ACS ORGANIC & INORGANIC Au
AN OPEN ACCESS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY



pubs.acs.org/orginorgau
Article

# Direct Organocatalytic Chemoselective Synthesis of Pharmaceutically Active 1,2,3-Triazoles and 4,5′-Bitriazoles

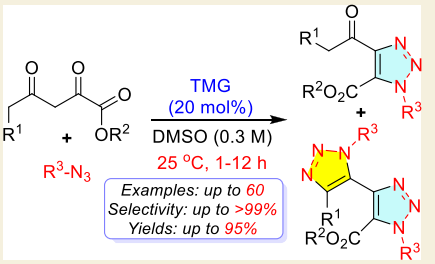
*Published as part of ACS Organic & Inorganic Au virtual special issue "Celebrating the 25th Anniversary of the Chemical Research Society of India".*

Badaraita Gorachand, Gundam Surendra Reddy, and Dhevalapally B. Ramachary*

Cite This: ACS Org. Inorg. Au 2024, 4, 534−544
Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

**ABSTRACT:** Carbonyl-containing 1,4,5-trisubstituted- and 1,4-disubstituted-1,2,3-triazoles are well-known for their wide range of applications in pharmaceutical and medicinal chemistry, but their high-yielding metal-free synthesis has always remained challenging, as no comprehensive protocol has been outlined to date. Owing to their structural and medicinal importance, herein, we synthesized various carbonyl-containing 1,4,5-trisubstituted- and 1,4-disubstituted-1,2,3-triazoles and unsymmetrical 4,5′-bitriazoles with high yields and chemo-/regioselectivity from the library of 2,4-diketoesters and azides in a sequential one-pot manner through the combination of organocatalytic enolization, in situ [3 + 2]-cycloaddition, and hydrolysis reactions. The commercial availability of the starting materials/catalysts, diverse substrate scope, performance in a one-pot manner, chemo-/regioselectivity of organo-click reaction, quick synthesis of unsymmetrical 4,5′-bitriazoles, a large number of synthetic applications, and numerous medicinal applications of carbonyl-containing 1,2,3-triazoles are the key attractions of this metal-free organo-click work.



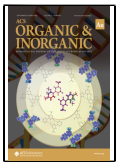

**KEYWORDS:** *azides, carbonyls, [3 + 2]-cycloaddition, organo-click, 1,2,3-triazoles, 4,5′-bitriazoles*

## INTRODUCTION

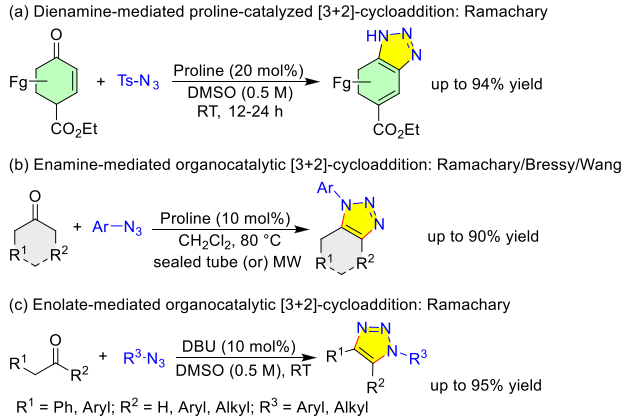
In recent years, chemists employed various strategies for the synthesis of functionalized 1,2,3-triazoles, as functionalized 1,2,3-triazoles found a wide range of applications in biological studies, therapeutic drug discovery, material chemistry, and agrochemical industry.[1−8] The thermally induced nonselective Huisgen azide−alkyne [3 + 2]-cycloaddition was transformed into the highly regiospecific 1,4-disubstituted-1,2,3-triazoles with high yields through the copper(I)-catalyzed azide−alkyne [3 + 2]-cycloaddition as click reaction by Sharpless and Meldal independently.[9−16] Apart from Cu-catalysis, azide−alkyne [3 + 2]-cycloadditions were also developed with ruthenium,[17−19] iridium,[20−22] nickel,[23−26] magnesium,[27] and also using strain-promoted[28−32] manner for the construction of functionalized 1,2,3-triazoles. Besides the transition metal-mediated azide−alkyne [3 + 2]-cycloaddition reaction for 1,2,3-triazoles synthesis, Ramachary, Bressy, Wang, Dehaen, Paixao, and other groups developed alternative green synthetic methods of azide-carbonyl [3 + 2]-cycloadditions employing a variety of amines as organocatalysts.[33−78]

In 2008, Ramachary and co-workers reported a proline-catalyzed [3 + 2]-cycloaddition reaction between Hagemann's ester derivatives and tosyl azide, which was the initial footstep toward the organocatalytic azide-carbonyl [3 + 2]-cycloaddition or organo-click reaction using a push−pull dienamine strategy.[33] Later in 2011, Wang and Bressy et al. reported independently an enamine-mediated [3 + 2]-cycloaddition for the synthesis of 1,2,3-triazoles using a variety of activated and unactivated cyclic and linear ketones with aryl azides (Scheme 1).[34−36] In 2014, enolate-mediated organocatalytic [3 + 2]-cycloaddition of a variety of activated carbonyls and aryl azides for the synthesis of 1,4,5-trisubstituted- and 1,4-disubstituted-1,2,3-triazoles was developed by Ramachary et al. (Scheme 1).[49−61] Previous studies showed that the alkyl trisubstituted 1,2,3-triazole systems have the least scope for further functional group modification because of the requirement of expensive reagents and harsh reaction conditions.[79−82] It is well-known that modification of the different substitutions on the 1,2,3-triazole system, by incorporation or removal of different functional groups, may work better, for a wider application in material, medicinal, and drug discoveries. It can be possible either by choosing functionalized starting materials or by further functionalization of the trisubstituted 1,2,3-triazoles by various reactions. Ester and carbonyl group-substituted 1,2,3-triazoles are the most fascinating scaffolds, as

Received: May 2, 2024
Revised: May 24, 2024
Accepted: May 24, 2024
Published: June 5, 2024



**Scheme 1. Previous Organocatalytic Azide-Carbonyl [3 + 2]-Cycloaddition Reactions**[a]




[a](a), (b), and (c) reproduced with permission from refs 33, 34, 49, and 50, respectively. Copyright 2008, 2011, 2014, and 2014 John Wiley & Sons, Inc.

the ester and the carbonyl groups can be converted very easily to other functional groups to produce biologically important molecules (Figure 1).[83−89] Despite a huge demand, there are

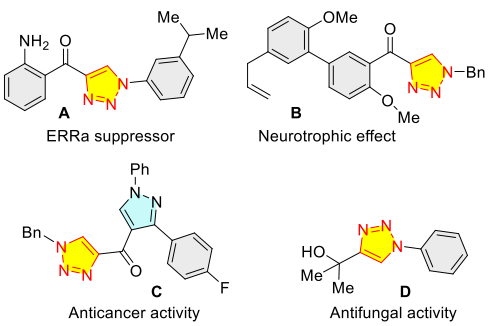



**Figure 1.** Biologically active carbonyl-containing 1,2,3-triazoles.

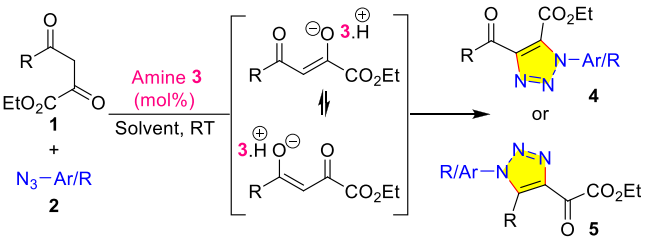
very less reports for the direct synthesis of acyl (ester and carbonyl)-substituted 1,2,3-triazoles through organocatalytic [3 + 2]-cycloaddition.[33−78] This may be due to an uncontrolled reactivity of the active methylene compound containing three carbonyl groups, which act as a potential synthon for 1,2,3-triazoles. To overcome the challenges and to understand the reactivity and regioselectivity of the unsymmetrical CH-acids containing three carbonyls toward [3 + 2]-cycloaddition with azides, we have designed/developed a suitable methodology to produce ester/ketone group-containing 1,4,5-trisubstituted-1,2,3-triazoles through 1,1,3,3-tetramethylguanidine (TMG)-catalyzed [3 + 2]-cycloaddition between the aryl/alkyl/vinyl azides and the 2,4-diketoesters at room temperature (Scheme 2).

## RESULTS AND DISCUSSION

### Reaction Optimization

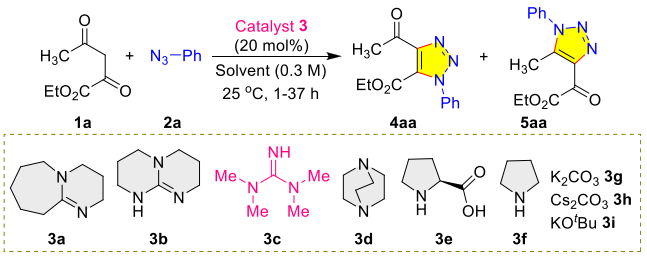
We started our optimization with the reaction between ethyl-2,4-dioxopentanoate **1a** (0.3 mmol) and 1.5 equiv of the phenyl azide **2a** in the presence of 20 mol % 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) **3a** as a catalyst/base in DMSO solvent at room temperature. Within 3 h, the reaction gave organo-click product 1,2,3-triazole **4aa** as a major product with 80% yield, and another click-product 1,2,3-

**Scheme 2. Reaction Design for the Chemoselective Organocatalytic Azide-Carbonyl [3 + 2]-Cycloaddition (OrgACC) Reaction**




triazole **5aa** was not observed (Table 1, entry 1). When the same organo-click reaction was carried out using a series of

**Table 1. Reaction Optimization for Chemoselective OrgAKC Reaction**[a]




| entry | catalyst 3 (20 mol %) | solvent (0.3 M) | T (h) | yield (%)[b] | ratio[c] (4/5) |
|---|---|---|---|---|---|
| 1 | **3a** | DMSO | 3 | 80 | >20:1 |
| 2 | **3b** | DMSO | 5 | 63 | >20:1 |
| 3 | **3c** | DMSO | 1 | 84 | >20:1 |
| 4 | **3d** | DMSO | 6 | 64 | >20:1 |
| 5 | **3e** | DMSO | 36 | 05 | >20:1 |
| 6 | **3f** | DMSO | 144 | 30 | >20:1 |
| 7 | **3g** | DMSO | 1.7 | 79 | >20:1 |
| 8 | **3h** | DMSO | 2 | 70 | >20:1 |
| 9 | **3i** | DMSO | 2 | 75 | >20:1 |
| 10[d] | **3a** | DMF | 37 | 50 | >20:1 |
| 11[d] | **3a** | $CHCl_3$ | 22 | 15 | >20:1 |
| 42[d] | **3a** | $CH_3CN$ | 37 | 15 | >20:1 |
| 13[e] | **3c** | DMSO | 1 | 71 | >20:1 |
| 14[f] | **3c** | DMSO | 2 | 64 | >20:1 |

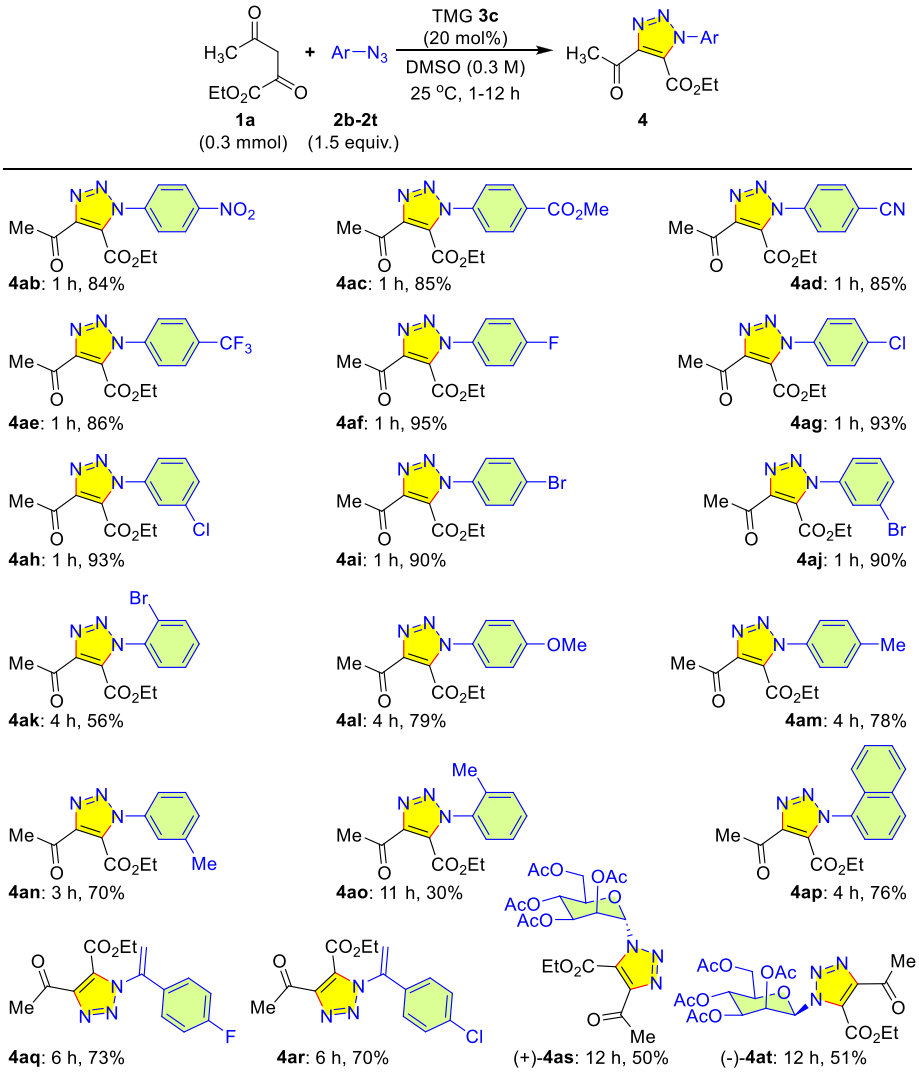
[a]Reaction was carried out in solvent (0.3 M) with **1a** (0.3 mmol), **2a** (1.5 equiv), and catalyst **3** (20 mol %). [b]Yield refers to the column-purified product. [c]Ratio of isomers **4aa**/**5aa** was determined by $^1$H NMR analysis of the crude reaction mixture. [d]Starting material **1a** was recovered in 50−70% yield. [e]Catalyst **3c** is used in 25 mol %. [f]Catalyst **3c** is used in 10 mol %.

different amine and base catalysts, like 20 mol % of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) **3b**, 1,1,3,3-tetramethylguanidine (TMG) **3c**, 1,4-diazabicyclo[2.2.2]octane (DABCO) **3d**, proline **3e**, pyrrolidine **3f**, $K_2CO_3$ **3g**, $Cs_2CO_3$ **3h**, and KO$^t$Bu **3i**, delightfully, we observed the slightly best yield with catalyst TMG **3c** affording 84% of only one 1,2,3-triazole **4aa** within 1 h (Table 1, entries 2−9). In the case of secondary amines, like proline **3e** and pyrrolidine **3f**, the yields of the organo-click product **4aa** were unexpectedly low (5 and 30%, respectively) with an unusually prolonged reaction time of 36 and 144 h, respectively (Table 1, entries 5 and 6).

This observation indicates that the in situ enolate chemistry was working faster than the enamine chemistry in our present


https://doi.org/10.1021/acsorginorgau.4c00032
ACS Org. Inorg. Au 2024, 4, 534−544

**Table 2. Reaction Scope with Different Azides for Chemoselective OrgAKC Reaction**[a,b]




[a]Reactions were carried out in DMSO (0.3 M) with 1.5 equiv of **2** relative to **1a** (0.3 mmol) in the presence of 20 mol % TMG **3c** at 25 °C. [b]Yield refers to the column-purified product.

protocol. After understanding the best catalyst relatively, we further moved on to screening different solvents like DMF, acetonitrile, and chloroform, but none of them performed better than DMSO (Table 1, entries 10−12) and in all the cases, the remaining starting material **1a** was recovered in a quantitative amount. Two more experiments were conducted to check the sensitivity and effectiveness of TMG **3c** via changing the catalytic loading from 20 mol % to 25 and 10 mol %, but no further improvement of yield was found (Table 1, entries 13 and 14). From the thorough investigation, we have concluded that ethyl-2,4-dioxopentanoate **1a** (0.3 mmol) and 1.5 equiv of the phenyl azide **2a** in the presence of 20 mol % TMG **3c** as a catalyst/base in DMSO at room temperature is the most favorable condition for the present chemoselective organo-click protocol (Table 1, entry 3).

## Reaction Scope with Different Azides

With the optimized conditions in hand, the scope of the aryl azides was investigated (Table 2). First, we decided to use aryl azides and vinyl azides, followed by sugar azides **2b−2t** in the **3c**-catalyzed organo-click reaction with **1a**. All of the electron-deficient aryl azides **2b−2e** reacted well with **1a**, within a short time of 1 h, forming the organo-click products **4ab−4ae**, with a very good yield of 84−86% (Table 2). The aryl azides **2f−2j**, substituted with halogens such as fluorine, chlorine, and bromine substituted at *para-*/*meta*-position on their phenyl ring, proceeded smoothly in this organo-click reaction to furnish 1,2,3-triazoles **4af−4aj** with an excellent yield of 90−95%, within 1 h (Table 2). With the bromine substitution at the *ortho*-position of the phenyl ring on the azide **2k**, the reaction furnished **4ak**, with a low yield of 56%, under a longer reaction time of 4 h, indicating a clear effect of increased steric factor (Table 2). The electron-rich *para*-methoxy substituted azide **2l**, afforded **4al**, with a yield of 79%, in 4 h (Table 2). When the substituent position varied from *para-*, *meta-* to *ortho*-methyl substituted aryl azides **2m−2o**, a clear effect of a steric factor was observed with a gradual decrement of the yields from 78% and 70 to 30% within 3, 4, and 11 h, respectively (Table 2). When, we explored the electron neutral 2-naphthyl azide **2p**, halogenated $\alpha$-azidostyrenes **2q** and **2r**, the reaction performed well, producing 1,2,3-triazoles **4ap**, **4aq**, and **4ar** in 76, 73, and 70% yield, respectively (Table 2). The $\alpha$-sugar azide **2s** and $\beta$-sugar azide **2t** also produced an


https://doi.org/10.1021/acsorginorgau.4c00032
ACS Org. Inorg. Au 2024, 4, 534−544

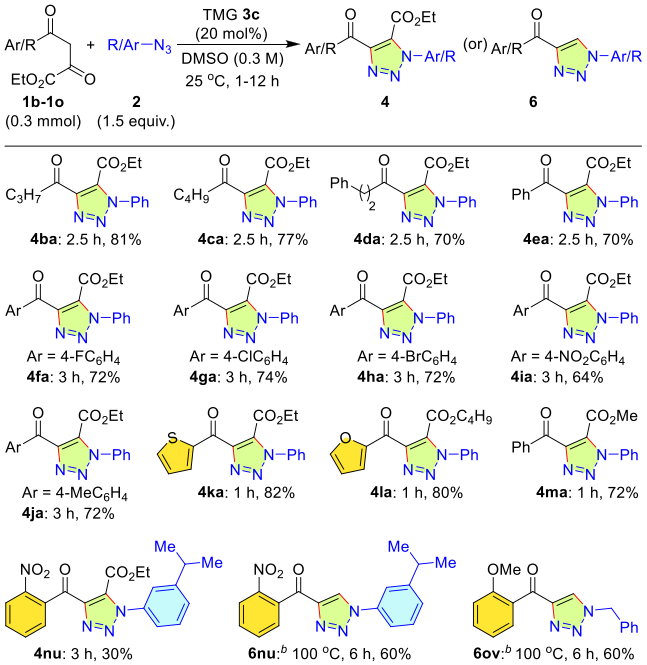
impressive yield of sugar substituted 1,2,3-triazoles (+)-**4as** and (−)-**4at** in 51 and 50% yield, respectively, within 12 h (Table 2). These results highlight the importance of TMG **3c**-catalyzed regio-/chemoselective azide-carbonyl [3 + 2]-cycloaddition for the synthesis of carbonyl-containing 1,2,3-triazoles **4ab**−**4at** in a short period of time with high yields under the ambient conditions (Table 2).

## Reaction Scope with Different 2,4-Diketoesters

After having a thorough investigation of organo-click reaction with different azides **2**, we further examined the scope of organo-click reaction with different substituted 2,4-diketoesters **1b**−**1o** (Table 3). When the alkyl-substituted 2,4-diketoesters **1m** were utilized in our present protocol to furnish the **4ka**, **4la**, and **4ma** in good yields of 82, 80 and 72%, respectively, within 1 h (Table 3). Applications in mind (see Figure 1), when the *o*-nitro substituted phenyl ring containing 2,4-dieketoester **1n** was treated with the 1.5 equiv of electron-rich *meta*-$^{i}$Pr substituted aryl azide **2u**, the [3 + 2]-cycloaddition reaction afforded the 1,4,5-trisubstituted 1,2,3-triazole **4nu** with only 30% yield in DMSO solvent within 3 h (Table 3). Fascinatingly, the [3 + 2]-cycloaddition reactions using $K_2CO_3$ as the catalyst, for **1n** with 1.5 equiv of **2u** in DMSO solvent and **1o** with 1.5 equiv of $BnN_3$ **2v** in DMF or EtOH solvent (as the reaction was not moving in DMSO) at 25 °C for 2 h followed by 100 °C for 4 h produced tandem [3 + 2]-cycloaddition/decarboxylation products **6nu** and **6ov** with 60% yield in both the cases in a one-pot manner (Table 3). Yields of **6nu** and **6ov** increased to 80% when we used 2.0 equiv of **2u**/**2v** under similar reaction conditions, as shown in Table 3. Organo-click products **6nu** and **6ov** are precursors or analogues for biologically active compounds **A** and **B** mentioned in Figure 1, highlighting the importance of catalytic one-pot tandem [3 + 2]-cycloaddition/decarboxylation reactions.

There are a few previous reports, which discuss the synthesis of 4,4′-bitriazoles or 5,5′-bitriazoles, through metal-mediated double azide−alkyne [3 + 2]-cycloaddition or azide−alkyne [3 + 2]-cycloaddition followed by oxidative dimerization of the resulting 1,2,3-triazoles using metal reagents.[11−15] After a preliminary understanding of this reaction, we intended to employ the present metal-free protocol for the synthesis of 4,5′-bitriazoles **7** in a one-pot manner by using suitably designed double methylene activated 2,4-diketoester **1**. For the same, we investigated the reaction of ethyl-2,4-dioxo-5-phenylpentanoate **1p**, which has two active methylene centers with different equivalents of phenyl azide **2a** under the optimized reaction conditions (Table 4). First, we performed the reaction of **1p** (0.15 mmol) with 1.0 equiv of **2a** under the 20 mol % of TMG **3c** in DMSO at 25 °C for 1 h furnished the monoclick product **4pa** in 73% yield and double-click 4,5′-bitriazole **7pa** in 10% yield (Table 4, entry 1). Treatment of **1p** (0.3 mmol) with 1.5 equiv of **2a** under the 20 mol % of TMG **3c** in DMSO at 25 °C for 2 h furnished the monoclick product

**Table 3. Reaction Scope with Different 2,4-Diketoesters for Chemoselective OrgAKC Reaction**[a]

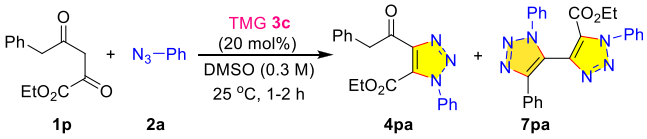



[a]Reactions were carried out in DMSO (0.3 M) with 1.5 equiv of **2** relative to **1** (0.3 mmol) in the presence of 20 mol % TMG **3c**. Yield refers to the column-purified product. [b]Reaction was performed under the 20 mol % of $K_2CO_3$ at 100 °C in DMSO (0.3 M) for **6nu** formation and in dry DMF or EtOH (0.3 M) for **6ov** formation, respectively.

**1b**−**1d** reacted with the phenyl azide **2a** in the presence of 20 mol % of TMG **3c** at 25 °C in the DMSO solvent, the reaction selectively furnished 1,2,3-triazoles **4ba**, **4ca** and **4da** in 81, 77 and 70% yields, within 2.5 h, respectively, without observation of other minor organo-click products of 1,2,3-triazoles **5** (Table 3).

We further extended our investigation to test different electronic factors, by using unsubstituted phenyl and halogen-substituted phenyl rings containing 2,4-diketoesters **1e**−**1h**, electron-withdrawing group such as *p*-$NO_2$ substituted 2,4-diketoester **1i** and electron donating group such as *p*-Me substituted 2,4-diketoester **1j**, which are reacted with phenyl azide **2a** in the presence of 20 mol % of TMG **3c** in DMSO solvent to selectively furnish 1,2,3-triazoles **4ea**−**4ja** in 64−81% yields within 3 h (Table 3). Under the same reaction condition, the heterocyclic aromatic ring containing 2,4-diketoesters **1k**, **1l**, and methyl 2,4-dioxo-4-phenylbutanoate

**Table 4. Reaction Optimization for 4,5′-Bitriazole 7pa Synthesis**[a]



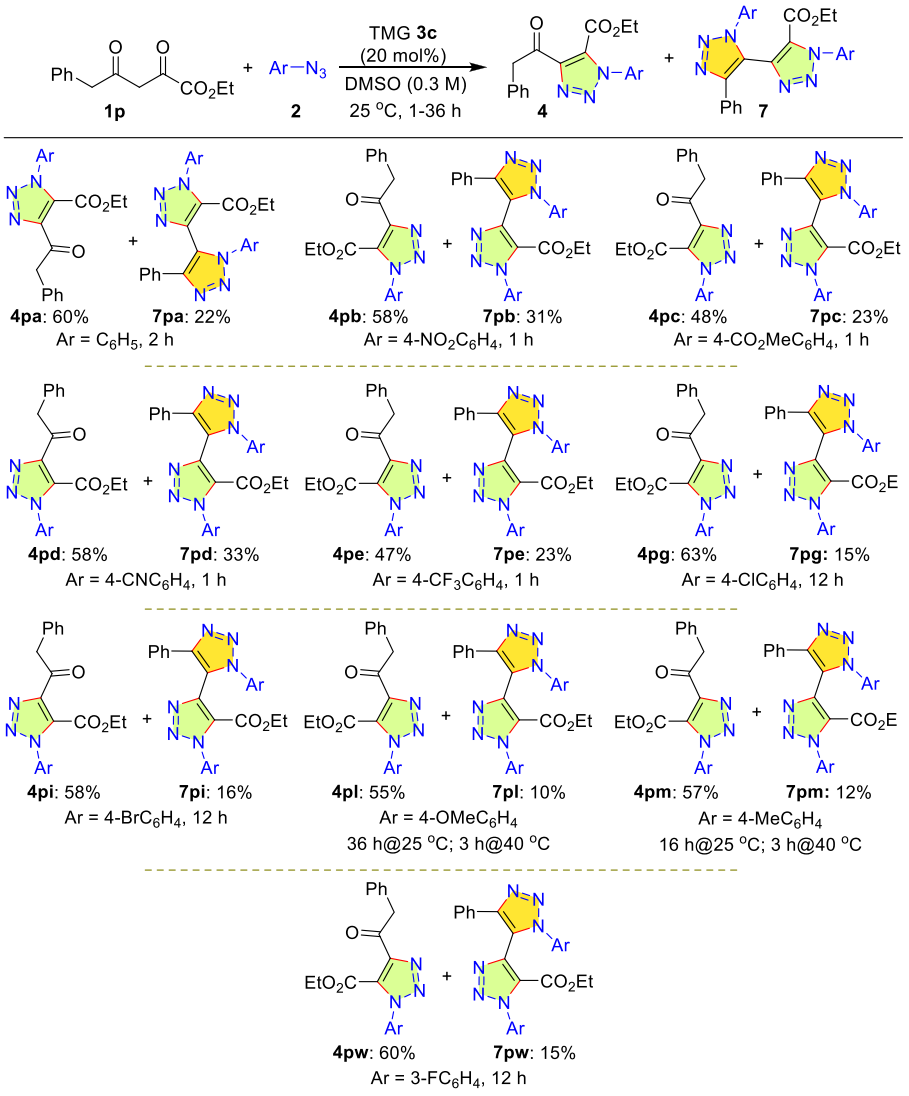

| entry | $PhN_3$ **2a** (equiv) | *t* (h) | yield **4pa** (%)[b] | yield **7pa** (%)[b] | ratio[c] (**4pa**/**7pa**) |
|---|---|---|---|---|---|
| 1 | 1.0 | 1 | 73 | 10 | 7.3:1 |
| 2 | 1.5 | 2 | 60 | 20 | 31 |
| 3 | 2.0 | 2 | 60 | 22 | 27:1 |
| 4 | 2.5 | 2 | 60 | 17 | 3.5:1 |
| 5 | 2.0 | 12 | 50 | 20 | 2.5:1 |
| 6[d] | 4.0 | 12 | 60 | 33 | 1.8:1 |

[a]Reactions were carried out in solvent (0.3 M) with **2a** relative to **1p** (0.15 or 0.2 or 0.3 mmol) in the presence of TMG **3c** (20 mol %). [b]Yields refers to the column-purified products. [c]Ratio is based on the isolated products. [d]Reaction performed with 30 mol % of **3c** at 70 °C.



https://doi.org/10.1021/acsorginorgau.4c00032
ACS Org. Inorg. Au 2024, 4, 534−544

**Table 5. Reaction Scope with 2,4-Diketoester 1p and 2 for Chemoselective OrgAKC**[a,b]




[a]Reactions were carried out in solvent (0.3 M) with 1.5 equiv of **2** relative to **1p** (0.3 mmol) in the presence of TMG **3c** (20 mol %). [b]Yields refers to the column-purified products.

**4pa** in 60% yield and double-click 4,5′-bitriazole **7pa** in 20% yield (Table 4, entry 2). Surprisingly, further reaction of **1p** (0.3 or 0.2 mmol) with 2.0 or 2.5 equiv of **2a** under the 20 mol % of TMG **3c** in DMSO at 25 °C for 2 h furnished the monoclick product **4pa** in 60% yield and double-click 4,5′-bitriazole **7pa** in only 22 or 17% yield, respectively (Table 4, entries 3 and 4). Even though after increasing the reaction time or equiv of azide **2a** or catalyst **3c** loading or temperature, the yield of double-click product **7pa** did not improve much and same time reaction become sluggish along with many unidentified byproducts in trace amounts (Table 4, entries 5 and 6). To further understand the kinetics of double-click reaction, we performed treatment of pure monoclick product **4pa** with 2.0 equiv of **2a** under the 20 mol % of TMG **3c** in DMSO at 25 °C for 6 h, furnished the double-click product **7pa** in only 40% yield, which is explaining the sensitive nature of this second click reaction and substrate **4pa** (result not shown in Table 4).

We further investigated the TMG **3c**-catalyzed organo-click reaction scope by choosing 1.0 or 1.5 equiv of different azides **2** with diketone **1p** (Table 5). The [3 + 2]-cycloaddition reaction between **1p** (0.3 mmol) and the electron-deficient aryl azides **2b**−**2e** (1.5 equiv) in the presence of 20 mol % of TMG **3c** in DMSO, produced both monotriazoles **4** and 4,5′-bitriazoles 7 of **4pb** (58%) and **7pb** (31%), **4pc** (48%) and **7pc** (23%), **4pd** (58%) and **7pd** (33%), and **4pe** (47%) and **7pe** (23%), respectively, within 1.0 h at 25 °C (Table 5). To further understand the reactivity of the diketone **1p** toward different azides, we performed the [3 + 2]-cycloaddition reactions between **1p** (0.3 mmol) and the halogenated aryl azides **2g**, **2i**, and **2w** (1.5 equiv) to furnish monotriazoles of **4pg**, **4pi**, and **4pw** in 63, 58, and 60% yields, respectively, along with 4,5′-bitriazoles **7pg**, **7pi**, and **7pw** as minor products in 15, 16, and 15% yields, respectively, for longer reaction times of 12 h at 25 °C (Table 5). In a further understanding, TMG **3c**-catalyzed reaction of diketone **1p** with electron-rich azides **2l** and **2m** (1.5 equiv) at 25 °C for 16−36 h and at 40 °C for 3 h furnished the monotriazole products **4pl** and **4pm** in 55 and 57% yields, respectively, and 4,5′-bitriazoles **7pl** and **7pm** were formed as minor products in 10 and 12% yields, respectively, as shown in Table 5. Monotriazoles **4** and 4,5′-bitriazoles 7 were well separated by silica-gel mediated column chromatography.


https://doi.org/10.1021/acsorginorgau.4c00032
ACS Org. Inorg. Au 2024, 4, 534−544

Surprisingly, when we performed TMG **3c**-catalyzed click reaction of **1p** (0.3 mmol) with 1.0 equiv of different less reactive azides **2g**, **2i**, **2w**, **2l** and **2m** at 25 °C for 1−2 h furnished the monotriazoles **4pg**, **4pi**, **4pw**, **4pl** and **4pm** in moderate (49, 50, 44, 44 and 51%) yields, respectively, along with 4,5′-bitriazoles **7pg**−**7pm** in only 5−9% yield (results not shown in Table 5). In support of the above results, we observed that after 1.0 h of TMG **3c**-catalyzed reaction between **1p** and **2a**, starting material **1p** was consumed totally, but azide **2a** was still there in the reaction medium, with multiple unidentified spots, along with the spots of compound **2a** and the organo-click products **4pa** and **7pa** in the TLC analysis, which clearly indicates the decomposition of **1p** during the course of organo-click reaction. The sensitive and highly reactive nature of 2,4-diketoester **1p** under the organo-click reaction conditions causes the less yield of **4pa** and **7pa**, and the same pattern is observed in the case of other azides **2g**, **2i**, **2w**, **2l**, and **2m** too (Table 5).

Functionalized 4,5′-bitriazoles **7** are structurally interesting compounds, which can have an axis of chirality due to the controlled rotation of the C−C bond between two triazole rings.[61] To test this phenomenon, we have tried a few compounds **7** to separate their possible atropisomers through the chiral HPLC analysis, but we have seen only one peak in many chiral columns. 4,5′-Bitriazoles **7** can have an axis of chirality, but the barrier for racemization is too low to isolate the chiral forms at 25 °C. This was further confirmed by performing the organo-click reaction of chiral diketone (−)-**1q** with aryl azide **2d** in DMSO under the TMG **3c**-catalysis at 25 °C for 8 h furnished the chiral 4,5′-bitriazole (−)-**7qd** in 60% yield with almost single diastereomer. The same organo-click reaction of (−)-**1q** with two different azides **2a**/**2g** also furnished the 4,5′-bitriazoles (−)-**7qa** in 43% yield and (−)-**7qg** in 52% yield with single diastereomer, respectively (Figure 2). These results confirm that the barrier for racemization is too low to isolate the diastereomers at 25 °C (Figure 2).[61]

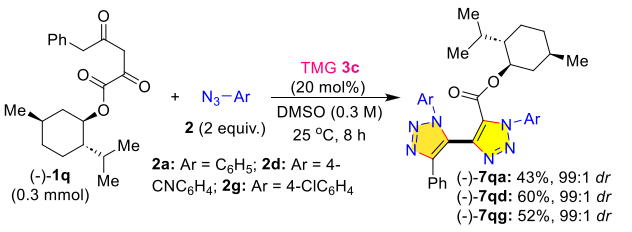
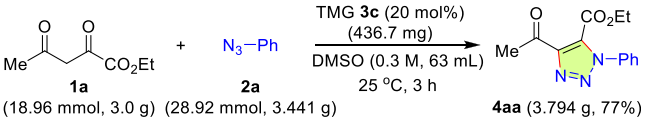



**Figure 2.** Selective one-pot synthesis of chiral 4,5′-bitriazoles **7**.

## Synthetic Applications

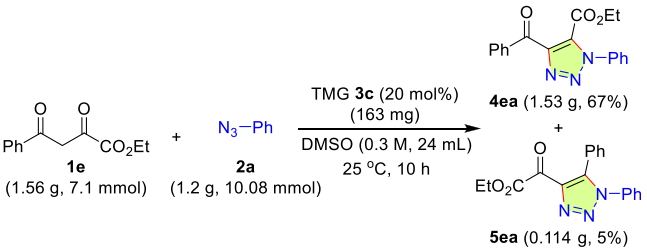
Applications in mind and at the same time to investigate the sustainability of the organocatalytic [3 + 2]-cycloaddition reaction through bulk scale, we planned a gram-scale reaction of ethyl 2,4-dioxopentanoate **1a** (3.0 g, 18.96 mmol) with phenyl azide **2a** (3.441 g, 28.92 mmol, 1.5 equiv) in DMSO (63 mL, 0.3 M) under the catalysis of TMG **3c** (20 mol %, 436.7 mg) at 25 °C for 3 h, which produced slightly reduced yield of **4aa** (3.794 g, 77%) compared to milligram scale in a highly chemoselective manner (Scheme 3). This gram-scale reaction under ambient conditions demonstrated the ease of use and importance of the enolate-mediated [3 + 2]-cycloaddition reaction for industrial applications (Scheme 3).

**Scheme 3. Gram-Scale Synthesis of the OrgAKC Product 4aa**




We performed another gram-scale reaction for the investigation of reactivity, sustainability, and selectivity between the ethyl-2,4-dioxo-4-phenylbutanoate **1e** (1.56 g, 7.1 mmol) and phenyl azide **2a** (1.2 g, 10.08 mmol) in DMSO (24 mL, 0.3 M) under the catalysis of TMG **3c** (20 mol %, 163 mg) at 25 °C for 10 h, which furnished 67% of the major organo-click product **4ea** (1.53 g) and 5% of the minor organo-click product **5ea** (0.114 g), as shown in Scheme 4.

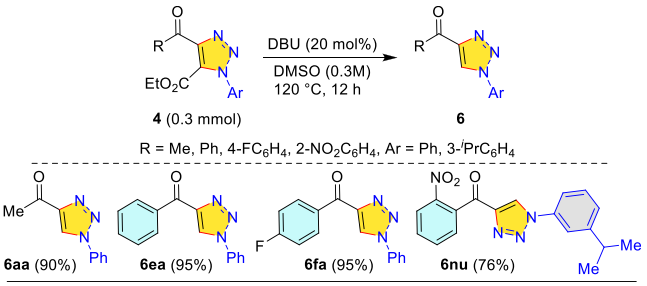
**Scheme 4. Gram-Scale Synthesis of the OrgAKC Product 4ea**




Surprisingly, we are able to observe formation of minor organo-click product **5ea** in gram-scale reaction only compared to milligram scale may be due to the less formation and same time decomposition nature (Scheme 4).

The excellence of the metal-free [3 + 2]-cycloaddition reactions was further demonstrated in the synthesis of a similar core structure of highly medicinally rich acylated 1,4-disubstituted-1,2,3-triazoles **6**.[1−8,83−89] We performed the decarboxylation reactions on the 1,4,5-trisubstituted-1,2,3-triazoles **4** using 20 mol % of DBU **3a** in DMSO at 120 °C to afford the 1,4-disubstituted-1,2,3-triazoles **6aa**, **6ea**, **6fa**, and **6nu** in good to excellent yields (90, 95, 95, and 76%, respectively) within 12 h (Scheme 5).

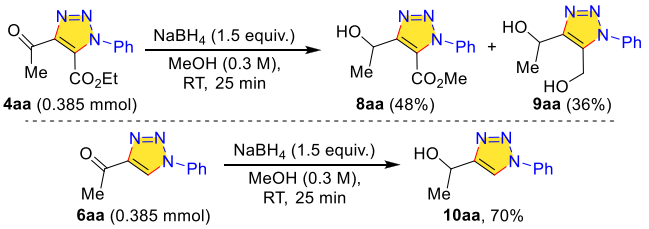
**Scheme 5. Synthesis of Carbonyl-Containing 1,4-Disubstituted-1,2,3-triazoles 6**




When the acylated 1,2,3-triazole **4aa** was treated with sodium borohydride in methanol solvent at room temperature, the corresponding secondary alcohol containing 1,2,3-triazole **8aa** was obtained in 48% yield along with the diol containing 1,2,3-triazole **9aa** in 36% yield, within 25 min (Scheme 6). Formation of diol-1,2,3-triazole **9aa** in the above reaction through ester reduction is surprising and may be due to the


https://doi.org/10.1021/acsorginorgau.4c00032
ACS Org. Inorg. Au 2024, 4, 534−544

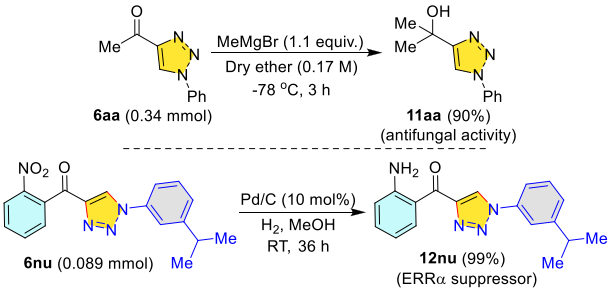
**Scheme 6. Reduction of Ketone and Ester Groups of 1,2,3-Triazoles 4aa/6aa**




neighboring secondary alcohol group induction or activation of the ester group. Similarly, 4-acetyl-1,2,3-triazole **6aa** was reduced to a secondary alcohol containing 1,2,3-triazole **10aa** in 70% yield, within 25 min (Scheme 6).

With further medicinal applications in mind, the decarboxylated 4-acetyl-1,2,3-triazole **6aa** (0.34 mmol) was treated with the methyl Grignard reagent of MeMgBr (1.1 equiv) in dry ether at −78 °C for 3 h to furnish the antifungal active scaffold of *tert*-hydroxyl-1,2,3-triazole **11aa** (**D**) with an excellent yield (Scheme 7 and Figure 1).[84] In a further application, hydrogen-

**Scheme 7. Synthesis of Biologically Active 1,2,3-Triazoles 11aa (D) and 12nu (A)**



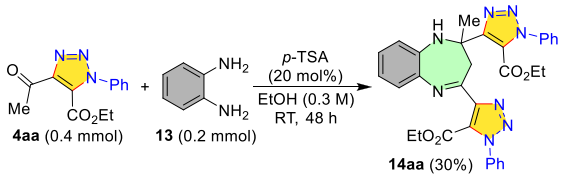

gas-mediated reduction of the nitro group of carbonyl-containing 1,2,3-triazole **6nu** (0.089 mmol) under the 10 mol % of Pd/C-catalysis in methanol (1.0 mL) at room temperature for 36 h furnished the ERR$\alpha$ suppressor **12nu** (**A**) in excellent yield (Scheme 7 and Figure 1).[85] Presently reported organocatalytic click reactions followed by simple synthetic transformations produced high-overall yields of biologically active 1,2,3-triazoles **11aa** (**D**) and **12nu** (**A**) compared to previous synthetic methods.[84,85]

As more nitrogen-containing molecules are predominantly showing different biological activities, herein, we try to utilize the two carbonyl groups of compounds **4** to undergo condensation with diamine to furnish highly nitrogen-rich molecules.[83−89] For the same, compound **4aa** was treated with *ortho*-phenylenediamine **13** (0.5 equiv) in the presence of 20 mol % of *p*-TSA in ethanol (0.3 M) at room temperature for 48 h to furnish a medicinally interesting seven-membered heterocyclic bis-triazole product **14aa** in 30% yield (Scheme 8).

## Reaction Mechanism

A plausible mechanism is proposed for the present organo-click protocol, which is going to explain the formation of different 1,2,3-triazole products **4**, **5**, and **7**. When 2,4-diketoester **1a** was treated with 20 mol % of TMG **3c**, two kinds of enolates **Ia** and **Ib** can be formed in situ in the course of the deprotonation reaction, which are tautomers in

**Scheme 8. Synthesis of Benzodiazipene-Containing 1,2,3-Triazole 14aa**




equilibrium (Scheme 9). Whether organo-click reaction is concerted or stepwise,[49] the first step will be nucleophilic polar addition of enolates **Ia** or **Ib** with aryl azides **2** to produce in situ 1,3-disubstituted 1,2,3-triazenes **IIa**, which further undergo the second step as chemoselective intramolecular cyclization with electrophilic carbonyl to produce 4,5-dihydro-1,2,3-triazoles through path-(a) or path-(b). TMG **3c**-mediated hydrolysis of in situ formed 4,5-dihydro-1,2,3-triazoles produces final 1,2,3-triazole products **4** and **5** (Scheme 9). Formation of 1,2,3-triazoles **4** as major products can be explained based on the thermodynamically feasible path-(a) due to the high electrophilic nature of $\alpha$-ketone to the ester group compared to $\gamma$-ketone (Scheme 9).[49]

In the case of 2,4-diketoester **1e**, two different tautomeric enolates, **Ic** and **Id**, can be formed in situ when treated with the amine base **3c**; even though both are in equilibrium, the enolate **Ic** or **Id** participated in the sequential [3 + 2]-cycloaddition followed by hydrolysis reactions with aryl azides **2** to furnish the 1,2,3-triazole **4** as major products selectively through path-(a) of intermediate **IIb**. However, relatively electrophilic $\gamma$-benzoyl ketone also can participate in the intramolecular cyclization followed by hydrolysis reaction through intermediate **IIb** to furnish the 1,2,3-triazole **5** as minor products (Scheme 9).

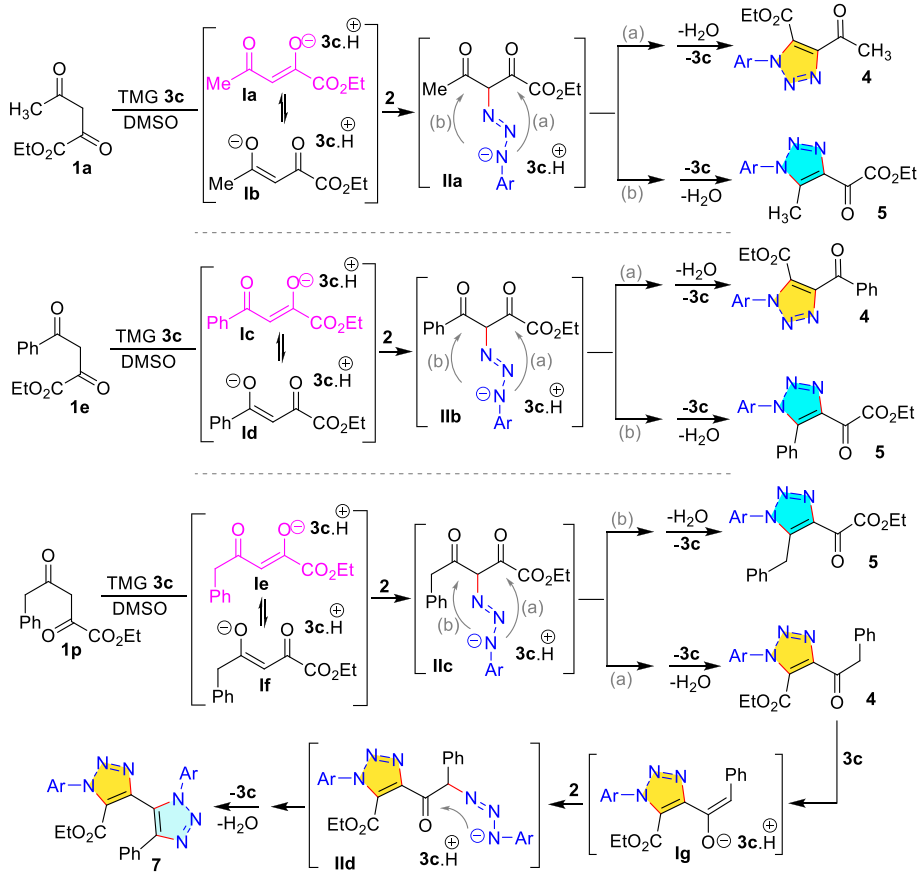
On the other hand, 2,4-diketoester **1p** has two active methylene centers and the reaction can produce three kinds of 1,2,3-triazoles **4**, **5**, and **7**. The formation of major 1,2,3-triazole products **4** can be explained through the participation of in situ generated tautomeric enolates of **Ie**/**If** from **1p** and **3c** with aryl azides **2** to produce 1,3-disubstituted 1,2,3-triazenes **IIc**, which further undergo chemoselective intramolecular cyclization with a highly electrophilic $\alpha$-ketone ester to produce 4,5-dihydro-1,2,3-triazoles through path-(a) followed by hydrolysis (Scheme 9). The formation of minor 4,5′-bitriazole products **7** can be explained through **the 3c**-catalyzed second [3 + 2]-cycloaddition followed by hydrolysis reactions of major carbonyl-containing 1,2,3-triazoles **4** with aryl azides **2** via the sequence of intermediates [**Ig** → **IId** → **7**] formation as shown in Scheme 9.

## CONCLUSIONS

In conclusion, we have developed a general and sustainable catalytic protocol for the high-yielding selective synthesis of carbonyl-containing 1,4,5-trisubstituted- and 1,4-disubstituted-1,2,3-triazoles and 4,5′-bitriazoles **4**/**5**/**6**/**7** from the readily available functionalized acyclic 2,4-diketoesters **1** and aryl/alkyl/vinyl azides **2** under 1,1,3,3-tetramethylguanidine (TMG)-catalysis under ambient conditions. In this manuscript, we have shown the simple and selective catalytic method for the synthesis of carbonyl-containing 1,2,3-triazoles as privileged building blocks for various applications. This work demonstrated the importance of mild organocatalytic in situ generation of acyclic enolate/dienolate reactivity compared to


https://doi.org/10.1021/acsorginorgau.4c00032
ACS Org. Inorg. Au 2024, 4, 534−544

**Scheme 9. Reaction Mechanism for the TMG-Catalyzed Enolate-Mediated Chemoselective [3 + 2]-Cycloaddition**




enamines/dienamines for carbonyl-mediated [3 + 2]-cycloaddition reactions with less reactive azides under ambient conditions. Furthermore, we demonstrated the gram-scale synthesis, followed by synthetic transformations on the resulting carbonyl-containing 1,4,5-trisubstituted- and 1,4-disubstituted-1,2,3-triazoles **4**/**5**/**6** into the pharmaceutically important compounds of **11aa** (**D**) and **12nu** (**A**). Many of these 1,2,3-triazole applications highlight that the metal-free catalytic protocol and same time will give inspiration to develop synthetic to medicinal applications of these functionally rich carbonyl-containing 1,2,3-triazoles in the near future. Presently, we are expanding the library of various functionalized carbonyl-rich azidophiles **1** for [3 + 2]-cycloaddition with various azides **2** through sustainable enolate/dienolate/polyenolate chemistry for synthesizing medicinally important 1,2,3-triazoles.

## EXPERIMENTAL SECTION

### General Procedure for the Organo-Click Synthesis of 1,2,3-Triazoles 4, 5, 6, and 7

To an ordinary glass vial equipped with a magnetic stirring bar were added 2,4-diketoester **1** (0.3 mmol, 1.0 equiv), azides **2** (0.45 mmol, 1.5 equiv), and tetramethyl guanidine TMG **3c** (6.9 mg, 0.06 mmol, 0.2 equiv, 20 mol %) in DMSO (1.0 mL, 0.3 M). The reaction mixture was allowed to stir until complete consumption of **1** (monitored by TLC) at room temperature. The corresponding organo-click products **4**, **5**, **6**, and/or **7** were purified by column chromatography (silica gel: 100−200 mesh; eluent: EA/hexanes).

A few of the reactions were performed using 2,4-diketoester **1** (0.3 mmol, 1.0 equiv) and azides **2** (0.45 mmol, 1.5 equiv) under the catalysis of $K_2CO_3$ **3g** (8.3 mg, 0.06 mmol, 0.2 equiv, 20 mol %) in dry ethanol or DMF (1.0 mL, 0.3 M) at 80 °C. After complete consumption of **1**, products **4**/**5**/**6**/**7** were purified by column chromatography (silica gel: 100−200 mesh; eluent: EA/hexanes).

### Decarboxylative Synthesis of Carbonyl-Containing 1,4-Disubstituted-1,2,3-triazoles 6

To an ordinary sealed tube equipped with a magnetic stirring bar were added compound **4** (0.3 mmol, 1.0 equiv), DBU **3a** (9.1 mg, 0.06 mmol, 0.2 equiv, 20 mol %), and DMSO (1.0 mL, 0.3 M). The reaction mixture was allowed to stir for 12 h at 120 °C. After complete consumption of compound **4** (monitored by TLC), workup was done by using saturated aqueous $NH_4Cl$, and the compound was extracted with DCM (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. Pure product **6** was obtained by column chromatography (silica gel, mixture of hexanes and ethyl acetate).

For all other procedures referring to the synthesis of 2,4-diketoesters **1**, azides **2**, carbonyl-containing 1,4,5-trisubstituted-1,2,3-triazoles, 1,4-disubstituted-1,2,3-triazoles, 4,5′-bitriazoles, and their synthetic derivatives **4** to **14**, see the Supporting Information.

## ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.4c00032.

Characterization data (including $^1H$ and $^{13}C$ NMR spectra) for all products, experimental procedures, characterization data of new compounds, substrate syntheses, procedures, and analytical data for click



https://doi.org/10.1021/acsorginorgau.4c00032
ACS Org. Inorg. Au 2024, 4, 534−544

reactions, details of controlled experiments, and X-ray crystal structures (PDF)

### Accession Codes

CCDC 2321526−2321528 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

## AUTHOR INFORMATION


### Corresponding Author

**Dhevalapally B. Ramachary** − *Catalysis Laboratory, School of Chemistry, University of Hyderabad, Hyderabad 500 046, India;* orcid.org/0000-0001-5349-2502; Email: ramsc@uohyd.ac.in, ramchary.db@gmail.com

### Authors

**Badaraita Gorachand** − *Catalysis Laboratory, School of Chemistry, University of Hyderabad, Hyderabad 500 046, India*

**Gundam Surendra Reddy** − *Catalysis Laboratory, School of Chemistry, University of Hyderabad, Hyderabad 500 046, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsorginorgau.4c00032


### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT: **Badaraita Gorachand** data curation, formal analysis, investigation, methodology, resources, writing-original draft; **Gundam Surendra Reddy** data curation, formal analysis, methodology; **Dhevalapally Buchi Ramachary** conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, visualization, writing-original draft, writing-review & editing.

### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

This work was made possible by a grant from the Department of Science and Technology (DST), SERB, New Delhi [Grant No.: CRG/2018/000775] and UoH-IoE grant [Grant No.: UoH/IoE/RC1/RC1-20-002]. B.G. thanks the Government of India, Ministry of Tribal Affairs, New Delhi, for his research fellowship [Ref. No. 201819-NFST-ODI-00372]. G.S.R. thanks the University Grants Commission (UGC), New Delhi, for his JRF/SRF research fellowship. We thank Prof. P. Raghavaiah, Central University of Karnataka, Gulbarga for X-ray structural analysis.

## REFERENCES


(1) Hitotsuyanagi, Y.; Motegi, S.; Fukaya, H.; Takeya, K. A *cis* Amide Bond Surrogate Incorporating 1,2,4-Triazole. *J. Org. Chem.* **2002**, *67*, 3266−3271.

(2) Horne, W. S.; Yadav, M. K.; Stout, C. D.; Ghadiri, M. R. Heterocyclic Peptide Backbone Modifications in an α-Helical Coiled Coil. *J. Am. Chem. Soc.* **2004**, *126*, 15366−15367.

(3) Hua, Y.; Flood, A. H. Click Chemistry Generates Privileged CH Hydrogen-bonding Triazoles: The Latest Addition to Anion Supramolecular Chemistry. *Chem. Soc. Rev.* **2010**, *39*, 1262−1271.

(4) Qin, A.; Lam, J. W. Y.; Tang, B. Z. Click Polymerization. *Chem. Soc. Rev.* **2010**, *39*, 2522−2544.

(5) Hanni, K. D.; Leigh, D. A. The Application of CuAAC 'Click' Chemistry to Catenane and Rotaxane Synthesis. *Chem. Soc. Rev.* **2010**, *39*, 1240−1251.

(6) Kantheti, S.; Narayan, R.; Raju, K. V. S. N. The Impact of 1,2,3-Triazoles in the Design of Functional Coatings. *RSC Adv.* **2015**, *5*, 3687−3708.

(7) Herrmann, L.; Hahn, F.; Grau, B. W.; Wild, M.; Niesar, A.; Wangen, C.; Kataev, E.; Marschall, M.; Tsogoeva, S. B. Autofluorescent Artemisinin-Benzimidazole Hybrids via Organo-Click Reaction: Study of Antiviral Properties and Mode of Action in Living Cells. *Chem. - Eur. J.* **2023**, *29*, No. e202301194.

(8) Herrmann, L.; Leidenberger, M.; Quadros, H. C.; Grau, B. W.; Hampel, F.; Friedrich, O.; Moreira, D. R. M.; Kappes, B.; Tsogoeva, S. B. Access to Artemisinin−Triazole Antimalarials via Organo-Click Reaction: High In Vitro/In Vivo Activity against Multi-Drug-Resistant Malaria Parasites. *J. Am. Chem. Soc. Au* **2024**, *4*, 951−957. and references cited therein.

(9) Tornoe, C. W.; Christensen, C.; Meldal, M. Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. *J. Org. Chem.* **2002**, *67*, 3057−3064.

(10) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective "Ligation" of Azides and Terminal Alkynes. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.

(11) Angell, Y.; Burgess, K. Base Dependence in Copper-Catalyzed Huisgen Reactions: Efficient Formation of Bistriazoles. *Angew. Chem., Int. Ed.* **2007**, *46*, 3649−3651.

(12) Monkowius, U.; Ritter, S.; König, B.; Zabel, M.; Yersin, H. Synthesis, Characterisation and Ligand Properties of Novel Bi-1,2,3-triazole Ligands. *Eur. J. Inorg. Chem.* **2007**, *2007*, 4597−4606.

(13) Oladeinde, O. A.; Hong, S. Y.; Holland, R. J.; Maciag, A. E.; Keefer, L. K.; Saavedra, J. E.; Nandurdikar, R. S. Click" Reaction in Conjunction with Diazeniumdiolate Chemistry: Developing High-Load Nitric Oxide Donors. *Org. Lett.* **2010**, *12*, 4256−4259.

(14) Tautz, M.; Saldias, C.; Gorrin, A. D. L.; Diaz, D. D. Use of a Bis-1,2,3-triazole Gelator for the Preparation of Supramolecular Metallogels and Stabilization of Gold Nanoparticles. *New J. Chem.* **2019**, *43*, 13850−13856.

(15) Zheng, Z.-J.; Wang, D.; Xu, Z.; Xu, L.-W. Synthesis of Bi- and Bis-1,2,3-triazoles by Copper-catalyzed Huisgen Cycloaddition: A Family of Valuable Products by Click Chemistry. *Beilstein J. Org. Chem.* **2015**, *11*, 2557−2576.

(16) Li, Y.-J.; Li, X.; Zhang, S.-X.; Zhao, Y.-L.; Liu, Q. Copper(II)-catalyzed Oxidative [3 + 2]-Cycloaddition Reactions of Secondary Amines with α-Diazo Compounds: A Facile and Efficient Synthesis of 1,2,3-Triazoles. *Chem. Commun.* **2015**, *51*, 11564−11567.

(17) Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. Ruthenium-Catalyzed Cycloaddition of Alkynes and Organic Azides. *J. Am. Chem. Soc.* **2005**, *127*, 15998−15999.

(18) Rasmussen, L. K.; Boren, B. C.; Fokin, V. V. Ruthenium-Catalyzed Cycloaddition of Aryl Azides and Alkynes. *Org. Lett.* **2007**, *9*, 5337−5339.

(19) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H.; Lin, Z.; Jia, G.; Fokin, V. V. Ruthenium-Catalyzed Azide−Alkyne Cycloaddition: Scope and Mechanism. *J. Am. Chem. Soc.* **2008**, *130*, 8923−8930.

(20) Luo, Q.; Jia, G.; Sun, J.; Lin, Z. Theoretical Studies on the Regioselectivity of Iridium-Catalyzed 1,3-Dipolar Azide−Alkyne Cycloaddition Reactions. *J. Org. Chem.* **2014**, *79*, 11970−11980.

(21) Ding, S.; Jia, G.; Sun, J.; et al. Iridium-Catalyzed Intermolecular Azide−Alkyne Cycloaddition of Internal Thioalkynes under Mild Conditions. *Angew. Chem., Int. Ed.* **2014**, *53*, 1877−1880.

(22) Rasolofonjatovo, E.; Theeramunkong, S.; Bouriaud, A.; Kolodych, S.; Chaumontet, M.; Taran, F. Iridium-Catalyzed Cycloaddition of Azides and 1-Bromoalkynes at Room Temperature. *Org. Lett.* **2013**, *15*, 4698−4701.
(23) Kim, W. G.; Kang, M. E.; Lee, J. B.; Jeon, M. H.; Lee, S.; Lee, J.; Choi, B.; Cal, P. M. S. D.; Kang, S.; Kee, J. M.; Bernardes, G. J. L.; Rohde, J. U.; Choe, W.; Hong, S. Y.; et al. Nickel-Catalyzed Azide−Alkyne Cycloaddition to Access 1,5-Disubstituted 1,2,3-Triazoles in Air and Water. *J. Am. Chem. Soc.* **2017**, *139*, 12121−12124.
(24) Kim, W. G.; Baek, S. Y.; Jeong, S. Y.; Nam, D.; Jeon, J. H.; Choe, W.; Baik, M. H.; Hong, S. Y. Chemo- and Regioselective Click Reactions through Nickel-Catalyzed Azide−Alkyne Cycloaddition. *Org. Biomol. Chem.* **2020**, *18*, 3374−3381.
(25) Liu, E. C.; Topczewski, J. J. Enantioselective Nickel-Catalyzed Alkyne−Azide Cycloaddition by Dynamic Kinetic Resolution. *J. Am. Chem. Soc.* **2021**, *143*, 5308−5313.
(26) Rao, H. S. P.; Chakibanda, G. Raney Ni Catalyzed Azide-Alkyne Cycloaddition Reaction. *RSC Adv.* **2014**, *4*, 46040−46048.
(27) Krasinski, A.; Fokin, V. V.; Sharpless, K. B. Direct Synthesis of 1,5-Disubstituted-4-magnesio-1,2,3-triazoles, Revisited. *Org. Lett.* **2004**, *6*, 1237−1240.
(28) Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. A Strain-Promoted [3 + 2] Azide−Alkyne Cycloaddition for Covalent Modification of Biomolecules in Living Systems. *J. Am. Chem. Soc.* **2004**, *126*, 15046−15047.
(29) Laughlin, S. T.; Baskin, J. M.; Amacher, S. L.; Bertozzi, C. R. In Vivo Imaging of Membrane-Associated Glycans in Developing Zebrafish. *Science* **2008**, *320*, 664−667.
(30) Gartner, Z. J.; Bertozzi, C. R. Programmed Assembly of 3-Dimensional Microtissues with Defined Cellular Connectivity. *Proc. Natl. Acad. Sci. U. S. A.* **2009**, *106*, 4606−4610.
(31) Debets, M. F.; Doelen, C. W. J. V.; Rutjes, F. P. J. T.; Delft, F. L. V. Azide: A Unique Dipole for Metal-Free Bioorthogonal Ligations. *Chembiochem* **2010**, *11*, 1168−1184.
(32) Shelbourne, M.; Chen, X.; Brown, T.; Sagheer, A. H. E. Fast Copper-free Click DNA Ligation by the Ring-Strain Promoted Alkyne-Azide Cycloaddition Reaction. *Chem. Commun.* **2011**, *47*, 6257−6259.
(33) Ramachary, D. B.; Ramakumar, K.; Narayana, V. V. Amino Acid-Catalyzed Cascade [3 + 2]-Cycloaddition/Hydrolysis Reactions Based on the Push−Pull Dienamine Platform: Synthesis of Highly Functionalized *N*H-1,2,3-Triazoles. *Chem.—Eur. J.* **2008**, *14*, 9143−9147.
(34) Belkheira, M.; Abed, D. E.; Pons, J.-M.; Bressy, C. Organocatalytic Synthesis of 1,2,3-Triazoles from Unactivated Ketones and Arylazides. *Chem.—Eur. J.* **2011**, *17*, 12917−12921.
(35) Danence, L. J. T.; Gao, Y.; Li, M.; Huang, Y.; Wang, J. Organocatalytic Enamide−Azide Cycloaddition Reactions: Regiospecific Synthesis of 1,4,5-Trisubstituted-1,2,3-Triazoles. *Chem.—Eur. J.* **2011**, *17*, 3584−3587.
(36) Wang, L.; Peng, S.; Danence, L. J. T.; Gao, Y.; Wang, J. Amine-Catalyzed [3 + 2] Huisgen Cycloaddition Strategy for the Efficient Assembly of Highly Substituted 1,2,3-Triazoles. *Chem.—Eur. J.* **2012**, *18*, 6088−6093.
(37) Seus, N.; Goncalves, L. C.; Deobald, A. M.; Savegnago, L.; Alves, D.; Paixao, M. W. Synthesis of Arylselanyl-1*H*-1,2,3-triazole-4-carboxylates by Organocatalytic Cycloaddition of Azidophenyl Arylselenides with *β*-Keto-esters. *Tetrahedron* **2012**, *68*, 10456−10463.
(38) Ramachary, D. B.; Shashank, A. B. Organocatalytic Triazole Formation, Followed by Oxidative Aromatization: Regioselective Metal-Free Synthesis of Benzotriazoles. *Chem.—Eur. J.* **2013**, *19*, 13175−13181.
(39) Li, W.; Jia, Q.; Du, Z.; Wang, J. Direct Access to Triazole-olefins through Catalytic Cycloaddition of Azides to Unsaturated Aldehydes. *Chem. Commun.* **2013**, *49*, 10187−10189.
(40) Yeung, D. K. J.; Gao, T.; Huang, J.; Sun, S.; Guo, H.; Wang, J. Organocatalytic 1,3-Dipolar Cycloaddition Reactions of Ketones and Azides with Water as a Solvent. *Green Chem.* **2013**, *15*, 2384−2388.
(41) Seus, N.; Goldani, B.; Lenardão, E. J.; Savegnago, L.; Paixão, M. W.; Alves, D. Organocatalytic Synthesis of (Arylselanyl)phenyl-1*H*-1,2,3-triazole-4-carboxamides by Cycloaddition between Azidophenyl Arylselenides and *β*-Oxo-amides. *Eur. J. Org. Chem.* **2014**, *2014*, 1059−1065.
(42) Li, W.; Du, Z.; Zhang, K.; Wang, J. Organocatalytic 1,3-Dipolar Cycloaddition Reaction of *α*, *β*-Unsaturated Ketones with Azides through Iminium Catalysis. *Green Chem.* **2015**, *17*, 781−784.
(43) Sangwan, R.; Javed; Dubey, A.; Mandal, P. K. Organocatalytic [3 + 2] Cycloadditions: Toward Facile Synthesis of Sulfonyl-1,2,3-Triazolyl and Fully Substituted 1,2,3-Triazolyl Glycoconjugates. *ChemistrySelect* **2017**, *2*, 4733−4743.
(44) Blastik, Z. E.; Klepetářová, B.; Beier, P. Enamine-Mediated Azide-Ketone [3 + 2] Cycloaddition of Azidoperfluoroalkanes. *ChemistrySelect* **2018**, *3*, 7045−7048.
(45) Bakulev, V. A.; Beryozkina, T.; Thomas, J.; Dehaen, W. The Rich Chemistry Resulting from the 1,3-Dipolar Cycloaddition Reactions of Enamines and Azides. *Eur. J. Org. Chem.* **2018**, *2018*, 262−294.
(46) Chrovian, C. C.; Soyode-Johnson, A.; Peterson, A. A.; Gelin, C. F.; Deng, X.; Dvorak, C. A.; Carruthers, N. I.; Lord, B.; Fraser, I.; Aluisio, L.; Coe, K. J.; Scott, B.; Koudriakova, T.; Schoetens, F.; Sepassi, K.; Gallacher, D. J.; Bhattacharya, A.; Letavic, M. A. A Dipolar Cycloaddition Reaction To Access 6-Methyl-4,5,6,7-tetrahydro-1*H*-[1,2,3]triazolo[4,5-c]pyridines Enables the Discovery Synthesis and Preclinical Profiling of a P2 × 7 Antagonist Clinical Candidate. *J. Med. Chem.* **2018**, *61*, 207−223.
(47) Li, W.; Du, Z.; Huang, J.; Jia, Q.; Zhang, K.; Wang, J. Direct Access to 1,2,3-Triazoles through Organocatalytic 1,3-Dipolar Cycloaddition Reaction of Allyl Ketones with Azides. *Green Chem.* **2014**, *16*, 3003−3006.
(48) Yuan, H.; Zhang, L.; Liu, Z.; Liu, Y.; Wang, J.; Li, W. A NHC-Catalyzed 1,3-Dipolar Cycloaddition Reaction of Allyl Ketones with Azides: Direct Access to 1,4,5-Trisubstituted 1,2,3-Triazoles. *Org. Biomol. Chem.* **2017**, *15*, 4286−4290.
(49) Ramachary, D. B.; Shashank, A. B.; Karthik, S. An Organocatalytic Azide−Aldehyde [3 + 2] Cycloaddition: High-Yielding Regioselective Synthesis of 1,4-Disubstituted 1,2,3-Triazoles. *Angew. Chem., Int. Ed.* **2014**, *53*, 10420−10424.
(50) Shashank, A. B.; Karthik, S.; Madhavachary, R.; Ramachary, D. B. An Enolate-Mediated Organocatalytic Azide−Ketone [3 + 2]-Cycloaddition Reaction: Regioselective High-Yielding Synthesis of Fully Decorated 1,2,3-Triazoles. *Chem.—Eur. J.* **2014**, *20*, 16877−16881.
(51) Li, W.; Wang, J. Lewis Base Catalyzed Aerobic Oxidative Intermolecular Azide−Zwitterion Cycloaddition. *Angew. Chem., Int. Ed.* **2014**, *53*, 14186−14190.
(52) Krishna, P. M.; Ramachary, D. B.; Sruthi, P. Azide−Acetonitrile "Click" Reaction Triggered by $Cs_2CO_3$: The Atom-Economic, High-Yielding Synthesis of 5-Amino-1,2,3-Triazoles. *RSC Adv.* **2015**, *5*, 62062−62066.
(53) Ramachary, D. B.; Krishna, P. M.; Gujral, J.; Reddy, G. S. An Organocatalytic Regiospecific Synthesis of 1,5-Disubstituted 4-Thio-1,2,3-triazoles and 1,5-Disubstituted 1,2,3-Triazoles. *Chem.—Eur. J.* **2015**, *21*, 16775−16780.
(54) Ramachary, D. B.; Reddy, G. S.; Peraka, S.; Gujral, J. Organocatalytic Vinyl Azide-Carbonyl [3 + 2] Cycloaddition: High-Yielding Synthesis of Fully Decorated N-Vinyl-1,2,3-Triazoles. *ChemCatChem.* **2017**, *9*, 263−267.
(55) Ramachary, D. B.; Gujral, J.; Peraka, S.; Reddy, G. S. Triazabicyclodecene as an Organocatalyst for the Regiospecific Synthesis of 1,4,5-Trisubstituted *N*-Vinyl-1,2,3-triazoles. *Eur. J. Org. Chem.* **2017**, *2017*, 459−464.
(56) Choi, H.; Shirley, H. J.; Hume, P. A.; Brimble, M. A.; Furkert, D. P. Unexpected Direct Synthesis of *N*-Vinyl Amides through Vinyl Azide−Enolate [3 + 2] Cycloaddition. *Angew. Chem., Int. Ed.* **2017**, *56*, 7420−7424.
(57) González-Calderón, D.; Fuentes-Benítes, A.; Díaz-Torres, E.; González-González, C. A.; González-Romero, C. Azide−Enolate 1,3-


https://doi.org/10.1021/acsorginorgau.4c00032
ACS Org. Inorg. Au 2024, 4, 534−544

Dipolar Cycloaddition as an Efficient Approach for the Synthesis of 1,5-Disubstituted 1,2,3-Triazoles from Alkyl/Aryl Azides and β-Ketophosphonates. *Eur. J. Org. Chem.* **2016**, *2016*, 668−672.
(58) Reddy, G. S.; Ramachary, D. B. Reaction Engineering and Photophysical Studies of Fully Enriched *C*-Vinyl-1,2,3-Triazoles. *Org. Chem. Front.* **2019**, *6*, 3620−3628.
(59) Reddy, G. S.; Kumar, A. S.; Ramachary, D. B. Organocatalytic Enone-Azide [3 + 2]-Cycloaddition: Synthesis of Functionally Rich *C*/*N*-Double Vinyl 1,2,3-Triazoles. *Org. Biomol. Chem.* **2020**, *18*, 4470−4478.
(60) Reddy, G. S.; Reddy, L. M.; Kumar, A. S.; Ramachary, D. B. Organocatalytic Selective [3 + 2] Cycloadditions: Synthesis of Functionalized 5-Arylthiomethyl-1,2,3-Triazoles and 4-Arylthio-1,2,3-Triazoles. *J. Org. Chem.* **2020**, *85*, 15488−15501.
(61) Vroemans, R.; Ribone, S. R.; Thomas, J.; Meervelt, L. V.; Ollevier, T.; Dehaen, W. Synthesis of Homochiral Sulfanyl- and Sulfoxide-Substituted Naphthyltriazoles and Study of the Conformational Stability. *Org. Biomol. Chem.* **2021**, *19*, 6521−6526.
(62) Berkel, S. S. V.; Brauch, S.; Gabriel, L.; Henze, M.; Stark, S.; Vasilev, D.; Wessjohann, L. A.; Abbas, M.; Westermann, B. Traceless Tosylhydrazone-Based Triazole Formation: A Metal-Free Alternative to Strain-Promoted Azide−Alkyne Cycloaddition. *Angew. Chem., Int. Ed.* **2012**, *51*, 5343−5346.
(63) Chen, Z.; Yan, Q.; Liu, Z.; Xu, Y.; Zhang, Y. Copper-Mediated Synthesis of 1,2,3-Triazoles from *N*-Tosylhydrazones and Anilines. *Angew. Chem., Int. Ed.* **2013**, *52*, 13324−13328.
(64) Cai, Z.-J.; Lu, X.-M.; Zi, Y.; Yang, C.; Shen, L.-J.; Li, J.; Wang, S.-Y.; Ji, S.-J. $I_2$/TBPB Mediated Oxidative Reaction of *N*-Tosylhydrazones with Anilines: Practical Construction of 1,4-Disubstituted 1,2,3-Triazoles under Metal-Free and Azide-Free Conditions. *Org. Lett.* **2014**, *16*, 5108−5111.
(65) Chen, Z.; Yan, Q.; Liu, Z.; Zhang, Y. Metal-Free C-N- and N-N-Bond Formation: Synthesis of 1,2,3-Triazoles from Ketones, *N*-Tosylhydrazines, and Amines in One Pot. *Chem.—Eur. J.* **2014**, *20*, 17635−17639.
(66) Thomas, J.; John, J.; Parekh, N.; Dehaen, W. A Metal-Free Three-Component Reaction for the Regioselective Synthesis of 1,4,5-Trisubstituted 1,2,3-Triazoles. *Angew. Chem., Int. Ed.* **2014**, *53*, 10155−10159.
(67) Ali, A.; Corrêa, A. G.; Alves, D.; Zukerman-Schpector, J.; Westermann, B.; Ferreira, M. A. B.; Paixao, M. W. An Efficient One-Pot Strategy for the Highly Regioselective Metal-Free Synthesis of 1,4-Disubstituted-1,2,3-Triazoles. *Chem. Commun.* **2014**, *73*, 11926−11929.
(68) Quan, X.-J.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. Iron-Catalyzed C−O Bond Activation for the Synthesis of Propargyl-1,2,3-Triazoles and 1,1-Bis-Triazoles. *Org. Lett.* **2014**, *16*, 5728−5731.
(69) Cheng, G.; Zeng, X.; Shen, J.; Wang, X.; Cui, X. A Metal-Free Multicomponent Cascade Reaction for the Regiospecific Synthesis of 1,5-Disubstituted 1,2,3-Triazoles. *Angew. Chem., Int. Ed.* **2013**, *52*, 13265−13268.
(70) John, J.; Thomas, J.; Parekh, N.; Dehaen, W. Tandem Organocatalyzed Knoevenagel Condensation/1,3-Dipolar Cycloaddition towards Highly Functionalized Fused 1,2,3-Triazoles. *Eur. J. Org. Chem.* **2015**, *2015*, 4922−4930.
(71) Thomas, J.; Goyvaerts, V.; Liekens, S.; Dehaen, W. Metal-Free Route for the Synthesis of 4-Acyl-1,2,3-Triazoles from Readily Available Building Blocks. *Chem.—Eur. J.* **2016**, *22*, 9966−9970.
(72) Anebouselvy, K.; Ramachary, D. B. Synthesis of Substituted 1,2,3-Triazoles through Organocatalysis. In *Click Reactions in Organic Synthesis*; Wiley-VCH, 2016; 99−139.
(73) Ramasastry, S. S. V.; et al. Enamine/Enolate-Mediated Organocatalytic Azide−Carbonyl [3+2] Cycloaddition Reactions for the Synthesis of Densely Functionalized 1,2,3-Triazoles. *Angew. Chem., Int. Ed.* **2014**, *53*, 14310−14312.
(74) Jalani, H. B.; Karagöz, A. C.; Tsogoeva, S. B. Synthesis of Substituted 1,2,3-Triazoles via Metal-Free Click Cycloaddition Reactions and Alternative Cyclization Methods. *Synthesis* **2016**, *49*, 29−41.
(75) Reddy, G. S.; Anebouselvy, K.; Ramachary, D. B. [3 + 2]-Cycloaddition for Fully Decorated Vinyl-1,2,3-Triazoles: Design, Synthesis and Applications. *Chem. Asian. J.* **2020**, *15*, 2960−2983.
(76) Thomas, J.; Jana, S.; John, J.; Liekens, S.; Dehaen, W. A General Metal Free Route Towards the Synthesis of 1,2,3-Triazoles from Readily Available Primary Amines and Ketones. *Chem. Commun.* **2016**, *52*, 2885−2888.
(77) Silveira-Dorta, G.; Jana, S.; Borkova, L.; Thomas, J.; Dehaen, W. Straightforward Synthesis of Enantiomerically Pure 1,2,3-Triazoles Derived from Amino Esters. *Org. Biomol. Chem.* **2018**, *16*, 3168−3176.
(78) Guo, N.; Liu, X.; Xu, H.; Zhou, X.; Zhao, H. A Simple Route Towards the Synthesis of 1,4,5-Trisubstituted 1,2,3-Triazoles from Primary Amines and 1,3-Dicarbonyl Compounds under Metal-Free Conditions. *Org. Biomol. Chem.* **2019**, *17*, 6148−6152.
(79) Xu, S.; Mao, L.; Ding, P.; Zhuang, X.; Zhou, Y.; Yu, L.; Liu, Y.; Nie, T.; Xu, T.; Xu, Y.; Liu, J.; Smaill, J.; Ren, X.; Wu, D.; Ding, K. 1-Benzyl-4-phenyl-1*H*-1,2,3-Triazoles Improve the Transcriptional Functions of Estrogen-Related Receptor γ and Promote the Browning of White Adipose. *Bioorg. Med. Chem.* **2015**, *23*, 3751−3760.
(80) Albuquerque, D. Y.; Moraes, J. R.; Schwab, R. S. Palladium-Catalyzed Aminocarbonylation Reaction to Access 1,2,3-Triazole-5-carboxamides Using Dimethyl Carbonate as Sustainable Solvent. *Eur. J. Org. Chem.* **2019**, *2019*, 6673−6681.
(81) Szuroczki, P.; Molnar, L.; Dornyei, A.; Kollar, L. Facile, High-Yielding Synthesis of 4-Functionalised 1,2,3-Triazoles via Amino- and Aryloxycarbonylation. *ChemistrySelect* **2020**, *5*, 448−451.
(82) Biagi, G.; Giorgi, I.; Livi, O.; Scartoni, V.; Betti, L.; Giannaccini, G.; Trincavelli, M. L. New 1,2,3-Triazolo[1,5-a]quinoxalines: Synthesis and Binding to Benzodiazepine and Adenosine Receptors. *Eur. J. Med. Chem.* **2002**, *37*, 565−571.
(83) Calderone, V.; Fiamingo, F. L.; Amato, G.; Giorgi, I.; Livi, O.; Martelli, A.; Martinotti, E. 1,2,3-Triazol-carboxanilides and 1,2,3-Triazol-(*N*-benzyl)-carboxamides as BK-Potassium Channel Activators. *XII. Eur. J. Med. Chem.* **2008**, *43*, 2618−2626.
(84) Neto, R. G. L.; Cavalcante, N. N. M.; Srivastava, R. M.; Junior, F. J. B. M.; Wanderley, A. G.; Neves, R. P.; Anjos, J. V. Synthesis of 1,2,3-Triazole Derivatives and *in Vitro* Antifungal Evaluation on *Candida* Strains. *Molecules* **2012**, *17*, 5882−5892.
(85) Xu, S.; Zhuang, X.; Pan, X.; Zhang, Z.; Duan, L.; Liu, Y.; Zhang, L.; Ren, X.; Ding, K. 1-Phenyl-4-benzoyl-1*H*-1,2,3-Triazoles as Orally Bioavailable Transcriptional Function Suppressors of Estrogen-Related Receptor α. *J. Med. Chem.* **2013**, *56*, 4631−4640.
(86) Altimari, J. M.; Niranjan, B.; Risbridger, G. P.; Schweiker, S. S.; Lohning, A. E.; Henderson, L. C. Preliminary Investigations into Triazole Derived Androgen Receptor Antagonists. *Bioorg. Med. Chem.* **2014**, *22*, 2692−2706.
(87) Moura, L. A.; Almeida, A. C. M.; Silva, A. V.; Souza, V. R.; Ferreira, V. F.; Menezes, M. V.; Kaiser, C. R.; Ferreira, S. B.; Fuly, A. L. Synthesis, Anticlotting and Antiplatelet Effects of 1,2,3-Triazoles Derivatives. *Med. Chem.* **2016**, *12*, 733−741.
(88) Gao, Z.; Du, Y.; Sheng, X.; Shen, J. Molecular Dynamics Simulations Based on 1-Phenyl-4-Benzoyl-1-Hydro-Triazole ERRα Inverse Agonists. *Int. J. Mol. Sci.* **2021**, *22*, 3724.
(89) Ahmed, D. M.; Chen, J. M.; Sanders, D. A. R. Pyrazole and Triazole Derivatives as *Mycobacterium tuberculosis* UDP-Galactopyranose Inhibitors. *Pharmaceuticals* **2022**, *15*, 197.


https://doi.org/10.1021/acsorginorgau.4c00032
*ACS Org. Inorg. Au* 2024, 4, 534−544