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Heterocyclic Synthesis

Metal-Free Route for the Synthesis of 4-Acyl-1,2,3-Triazoles from Readily Available Building Blocks

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Abstract: Functionalized 1,2,3-triazole heterocycles have been known for a long time and hold an extraordinary potential in diverse research areas ranging from medicinal chemistry to material science. However, the scope of therapeutically important 1-substituted 4-acyl-1H-1,2,3-triazoles is much less explored, probably due to the lack of synthetic methodologies of good scope and practicality. Here, we describe a practical and efficient one-pot multicomponent reaction for the synthesis of α-ketotriazoles from readily available building blocks such as methyl ketones, *N*,*N*-dimethylformamide dimethyl acetal, and organic azides with 100% regioselectivity. This reaction is enabled by the in situ formation of an enaminone intermediate followed by its 1,3-dipolar cycloaddition reaction with an organic azide. We effectively utilized the developed strategy for the derivatization of various heterocycles and natural products, a protocol which is difficult or impossible to realize by other means.

In the last decade, 1,2,3-triazole heterocycles have found wide applications in almost every area of chemistry.[1] One of the most popular reactions commonly used for the synthesis of triazole heterocycles is the copper(I)-catalyzed azide-alkyne [3+2] cycloaddition (CuAAC) reaction, often referred to as the premier example of click chemistry.[2] Recently, several metal-free strategies have emerged as an alternative synthetic approach.[3] Among these, organocatalytic cycloaddition reactions of azides with enolizable ketones or aldehydes via an enolate, enamine, or iminium ion intermediate have recently received wide attention.[4] Very recently, our group designed two general and powerful strategies to synthesize triazole heterocycles.[5] The first method involves an organocatalytic three-component reaction for synthesizing fully functionalized triazoles from aldehydes, organic azides, and nitroalkanes,[5a,b] whereas the second approach involves a metal-free route towards the synthesis of fully functionalized or 1,5-disubstituted 1,2,3-triazoles from primary amines, ketones, and 4-nitrophenyl azide as a renewable source of dinitrogen through an organocascade process.[5c]

In the context of this program to develop new synthetic protocols towards 1,2,3-triazole skeletons having medicinal and supramolecular characteristics, we thought of synthesizing 1-substituted 4-acyl-1H-1,2,3-triazoles, for which the synthetic pathways are poorly represented in the literature.[6] It is well documented that α-ketotriazole building blocks display various interesting biological properties (Figure 1).[7] Recently, these compounds have been employed as hybridization probes for applications in nucleic acid chemistry, such as the development of triazole-linked DNA.[7f]

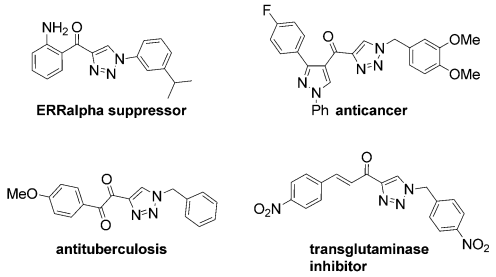

Figure 1. Illustration of pharmaceutically active 4-acyl-1H-1,2,3-triazoles.[7]

Generally, the synthesis of these triazoles involves a CuAAC reaction of different dipolarophiles, either acetylenic carbinols, followed by the oxidation of the 1,2,3-triazolic intermediate,[6e] or via unstable ynones.[6,7] The synthesis of these dipolarophiles may require multiple steps, a large amount of reagents, and expensive metal-catalyzed reactions, all of which may be a limiting factor especially when diverse and large collections of compounds are required (Figure 2). Given the increasing demand for novel α-ketotriazole-based entities in current synthesis, general reactions that allow easy access to a large library of these compounds are of significant interest.

A solution to overcome these drawbacks has emerged from the realization that enaminones can be considered as a synthetic equivalent to ynones.[8] We envisioned that enaminone dipolarophiles prepared in situ by a condensation reaction of the corresponding enolizable ketones, containing three α-hydrogens, with *N*,*N*-dimethylformamide dimethyl acetal (DMF dimethyl acetal, **2**),[9] may undergo a regioselective enamine-mediated cycloaddition reaction with organic azides. Aromati-

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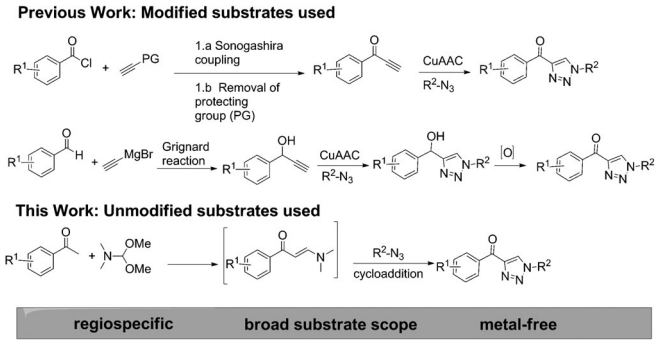
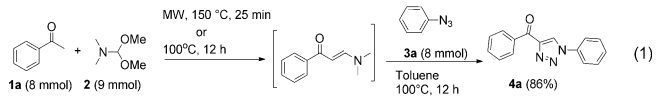


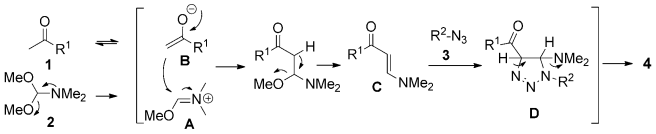
Figure 2. Summary of previous[6,7] and present work.

zation by spontaneous elimination of dimethylamine eventually results in the assembly of the α-ketotriazoles. Obviously, this approach features significant advantages: 1) the use of readily available building blocks such as methyl ketones is appealing because they are inexpensive (the price of acetophenone and *N*,*N*-dimethylformamide dimethyl acetal combined is 225 times lower than the price of analogous 1-phenyl-2-propyn-1-one) and abundantly present in biologically active natural products, 2) metal-free synthesis and 3) the rapid and convergent synthesis of triazole heterocycles without isolation of the intermediate species, which facilitates the structure–activity relationship studies of bioactive/drug-like molecules.

We decided to use readily available acetophenone **1a**, **2**, and phenyl azide **3a** as the model substrates for optimizing the reaction conditions (see Supporting Information). The optimized conditions involve the in situ synthesis of the enaminone intermediate from **1a** and **2** either by microwave (MW) irradiation at 150 °C over a period of 25 min, or by conventional heating (Δ) at 100 °C over a period of 12 h in a sealed tube. This is followed by the addition of one equivalent of phenyl azide **3a** in toluene and continued heating at 100 °C over a period of 12 h. These optimized conditions allowed for compound **4a** to be isolated with a yield of 86% and 100% regioselectivity (Reaction 1). On a preparative scale (17 mmol), it was possible to achieve **4a** using only conventional heating conditions. We started the reaction with 2 g of **1a**, and produced 3.4 g of **4a** in a comparable yield of 82%.



A possible reaction mechanism is depicted in Scheme 1. In the first step, a molecule of methoxide is expelled from **2**, giving rise to the iminium ion **A**. The enolate **B**, which is formed after deprotonation of **1**, can attack the iminium carbon of **A** to generate the enaminone **C** after the loss of another molecule of methanol.[9] This enaminone species acts as the electron-rich olefinic partner in the reaction with the azide dipole **3** by an inverse-electron-demand [3+2] cycloaddition process with complete regioselectivity, to form **4**. The aromatization of the triazoline intermediate **D** through a *syn*-elimination of dimethylamine is the plausible driving force for the final step. Based on this postulated reaction mechanism, the rate of the 1,3-dipolar cycloaddition reaction is strongly dependent on the electronic nature of the dipole and the dipolarophile. For instance, increasing the electron-donating character of enaminone and the electron-withdrawing character of azide will lower the $HOMO_{dipolarophile}$–$LUMO_{dipole}$ gap, which in turn increases the reaction rate and vice versa.[10]

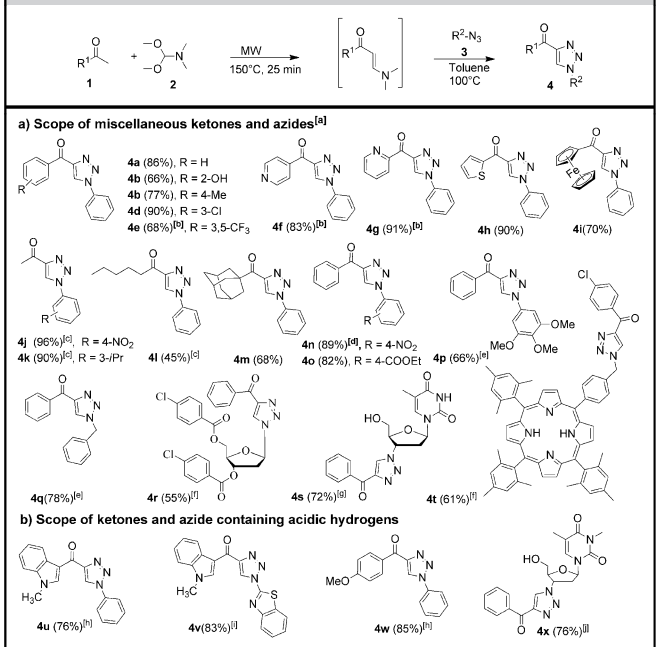


Scheme 1. Proposed reaction mechanism.

With this optimized reaction in hand, we first explored the generality of this protocol to a variety of acetophenones having both electron-donating and electron-withdrawing groups (Table 1, **4a**–**4e**). Very interestingly, the library was further extended to triazoles containing heterocyclic moieties such as pyridines (**4f** and **4g**) and thiophene **4h** in excellent yields. To our delight, the transformation of acetylferrocene to 4-ferrocenoyl-decorated 1,2,3-triazole **4i** occurred in good yield, providing access to triazole derivatives that are otherwise difficult to synthesize. However, the reaction with aliphatic methyl ketones, such as acetone, resulted in a diminished yield under the optimized reaction conditions. A possible explanation is undesirable aldol condensation during the microwave irradiation with **2**. Fortunately, by using an excess of acetone (three equivalents), the expected 4-acetyl-triazoles **4j** and **4k** were obtained with excellent yields. Under similar circumstances, an unsymmetrical ketone, such as 2-heptanone, only gave 45% of the product **4l**. In the light of this result, we reasoned that a competition exists between the two possible places for enaminone formation, where only the less substituted enaminone will give the anticipated product. We were pleased to find that 1-adamantyl methyl ketone also delivered the corresponding triazole **4m** in a good yield of 68%.

Next, a variety of aromatic and aliphatic azides could be converted to the corresponding triazoles in moderate to high yields ((Table 1, **4n**–**4q**). Generally, in contrast to the acetylenic carbinol and the ynone pathways,[6–8] aryl azides bearing electron-withdrawing functional groups exhibit higher reaction rates and yields when compared to aliphatic and electron-donating aromatic azides. Interestingly, a protected sugar bearing sterically demanding secondary azide could be effectively transformed into its triazole analogue **4r** using the current conditions. Moreover, applicability of this synthetic methodology to the conversion of azidothymidine (AZT, an antiretroviral medication used to prevent and treat HIV/AIDS) to the corresponding 4-acyl-1,2,3-triazole **4s** was demonstrated with an isolated yield of 72%.[11a] Worth noting is that a metal-free tetraarylporphyrin functionalized with 4-acyl-triazole **4t** was synthesized in 61% yield with this protocol, whereas applying the

Table 1. Generality of triazole synthesis.[a]

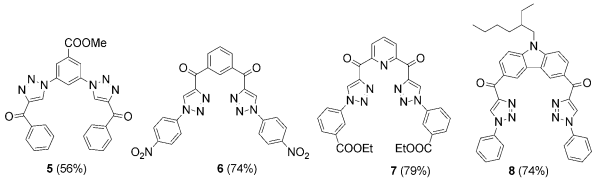


[a] Reaction conditions: **1** (1.0 equiv), **2** (1.2 equiv), **3** (1.0 equiv), MW, 150 °C, 25 min and Δ, 100 °C, 12 h; isolated yields provided. [b] Δ, 100 °C, 24 h. [c] 3.0 equiv of **1**. [d] Δ, 100 °C, 2 h. [e] Δ, 100 °C, 48 h. [f] Δ, 100 °C, 72 h. [g] DMF, Δ, 100 °C, 72 h. [h] **2** (2.4 equiv), Δ, 100 °C, 12 h. [i] **2** (2.4 equiv), Δ, 100 °C, 6 h. [j] **2** (2.4 equiv), DMF, Δ,100 °C, 72 h.

CuAAC reaction would have led to undesired Cu^{II}-metalated porphyrinate.[11d]

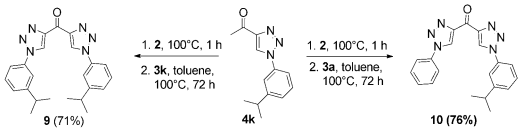
We further examined the scope of the reaction with respect to ketones containing acidic hydrogens. Surprisingly, subjecting the substrate 3-acetylindole **1u** to the standard reaction conditions resulted in an unexpected methylation of indole that eventually leads to the triazole derivative **4u** in 43% yield together with 48% of unreacted starting material. We speculate that the methylating agent could be the intermediate **A** (Scheme 1) formed from **2** under the reaction circumstances, and the presence of the unreacted starting material indicates that the alkylation occurs only after the enaminone formation. When the reaction was repeated with excess of **2**, the yield of **4u** was improved to 76%. Similarly, 4-hydroxyacetophenone led to the expected methoxy analogue **4w**. Also, repeating the reaction with AZT but with an excess of **2** led to the methylated thymidine nucleoside (**4x**). It is interesting to note that the alkylation does not occur in the case of the enaminone intermediate derived from 2-hydroxyacetophenone **1b** (**4b**, Table 1). This can be explained by considering the difficulty in abstracting the proton of the aromatic OH group due to the strong intramolecular H-bonding with the neighboring oxygen atom of the oxo functionality.[9b]

By using a bifunctional building block containing multiple-acetyl/azide functional groups, more than one triazole moiety can be incorporated in a single molecule. A possible application for these multicomponent reactions (MCRs) lies within the field of supramolecular chemistry.[12] For instance, different bond angles and the relatively acidic C-4 proton of the 4-benzoyl-substituted 1,2,3-triazole, when compared to its aryl-derivative, can give a different perspective towards the development of novel anion-binding receptors or metal chelators by the cooperative effect of having two or more of these triazole heterocycles within the same molecule.[12] As a proof of the synthetic viability, novel oligotriazole bidentate ligands **5**–**8** were obtained in good to acceptable yields from readily available starting materials in a single step (Reaction 2). A preliminary investigation of the pentad receptor **5** towards the affinity of anions using ^{1}H NMR spectroscopic studies indicates that it can bind chloride anion due to the cumulative binding effects of the triazole CHs and the benzene CHs (see Supporting Information). An upcoming study will focus on the supramolecular anion-binding properties and solid-state features of these materials. The pyridoyl derivative **7** can be considered as an analogue of the well-known ligand [2,6-bis(1,2,3-triazol-4-yl)pyridine] (BTP), which has been extensively studied as a complexing agent for several applications in coordination chemistry.[12b]



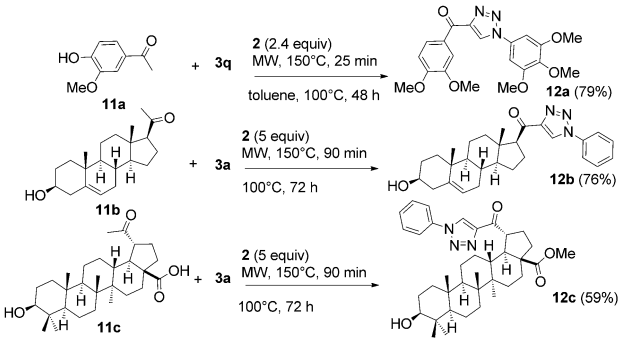
(2)

The versatility of this methodology was further exemplified by synthesizing previously inaccessible symmetrical and asymmetrical diphenylditriazole ketones **9** and **10** starting from the acyl-triazole **4k** in reasonable yields (Reaction 3). It is worth mentioning that this class of unique triazole skeletons cannot be easily accessed by existing methods, which highlights the synthetic utility of this approach.



(3)

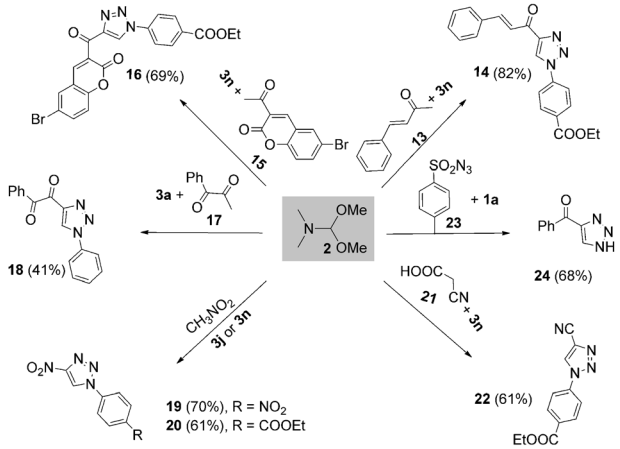
Encouraged by the broad applicability of this methodology, we further targeted the transformation of bioactive natural products, containing an acetyl functional group, to the corresponding α-ketotriazole derivatives, which could for instance facilitate the structure–activity relationship studies of bioactive/drug-like molecules (Scheme 2). Accordingly, triazolization of acetovanillone with an excess of **2** led to the corresponding 1,2,3-combretatriazole derivative **12a** after the methylation of the hydroxyl group.[7g] Applying this approach to the neuroactive endogenous steroid hormone, pregnenolone **11b**, provided the expected product **12b** furnished with an α-ketotriazole heterocycle in 76% yield[11c] Platanic acid **11c** is a naturally occurring pentacyclic triterpenoid and has gained much attention in natural product chemistry because of its potent anti-HIV activity. However, 1,2,3-triazole derivatives of these triterpe-



Scheme 2. Scope with respect to the natural products.

noids have not been investigated to date. Application of this synthetic methodology to platanic acid delivered the methyl ester of the expected product **12 c** in good yield.[11b]

Given the success of this reaction for the synthesis of α-ketotriazoles, the generality of this protocol was further tested. The application of this strategy to the α,β-unsaturated ketone **13** led to the synthesis of a chalcone derivative **14** with excellent yield (Scheme 3). These classes of compounds were shown to have reversible tissue transglutaminase inhibitor activity and are usually synthesized using a multistep strategy.[7f] Interestingly, the reaction also worked well with 3-acetylcoumarin **15**, which afforded the useful material **16**. 1-Phenyl-propane-1,2-dione **17** was also successfully employed in this reaction for the synthesis of α,β-diketotriazole **18**, albeit in slightly lower yield. Previously, this class of compounds was obtained in a multi-step procedure by the catalytic oxidation of α-ketotriazole, which was synthesized by an ynone-mediated cycloaddition reaction.[6d] It is worth mentioning that in the case of the activated ketones depicted in Scheme 3, conventional heating gave better results for the generation of the respective enaminone intermediate than the microwave conditions. Next, we investigated the scope of this reaction towards the synthesis of 4-nitro-substituted 1,2,3-triazoles **19** and **20** from nitromethane, which involved in situ generation of 1-(dimethylamino)-2-nitroethylene and its subsequent cycloaddition reaction with an organic azide, followed by the elimination of dimethyl amine instead of HNO_2. We then examined the possibility to employ cyanoacetic acid as one of the starting materials to develop a general method to synthesize 1,4-disubstituted 4-cyano-1,2,3-triazole **22** by in situ generation of the corresponding enaminone intermediate proceeding through a decarboxylative pathway.[9a] We envisioned that the latter two examples have a broad substrate scope and can be used as synthetic precursors for the construction of various amino-1,2,3-triazoles. The versatility of these MCRs was further demonstrated by synthesizing 4-benzoyl-1,2,3-(NH)-triazole **24** by using tosyl azide **23** as nitrogen source.[8b] The final step of this reaction was the elimination of *N*,*N*-dimethyl-*p*-toluenesulfonamide. These examples once again demonstrate the tolerance of this method towards various reactive substrates for the generation of triazole heterocycles decorated with sensitive functional groups that are otherwise difficult to synthesize or not even accessible by other methods.



Scheme 3. Miscellaneous multicomponent reactions.

To summarize, we have developed a straightforward and practical way to access 1,4-disubstitued 4-acyl-1,2,3-triazoles from readily available building blocks such as ketones, DMF acetal, and organic azides using a one-pot MCR. In contrast to other methods, this elegant strategy offers an operationally simple single-step procedure, metal-free conditions, and demonstrates a broad substrate scope. We also established the importance of this reaction in various natural products. Furthermore, different bi- and tridentate ligands having supramolecular interest were also synthesized. Beyond the broad usefulness of this new strategy, the method also offers a new avenue for regiospecific installation of various delicate scaffolds and functional groups on triazole heterocycles with high efficiency. Altogether, we anticipate that the present work will provide a valuable route in the construction of medicinally important compounds as well as in the development of supramolecular functional systems.

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Keywords: cycloaddition · host–guest systems · metal-free · multicomponent reactions · triazoles

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COMMUNICATION

Heterocyclic Synthesis

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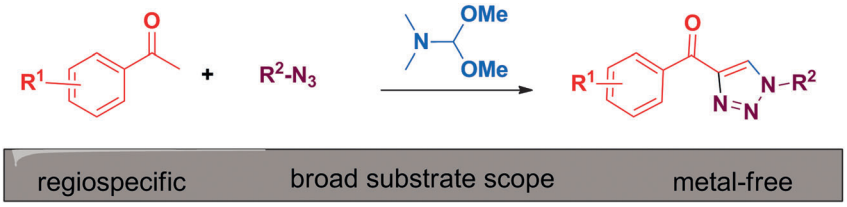
Metal-Free Route for the Synthesis of 4-Acyl-1,2,3-Triazoles from Readily Available Building Blocks



A metal-free route towards therapeutically important 1-substituted 4-acyl-1H-1,2,3-triazoles was accomplished using cheap and readily available ketones, *N*,*N*-dimethylformamide dimethyl acetal, and organic azides. This reaction is very general and was extended to the synthesis of various supramolecular receptors as well as to the functionalization of different natural products with α-ketotriazoles, all of which is otherwise not possible by known methods.