A Convenient Synthesis of 1-Substituted 1,2,3-Triazoles via CuI/Et_3N Catalyzed 'Click Chemistry' from Azides and Acetylene Gas

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Abstract: Copper(I)-catalyzed 'click chemistry' using acetylene gas was successfully explored under mild conditions. 1-Substituted-1,2,3-triazoles were conveniently synthesized from the corresponding aromatic and aliphatic azides.

Key words: azides, copper(I) catalysis, click chemistry, acetylene gas, 1,2,3-triazoles

1,2,3-Triazole derivatives have displayed an ample range of application in pharmaceutical, agrochemical, and material sciences.[1] Since Fokin and Sharpless developed Cu(I)-catalyzed 1,3-dipolar Huisgen cycloaddition reaction of azides with alkynes,[2] 'click chemistry' has received growing interest in the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles.[3] The formation of triazoles in 'click chemistry' has represented definitive advances: reliable, effective, benign in reaction conditions, and high tolerance to many functional groups. Through this reaction, a wide variety of compounds with an inert triazole heterocycle could be prepared that are of interest in medicinal chemistry and material science.[4]

Due to the contributions from Sharpless group and others, most reports were focused on the preparations of 1,4-disubstituted 1,2,3-triazoles.[3,5] To our best knowledge, synthesis of 1-substituted-1,2,3-triazole received little attention.[6] One of the most convenient entries is the 1,3-dipolar Huisgen cycloaddition reaction of azides with acetylene gas.[7] However, the typical Huisgen cycloaddition processes required elevated temperature, high pressure, and special reaction vessel. Reviewing the mechanism of the 'click chemistry', 1-substituted-1,2,3-triazole compounds would be similarly produced when acetylene gas was used as substrate. It was recently reported that 1-substituted-1,2,3-triazoles were successfully synthesized under the 'click' conditions from trimethylsilylacetylene and azides.[6a] However, deprotection of trimethylsilylacetylene made this process less atom economic. Motivated by our interesting in the 'click chemistry',[8] we examined the feasibility to synthesize 1-substituted-1,2,3-triazole via 'click' approach by direct usage of acetylene gas under mild conditions. Herein, we wish to report our results in this paper.

In preliminary experiments, benzyl azide (**1a**) was chosen for the template reaction with acetylene gas. The results are summarized in Table 1. Initially, acetone was chosen as the solvent. No product was isolated when the reaction was conducted at room temperature even for 24 hours in the presence of 10 mol% CuI (entry 1, Table 1). It was reported that organic bases could help the formation of the active copper acetylide complex, and promoted the 'click' reaction.[2b,4e,9] Therefore, we tried adding 40 mol% Et_3N into the reaction system. To our delight, the reaction gave the corresponding compound **2a** in 38% yield (entry 2, Table 1). Encouraged by this positive result, other polar solvents were also investigated (entries 3–9, Table 1). Clearly, the reaction was dramatically affected by solvent.[10] Dimethyl sulfoxide was found to be one of the best solvents to give good yields. It should be pointed out that MeCN and DMSO–H_2O both gave excellent results in the model reaction (entries 6 and 9, Table 1), but only medium yields were obtained when other azides were exploited as the reactant.[11] Thus, DMSO was chosen as the typical solvent in subsequent experiments. Other Cu(I) catalysts were investigated, which showed lower activity (entries 10–12, Table 1). Decreasing the reaction time from 24 hours to 14 hours gave rise to a reduction of the yield (entry 13, Table 1). The loading of Et_3N was also examined (entries 14 and 15, Table 1). When 20 mol% Et_3N were used, the yield of the product was reduced to 69%. Adding 1.0 equivalent Et_3N to the reaction system did not significantly improve the result. Other organic bases were also introduced into the reaction mixture and gave slightly lower yields (entries 16–18, Table 1). In comparison with the base-free conditions, inorganic base (K_2CO_3) did not improve the result (entries 19 and 20, Table 1). Reducing the amount of catalyst CuI to 5 mol% again led to a drop of product yield to 72% (entry 21, Table 1). The reaction did not proceed without the presence of catalyst (entry 22, Table 1).

With the optimal conditions in hand, a variety of azides were explored in this 'click' process. Generally, as shown in Table 2, the reactions were highly influenced by steric and electronic effects. Both electron-rich and electron-deficient aromatic azides, bearing substituents at *meta*- and *para*-position, afforded the product in excellent yields. It should be noted that the reaction of electron-rich azide (4-methoxy-phenyl azide) was slower than other

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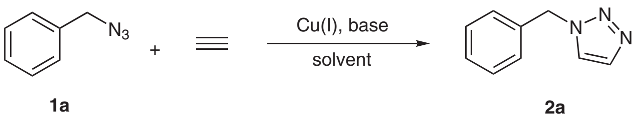
Table 1 Optimization of the Reaction Conditions[a]



Entry	Solvent	Cu(I) (10 mol%)	Base (mol%)	Yield (%)[b]
1	acetone	CuI	–	0
2	acetone	CuI	Et_3N (40)	38
3	THF	CuI	Et_3N (40)	23
4	MeOH	CuI	Et_3N (40)	31
5	DMF	CuI	Et_3N (40)	44
6	MeCN	CuI	Et_3N (40)	89
7	DMSO	CuI	Et_3N (40)	85
8	dioxane	CuI	Et_3N (40)	17
9	DMSO/H_2O[c]	CuI	Et_3N (40)	85
10	DMSO	CuBr	Et_3N (40)	78
11	DMSO	CuCl	Et_3N (40)	76
12	DMSO	$CuSO_4$/Vc[d]	Et_3N (40)	31
13[e]	DMSO	CuI	Et_3N (40)	80
14	DMSO	CuI	Et_3N (20)	69
15	DMSO	CuI	Et_3N (40)	83
16	DMSO	CuI	2,6-lutidine (40)	80
17	DMSO	CuI	pyridine (40)	78
18	DMSO	CuI	i-Pr_2NEt (40)	77
19	DMSO	CuI	K_2CO_3 (40)	54
20	DMSO	CuI	–	59
21[f]	DMSO	CuI	Et_3N (40)	72
22	DMSO	–	–	0

[a] Unless otherwise noted, all reactions were performed with 0.4 mmol Et_3N, 1.0 mmol of azide, 1.5 mL of solvent, and 0.1 mmol catalyst under a balloon pressure of acetylene atmosphere at r.t.

[b] Isolated yield.

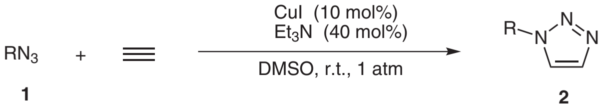
[c] $V_{DMSO}/V_{H2O} = 4:1$.

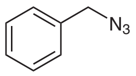
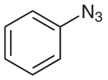
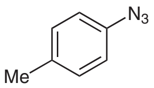
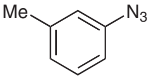
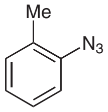
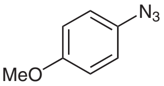
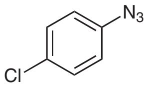
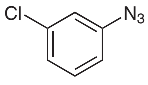
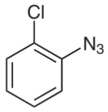
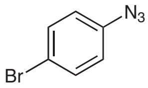
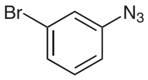
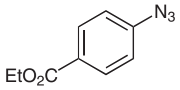
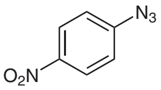
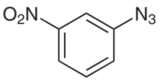
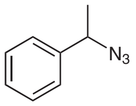
[d] Vc = sodium ascorbate.

[e] 14 h.

[f] The amount of 5 mol% CuI was used.

Table 2 Reaction of Acetylene Gas with Different Azides[a]



Entry	Azide	Time (h)	Triazole[12,13]	Yield (%)[b]
1		24	**2a**	85
2		24	**2b**	92
3		24	**2c**	93
4		24	**2d**	93
5		48	**2e**	45
6		48	**2f**	90
7		24	**2g**	92
8		24	**2h**	93
9		24	**2i**	54
10		24	**2j**	89
11		24	**2k**	86
12		24	**2l**	90
13		24	**2m**	91
14		24	**2n**	92
15		24	**2o**	76
16	n-C_8H_{17}—N_3	24	**2p**	97

[a] All reactions were performed with 0.4 mmol Et_3N, 1.0 mmol of azides, 1.5 mL of DMSO, and 0.1 mmol CuI under a balloon pressure of acetylene atmosphere at r.t., unless otherwise noted.

[b] Isolated yield.

4-substitued phenyl ones; the yield of 90% was isolated by prolonging the reaction time to 48 hours (entry 6, Table 2).

ortho-Substituted aromatic azides, 2-methylphenyl azide and 2-chlorophenyl azide, provided moderate yields in 45% and 54%, respectively (entries 5 and 9, Table 2). Compared with benzyl azide, the reaction of methyl benzyl azide gave a lower yield (76%, entry 15, Table 2), which was due to higher steric hindrance. In the case of aliphatic azide (*n*-octanyl azide) the reaction worked well to give the triazole in 97% yield (entry 16, Table 2).

In summary, CuI and Et_3N in DMSO proved to be an effective and convenient catalytic system for 'click chemistry' with acetylene gas. The reaction produced a series of 1-substituted-1,2,3-triazoles in moderate to excellent yields from both aliphatic and aromatic azides.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) The present reaction exhibited strong solvent effect, which is greatly different from the typical 'click chemistry'. The discrepancy was presumed to cause by the acetylene gas. In the reactions, abundant reddish-brown precipitate was formed.

(11) Acetonitrile and DMSO–H_2O both gave excellent results in the template reaction. But when other azides used, the yields decreased significantly. In MeCN, **2b** and **2c** were obtained, respectively, in 52% and 63% after 24 h. In DMSO–H_2O (4:1), 4-methylphenyl azide was tried, but the yield was only poor 40%. Therefore, we chose DMSO as typical solvent in subsequent experiments. The reason of the discrepancy is unknown.

(12) **Typical Procedure for Compound 2**.
To a 5 mL flask with Et_3N (0.4 mmol), azides **1** (1.0 mmol), and solvent (1.5 mL), CuI (0.1 mmol) was added into the mixture under N_2 atmosphere. The flask was purged with acetylene for several times. Then the mixture was stirred under a balloon pressure of acetylene at r.t. After the designed time, the mixture was diluted with 25 mL EtOAc, and washed by 10 mL H_2O for four times then by brine. The organic phase dried over anhyd Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified on SiO_2 with PE–EtOAc (4:1 to 1:2). *Caution*: Azides are potentially explosive compounds and should be handled with great care.

(13) **Analytical Data of Selected Products**

Compound **2a**: white solid, mp 51–53 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (s, 1 H), 7.48 (s, 1 H), 7.37 (m, 3 H), 7.27 (m, 2 H), 5.57 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.6, 134.0, 128.9, 128.5, 127.8, 123.3, 53.7 ppm. MS (EI): *m/z* = 159 [M$^+$], 130, 104, 91, 77.

Compound **2b**: pale yellow solid, mp 52–53 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 1 H), 7.88 (s, 1 H), 7.77 (m, 2 H), 7.56 (m, 2 H), 7.47 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5, 135.7, 130.0, 129.0, 122.8, 121.0 ppm. MS (EI): *m/z* = 145 [M$^+$].

Compound **2c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (s, 1 H), 7.80 (s, 1 H), 7.59 (d, *J* = 6.8 Hz, 2 H), 7.28 (d, *J* = 6.8 Hz, 2 H), 2.39 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 134.5, 134.0, 130.0, 121.6, 120.2, 20.8 ppm. MS (EI): *m/z* = 159 [M$^+$].

Compound **2d**: yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (s, 1 H), 7.79 (s, 1 H), 7.54 (s, 1 H), 7.47 (d, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* = 7.6 Hz, 1 H), 7.20 (d, *J* = 7.2 Hz, 1 H), 2.40 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8, 136.8, 134.2, 129.34, 129.33, 121.7, 121.1, 117.5, 21.2 ppm. MS (EI): *m/z* = 159 [M$^+$].

Compound **2f**: white solid, mp 78–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (s, 1 H), 7.85 (s, 1 H), 7.65 (dd, J_1 = 6.9 Hz, J_2 = 2.1 Hz, 2 H), 7.03 (dd, J_1 = 6.9 Hz, J_2 = 2.1 Hz, 2 H), 3.88 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 135.7, 131.1, 123.0, 122.6, 115.1, 55.9 ppm. MS (EI): *m/z* = 175 [M$^+$].

Compound **2g**: pale yellow solid, mp 111–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (s, 1 H), 7.85 (s, 1 H), 7.70 (d, *J* = 8.8 Hz, 2 H), 7.50 (d, *J* = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 134.5, 134.0, 130.0, 121.6, 120.2, 20.8 ppm. MS (EI): *m/z* = 179 [M$^+$].

Compound **2h**: pale yellow solid, mp 91–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (s, 1 H), 7.85 (s, 1 H), 7.79 (s, 1 H), 7.65 (d, *J* = 7.6 Hz, 1 H), 7.46 (d, *J* = 8.0 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.7, 135.4, 134.6, 130.8, 128.7, 121.7, 120.7, 118.5 ppm. MS (EI): *m/z* = 179 [M$^+$].