Synthesis of 1,4-Disubstituted 1,2,3-Triazoles *via* a Three-Component Reaction in Water in the Presence of CuX (X = Cl, I)

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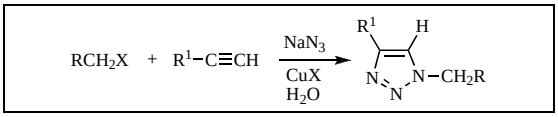

Three-component reaction of alkyl halides, sodium azide and alkynes in water in the presence of CuX (X = Cl, I) afforded 1,4-disubstituted 1,2,3-triazoles in high yields. These reactions do not require any special precautions or existence of a reducing agent. The bistriazoles formed during the reaction can efficiently enhance the catalytic activity of the Cu(I) salts.

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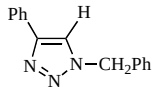
INTRODUCTION

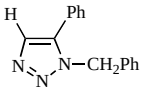
Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction of terminal alkynes and azides has attracted much attention [1-3]. This reaction shows high regioselectivity, wide substrate scope and excellent yields, and quickly found applications in medicinal chemistry [4], biological and biomedical research [5], combinatorial chemistry [6] and materials and surface science [7]. Recently, Cu(I)-catalyzed one-pot synthesis of 1,4-disubstituted 1,2,3-triazoles from alkyl halides, sodium azide and alkynes was reported [8]. These two- or three-component reactions were usually carried out in a mixed solvent of water and organic solvents in the presence of Cu(I) catalyst prepared *in situ* [1,8]. It was indicated that copper(I) salts such as CuI, $CuOTf{\cdot}C_6H_6$ and $[Cu(NCCH_3)_4][PF_6]$ can also catalyze the cycloaddition reactions. These copper(I) salts-catalyzed reactions usually require one equiv of a nitrogen base, and could form undesired by-products [1,3g,5e,9]. However, we found that reaction of organic azides and terminal alkynes can be efficiently catalyzed by CuI in water without the need for any other reagents or co-solvents, affording 1,4-disubstituted 1,2,3-triazoles in excellent yields [10]. Further we investigated three-component reaction of alkyl halides, sodium azide and terminal alkynes catalyzed by CuX (X = Cl, I) in water. Herein we report the results.

RESULTS AND DISCUSSION

The mixture of benzyl chloride, sodium azide and phenylacetylene in distilled water in the presence of CuI was heated to form 1-benzyl-4-phenyl 1,2,3-triazole **1a** (Figure 1). The reaction was affected by the amount of CuI, reaction time and reaction temperature (Table 1). When 0.1 mol % of CuI was employed, the reaction at 65 ℃ (bath temperature) afforded **1a** in 78% yield, and at 110 ℃ gave a mixture of 1,4- and 1,5-disubstituted 1,2,3-triazoles in 91% yield (**1a**:**1b** = 4:1). This shows that higher reaction temperature can enhance the reaction yield, but is disadvantageous to the regioselectivity. The use of 0.25 mol % of CuI at 65 ℃ increased the yield up to 91% and resulted in the formation of single 1,4-disubstituted triazole. The reaction was without the need for any reducing agent and protection from oxygen, and the product was separated by simple filtration.



1a



1b

Figure 1

Table 1

Three-component reaction of benzyl chloride, sodium azide and phenylacetylene in distilled water in the presence of CuI.

entry	CuI (mol%)	temp (℃)	time (h)	product	yield (%)
1	0.1	65	12	**1a**	78
2	0.1	110	10	**1a**+**1b** (4:1)	91
3	0.25	65	12	**1a**	91
4	0.5	65	10	**1a**	91
5	1	65	5	**1a**	90

We next investigated the reaction using different alkyl halides and different alkynes and the results are summarized in Table 2. Each of the reactions shown in Table 2 gave 1,4-disubstituted 1,2,3-triazole in high yield under the optimized conditions. The amount of the catalyst was from 0.25 mol % to 2.5 mol % depending on the reaction substrates. Aliphatic alkynes were found to be less reactive than phenylacetylene. The former needed more CuX catalyst to finish the reactions. Both benzylic and allylic chlorides can be applied in the three-component reactions. For example, 2-methylallyl chloride reacted with sodium azide and phenylacetylene in the presence of 0.3 mol % of CuI at 65 ℃ to yield 1,4-disubstituted 1,2,3-triazole **12a** in 90% yield. Methyl

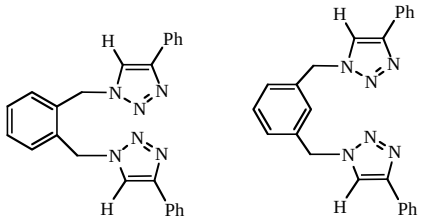
Table 2

Three-component reaction of alkyl chlorides, sodium azide and alkynes in distilled water in the presence of CuX (X = Cl or I).

entry	halide	alkyne	catalyst (mol%)	temp (℃)	time (h)	product	Yield (%)
1	$PhCH_2Cl$	PhC≡CH	CuI (0.25)	65	12	**1a**	91
2	*o*-$MeC_6H_4CH_2Cl$	PhC≡CH	CuI (1)	70	12	**2a**	89
3	*m*-$MeC_6H_4CH_2Cl$	PhC≡CH	CuI (1)	70	12	**3a**	87
4	*o*-$ClC_6H_4CH_2Cl$	PhC≡CH	CuI (1.5)	80	12	**4a**	85
5	*p*-$ClC_6H_4CH_2Cl$	PhC≡CH	CuI (1.5)	80	12	**5a**	88
6	$PhCH_2Cl$	$HOCH_2C$≡CH	CuI (1)	70	12	**6a**	93
7	*o*-$MeC_6H_4CH_2Cl$	$HOCH_2C$≡CH	CuI (2.5)	70	12	**7a**	93
8	*o*-$ClC_6H_4CH_2Cl$	$HOCH_2C$≡CH	CuI (2.5)	70	12	**8a**	94
9	$PhCH_2Cl$	$PhOCH_2C$≡CH	CuI (2.5)	70	12	**9a**	93
10	*o*-$(ClCH_2)_2C_6H_4$	PhC≡CH	CuI (0.2)	100	10	**10a**	96
11	*m*-$(ClCH_2)_2C_6H_4$	PhC≡CH	CuI (0.2)	100	10	**11a**	97
12	CH_2=C(Me)CH_2Cl	PhC≡CH	CuI (0.3)	60	12	**12a**	90
13	MeI	PhC≡CH	CuI (1)	55	24	**13a**	81
14	$PhCH_2Cl$	PhC≡CH	CuCl (0.26)	65	12	**1a**	90
15	*o*-$ClC_6H_4CH_2Cl$	PhC≡CH	CuCl (1.5)	80	12	**4a**	85
16	$PhCH_2Cl$	$HOCH_2C$≡CH	CuCl (1)	70	12	**6a**	90
17	*m*-$(ClCH_2)_2C_6H_4$	PhC≡CH	CuCl (0.2)	100	10	**11a**	96

iodide also exhibited good reactivity (Table 2, entry 13). Among the benzylic chlorides that we tested, substituted benzyl chlorides, including *o*- and *p*-chlorobenzyl chlorides and *o*- and *m*-methylbenzyl chlorides, were less reactive than benzyl chloride. The former required more CuI or CuCl catalyst to insure reasonable yields and high regioselectivity (Table 2, entries 2-5, 7, 8, 14 and 15). However, the reactions of *o*- and *m*-bis(chloromethyl) benzene with sodium azide and phenylacetylene could reach completion in the presence of only 0.2 mol % of CuI or CuCl, giving almost quantitative regioselective products (Table 2, entries 10, 11 and 17). This is ascribed to the acceleration of the bistriazoles (Figure 2, **10a** and **11a**) formed during the reaction (*cf.* the reaction of sodium azide and phenylacetylene with *o*-methylbenzyl chloride at 100℃ in the presence of 0.2 mol % of CuI produced a mixture of 1,4- and 1,5-disubstituted triazoles in 82% yield, and with *o*-chlorobenzyl chloride under the same conditions gave a mixture of two regioisomers in 75% yield). Similar ligand-accelerating effect has been reported in literature [11]. These bistriazoles can also promote other three-component reactions (Table 3). For example, in the reaction of *o*-chlorobenzyl chloride, sodium azide and phenylacetylene, the use of 1.5 mol % of CuI was necessary to insure the yield and regio-selectivity of the product (Table 2, entry 4). However, if 0.5 mol % of **10a** was added into the reaction system, 0.5 mol % of CuI could catalyze the reaction to reach completion and gave single 1,4-disubstituted product **4a** in 89% yield (Table 3, entry 2).

In the reactions already reported, the Cu(I) catalysts were usually prepared *in situ* by reduction of Cu(II) salts with a reducing agent such as sodium ascorbate. Excess reducing agent was often used to prevent formation of by-products. However, in aqueous medium the reactions catalyzed by CuX can proceed smoothly and do not require existence of a reducing agent. The heterogeneous nature of the reaction in water may be responsible for higher turnover rates and protection of the catalyst from oxidation.



10a **11a**

Figure 2

Table 3

CuI-catalyzed three-component reaction of benzylic chlorides ($ArCH_2Cl$), sodium azide and alkynes (RC≡CH) in water in the presence of bistriazole **10a** or **11a**.

entry	Ar	R	co-catalyst (mol %)	Temp (℃)	yield (%)
1	*o*-MeC_6H_4	Ph	**10a** (0.5)	80	88
2	*o*-ClC_6H_4	Ph	**10a** (0.5)	80	89
3	*o*-ClC_6H_4	CH_2OH	**10a** (0.8)	70	92
4	*o*-MeC_6H_4	Ph	**11a** (0.5)	80	87
5	*o*-ClC_6H_4	Ph	**11a** (0.5)	80	89
6	*o*-ClC_6H_4	CH_2OH	**11a** (0.8)	70	93

In summary, three-component reaction of alkyl halides, sodium azide and terminal alkynes in water can be efficiently catalyzed by CuX (X = Cl, I), giving single 1,4-disubstituted 1,2,3-triazoles in high yields. Both CuI and CuCl exhibited high catalytic activity. The reactions of *o*- and *m*-bis(chloromethyl)benzene were autocatalytic through the complexation to Cu(I) of the bistriazoles formed during the reactions. These bistriazoles were also

proved to promote other three-component reactions catalyzed by CuX. These aqueous medium reactions do not require any special precautions or existence of a reducing agent. Hence, the process is convenient and environmentally benign.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 NMR spectrometer at ambient temperature and the chemical shifts of ^{1}H and ^{13}C NMR spectra are referenced to internal solvent resonances. IR spectra were recorded on a Bruker VECTOR-22 spectrometer. Elemental analyses were performed by the Analytical Center of University of Science and Technology of China. *o*-$MeC_6H_4CH_2Cl$, *m*-$MeC_6H_4CH_2Cl$, *o*-$ClC_6H_4CH_2Cl$, *p*-$ClC_6H_4CH_2Cl$, *o*-$(ClCH_2)_2C_6H_4$, *m*-$(ClCH_2)_2C_6H_4$ and $PhOCH_2C{\equiv}CH$ were prepared according to reported procedures [12,13]. Other reagents were commercially obtained and used without further purification.

General Procedure. A mixture of alkyl halide (5 mmol for monohalides or 2.5 mmol for *o*- and *m*-bis(chloromethyl)-benzene), alkyne (5 mmol), NaN_3 (5 mmol) and CuX (X = I, Cl) (0.01- 0.125 mmol) in distilled water (5 mL) was stirred at 65-100ºC (bath temperature) for 5-24h. After cooling to room temperature, the precipitate was collected by filtration and washed successively with dilute NH_4OH (3 mL), cold water (2 × 5 mL) and petroleum ether (3 mL), and dried in air. In addition, reactions carried out in tap water gave the same results.

1-Benzyl-4-phenyl-1*H*-1,2,3-triazole (**1a**). Off-white solid, m.p. 120-122ºC (lit. [14]: 126-127ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.52 (s, 2H, CH_2), 7.23-7.35 (m, 8H, Ph), 7.60 (s, 1H, CH), 7.73 (d, *J* = 7.3 Hz, 2H, Ph).

1-(2-Methylbenzyl)-4-phenyl-1*H*-1,2,3-triazole (**2a**). White powder, m.p. 94-95ºC (lit. [15]: 92-94ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 3H, Me), 5.53 (s, 2H, CH_2), 7.15-7.33 (m, 7H, Ph+C_6H_4), 7.47 (s, 1H, CH), 7.72 (d, *J* = 7.2Hz, 2H, Ph).

1-(3-Methylbenzyl)-4-phenyl-1*H*-1,2,3-triazole (3a). White powder, m.p. 95-96ºC (lit. [15]: 200-202ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, Me), 5.47 (s, 2H, CH_2), 7.03-7.36 (m, 7H, Ph+C_6H_4), 7.60 (s, 1H, CH), 7.74 (d, *J* = 7.4Hz, 2H, Ph).

1-(2-Chlorobenzyl)-4-phenyl-1*H*-1,2,3-triazole (**4a**). White powder, m.p. 90-91ºC (lit. [15]: 89-90ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.72 (s, 2H, CH_2), 7.26-7.440 (m, 7H, Ph+C_6H_4), 7.77 (s, 1H, CH), 7.80-7.83 (m, 2H, Ph).

1-(4-Chlorobenzyl)-4-phenyl-1*H*-1,2,3-triazole (**5a**). White powder, m.p.143-144ºC (lit. [15]: 146-147ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.48 (s, 2H, CH_2), 7.17-7.36 (m, 7H, Ph+C_6H_4), 7.59 (s, 1H, CH), 7.72 (d, *J* = 7.8Hz, 2H, Ph).

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methanol (**6a**). Off-white solid, m.p. 73-75ºC (lit.[16]: 76-77ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.22 (b, 1H, OH), 4.75 (d, *J* = 4.3Hz, 2H, CH_2), 5.50 (s, 2H, CH_2), 7.24-7.37 (m, 5H, Ph), 7.42 (s, 1H).

(1-(2-Methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methanol (**7a**). White powder, m.p. 116-118ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.10 (t, *J* = 5.0 Hz, 1H, OH), 2.21 (s, 3H, Me), 4.68 (d, *J* = 5.0Hz, 2H, CH_2), 5.46 (s, 2H, CH_2), 7.08-7.23 (m, 4H, C_6H_4), 7.25 (s, 1H, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.07, 52.45, 56.40, 121.72, 126.77, 129.29, 129.58, 131.15, 132.48, 137.03. IR (KBr): ν (cm^{-1}) 3238vs, 3120s, 3074m, 2959m, 2870m, 1633w, 1550w, 1498w, 1464m, 1436m, 1377w, 1434m, 1219s, 1132m, 1107w, 1063m, 1040s, 1017s, 861w, 846w, 805w, 769m, 747s, 711w, 679w, 652w. *Anal*. Calcd. for $C_{11}H_{13}N_3O$: C, 64.99; H, 6.45; N, 20.68. Found: C, 64.96; H, 6.43; N, 20.87.

(1-(2-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methanol (**8a**). White solid, m.p. 110-112ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 (b, 1H, OH), 4.72 (s, 2H, CH_2), 5.59 (s, 2H, CH_2), 7.15-7.25 (m, 3H, C_6H_4), 7.36-7.39 (m, 1H, C_6H_4), 7.49 (s, 1H, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 51.56, 56.49, 122.19, 127.75, 130.07, 130.43, 130.56, 132.47, 133.65. IR (KBr): ν (cm^{-1}) 3223vs, 3121m, 3072m, 2940m, 2867m, 1626w, 1549w, 1477m, 1447m, 1376w, 1352w, 1224m, 1193w, 1122m, 1106w, 1041vs, 1016m, 861w, 837w, 802w, 759s, 681m. *Anal*. Calcd. for $C_{10}H_{10}ClN_3O$: C, 53.80; H, 4.52; N, 18.83. Found: C, 53.77; H, 4.51; N, 19.02.

1-Benzyl-4-phenoxymethyl-1*H*-1,2,3-triazole (**9a**) [1]. White solid, m.p. 118-120ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.12 (s, 2H, CH_2), 5.47 (s, 2H, CH_2), 6.88-6.91 (m, 3H, Ph), 7.19-7.31 (m, 7H, Ph), 7.50 (s, 1H, CH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 54.18, 62.04, 114.82, 121.27, 122.70, 128.10, 128.78, 129.13, 129.54, 134.56, 144.63, 158.25. IR (KBr): ν (cm^{-1}) 3133m, 3095w, 3065w, 3033w, 3012w, 2993vw, 2957vw, 2922m, 2872m, 1599vs, 1585s, 1560w, 1495vs, 1489vs, 1466s, 1456s, 1429m, 1384s, 1361w, 1351w, 1332m, 1292wm, 1243vs, 1222vs, 1179s, 1152m, 1120s, 1080s, 1054vs, 1030vs, 1006vs, 988vs, 890m, 857s, 818s, 757vs, 717vs, 705s, 694s, 640w, 614vw. *Anal*. Calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.59; H, 5.53; N, 15.97.

1,1'-(*o*-Phenylenedimethylene)bis[4-phenyl-1*H*-1,2,3-triazole] (**10a**) [17,18]. White solid, m.p. 180-182ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.64 (s, 4H, CH_2), 7.25-7.35 (m, 10H, Ph+C_6H_4), 7.48 (s, 2H, CH), 7.65-7.68 (m, 4H, Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 51.49, 119.85, 125.84, 128.42, 128.94, 130.06, 130.32, 130.82, 133.49, 148.54. IR (KBr): ν (cm^{-1}) 3124m, 3080m, 3028m, 1609m, 1483m, 1463s, 1435m, 1357w, 1221s, 1078s, 1045m, 977w, 941w, 814w, 765vs, 735vs, 695vs. *Anal*. Calcd. for $C_{24}H_{20}N_6$: C, 73.45; H, 5.14; N, 21.41. Found: C, 73.26; H, 5.32; N, 21.45.

1,1'-(*m*-Phenylenedimethylene)bis[4-phenyl-1*H*-1,2,3-triazole] (**11a**) [17,18]. White solid, m.p. 158-160ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.51 (s, 4H, CH_2), 7.21-7.36 (m, 10H, Ph+C_6H_4), 7.63 (s, 2H, CH), 7.72-7.75 (m, 4H, Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 53.88, 119.77, 125.82, 127.47, 128.36, 128.40, 128.97, 130.13, 130.46, 148.48. IR (KBr): ν (cm^{-1}) 3130s, 3089m, 2923m, 2853vw, 1610m, 1483m, 1461m, 1435m, 1356w, 1222m, 1192m, 1157vw, 1075s, 1048m, 976w, 915vw, 821w, 764vs, 742s, 695vs. *Anal*. Calcd. for $C_{24}H_{20}N_6$: C, 73.45; H, 5.14; N, 21.41. Found: C, 73.15; H, 5.31; N, 21.55.

1-(2-Methylallyl)-4-phenyl-1*H*-1,2,3-triazole (**12a**). Yellowish solid, m.p. 78-79ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.67 (s, 3H, Me), 4.88 (s, 2H, CH_2), 4.90 (s, 1H, =CH), 5.00 (s, 1H, =CH), 7.24-7.30 (m, 1H, Ph), 7.36 (t, *J* = 7.1 Hz, 2H, Ph), 7.69 (s, 1H, CH), 7.76-7.79 (m, 2H, Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.78, 56.44, 115.50, 119.65, 125.78, 128.22, 128.89, 130.71, 139.51, 148.10. IR (KBr disk) *ν* (cm^{-1}) 3126m, 3090w, 2980w, 2925w, 2854w, 1656m, 1610w, 1462s, 1439vs, 1360w, 1225s, 1201m, 1156w, 1078m, 1049m, 1022w, 975w, 894s, 825m, 767vs, 696vs. *Anal*. Calcd. for $C_{12}H_{13}N_3$: C, 72.34; H, 6.58; N, 21.09. Found: C, 72.19; H, 6.41; N, 20.92.

Synthesis of 1-methyl-4-phenyl-1*H*-1,2,3-triazole (13a). White powder, m.p. 126-127ºC (lit.[19]: 127ºC). ^{1}H NMR (300

MHz, $CDCl_3$): δ 4.15 (s, 3H, Me), 7.31-7.36 (m, 1H, Ph), 7.40-7.45 (m, 2H, Ph), 7.74 (s, 1H, CH), 7.81-7.84 (m, 2H, Ph).

Bistriazole Promoted Three Component Reaction of Alkyl Chloride, Alkyne and NaN_3 in Water in the Presence of CuI. A mixture of *o*-chloro or *o*-methylbenzyl chloride (5 mmol), alkynne (5 mmol), NaN_3 (5 mmol), CuI (0.025–0.04 mmol) and **10a** or **11a** (0.025–0.04 mmol) in water (5 mL) was stirred at 70 –80ºC (bath temperature) for 12 h. After cooling to room temperature, the precipitate was collected by filtration and washed successively with dilute NH_4OH (3 mL), cold water (2×5 mL) and petroleum ether (3 mL). After drying in air, corresponding product was obtained (see table 3).

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