Greener and Expeditious Synthesis of 1,4-Disubstituted 1,2,3-Triazoles from Terminal Acetylenes and in situ Generated α-Azido Ketones

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Abstract: A convenient and mild protocol for the one-pot regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles in aqueous PEG 400 has been reported. The methodology involves the one-pot reaction of α-bromo ketones, sodium azide, and terminal acetylenes catalyzed by Cu(I) in aqueous PEG 400 at room temperature. Prominent features of our approach are mild reaction conditions, use of readily available α-bromo compounds, aqueous PEG 400 as a benign reaction medium, avoiding the isolation of labile α-azido ketones, simple workup, and good yields.

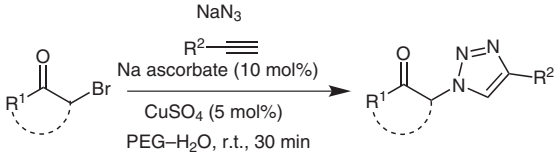
Key words: 1,2,3-triazoles, α-bromo ketones, click chemistry, α-azido ketones

The 1,2,3-triazole, a five-membered, nitrogen-containing heterocycle, is often encountered as a structural unit of compounds possessing diverse biological activities including herbicidal, fungicidal, antibacterial, antiallergic, selective β_3 adrenergic receptor agonism, anti-HIV, and anti-convulsant.[1] Many 1,2,3-triazoles are also used as dyes, optical brightners, agrochemicals, photographic materials, and corrosion inhibitors.[1c–1e,2] Stability towards metabolic degradation and capability of hydrogen-bond formation make 1,2,3-triazoles an attractive connecting unit to discover novel biologically interesting chemical entities.[3]

Organic reactions in environmentally benign media have attracted significant interest among researchers due to the detrimental impact of toxic and volatile solvents on the environment.[4] In the past, without losing reaction efficiency, chemists have demonstrated the utility of benign alternative solvents such as ionic liquids, water, and polyethylene glycol (PEG) as a replacement for toxic and volatile organic solvents.[5] Multicomponent reactions (MCR) involving sequential reactions among three or more substrates have emerged as a powerful synthetic strategy to achieve diversely substituted organic compounds.[6] Owing to many advantages in terms of molecular complexity, operational simplicity, isolation and handling of intermediates, purification, and atom economy, MCR comply with most of the stringent requirements of green chemistry.

In the past, various methods were developed for the synthesis of 1,2,3-triazoles. Of the existing procedures, the 1,3-dipolar cycloaddition reaction of azides with alkynes is a very useful organic transformation which has been extensively studied by Huisgen et al.[7] Recently, Sharpless and co-workers have reported remarkable high-yielding syntheses of 1,2,3-triazoles with excellent regioselectivity.[1b]

α-Bromo ketones can be easily prepared by the selective α-bromination of the appropriate acetyl compound.[8] Isolation and purification of some α-azido ketones from the reaction of α-bromo ketones and sodium azide is difficult due to incomplete conversion.[9] Therefore, a method which avoids the isolation and handling of α-azido ketones via in situ generation from the reaction of α-bromo ketones with sodium azide is highly attractive and safe. In our efforts to prepare a novel and diverse library of 1,4-disubstituted 1,2,3-triazoles, we report herein a one-pot synthesis of these interesting compounds using Cu(I)-catalyzed reaction of α-bromo ketones, terminal acetylenes, and sodium azide in aqueous PEG 400 at room temperature (Scheme 1).[10]



Scheme 1 Synthesis of 1,2,3-triazoles **2**

We first tested the three-component reaction involving α-bromo ketones, sodium azide, and phenylacetylene in various solvents such as water, DMF, DMSO, and PEG 400 and their different combinations in the presence of the Cu(I) at room temperature. After varying the reaction conditions, it was found that aqueous PEG 400 (1:1) is the solvent of choice for this three-component reaction.

Under these optimized conditions, reaction of α-bromo acetophenone, sodium azide, and phenylacetylene resulted in the exclusive formation of 1-phenyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethanone (**2a**) in 90% yield at room temperature in 30 minutes. The IR spectrum of **2a** (Table 1) displayed a strong band at about 1690 cm^{-1} indicating the presence of a ketone group. The ^1H NMR spectrum of **2a** displayed a distinct singlet at $\delta = 8.19$ ppm for the triazolyl C_5–H proton. The mass spectra of this compound exhibits the molecular ion peak at $m/z = 264.3$ $[M + H]^+$, which is in agreement with the calculated value.

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Table 1 Synthesis of 1,4-Disubstituted 1,2,3-Triazoles **2**

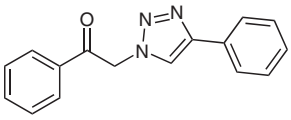
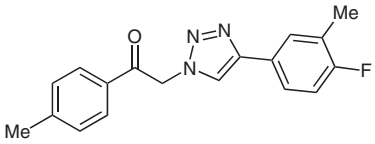
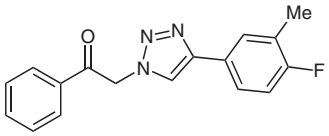
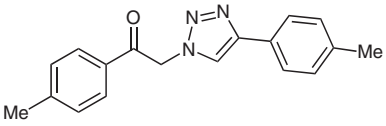
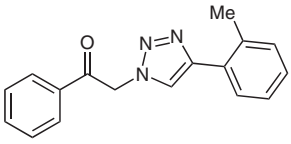
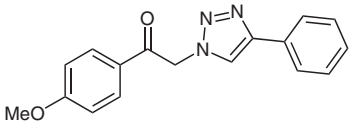
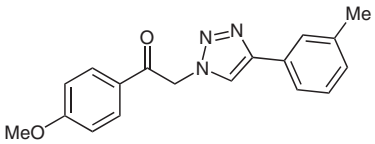
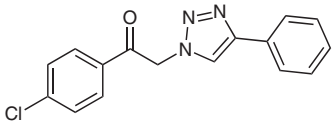
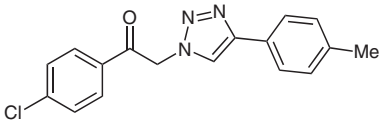
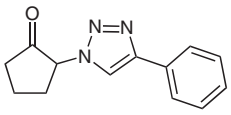
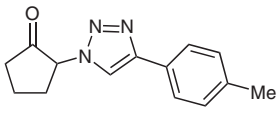
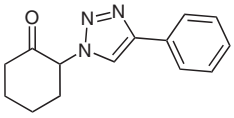
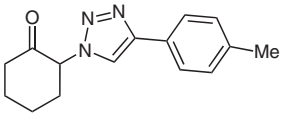
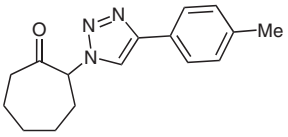
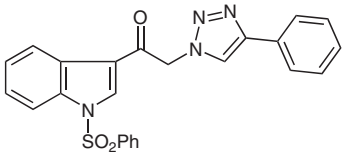
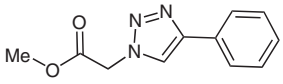
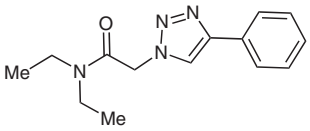
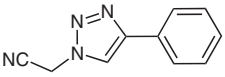
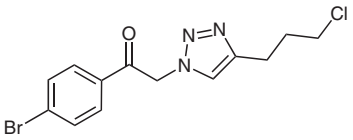
Product		Yield (%)[a]
2a		90
2b		88
2c		86
2d		90
2e		85
2f		86
2g		84
2h		87
2i		85
2j		86
2k		81
2l		83

Table 1 Synthesis of 1,4-Disubstituted 1,2,3-Triazoles **2** (continued)

Product		Yield (%)[a]
2m		85
2n		81
2o		80
2p		77
2q		78
2r		79
2s		75

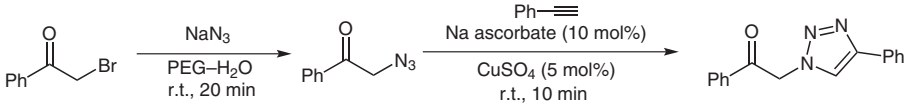
[a] Yields refer to pure and isolated products.

Encouraged by the success with initial efforts, we decided to extend the scope of this one-pot protocol by choosing various α-halo compounds and terminal acetylenes.

All the α-bromo ketones, α-bromoacetonitrile, α-bromo-*N*,*N*-dimethylacetamide, and terminal acetylenes reacted smoothly to afford diverse 1,4-disubstituted 1,2,3-triazoles **2b**–**s** in good yields (Table 1). Regioselective syntheses of 1,4-disubstituted 1,2,3-triazole analogues with diverse functionalities further demonstrates the usefulness of this protocol. After completion of the reaction, the products were isolated by simple filtration or percolating the crude product through a bed of silica gel. All the products were characterized by IR, NMR, and MS data.

To check the reusability of the catalyst and aqueous PEG 400 system, after the removal of product **2a**, the solution obtained was recycled for successive reactions. Almost similar results were obtained in the second and third successive recycles in terms of product yield and reaction time.

Formation of 1,4-disubstituted 1,2,3-triazoles **2** probably involve first in situ generation of α-azido ketones by the reaction of α-bromo ketone with sodium azide. Subse-



Scheme 2 Stepwise synthesis of 1,2,3-triazoles **2**

quently, cycloaddition reaction of α-azido ketones and terminal acetylenes generates **2**. Higher solubility of reactants in aqueous PEG 400 and formation of PEG 400–sodium cation complex may be responsible for the faster reaction.[11] The reaction pathway was further unambiguously confirmed by the preparation of **2** from the reaction of α-azidoacetophenone with phenylacetylene (Scheme 2).

In summary, we have developed a rapid and high yielding one-pot regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles in aqueous PEG 400 system at room temperature. Use of easily available α-bromo ketones, α-bromoacetonitrile, α-bromo-*N*,*N*-dimethylacetamide, and terminal acetylenes makes this protocol very useful for the preparation of diverse 1,4-disubstituted 1,2,3-triazoles. Simple experimentation, solvent and catalyst reusability, benign reaction solvent, mild reaction conditions, and high yields make this method attractive.

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(10) **General Procedure**
To a solution of α-halo compound **1** (1.0 mmol), NaN_3 (1.2 mmol), and terminal acetylene (1.0 mmol) in aq PEG 400 (2 mL) was added sodium ascorbate (19.8 mg, 10 mol%) and 1 M $CuSO_4$ (50 μL, 5 mol%) solution. The reaction mixture was allowed to stir at r.t. for 30 min. After the reaction was complete, as indicated by TLC, the solid product was filtered, washed, and dried to afford pure product.
Analytical Data for Selected Compounds
Compound **2a**:[7c] IR (KBr): 1690 (CO) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 8.04–8.00 (2 H, m), 7.95 (1 H, s), 7.89–7.84 (2 H, m), 7.73–7.65 (1 H, m), 7.59–7.31 (5 H, m), 5.91 (2 H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 195.0 (CO), 152.4, 139.0, 138.2, 134.5, 133.5, 133.2, 132.7, 132.5, 130.1, 126.4, 59.9. MS (EI): *m/z* calcd for $C_{16}H_{14}N_3O$ $[M + H]^+$: 264.1; found: 264.3.
Compound **2h**: IR (KBr): 1680 (CO) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.53 (1 H, s), 8.11 (2 H, d, *J* = 8.0 Hz),

7.88 (2 H, d, J = 8.0 Hz), 7.70 (2 H, d, J = 8.0 Hz), 7.48–7.45 (2 H, m), 7.37–7.35 (1 H, m), 6.27 (2 H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 191.4 (CO), 146.3, 139.2, 132.8, 130.7, 130.1, 129.1, 128.9, 127.9, 125.1, 123.0, 56.0. MS (EI): *m/z* calcd for $C_{16}H_{13}ClN_3O$ [M + H]$^+$:298.0747; found: 297.9593.

Compound **2l**: IR (KBr): 1720 (CO) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.56 (1 H, s), 7.85 (2 H, d, J = 8.0 Hz), 7.47–7.44 (2 H, m), 7.35–7.32 (1 H, m), 5.76–5.71 (1 H, m), 2.75–2.67 (1 H, m), 2.45–2.32 (3 H, m), 2.11–2.09 (1 H, m), 1.96–1.92 (2 H, m), 1.76–1.68 (1 H, m). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 204.1 (CO), 145.9, 130.8, 128.9, 127.8, 125.0, 121.3, 66.8, 40.4, 33.4, 26.4, 23.6. MS (EI): *m/z* calcd for $C_{14}H_{16}N_3O$ [M + H]$^+$: 242.1293; found: 242.0473.

Compound **2o**: IR (KBr): 1685 (CO) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.17 (1 H, s), 8.61 (1 H, s), 8.20 (2 H, d, J = 8.0 Hz), 8.15 (1 H, d, J = 8.0 Hz), 8.02 (1 H, d, J = 8.0 Hz), 7.90 (2 H, d, J = 8.0 Hz), 7.80–7.76 (1 H, m), 7.69–7.65 (2 H, m), 7.49–7.33 (5 H, m), 6.26 (2 H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 187.9 (CO), 146.3, 136.3, 135.4, 134.8, 133.9, 130.7, 130.2, 128.9, 127.9, 127.3, 126.8, 126.2, 125.2, 125.1, 123.2, 122.0, 117.5, 113.1, 56.0. MS (EI): *m/z* calcd for $C_{24}H_{19}N_4O_3S$ [M + H]$^+$: 443.1178; found: 443.0073.

Compound **2p**: IR (KBr): 1759 (CO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.82 (3 H, m), 7.42–7.27 (3 H, m), 5.21 (2 H, s), 3.80 (3 H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8 (CO), 148.2, 130.4, 128.9, 128.3, 125.8, 121.1, 53.0, 50.8. MS (EI): *m/z* calcd for $C_{11}H_{12}N_3O_2$ [M + H]$^+$: 218.1; found: 218.3.

Compound **2q**: IR (KBr): 1651 (CO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (1 H, s), 7.85–7.83 (2 H, m), 7.44–7.39 (2 H, m), 7.39–7.30 (1 H, m), 5.23 (2 H, s), 3.46–3.39 (4 H, m), 1.25 (3 H, t, J = 7.15 Hz), 1.15 (3 H, t, J = 7.10 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.0 (CO), 148.0, 130.7, 128.8, 128.1, 125.8, 121.4, 50.9, 42.0, 41.0, 14.4, 12.8. MS (EI): *m/z* calcd for $C_{14}H_{19}N_4O$ [M + H]$^+$: 259.2; found: 259.3.

Compound **2r**: IR (KBr): 2286 (CN) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.00 (1 H, s), 7.86–7.81 (2 H, m), 7.51–7.38 (3 H, m), 5.40 (2 H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 149.6, 129.9, 129.4, 129.3, 126.3, 120.3, 113.1, 38.0. MS (EI): *m/z* calcd for $C_{10}H_9N_4$ [M + H]$^+$: 185.1; found: 185.2.

Compound **2s**: IR (KBr): 1693 (CO) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.86 (2 H, d, J = 8.49 Hz), 7.68 (2 H, d, J = 8.49 Hz), 7.51 (1 H, s), 5.79 (2 H, s), 3.65–3.58 (2 H, m), 2.96–2.91 (2 H, m), 2.24–2.15 (2 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 189.7 (CO), 146.8, 132.7, 132.6, 130.0, 129.6, 123.0, 55.3, 44.2, 31.8, 22.7. MS (EI): *m/z* calcd for $C_{13}H_{14}BrClN_3O$ [M + H]$^+$: 342.0; found: 342.0.

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