Preparation of 1H-1,2,3-Triazoles by Cuprous Ion Mediated Cycloaddition of Terminal Alkyne and Sodium Azide

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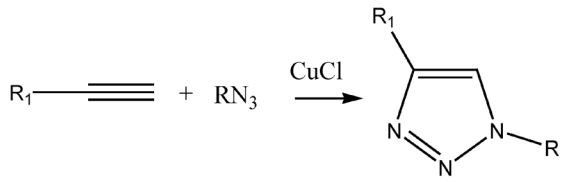
1H-1,2,3-triazoles can be prepared in good yield by the reaction of terminal alkyne and sodium azide in the presence of cuprous chloride at a temperature higher than 70 °C. The alkyne is unactivated and the reaction has to be carried out under inert gas. At room temperature, the reaction first gives a Cu(I)-azide complex which is converted to a Cu-alkyne complex when the temperature is raised to higher than 70 °C. The reaction of Cu(I)-alkyne complex and azide ion dissociated from or coordinated to Cu(I) then gives 1H-1,2,3-triazoles.

Keywords: 1H-1,2,3-Triazole; Alkyne; Cuprous chloride; Sodium azide.

INTRODUCTION

N-substituted 1,2,3-triazoles are useful as dyestuffs, photostabilizers, corrosion inhibitors, pharmaceuticals and agrochemicals.[1] Many methodologies for preparing these compounds have been developed.[1] Recently, the reaction of alkyl azide and terminal alkyne catalyzed by Cu(I), known as click chemistry, was often used to prepare N-substituted 1,2,3-triazoles for a variety of purposes (Scheme I(a)).[2]

Scheme I



(a) N-substituted 1,2,3-triazoles prepared by click chemistry, R = alkyl.
(b) 1H-1,2,3-triazoles prepared by the reaction of terminal alkyne and sodium azide, R = Na.

N-unsubstituted 1,2,3-triazoles also are found to have many applications.[3] For example, many N-unsubstitued 4-aryl-1,2,3-triazoles are methionine aminopeptidase 2 inhibitors and can inhibit angiogenesis in vivo.[3a] Many compounds having N-unsubstituted moiety are found to be biologically active and useful as ihibitors against tuberculosis,[3b] as neurokinin-1 receptor antagonists,[3c] as HIV-protease inhibitors,[3d] and as anticancer agents.[3e] The method used to prepare N-substituted 1,2,3-triazoles may not be applicable to their N-unsubstituted counterpart. Therefore, methodologies for preparing N-substituted 1,2,3-triazoles are still receiving attention. In the literature, the preparations of N-unsubstituted 1,2,3-triazoles can be classified into three categories: (a) By the rearrangement of propargyl azide (Banert cascade);[4] (b) By the reaction of an alkyne and an organic azide to obtain a preformed N-substituted 1,2,3-triazole followed by removing the substituent on nitrogen.[5] The organic azides used therein include trimethylsilyl azide,[5a,5c] pivaloyloxymethyl azide,[5b] tropylium azide[5d] and β-tosylethylazide;[5e] (c) By addition of hydrazoic acid or an azide ion to alkyne.[6] In (c), the alkyne usually is activated by an electron-withdrawing group and the reaction is usually carried out at high temperature (> 90 °C).

In this report, a convenient and efficient preparation of N-unsubstituted 1,2,3-triazoles by cuprous ion mediated cycloaddition of nonactivated terminal alkynes and sodium azide is described.

RESULTS AND DISCUSSION

4-Phenyl-1H-1,2,3-triazole (**2a**) can be prepared in a yield of 81% by refluxing the mixture of phenylacetylene (1 equivalent), cuprous chloride (1.0 equivalent) and sodium azide (1.5 equivalent) in a co-solvent of methanol and 1,4-dioxane (1:2) under nitrogen for two days. In studying this reaction, we noticed:

(a) There is only one compound obtained in the crude product as observed by ^{1}H-NMR spectroscopy. The ^{1}H-NMR and ^{13}C-NMR spectra of this compound are identical to that of 4-phenyl-1H-1,2,3-triazole.[6a] Therefore, this re-

action is regiospecific.

(b) The reaction has to be carried out under inert gas; otherwise, phenylacetylene dimer (1,4-diphenylbutadiyne) produced from oxidative coupling is the major product and **2a** is obtained only in less than 10% yield.[7]

(c) The reaction temperature has to be higher than 70 °C. If the reaction is carried out at 50 °C, the yield of **2a** is lower than 34%.

(d) The yield of **2a** is dependent on the amount of cuprous chloride used in the reaction. If the molar ratio of cuprous chloride to phenylacetylene in the reaction is 1:4, then the yield of the triazole is down to 26%.

(e) The color of the reaction mixture is changing in the reaction. It is brownish-red at the beginning when the mixture is at room temperature. As the reaction temperature is raised to 70 °C, the color of the slurry formed gradually changes to yellow. After refluxing for two days, a white precipitate is obtained.

(f) Mixing only sodium azide and cuprous chloride using methanol-dioxane as the solvent produces sparingly soluble red-brown precipitate which presumably is a Cu(I)-azide complex.

(g) Mixing phenylacetylene and cuprous chloride using methanol-dioxane as the solvent produces insoluble yellow precipitate which is presumably a Cu(I)-phenylacetylene complex.

From (e), (f) and (g), it seems that at the beginning, a Cu(I)-azide complex is formed. When the temperature is raised to about 70 °C, a Cu-phenylacetylene complex is produced at the expense of Cu(I)-azide complex. **2a** is obtained from the reaction of alkyne-Cu(I) complex and free azide ion dissociated from Cu(I)-azide complex or azide ion coordinated to Cu(I) (Scheme II).

To test this hypothesis, CuCl and phenylacetylene are first mixed under nitrogen to obtain a yellow precipitate; sodium azide is then added to the suspension of yellow precipitate in dioxane-methanol co-solvent. After the reaction temperature is raised to 70 °C, the color of the suspension changes gradually from yellow to light yellow and eventually to white in two days. After work-up, **2a** is obtained in a yield of 79%. This yield is comparable to that when the reaction is carried out in one pot. This result supports our speculation that **2a** is formed from the reaction of Cu(I)-alkyne complex and coordinated or free azide ion.

Table 1. The yields of 1H-1,2,3-triazoles from the reaction of terminal alkynes and sodium azide in the presence of cuprous chloride (Scheme I(b))

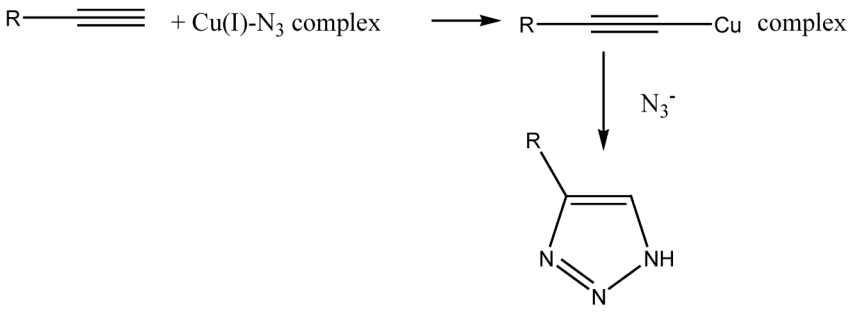
	R_1	Yield (%)
2a	C_6H_5-	81
2b	n-C_4H_9-	91
2c	$HOCH_2$-	82
2d	1-(cyclohexanol)yl	91
2e	1-cyclohexenyl	78
2f	CH_2=C(CH_3)-	75
2g	p-CH_3O-C_6H_4-	78
2h	$CH_3CH_2COOCH_2$-	70
2i	p-CH_3-C_6H_4-	72

The same procedure was used to prepare several other 1H-1,2,3-triazoles (**2b**-**2i**) in good yields from terminal alkynes, cuprous chloride and sodium azide (Table 1). In these reactions, the color changes from red brown to white or yellow for the mixture in the course of reaction are also observed. Therefore, the same reaction path as in the preparation of **2a** should also occur in these cases. The yields of **2a**-**2i** by this method are comparable to that of the corresponding cases by other methods.[4d,5b,5c,6d,8]

For nonterminal alkynes such as diphenylacetylene and 3-hexyne, only starting materials were recovered using the same procedure. These negative results are further support for the mechanism proposed in Scheme II.

In our preparation of 1H-1,2,3-triazole, the reaction conditions are mild, the alkynes are not activated and inex-

Scheme II



pensive sodium azide, instead of organic azide as in category (b), is used. Furthermore, the step of removing the N-substituent group is also avoided.

CONCLUSION

In conclusion, 1H-1,2,3-triazoles can be prepared in good yields by refluxing the mixture of nonactivated terminal alkynes, cuprous chloride and sodium azide using methanol and dioxane as the co-solvent. In this reaction, a Cu(I)-azide complex is produced at low temperature; Cu-alkyne complex is then formed when the temperature is raised to higher than 70 °C, 1H-1,2,3-triazoles are finally produced from the reaction of Cu(I)-alkyne complexes and azide ion dissociated from or coordinated to Cu(I).

EXPERIMENTAL SECTION

Commercially available reagents from Aldrich, Merck or Acros were used without further purification. Solvents were dried by standard procedures. NMR spectra were recorded using a Bruker ACE-300 FT-NMR spectrometer. J values were recorded in Hz, and multiplicities were expressed by usual conventions. Mass spectra were obtained with an Agilent 5973 mass spectrometer. HRMS were obtained with a JMS-700 HRMS high resolution mass spectrometer. Melting points were determined on a Yanagimoto micromelting point apparatus and are reported uncorrected.

Procedure of preparing 4-phenyl 1H-1,2,3-triazole (2a)

The mixture of phenylacetylene (0.51 g, 5 mmole), cuprous chloride (0.495 g, 7.5 mmole) and sodium azide (0.487 g, 7.5 mmole) in a mixed solvent of methanol and dioxane (1:2, 50 mL) was purged with nitrogen gas. The temperature of the mixture is raised to 80 °C and refluxed for 2 days. The color of the mixture was red brown in the beginning, gradually turned yellow and finally became white in two days. The mixture then was bubbled with hydrogen sulfide and the precipitate was filtrated off. The solvent was removed from the filtrate and a precipitate as crude product was obtained. The crude product was then dissolved in acetonitrile and insoluble solid was filtered off. A yellowish white precipitate was obtained after evaporation of the solvent. The product can be further purified by column chromatography using silica gel as the stationary phase and a mixture of ethyl acetate and n-hexane (1:1~6:1) as eluent.

2b, **2c**, **2d**, **2e**, **2f**, **2g** are prepared following the same procedure.

Compounds **2a**,[8] **2b**,[6d] **2c**,[4d] **2d**,[8] **2f**[5c] and **2g**[5b] are known in the literature.

1H-1,2,3-Triazole, 4-(phenyl) (2a)

White solid. 81% yield: mp: 147-148 °C. (literature:[6d] 148 °C); ^{1}H-NMR spectrum is identical to that reported in literature.[7] ^{13}C NMR (DMSO-d_6, δ ppm): 125.9, 127.1, 128.7, 129.4, 130.2, 145.5.

1H-1,2,3-Triazole, 4-(n-butyl) (2b)

Liquid, 91% yield. ^{1}H-NMR ($CDCl_3$, δ ppm): 0.90 (t, 3H, J = 7.3 Hz), 1.36 (sextet, 2H, J = 7.7 Hz), 1.36 (quintet, 2H, J = 7.7 Hz), 2.74 (t, 2H, J = 7.7 Hz), 7.53 (s, 1H); ^{13}C-NMR (CD_3OD, δ ppm): 13.7, 22.2, 24.2, 31.2, 130.2, 146.0; MS *m/z* (EI): 125 (M^+, 6%).

1H-1,2,3-Triazole, 4-(hydroxymethyl) (2c)

Liquid, 82% yield. ^{1}H-NMR and ^{13}C-NMR spectra are identical to that reported in literature.[4e]

1H-1,2,3-Triazole, 4-(1-hydroxy-1-cyclohexyl) (2d)

White solid, 91% yield: mp: 128~129 °C.

^{1}H-NMR spectrum is identical to that reported in literature.[9] ^{13}C-NMR (CD_3OD, δ ppm): 21.6 (CH_2), 25.1 (CH_2), 37.6 (CH_2), 68.6 (C), 126.4 (CH), 152.5 (C); MS *m/z* (EI): 168 ($M+H^+$, 30%).

1H-1,2,3-Triazole, 4-(1-cyclohexenyl) (2e)

White solid, 78% yield: mp: 103~104 °C. ^{1}H-NMR (CD_3OD, δ ppm): 1.70~1.57 (m, 4H), 2.13~2.10 (m, 2H), 2.34~2.30 (m, 2H), 7.68 (s, 1H). ^{13}C-NMR (CD_3OD, δ ppm): 21.7, 22.0, 24.9, 25.8, 125.6, 125.9, 126.1, 145.5; MS *m/z* (EI): 150 ($M+H^+$, 100%); HRMS calcd. for $C_8H_{11}N_3$: 149.0954; Found: 149.0956.

1H-1,2,3-Triazole, 4-(1-methylethenyl) (2f)

Yellow oil, 75% yield. ^{1}H-NMR (CD_3OD, δ ppm): 2.12 (s, 3H), 5.15 (d, 1H, J = 1.0 Hz), 5.59 (d, 1H, J = 1.0 Hz), 7.74 (s, 1H). ^{13}C-NMR (CD_3OD, δ ppm): 20.6, 114.2, 128.3, 132.8, 146.7; MS *m/z* (EI): 109 (M^+, 100%).

1H-1,2,3-Triazole, 4-(4-methoxyphenyl) (2g)

White solid, 78% yield: mp: 168-169 °C (literature:[5b] 166 °C). ^{1}H-NMR spectrum is identical to that reported in literature.[5b] ^{13}C NMR ($CDCl_3$, δ ppm): 54.4 (CH_3), 114.0 (CH), 122.0 (C), 125.6 (C), 126.9 (CH), 145.0 (C), 160.0 (CH).

1H-1,2,3-Triazole-4-methanol propanoate (2h)

^{1}H-NMR (CD_3OD, δ ppm): 1.07 (t, 3H, J = 7.2 Hz), 2.30 (q, 2H, J = 7.2 Hz), 5.22 (s, 2H), 7.74 (s, 1H); ^{13}C NMR ($CDCl_3$, δ ppm): 8.83 (CH_3), 27.3 (CH_2), 56.9 (CH_2), 130.2 (CH), 141.8 (C), 174.6 (C=O); MS *m/z* (EI): 155. (M^+, 3%); HRMS calcd. for $C_6H_9N_3O_2$: 155.0695; Found:

155.0700.

1H-1,2,3-Triazole-4-(p-tolyl) (2i)

mp: 134-136 °C, ^{1}H-NMR and ^{13}C NMR spectra are identical to that in reported literature.[5c]

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