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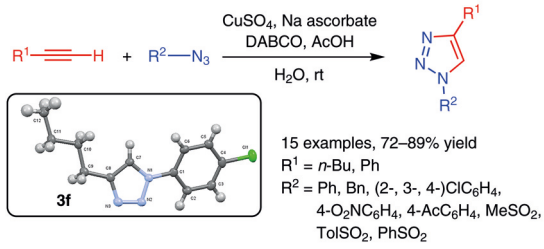
DABCO/AcOH Jointly Accelerated Copper(I)-Catalysed Cycloaddition of Azides and Alkynes on Water at Room Temperature

Prashant B. Sarode
Sandeep P. Bahekar
Hemant S. Chandak*

Department of Chemistry, G. S. Science, Arts and Commerce College, Khamgaon 444303, India
chemants@gmail.com
hschandak@gsck.ac.in



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Abstract An expeditious room temperature protocol for the synthesis of 1,4-disubstituted 1,2,3-triazoles from terminal alkynes and substituted azides has been achieved using the combination of $CuSO_4$-ascorbate/1,4-diazabicyclo[2.2.2]octane/acetic acid. This expeditious protocol is applicable to aryl, alkyl, and sulfonyl azides. Acetic acid accelerates the protonation of cuprated triazole and thus avoids the possible side reactions. Devoid of acetic acid, the reaction pathway alters to the ketinimine route and results in the formation of sulfonamides.

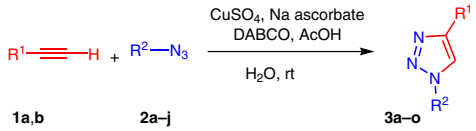
Key words CuAAC, DABCO, alkynes, azides, 1,4-disubstituted 1,2,3-triazole

Copper-catalysed azide–alkyne cycloaddition (CuAAC) has been the ultimate in click chemistry since the Huisgen [3+2] cycloaddition under catalytic condition was rediscovered independently by the groups of Sharpless[1] and Meldal.[2] Many research groups have devoted attention to finding different catalytic systems and studying the mechanistic aspects of the reaction. A literature survey reveals that there is plethora of catalytic systems using different copper(I) sources,[2,3] solvents,[4] and additives for CuAAC when alkyl or aryl azides are used. However, electron-deficient azides are challenging substrates since they frequently do not provide the corresponding 1,2,3-triazoles. *N*-Sulfonyl azides usually react with alkynes in the presence of the corresponding catalytic system giving amidines, imidates, or amides via a ketinimine intermediate.[5]

The reaction rate and product distribution of CuAAC depends upon the copper(I) source, solvent, ligand used, and the type of azide used. It is well-known that use of ascorbate as a mild reductant for the in situ generation of copper(I) has provided a convenient and practical protocol. Water is the solvent of choice as it is capable of supporting the in situ generated copper(I) acetylide in a reactive state. Furthermore, in aqueous medium the ability of copper(I) to engage the terminal alkyne by σ-and π-interactions and the rapid exchange of these with other ligands in its coordination sphere becomes pronounced.[6] A delay in the onset of catalysis by copper(I) is observed in some cases, due to the formation of unreactive polynuclear copper(I) acetylide clusters.[7]

Previous experimental and DFT investigations[8] of the mechanism of CuAAC suggest that formation of unreactive copper(I) acetylide clusters and delay in the protonation of cuprated triazole constitute bottlenecks in the development of an efficient protocol for the formation of triazoles. Overcoming these two hurdles should therefore enhance the rate of the reaction as well as minimizing the formation of side products such as diacetylenes, bistriazoles, and 5-hydroxytriazole.[9] The addition of an electron-rich ligand increases the electron density at copper and N1 and decreases the binding energy of the C5–Cu bond, which improves the stability of the N1–N2 bond.[10] Acetic acid (AcOH) is known to be the best proton source for the protonation of cuprated triazole and it accelerates both cycloaddition and protonation steps.[3a,10,11]

We speculated that 1,4-diazabicyclo[2.2.2]octane (DABCO) could primarily prevent the formation of the unreactive polynuclear copper(I) acetylide and facilitate the coordination of azide to copper during the ligand exchange step. Acetic acid may accelerate the conversion of the copper-metallated triazole to triazole and buffer the basicity of DABCO. With the aim of designing a simple, efficient, and expeditious protocol that should be modular with respect to aryl/alkyl/sulfonyl azides, we present herein a DABCO–AcOH accelerated aqueous ascorbate method for the synthesis of 1,4-disubstituted 1,2,3-triazoles (Scheme 1).



Scheme 1 DABCO–AcOH accelerated CuAAC

To confirm our hypothesis, control experiments were undertaken as shown in Table 1. In preliminary experiments, CuAAC reactions were conducted in $CuSO_4{\cdot}5H_2O$ (10 mol%), sodium ascorbate (40 mol%), and a binary mixture of solvents. In an *i*-PrOH–H_2O system (1:1) product **3a** was obtained in moderate yield; while CH_2Cl_2–H_2O system (1:1) and THF resulted in lower yields. However, when DABCO was added to the reaction system, the substrates reacted within four hours to give **3a** in moderate yield (Table 1, entry 6). Addition of triethylamine as an additive hampered the reaction resulting in a lower yield (Table 1, entry 7). Various commercially available copper(I) salts such as CuCl and CuI were also tested in the presence of DABCO (20 mol%) and AcOH (20 mol%), however, the outcomes were not encouraging. In addition to this, formation of the diacetylene product via Glaser–Hay coupling[12] was also observed.

To our satisfaction, the $CuSO_4$-ascorbate/DABCO/AcOH catalytic system effectively catalysed the reaction and complete conversion of the starting alkyne and azide was observed within 15 minutes, resulting in a 86% yield of **3a** (Table 1, entry 12). The reaction with this catalyst system ($CuSO_4{\cdot}5H_2O$/sodium ascorbate/DABCO/AcOH) in different proportions (Table 1, entries 13–15) was studied, and it was observed that the catalytic system with a 1:4:2:2 proportion proved most productive (Table 1, entry 14).

To explore the generality of this protocol, cycloaddition between various alkynes and azides was tested. Benzyl- and substituted phenyl azides react smoothly in this acid and base jointly accelerated CuAAC reaction to afford 1,4-disubstituted 1,2,3-triazoles within 15 minutes in water with excellent yields (Scheme 2, 3a–i).[13] The structure of compound **3f** was confirmed unequivocally by X-ray crystallographic analysis (Figure 1).[14]

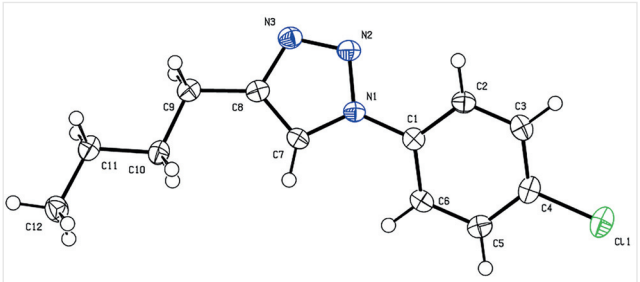
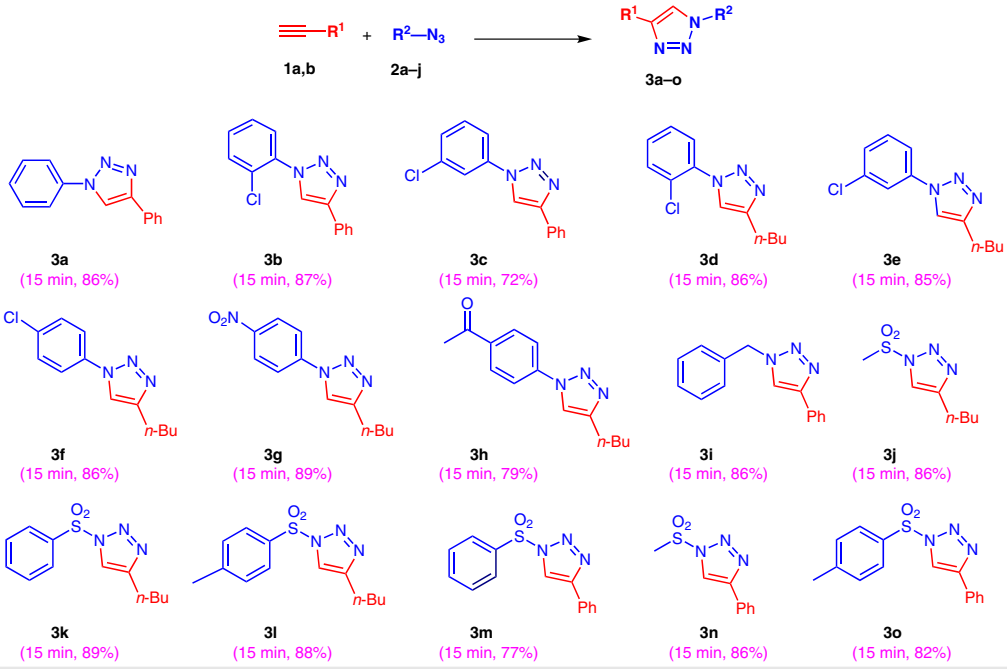


Figure 1 ORTEP diagram of **3f** (CCDC 1479799)

Table 1 Screening of Catalyst, Additive, and Solvent for the Synthesis of **3a**[a]

Entry	Copper source (mol%)	Reducing agent (mol%)	Solvent	Additive (mol%)	Proton source	Time (h)	Yield (%)[b]
1	$CuSO_4{\cdot}5H_2O$ (10)	Na ascorbate (40)	*i*-PrOH–H_2O (1:1)	–	–	3	59
2	$CuSO_4{\cdot}5H_2O$ (10)	Na ascorbate (40)	CH_2Cl_2–H_2O (1:1)	–	–	20	56
3	$CuSO_4{\cdot}5H_2O$ (10)	Na ascorbate (40)	THF	–	–	12	20
4	$CuSO_4{\cdot}5H_2O$ (10)	Na ascorbate (40)	CH_2Cl_2–H_2O (1:1)	DABCO (20)	–	6	59
5	$CuSO_4{\cdot}5H_2O$ (10)	Na ascorbate (40)	EtOH–H_2O (1:1)	DABCO (20)	–	6	59
6	$CuSO_4{\cdot}5H_2O$ (10)	Na ascorbate (40)	H_2O	DABCO (20)	–	4	63
7	$CuSO_4{\cdot}5H_2O$ (10)	Na ascorbate (40)	H_2O	Et_3N (20)	–	4	45
8	$CuSO_4{\cdot}5H_2O$ (10)	Na ascorbate (40)	H_2O	DABCO (20)	AcOH (20)	0.25	86
9	CuCl (10)	–	DMSO–H_2O (1:1)	Na_2CO_3	–	5	50
10	CuCl (10)	–	H_2O	DABCO (20)	AcOH (20)	1	66
11	CuI (10)	–	H_2O	DABCO (20)	AcOH (20)	1	36
12	$CuSO_4{\cdot}5H_2O$ (5)	Na ascorbate (20)	H_2O	DABCO (10)	AcOH (10)	0.25	86
13	$CuSO_4{\cdot}5H_2O$ (4)	Na ascorbate (16)	H_2O	DABCO (8)	AcOH (8)	0.25	86
14	$CuSO_4{\cdot}5H_2O$ (3)	Na ascorbate (12)	H_2O	DABCO (6)	AcOH (6)	0.25	86
15	$CuSO_4{\cdot}5H_2O$ (2)	Na ascorbate (8)	H_2O	DABCO (4)	AcOH (4)	0.25	70

[a] A mixture of **1a** (1 equiv) and **2a** (1 equiv) was tested at r.t.
[b] Isolated yields.

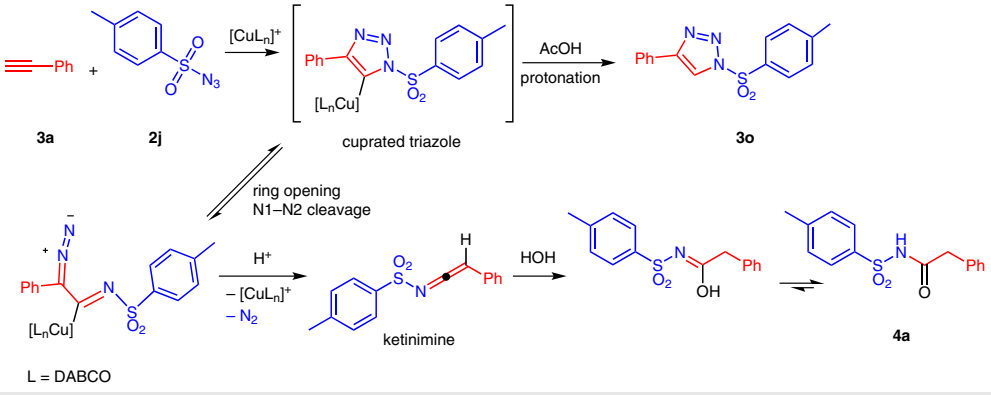


Scheme 2 Synthesis of 1,4-disubstituted -1,2,3-triazole from various alkynes and azides

To improve the substrate scope of the process further, various sulfonyl azides (**2h–j**) were also tested. *N*-Sulfonyltriazoles arising from the reaction of sulfonyl azides and alkynes can undergo rearrangement leading to the formation of mixture of triazoles and their ring-opened α-diazoimino tautomers.[15] We found the present catalytic system (DABCO/AcOH) to work well with sulfonyl azides and solely afford *N*-sulfonyltriazoles with excellent yields (Scheme 2, entries **3j–o**).

To confirm the role of AcOH in the reaction, a control experiment for the reaction of phenyl acetylene (**1a**) and 4-methylbenzenesulfonyl azide (**2j**) was performed using the optimized reaction conditions but excluding AcOH.[16] *N*-Sulfonyl amide **4a** was obtained exclusively instead of the desired *N*-sulfonyltriazole (**3o**). The pathways for formation of both cyclic product **3o** and chain product **4a** share the 5-cuprated 1,2,3-triazole as a common intermediate (Scheme 3). In the presence of AcOH subsequent protonation of this intermediate results in the formation of *N*-sulfonyl triazole (**3o**) but in the absence of AcOH, the protonation step is delayed and consequently, N1–N2 bond cleavage takes place to give the *N*-sulfonyl amide via the ketinimime intermediate.

In summary, we have developed a robust and highly efficient catalytic system of copper(I)/DABCO/AcOH for the synthesis of 1,4-disubstituted 1,2,3-triazoles. The DABCO/AcOH combination provides a buffer and dramatically decreases the reaction time from hours to minutes. The de-



Scheme 3 Mechanistic steps involved in the formation of *N*-sulfonyl amide

veloped protocol is versatile and tolerant of most functional groups. The addition of DABCO improves the stability of the N1–N2 bond by increasing the electron density at copper and N1 and decreasing the binding energy of the C5-Cu bond. AcOH accelerates the protonation of cuprated triazole and buffers the basicity of DABCO. We further conclude that delay in the protonation of the cuprated triazole intermediate results in ring opening with the cleavage of the N1–N2 bond to form the ketinimine intermediate which is trapped with water to form *N*-sulfonyl amides. This study demonstrates the role of AcOH in the development of an expeditious protocol for CuAAC and also opens a way to control the selectivity of formation of ring with regard to ring-opened product during the reaction of electron-deficient azides with alkynes.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588590.

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(13) **1,4-Diphenyl-1*H*-1,2,3-triazole (3a)**
A mixture of $CuSO_4{\cdot}5H_2O$ (0.03 mmol), sodium ascorbate (0.12 mmol), and DABCO (0.06 mmol) in H_2O (2 mL) was stirred vigorously at r.t. for 5 min. To this, AcOH (0.06 mmol), phenylacetylene (**1a**) (1 mmol), and phenyl azide (**2a**, 1 mmol) were added sequentially, and the resultant mixture was stirred until the substrates had been completely consumed (TLC monitoring). The reaction mixture was diluted by adding EtOAc (5 mL) and aq NH_4Cl solution (3 mL). The mixture was stirred for an additional 30 min, and the two layers were separated. The aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated. The crude product thus obtained was recrystallized from EtOH to afford pure 1,4-diphenyl-1,2,3-triazole (**3a**) as a pale yellow solid; yield 0.160 g, 86%; mp 182–183 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.20 (s, 1 H), 7.93–7.91 (m, 2 H), 7.81–7.79 (m, 2 H), 7.58–7.54 (m, 2 H), 7.48–7.45 (m, 3 H), 7.39–7.36 (m, 1 H).
(14) CCDC 1479799 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.
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(16) **2-Phenyl-*N*-tosylacetamide (4a)**
A mixture of $CuSO_4{\cdot}5H_2O$ (0.03 mmol), sodium ascorbate (0.12 mmol), and DABCO (0.06 mmol) in H_2O (2 mL) was stirred vigorously at r.t. for 5 min. Alkyne **1a** (1 mmol) and *p*-toluenesulfonyl azide (**2j**, 1 mmol) were added sequentially, and the resultant mixture was stirred until the substrates had been completely consumed (TLC monitoring). The reaction mixture was diluted by adding EtOAc (5 mL) and aq NH_4Cl solution (3 mL), the mixture was stirred for an additional 30 min, and the two layers were separated. The aqueous layer was extracted with EtOAc (2 × 5 mL), the combined organic layers were dried over Na_2SO_4, filtered, and evaporated. The crude product so obtained was purified by recrystallization from EtOH to afford pure 2-phenyl-*N*-tosylacetamide (**4a**) as a white solid; yield 0.095 g, 64%; mp 148–149 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.87 (d, 2 H), 7.81 (br s, 1 H), 7.33 (m, 5 H), 7.14 (d, 2 H) 3.58 (s, 2 H), 2.44 (s, 3 H).