furthermore, this efficient methodology also enables the synthesis of fully functionalized and fused N-substituted heterocycles.

In recent years, 1,2,3-triazole-containing molecules have received attention in diverse fields.[1] Currently, the most publicized ways to access 1,4- and 1,5-disubstituted 1,2,3-triazoles are the Cu- and Ru-catalyzed azide-alkyne cycloaddition reactions, respectively.[2] However, the limited access to terminal alkynes and the toxicity of the heavy metal catalysts hampers a wider exploration.[3] Several metal-free methods have been developed for the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles.[4] Nevertheless, selective pathways towards 1,5-disubstituted triazoles are rather scarce.[5] It is well documented that the *cis*-locked geometry present in 1,5-disubstituted triazoles could be an advantage to increase biological activity and binding affinity towards several biological targets.[6] Unfortunately, the lack of an efficient and very general synthetic route to achieve a diverse library of these isomers limits their applications in medicinal chemistry.[6c]

More recently, significant attention has been given to the preparation of diversely functionalized 1,2,3-triazoles *via* organocatalysis rather than metal catalyzed routes.[7-8] Unfortunately, the scope of these reactions is mostly limited to aromatic groups at the N1-position of the triazole heterocycles and extension to aliphatic substituents is cumbersome. Moreover, most transformations reported so far relied on organic azides that are mostly non-commercial and potentially hazardous. Other major limitations are the low substrate scope of the other component with reactivity limited mostly to activated carbonyl compounds. A very general and metal-free procedure to synthesize 1,5-disubstituted 1,2,3-triazoles is still lacking. Also, none of these methodologies have yet beenapplied to synthesize triazole derivatives of readily available natural products which could for instance facilitate structure activity relationship studies of bioactive/drug-like molecules.

In 1965, Pocar *et al.* described the reaction of an isolated imine/enamine (derived from acetone and propylamine) with 4-nitrophenyl azide (**3a**) which yielded 1-propyl-5-methyl-1,2,3-triazole in moderate yield.[9a] Surprisingly, this report remained virtually unnoticed, and no further attempts were made towards the further development of this protocol. One of the central challenges that could be associated with this method is the reversibility of the imine/enamine formation, hampering its isolation. This led us to the design of a multicomponent reaction starting from an enolizable ketone, primary amine and **3a**. We surmised that both the imine formation and the isomerization to enamine can be accelerated by a catalytic amount of an organic acid. The reaction would proceed *via* a sequence of, (a) Schiff base formation, (b) tautomerisation to the enamine, (c) 3+2 cycloaddition reaction with **3a**, and (d) aromatization with the loss of 4-nitroaniline (**5a**). Such a cascade process that combines multiple individual transformations in one operation is particularly attractive in triazole synthesis because isolation of the intermediate species, which may be difficult and time consuming especially when large collections of compounds are required, is avoided. Moreover, amines and ketones are inexpensive and abundantly present in biologically active natural products. Even more alluring is that this could lead to previously inaccessible 1,5-disubstitued 1,2,3-triazoles *via* a metal-free pathway.[7f-h]

In order to validate this synthetic design, we have chosen acetophenone (**1a**), 4-methoxybenzylamine (**2a**) and **3a** as model substrates. After some optimization (see supporting information), we found that the three-component reaction of **1a**, **2a** and **3a** in a respective molar ratio of 1:1.4:1 using 30 mol% of acetic acid as catalyst over 4 Å molecular sieves in 1M solution of toluene at 100°C were the reaction conditions of choice. The desired product **4a** was obtained after 12 h with an isolated yield of 93%. As expected, quantitative conversion of **3a** to **5a** was also observed. Importantly, this reaction also worked fine under acid free

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See

conditions without significantly affecting the yield of **4a** (85%) although the required reaction time was longer (24 h). To check the synthetic utility of the method at a larger scale, the optimized reaction was carried out on a five gram scale of **1a**. Indeed, the reaction proceeded efficiently and furnished the desired product in an undiminished yield of 88%. An even more interesting aspect of the bulk synthesis was the easiness of purification of **4a** in an atom economic way simply by the diazotization of the eliminated **5a** to its diazonium salt from the crude reaction mixture itself followed by its extraction to the aqueous layer and the pure product **4a** to the organic layer. Finally, treatment of the diazonium salt with NaN_3 lead to the regeneration of **3a** in high yield (82%), which could then be reused (Fig. 1).

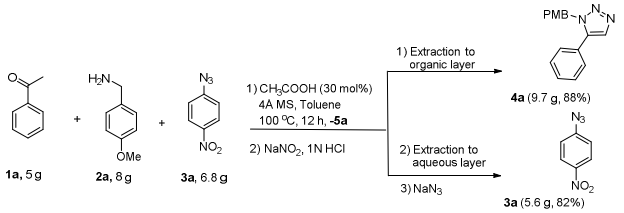


Figure 1. Bulk synthesis of 1,2,3-triazole **4a** and the regeneration of the 4-nitrophenyl azide **3a**. PMB= 4-methoxybenzyl.

We conducted several control experiments (see supporting information and Fig. 2) to understand the mechanism of the reaction. [9]

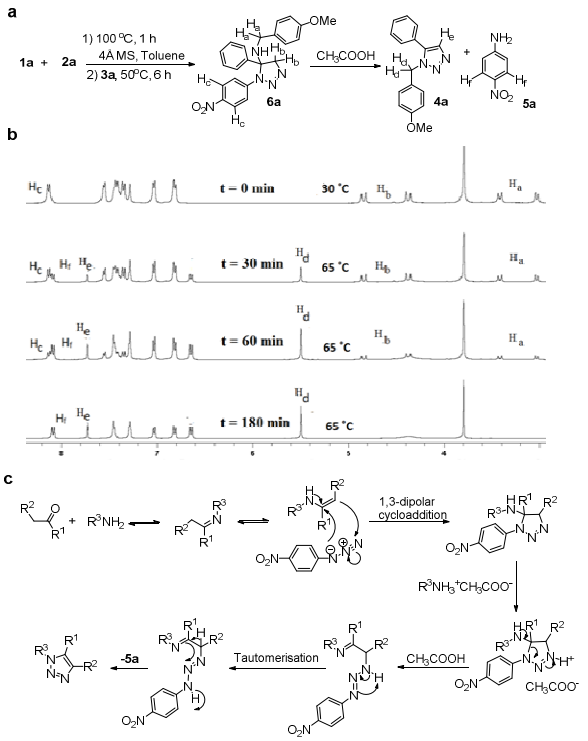
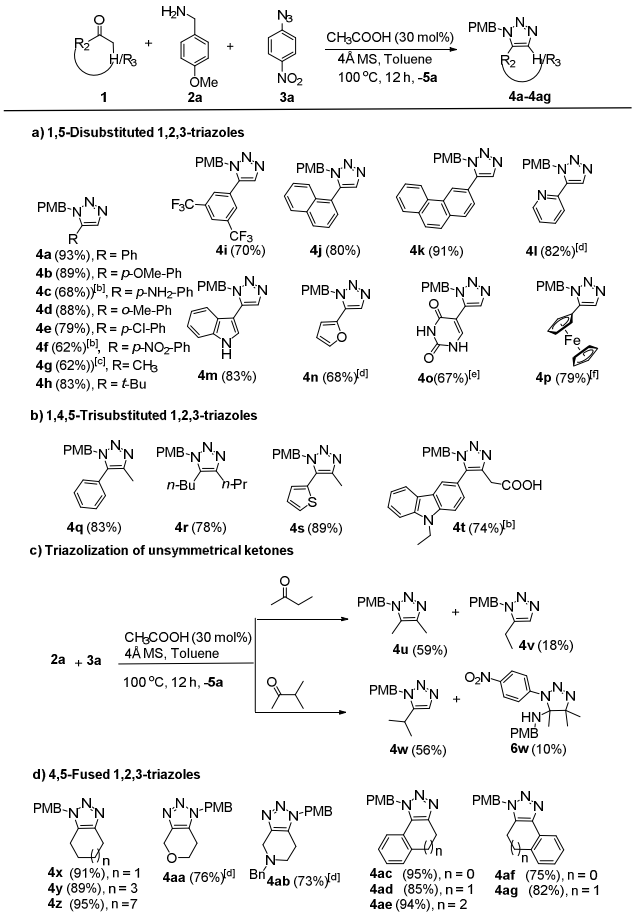


Figure 2. Proposed mechanistic experiments and catalytic cycles. [a] Scheme showing the synthesis of the triazoline intermediate **6a** and its conversion to **4a** and **5a**. [b] The ^{1}H NMR spectra showing the clean formation of the triazole **4a** and **5a** upon heating the triazoline intermediate **6a** in presence of 8 mol% of CH_3COOH in $CDCl_3$ at 65° C. [c] Postulated mechanism. $R^3NH_3^+CH_3COO^-$ indicates the *in situ* formation of the organic salt when CH_3COOH reacts with R^3NH_2.

With this newly developed metal-free three-component protocol we first set out to survey the scope and limitations of this methodology with a variety of aromatic and aliphatic enolizable ketones. Acetophenones with both electron-donating and electron-withdrawing groups smoothly underwent these transformations (**4a**-**4i**) (Table 1a). To our delight, various interesting heterocyclic moieties were amenable to the reaction providing access to triazole derivatives which are otherwise difficult to synthesize (**4l**-**4n**). The utility of this reaction was further demonstrated by the transformation of acetyl ferrocene and 6-acetyl uracil. It is worth mentioning that these reactions failed under an acidic environment but fortunately under acid-free conditions the expected products **4o** and **4p** were obtained in good yields.

Table 1. Scope with respect to the ketones.[a]



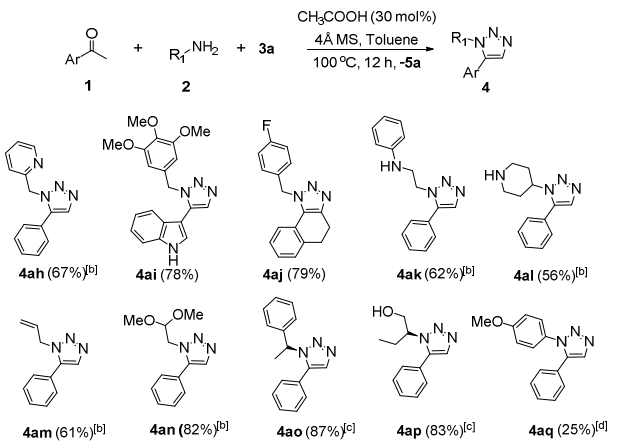
[a] Reaction conditions: **1** (1.0 equiv.), **2a** (1.3 equiv.), **3a** (1.0 equiv.), CH_3COOH (30 mol%), toluene (0.4 mL), 100 °C, 12 h, Isolated yield. [b] 40 h. [c] 3.0 equivalents of **1g**. [d] CH_3COOH (0 mol%), 24 h. [e] CH_3COOH (0 mol%), DMF (0.6 mL), 12 h. [f] Reaction Conditions: **1p** (1.0 equiv.), **2a** (2.8 equiv.), **3a** (2.0 equiv.), toluene (1.5 mL), 100 °C, 72 h. [e] 24 h.

Next, we investigated the scope of this reaction towards the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles (Table 1b). For instance, aryl or alkyl ketone precursors such as aryl propanones or 5-nonanone lead to the expected trisubstituted triazoles in

excellent yield (**4q**-**4t**). However, the extension of this reaction to activated methylene ketones such as ethyl benzoylacetate leads to the well-known Dimroth product formed by the 3+2 cycloaddition of **3a** with either the enolate or enamine intermediate.[10] An initial investigation with an unsymmetrical ketone, for example 2-butanone, gave mostly the expected product **4u** together with a noticeable amount of 18% of the other regioisomer **4v** (Table 1c). In light of these results, we reasoned that during the course of the reaction an equilibrium mixture of the two enamines will form and the composition of this is in favor of the most substituted enamine. This eventually gives **4u** as the major isomer. On the other hand, the ease of attack onto the less hindered enamine leads to a minor amount of the kinetic product **4v**. Interestingly, methyl isopropyl ketone led to 10% of the stable triazoline intermediate **6w** derived from the more substituted enamine together with 56% of the kinetic product **4w**. We then examined the scope of this reaction with respect to different cyclic ketones (Table 1d). The synthesis of N1-alkyl derivatives of carbo- as well as O- and N-heterocyclic fused triazole derivatives is scarcely reported (**4x**-**4ab**). Additionally, different aromatic bicyclic ketones were also compatible with the reaction (**4ac-4ag**). The high regioselectivity obtained with 2-tetralone shows that cycloaddition occurs with the most stable enamine, thus yielding **4ag** as the sole product.

In a next series of experiments the substitution pattern in the amine part was varied (**4ah-4aq**). More importantly, substrates bearing unprotected secondary amines such as **4ak** and **4al** could be effectively transformed using the current conditions. Remarkable functional group tolerance was observed in the case of allyl amine and 2,2-dimethoxyethylamine where the alkene and acetal functionalities remained intact under acid-free conditions (**4am**&**4an**). This elegant strategy was also applied to synthesize chiral-unit-containing triazoles by using different chiral amines (**4ao**&**4ap**). As expected, the extension of our protocol to aromatic amines gave a dissatisfactory yield of only 25% (**4aq**) caused by the lower reactivity of the intermediate enamines. However, the N-aryl triazoles are easily obtained by other methods. [5,7-8]

Table 2. Scope with respect to the amines.[a]



[a] Reaction conditions: **1** (1.0 equiv.), **2a** (1.3 equiv.), **3a** (1.0 equiv.), CH_3COOH (30 mol%), toluene (0.4 mL), 100 °C, 12 h, Isolated yield. [b] CH_3COOH (0 mol%), 24 h. [c] 48 h, CH_3COOH (30 mol%). [d] 48 h.

To demonstrate the utility of this reaction in material science, novel oligotriazole derivatives **7**&**8** derived from bi/tri-acetyl compounds could be generated in good yields after multiple MCRs without being affected by any steric hindrance (Fig. 3). Polymeric or dendritic triazole materials are of current interest.[1] The need for building blocks having multiple azide groups may be a limiting factor since they are potentially shock-sensitive compounds.[11] We surmised that the present approach is a safer alternative. Accordingly, readily available tris(2-aminoethyl)amine was subjected to reaction conditions to afford the C3-symmetric derivative **9** in good yield. To further demonstrate the utility of this approach to dendrimer chemistry, the modification of the 2nd generation dendron **10** with cyclohexanone was considered. Clean conversion to a monodisperse fused polytriazole amine **11** in reasonable yield was observed.

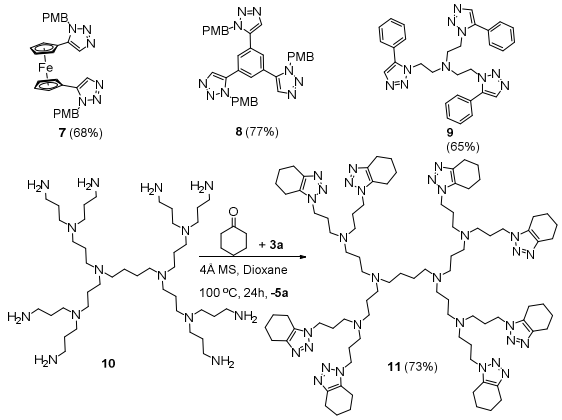
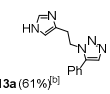
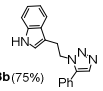
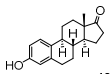
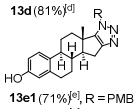
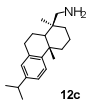
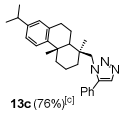
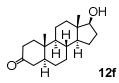
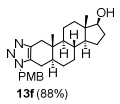


Figure 3. Substrate scope of the various multifunctional building blocks.

To fully exploit the versatility of this MCR, bioactive natural products containing functional groups such as primary amines and enolizable ketones were investigated to access novel and unique triazole-containing natural products which are expected to enable SAR studies facilitating subsequent drug developments for human diseases (Table 3). The application of the triazolation condition to the histamine **12a** and tryptamine **12b** led to the expected 1,5-disubstituted 1,2,3-triazoles in reasonable yields (**13a** and **13b**). Leelamine **12c** (an optically active diterpene amine which binds weakly to human cannabinoid receptors) was also structurally modified to new triazole entities **13c**.[12] Addtionally sphingoid base, phytosphingosine **12d** was easily modified to non-hydrolysable ceramide analogue **13d** (amide bond of ceramide was replaced by bioisosteric 1,2,3-triazole functionality) in a single step without doing a laborious protection/deprotection strategy.[13] Several D-ring tethered heterocyclic compounds of estrone **12e** were identified as useful templates for the design of inhibitors of steroidogenic enzymes such as 17β-hydroxysteroid dehydrogenases.[14] This

inspired us to synthesize estrone 16,17-fused 1,2,3-triazole derivatives **13e1** and **13e2** *via* this strategy using slightly modified reaction circumstances to surpass the steric effects of the reactants. As expected, the less sterically hindered butylamine gave a better conversion as compared to **2a**. The male hormone analogue, dihydrotestosterone **12f** gave excellent regio-selective triazolization on the A-ring leading to **13f** as a single product in 88% isolated yield.

Table 3. Scope with respect to the natural products.[a]

Natural product	Derivatives	Natural product	Derivatives
 **12a**	 **13a** (61%)[b]	 **12d**	 **13d** (81%)[d]
 **12b**	 **13b** (75%)	 **12e**	 **13e1** (71%)[e], R = PMB **13e2** (88%)[e], R = *n*-Bu
 **12c**	 **13c** (76%)[c]	 **12f**	 **13f** (88%)

[a] Reaction Conditions: **1**or **12** (1.0 equiv.), **12** or **2a** (1.3 equiv.), **3a** (1.0 equiv.), CH_3COOH (30 mol%), toluene (0.4 mL), 100 °C, 12 h, Isolated yield. [b] CH_3COOH (0 mol%), 24 h. [c] 48 h. [d] CH_3COOH (0 mol%), 48h. [e] **12** (1 equiv.), **2** (2.8 equiv.), **3a** (2.0 equiv.), CH_3COOH (30 mol%), toluene (1 mL), 100 °C, 72 h.

In conclusion, we have developed a universal approach to access 1,2,3-triazole derivatives in a single step from simple and readily available enolizable carbonyl compounds and amines which could be considered not as the end point, but as the initial point for the rapid generation of complex triazole derivatives that are inaccessible by other means. In contrast to other well-established 1,5- or fused triazole syntheses where different organic azides that are non-commercial and potentially dangerous are used to bring diversity, this strategy makes use of a readily available organic azide (**3a**) and readily available aliphatic amines as the sources of nitrogen of the triazole heterocycles. We successfully illustrated the utility of this reaction in natural products by systematically transforming them into diverse triazole derivatives. The fifty-five examples of this unprecedented triazole synthesis show the scope and limitations of this strategy.

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