1,2,3-Triazoles

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An Organocatalytic Azide–Aldehyde [3+2] Cycloaddition: High-Yielding Regioselective Synthesis of 1,4-Disubstituted 1,2,3-Triazoles**

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Abstract: *An organocatalytic azide–aldehyde [3+2] cycloaddition (organo-click) reaction of a variety of enolizable aldehydes is reported. The organo-click reaction is characterized by a high rate and regioselectivity, mild reaction conditions, easily available substrates with simple operation, and excellent yields with a broad spectrum of substrates. It constitutes an alternative to the previously known CuAAC, RuAAC, and IrAAC click reactions.*

1,4-Disubstituted 1,2,3-triazoles have emerged as an important class of organic compounds, displaying a vast spectrum of properties and are widely used as pharmaceuticals.[1] Many 1,2,3-triazoles have found medicinal applications, such as HIV protease inhibitors, anticancer drugs, antituberculosis drugs, antifungal agents, antibacterial drugs, histone deacetylase inhibitors, and bioorthogonal probes, and are also used as corrosion inhibitors, lubricants, dyes, and photostabilizers (Figure 1).[1] Thus, the development of green methods for the preparation of these compounds is of significant interest.[2]

The regioselective formation of 1,4- and 1,5-disubstituted 1,2,3-triazoles can be accomplished by copper-catalyzed azide-alkyne [3+2] cycloaddition (CuAAC) reactions [Eq. (a), Scheme 1],[3] and ruthenium-catalyzed azide-alkyne [3+2] cycloaddition (RuAAC) reactions, respectively.[4] Recently, a strain-promoted [3+2] cycloaddition reaction of substituted cyclooctyne with aryl azides was reported to furnish 1,4,5-trisubstituted 1,2,3-triazoles [Eq. (b), Scheme 1], which have become good bioorthogonal probes.[5] Very recently, an enamine-mediated amino acid or amine catalyzed [3+2] cycloaddition reaction of different carbonyl compounds (enones, β-keto esters, ketones, and enals) with aryl azides was reported to furnish 1,4,5-trisubstituted 1,2,3-triazoles in good yields [Eq. (c), Scheme 1].[6]

In all the above three methods, the authors either used expensive or not commercially available alkynes, or less reactive carbonyl compounds other than simple aldehydes as the starting materials along with aryl azides. Furthermore,

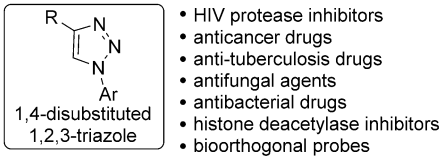
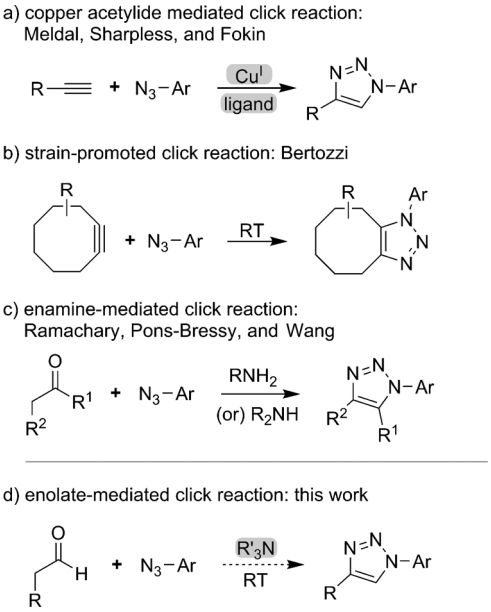


Figure 1. Potential applications based on the 1,2,3-triazoles.



Scheme 1. Background and design of the enolate-mediated organocatalytic azide–aldehyde [3+2] cycloaddition reaction.

CuAAC only gave 1,4-disubstituted 1,2,3-triazoles, and the remaining two methods gave 1,4,5-trisubstituted 1,2,3-triazoles. Even though the CuAAC reaction has become a paradigm of the "click reaction", its use for the labeling of biomolecules in live cells is prohibited because of the cytotoxicity of the copper catalyst.[3d,5a–c] Alkynes used in CuAAC or RuAAC click reactions are more expensive than the corresponding aldehydes. For example, the price of phenylacetylene is $76 for 100 mL, whereas that of phenylacetaldehyde is only $33 for 100 mL. These obstacles inspired us to develop a novel green method for the high-yielding regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles based upon enolate-mediated organocatalytic azide–aldehyde [3+2] cycloaddition (organo-click) reaction from commercially available enolizable aldehydes, aryl azides, and a catalytic amount of a tertiary amine [Eq. (d), Scheme 1]. Although simple enolizable aldehydes and active methylenes

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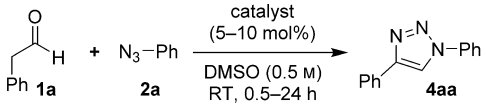
were previously used in reactions with aryl azides to furnish 1,2,3-triazoles through the formation of enolates or enamines with strong bases/amines, further development is required because the known protocols require an excess amount of amine/base and harsh reaction conditions.[7] Herein, we present the organocatalytic enolate-mediated synthesis of 1,2,3-triazoles from aldehydes and aryl azides.

We initiated our preliminary optimization of the organo-click reaction by screening a number of known simple organocatalysts for the click reaction of phenylacetaldehyde (**1a**) with 1.0 to 1.5 equiv of phenyl azide (**2a**) (Table 1). Interestingly, the reaction of **1a** with 1.5 equiv of **2a** in DMSO catalyzed by 10 mol% of proline (**3a**) furnished the product **4aa** as a single regioisomer in moderate yield (53%; Table 1, entry 1). The same reaction catalyzed by 10 mol% of diethyl amine (**3b**) or pyrrolidine (**3c**) did not furnish the 1,2,3-triazole **4aa**, but **1a** is consumed completely (Table 1, entries 2 and 3). After obtaining discouraging results for the enamine-mediated reaction with catalysts **3a–c**, we investigated the reaction via enolates, which were formed in situ with tertiary amines **3d–g**. Intriguingly, the reaction of **1a** with 1.5 equiv of **2a** in DMSO catalyzed by 10 mol% of DBU (**3d**) at 25°C for 0.5 h furnished **4aa** in 95% yield (Table 1, entry 4). Deviations from these reaction conditions by switching the solvent to DMF, using 5 mol% of **3d** as the catalyst, or using 1.0 equiv of **2a** was not so successful in promoting the high-yielding organo-click reaction (Table 1, entries 5, 6, and 7). These results clearly support our hypothesis of the formation of reactive enolates. The use of less basic tertiary amines, such as DABCO (**3e**), DMAP (**3f**), and Et_3N (**3g**), resulted in the formation of 1,2,3-triazole **4aa** with moderate yields compared to the use of **3d** (Table 1, entries 8 to 10), and no reaction was observed without the catalyst in DMSO for 24 h at 25°C (Table 1, entry 13). The same reaction catalyzed by 10 mol% of non-amine bases K_2CO_3 and *t*BuOK also furnished the 1,2,3-triazole **4aa** in moderate to good yields (Table 1, entries 11,12). The DBU-promoted organo-click reaction is dependent on the solvent, as it works well in aprotic polar solvents such as DMSO and DMF, but in other solvents, such as EtOH and H_2O, less than 5% of the product is formed (results not shown in the Table). The optimized conditions for the reaction comprise the catalysis by 10 mol% of **3d** at 25°C in DMSO to furnish the single 1,2,3-triazole **4aa** in 95% yield from **1a** and **2a** (Table 1, entry 4).

With the optimized conditions in hand, the scope and generality of the DBU-catalyzed organo-click reactions were investigated. A variety of functionalized azides **2b–r** were reacted with **1a** for 0.5 h (Table 2). Interestingly, aryl azides **2b—o**, which contain functional groups, such as NO_2, CO_2Et, CN, CF_3, CHO, halogen, alkyl, and OMe, at different positions of the aromatic ring, furnished the expected 1,2,3-triazoles **4ab–ao** in excellent to good yields within 0.5 h (Table 2). The yields of products **4ab–ao** were dependent on the substituent at the *para* position of **2**, increasing with electron-withdrawing groups, and slightly decreasing with

Table 1: Optimization of reaction conditions.[a]



Entry	Catalyst	Catalyst pK_a[b]	*t* [h]	Yield **4aa** [%][c]
1	**3a** (10 mol%)	10.64	24	53
2[d]	**3b** (10 mol%)	10.84	0.5	–
3[d]	**3c** (10 mol%)	11.31	0.5	–
4	**3d (10 mol%)**	**12**	**0.5**	**95**
5[e]	**3d** (10 mol%)	12	0.5	70
6	**3d** (5 mol%)	12	0.5	70
7[f]	**3d** (10 mol%)	12	0.5	75
8	**3e** (10 mol%)	8.8	24	45
9	**3f** (10 mol%)	9.2	24	40
10	**3g** (10 mol%)	10.75	10	45
11	K_2CO_3 **3h** (10 mol%)	10.33	0.5	65
12	*t*BuOK **3i** (10 mol%)	29.4	0.5	87
13	–	–	24	–

[a] Reactions were carried out in solvent (0.5 M) with 1.5 equiv of **2a** relative to **1a** (0.5 mmol) in the presence of 5–10 mol% of the catalyst. [b] pK_a values refer to the conjugate acid of the amine/base. [c] Yields of products purified by column chromatography on silica gel. [d] **1a** was consumed completely. [e] DMF was used as solvent. [f] 1.0 equiv of **2a** was used relative to **1a** (0.5 mmol). Entry in bold marks optimized reaction conditions.

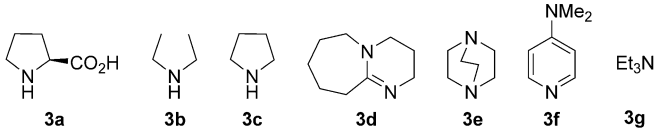
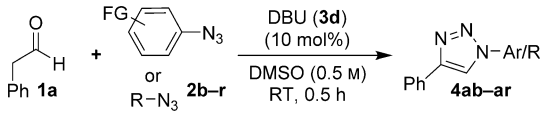


Table 2: Azide substrate scope.[a]



Entry	Substrate **2**	Yield (**4**) [%][b]
1	**2b** (FG = 2-NO_2)	93 (**4ab**)
2	**2c** (FG = 4-NO_2)	95 (**4ac**)
3	**2d** (FG = 4-CO_2Et)	93 (**4ad**)
4	**2e** (FG = 4-CN)	95 (**4ae**)
5	**2f** (FG = 4-CF_3)	95 (**4af**)
6	**2g** (FG = 3-CHO)	90 (**4ag**)
7	**2h** (FG = 4-F)	90 (**4ah**)
8	**2i** (FG = 4-Cl)	95 (**4ai**)
9	**2j** (FG = 3-Cl)	93 (**4aj**)
10	**2k** (FG = 4-Br)	93 (**4ak**)
11	**2l** (FG = 2-Br)	90 (**4al**)
12	**2m** (FG = 4-Me)	85 (**4am**)
13	**2n** (Ar = 1-naphthyl)	90 (**4an**)
14	**2o** (FG = 4-OMe)	75 (**4ao**)
15[c]	**2o** (FG = 4-OMe)	80 (**4ao**)
16[c]	**2p** (R = $PhCH_2$)	15 (**4ap**)
17[c,d]	**2q** (R = $EtCO_2$)	60 (**4aq**)
18	**2r** (R = Ts)	– (**4ar**)

[a] Reactions were carried out in DMSO (0.5 M) with 1.5 equiv of **2b–r** relative to **1a** (0.5 mmol) in the presence of 10 mol% of **3d**. [b] Yields of products purified by column chromatography on silica gel. [c] Catalyzed by *t*BuOK at RT for 1–3 h. [d] Decarboxylated 1*H*-1,2,3-triazole **4aq** was obtained.

alkyl and electron-donating groups. For example, the DBU-catalyzed organo-click reactions of aryl azides **2m** and **2o** with **1a** furnished the expected 1,2,3-triazoles **4am** and **4ao** in 85% and 75% yield, respectively (Table 2, entries 12 and 14). Interestingly, the reaction of **1a** with **2o** catalyzed by 10 mol% of the more basic **3i** furnished **4ao** in a slightly improved yield (80%, Table 2, entry 15). On the other hand, the **3d**-catalyzed organo-click reaction of **1a** with alkyl, acyl, and tosyl azides **2p–r** did not furnish the expected products **4**, but the same reactions catalyzed by **3i** gave **4ap** in less than 15% and decarboxylated product **4aq** in 60% yield, respectively, while **4ar** was not formed at all (Table 2, entries 16–18). The structures of organo-click products **4ab–aq** were confirmed by NMR and X-ray structure analysis on **4ab**, as shown in Figure S1 (see the Supporting Information).[8]

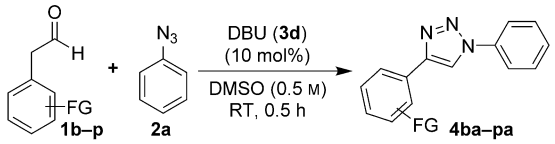
After investigating the effects of the electronic factors of substrates **2** on the [3+2] cycloaddition reaction, we next turned our attention to the reaction scope with different 2-arylacetaldehydes **1b–p** in the organo-click reaction with PhN_3 **2a** (Table 3). In this reaction, **1b–p** containing different functional groups, such as NO_2, halogen, alkyl, heteroaryl, and OMe, were used as substrates in the organocatalytic synthesis of the single isomers of 1,2,3-triazoles **4ba–pa**, which were obtained in excellent to good yields within 0.5 h (Table 3). These results demonstrate the broad scope of this novel methodology, covering a structurally diverse group of 2-arylacetaldehydes **1b–p** and phenyl azide **2a**. Many of the organo-click products **4** were obtained in very good yields compared to other routes (Table S1, see the Supporting Information).

To further understand the importance of the electronic or acidic nature of the α-methylene group of aldehydes **1** in the organo-click reaction, we investigated simple aliphatic aldehydes **1q–x**, which have less acidic α-methylene groups compared to 2-arylacetaldehydes **1a–p** (Table 4). Surprisingly, the DBU-catalyzed reaction of 3-phenylpropanaldehyde (**1q**) with **2c** furnished the expected 1,2,3-triazole **4qc** in 95% yield (Table 4, entry 1). In a similar manner, the DBU-catalyzed reaction of butyraldehyde (**1r**) with **2c** furnished the 1,2,3-triazole **4rc** in 70% yield (Table 4, entry 3). We tested six more aliphatic aldehydes **1q–w** as substrates for the organo-click reaction with **2c**/**2e**, and obtained the expected 1,2,3-triazoles **4** in good to excellent yields (Table 4, entries 2–8). Surprisingly, the reaction of 2-succinimidoacetaldehyde (**1x**) with **2c** catalyzed by **3d** or **3i** did not give the desired product (Table 4, entry 9). The organo-click reaction of 3-phenylpropanaldehyde (**1q**) with less reactive aryl azides **2a**, **2f**, and **2k** catalyzed by **3d** or **3i** at 25 °C for 1 h furnished the 1,2,3-triazoles **4qa–qk** in 60–65% yields (Table 4, entries 10–12). The industrial scope of this reaction was investigated by performing the syntheses of 1,2,3-triazoles **4aa** and **4ag** on a gram scale without compromising the reaction rates, yields, and purity of the products [Eq. S1,S2, see the Supporting Information].

The possible mechanism for the regioselective synthesis of **4** from **1** and **2** catalyzed by **3d** is illustrated in Scheme 2. The reaction of catalyst **3d** ($pK_a = 12$) with aldehyde **1** generates enolate **5**, which on in situ treatment with probably the major contributing mesomeric structure of Ar-N_3 **2′** selectively furnishes the adduct 1,2,3-triazolines **6** through a concerted [3+2] cycloaddition or stepwise amination–cyclization reaction.[7] Adduct **6** further transforms into the 1,2,3-triazole **4** through the rapid elimination of water induced by the basic nature of **3d**.

In summary, we have developed the metal-free DBU-catalyzed regioselective synthesis of 1,4-disubstituted 1,2,3-

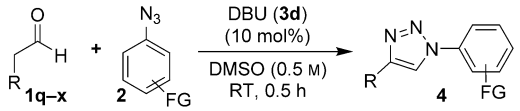
Table 3: Aldehyde substrate scope: 2-arylacetaldehydes.[a]



Entry	Ar-CH_2CHO **1**	Yield (**4**) [%][b]
1	**1b** (Fg = 2-NO_2)	90 (**4ba**)
2	**1c** (Fg = 4-F)	90 (**4ca**)
3	**1d** (Fg = 4-Cl)	90 (**4da**)
4	**1e** (Fg = 2-Cl)	90 (**4ea**)
5	**1f** (Fg = 4-Br)	95 (**4fa**)
6	**1g** (Fg = 2-Br)	92 (**4ga**)
7	**1h** (Fg = 4-Me)	93 (**4ha**)
8	**1i** (Fg = 2-Me)	90 (**4ia**)
9	**1j** (Ar = 2-naphthyl)	95 (**4ja**)
10	**1k** (Ar = 1*H*-indol-3-yl)	75 (**4ka**)
11	**1l** (Ar = thiophen-2-yl)	88 (**4la**)
12	**1m** (Fg = 4-OMe)	90 (**4ma**)
13	**1n** (Fg = 3-OMe)	80 (**4na**)
14	**1o** (Fg = 2-OMe)	90 (**4oa**)
15	**1p** (Fg = 3,4-$(OMe)_2$)	75 (**4pa**)

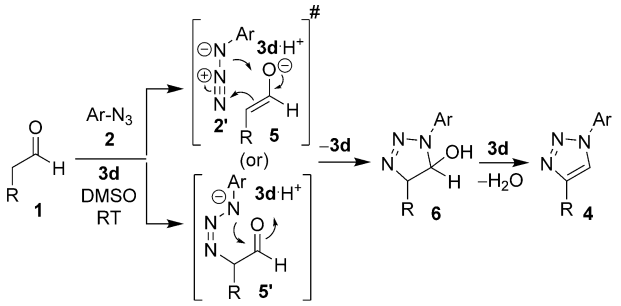
[a] Reactions were carried out in DMSO (0.5 M) with 1.5 equiv of **2a** relative to **1b–p** (0.5 mmol) in the presence of 10 mol% of **3d**. [b] Yields of products purified by column chromatography on silica gel.

Table 4: Aldehyde substrate scope: other aldehydes.[a]



Entry	Substrate **1** (R)	**2**	Yield (**4**) [%][b]
1	**1q** ($PhCH_2$)	**2c**	95 (**4qc**)
2	**1q** ($PhCH_2$)	**2e**	90 (**4qe**)
3	**1r** ($MeCH_2$)	**2c**	70 (**4rc**)
4	**1s** ($MeCH_2CH_2$)	**2c**	75 (**4sc**)
5	**1t** ($MeCH_2CH_2CH_2$)	**2c**	75 (**4tc**)
6	**1u** ($MeCH_2CH_2CH_2CH_2$)	**2c**	80 (**4uc**)
7	**1v** (CH_3)	**2c**	80 (**4vc**)
8	**1w** (H)	**2c**	80 (**4wc**)
9	**1x** (1,3-isoindoledione)	**2c**	– (**4xc**)
10[c]	**1q** ($PhCH_2$)	**2a**	60 (**4qa**)
11[d]	**1q** ($PhCH_2$)	**2f**	65 (**4qf**)
12[c]	**1q** ($PhCH_2$)	**2k**	60 (**4qk**)

[a] Reactions were carried out in DMSO (0.5 M) with 1.5 equiv of **2** relative to **1q–x** (0.5 mmol) in the presence of 10 mol% of **3d**. [b] Yields of products purified by column chromatography on silica gel. [c] Catalyzed by *t*BuOK at RT for 1 h. [d] Catalyzed by DBU at RT for 0.5 h and at 60 °C for 1 h.



Scheme 2. Mechanism of the organo-click reaction.

triazoles **4** from the simple aldehydes **1** and aryl azides **2** through a [3+2] cycloaddition reaction. This organo-click reaction proceeds with a high rate and selectivity within 0.5 h at room temperature, giving the desired products in very good yields. Further work is in progress to develop organocatalytic enolate-mediated [3+2] cycloaddition reactions.

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[8] CCDC 1005119 (**4ab**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.