Copper-Catalyzed Synthesis of *N*-Unsubstituted 1,2,3-Triazoles from Nonactivated Terminal Alkynes

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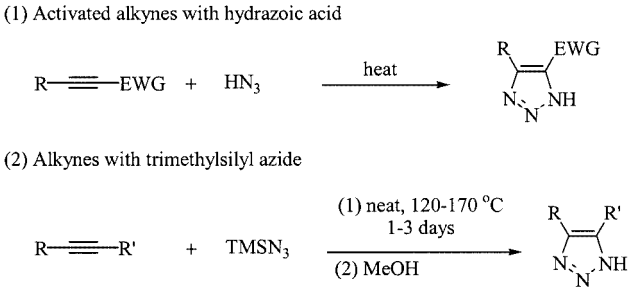
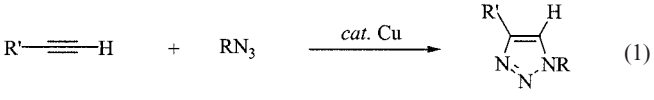
The [3+2] cycloaddition of nonactivated terminal alkynes and trimethylsilyl azide proceeded smoothly in the presence of Cu^{I} catalyst and DMF/MeOH, to give the corresponding *N*-unsubstituted triazoles in good to high yields. The reaction most probably proceeds through the in situ formation of a copper acetylide species and hydrazoic acid, followed by a successive [3+2] cycloaddition reaction.

Introduction

1,2,3-Triazoles have found broad use in agrochemicals and industrial applications such as dyes and corrosion inhibitors, and have been regarded as an interesting unit in terms of biological activity.[1] Because of their potent usefulness, several synthetic methods have been developed recently;[2] especially, the copper catalyzed addition of organoazide (RN_3) to terminal alkynes has become a useful and widely applicable method for the synthesis of *N*-substituted triazoles [Equation (1)].[3] However, deprotection of the R group from the triazole framework is difficult in the case of R = alkyl and aryl. Since the parent compounds *N*-unsubstituted 1,2,3-triazoles have also received much attention because of their wide utilities,[4] we have been interested in the synthesis of unsubstituted triazoles. The [3+2] cycloaddition between alkynes and metal azides has been well investigated for the construction of *N*-unsubstituted triazoles (Scheme 1): the direct addition of dangerous and harmful hydrazoic acid, which is generated in situ by cautiously reacting NaN_3 with an acid,[5] to alkynes bearing electron-withdrawing groups is straightforward.[6] Alternatively, the addition of trimethylsilyl azide to terminal and internal alkynes under harsh conditions and subsequent removal of silyl group provides a much safer procedure.[7] In the standard procedures[5−7] for the formation of unsubstituted triazoles, it is usually required that starting alkynes are substituted with an activating functional group, and the reactions are often conducted at high temperatures for a prolonged period of time. Therefore, it is desirable to develop a new and efficient synthetic approach for the formation of *N*-unsubstituted 1,2,3-triazoles.[8] We now report the synthesis of *N*-unsubstituted triazoles **3** by the copper-catalyzed [3+2] cycloaddition reaction of nonactivated terminal alkynes **1** and trimethylsilyl azide **2** in the presence of MeOH/DMF [Equation (2)].



Scheme 1. General methods for the formation of *N*-unsubstituted 1,2,3-triazoles by [3+2] cycloaddition reactions



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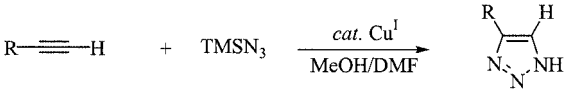

(2)

1 **2** **3**

Results and Discussion

In the cycloaddition between 4-ethynyltoluene **1a** with **2**, we investigated the effect of solvents and copper salts on the formation of the triazole **3a** (Table 1). Among the solvents that we tested (under a catalytic amount of CuCl),

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protic solvents gave better results (Entries 1 and 2), and a 1:1 mixture of DMF and MeOH improved the yield of **3a** (Entry 3). Other protic solvents such as EtOH and PrOH gave similar results. We next investigated the effect of the copper catalysts. Among the copper catalysts that we tested, CuI gave the highest yield of **3a** (Entry 4). Other copper catalysts such as $CuBr_2$ and Cu powder were also effective (Entries 5 and 6). The reaction without a copper catalyst gave a low yield of **3a** (Entry 7). Other metal catalysts such as $AuCl_3$, AgCl, and $ZnCl_2$ were not effective (Entries 8−10). Very interestingly, the use of 5 mol % of CuI increased the yield up to 88% (Entry 11). To our surprise, the use of 5 mol % of CuI in a mixture of DMF and H_2O also gave **3a** in a similar yield (Entry 12), and copper powder exhibited high catalytic activity under the same conditions, although a slightly prolonged reaction time was needed (Entry 13).

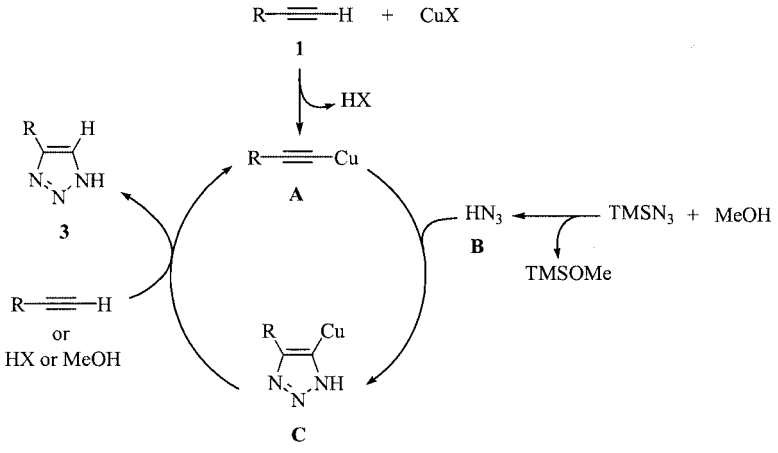
Table 1. Effect of catalysts and solvents on the formation of the triazole **3a** from **1a**

Entry[a]	Catalyst	Solvent	Yield (%)[b]
1	CuCl (20 mol %)	DMF	14
2	CuCl (20 mol %)	MeOH	(55)
3	CuCl (20 mol %)	DMF/MeOH (1:1)	(64)
4	CuI (20 mol %)	DMF/MeOH (1:1)	(69)
5	$CuBr_2$ (20 mol %)	DMF/MeOH (1:1)	59
6	Cu powder (20 mol %)	DMF/MeOH (1:1)	(64)
7	none	DMF/MeOH (1:1)	13
8	$AuCl_3$ (20 mol %)	DMF/MeOH (1:1)	0
9	AgCl (20 mol %)	DMF/MeOH (1:1)	0
10	$ZnCl_2$ (20 mol %)	DMF/MeOH (1:1)	0
11[c]	CuI (5 mol %)	DMF/MeOH (9:1)	88
12[c]	CuI (5 mol %)	DMF/H_2O (9:1)	87
13[c]	Cu powder (5 mol %)	DMF/H_2O (9:1)	86

[a] Unless otherwise noted, the reaction of alkyne **1a** with $TMSN_3$ (4.0 equiv.) was carried out in the presence of catalyst (20 mol %) in MeOH/DMF (1:1, 0.5 M) at 100 °C for 12 h. [b] ^1H NMR spectroscopic yield using dibromomethane as an internal standard. Isolated yield is shown in parenthesis. [c] 1.5 equiv. $TMSN_3$ was used.

The results of the [3+2] cycloaddition of various terminal alkynes **1** with **2** are summarized in Table 2. The reaction of ethynyltoluene **1a** with trimethylsilyl azide **2** was carried out in a mixture of DMF and MeOH (9:1) at 100 °C in the presence of 5 mol % CuI. The reaction was completed in 12 h to afford 4-tolyl-1,2,3-triazole **3a** in 83% yield (Entry 1). As can be seen from the results of Entries 2−5, the [3+2] cycloaddition of aryl acetylenes **1b**−**1e** gave the corresponding triazoles **3b**−**3e**, respectively, in good to high yields, indicating that the EWG and/or EDG at the *para*-position did not exert a significant influence on the reaction progress. The reaction of alkylacetylenes such as 1-dodecyne (**1f**) and *tert*-butylacetylene (**1g**) afforded the desired triazoles **3f** and **3g** in high yields, although prolonged reaction times were required (Entries 6 and 7). We then examined the reactions of the conjugated enyne **1h** and diyne **1i** (Entries 8 and 9). The reaction took place selectively at the terminal alkyne moiety to give the triazoles **3h** and **3i** in 55% and 84% yields, respectively. The alkynes **1j** and **1k**, which have a heteroatom substituent at the propargyl-position gave the corresponding triazoles **3j** and **3k** in good to high yields (Entries 10 and 11). Sterically bulky (triisopropylsilyl)acetylene (**1l**) also reacted without any problems to give the corresponding triazole **3l** in high yield (Entry 12).

A proposed mechanism for the reaction forming *N*-unsubstituted 1,2,3-triazole in the presence of copper catalyst and MeOH (or H_2O) is shown in Scheme 2. At the initial stage of the catalytic cycle, the reaction of terminal alkynes **1** with CuX produces the copper acetylide A and HX; besides, HN_3 B forms in situ from the reaction of $TMSN_3$ and MeOH.[9] The [3+2] cycloaddition between the C−C triple bond of the copper acetylide A and HN_3 B takes place readily to form the intermediate C. The C−C triple bond is activated by forming a copper acetylide species, which makes the [3+2] cycloaddition feasible.[3,8a,8b] Protonolysis of the C−Cu bond of intermediate C by the terminal alkynes **1**, HX or MeOH affords the *N*-unsubstituted 1,2,3-triazoles **3**.



Scheme 2. Proposed mechanism for the formation of *N*-unsubstituted 1,2,3-triazoles **3**

Table 2. Synthesis of 1,2,3-triazoles **3** under copper catalyst

Entry[a]	R	**1**	Time (h)	**3**	Yield (%)[b]
1	*p*-Me-C_6H_4	**1a**	12	**3a**	83
2	*p*-MeO-C_6H_4	**1b**	12	**3b**	89
3	C_6H_5	**1c**	11	**3c**	87
4	*p*-Cl-C_6H_4	**1d**	10	**3d**	70
5	*p*-CO_2Me-C_6H_4	**1e**	10	**3e**	95
6	$CH_3(CH_2)_9$	**1f**	18	**3f**	80
7	*t*Bu	**1g**	24	**3g**	80
8	isopropenyl	**1h**	24	**3h**	55
9	$iPr_3SiO(CH_2)_4C{\equiv}C$	**1i**	20	**3i**	84
10	$BnOCH_2$	**1j**	10	**3j**	70
11	$PhSO_2(Me)NCH_2$	**1k**	10	**3k**	86
12	iPr_3Si	**1l**	24	**3l**	94

[a] The reaction of the terminal alkynes **1** and $TMSN_3$ (1.5 equiv.) was conducted in DMF/MeOH (9:1, 0.5 M) in the presence of a catalytic amount of CuI (5 mol %) at 100 °C for the time shown in Table 2. [b] Isolated yield.

Conclusion

Irrespective of the precise mechanism, we are now in a position to synthesize various *N*-unsubstituted 1,2,3-triazoles, which are not easily available from previously known methodologies, through the new and efficient copper-catalyzed [3+2] cycloaddition reaction. Further studies on the application of the present methodology to the synthesis of biological active compounds and on the extension of the present findings to tetrazole synthesis are under investigation.

Experimental Section

The Procedure for the Synthesis of *N*-Unsubstituted 1,2,3-Triazole 3a from 1a: Trimethylsilyl azide (0.1 mL, 0.75 mmol) was added to a DMF and MeOH solution (1 mL, 9:1) of CuI (4.8 mg, 0.025 mmol) and ethynyltoluene (**1a**) (58 mg, 0.5 mmol) under Ar in a pressure vial. The reaction mixture was stirred at 100 °C for 12 h. After consumption of **1a**, the mixture was cooled to room temperature and filtered through a short Florisil pad and concentrated. The residue was purified with silica gel column chromatography (*n*-hexane/EtOAc, 10:1 to 2:1) to afford 4-(*p*-tolyl)-1,2,3-triazole (**3a**) in 83% yield (66 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3 H), 7.27−7.24 (m, 2 H), 7.72−7.67 (m, 2 H), 7.93 (s, 1 H), 11.88 (br. s, 1 H) ppm. ^{13}C NMR (67.80 MHz, CD_3OD): δ = 21.25, 126.82, 127.18, 128.17, 130.54, 139.54, 146.67 ppm. IR (KBr): $\tilde{\nu}$ = 3156, 3124, 2898, 1479, 1076, 821 cm^{-1}. $C_9H_9N_3$ (159.2): calcd. C 67.57, H 5.67, N 26.26; found C 67.69, H 5.75, N 26.55. HRMS (EI): calcd. for $C_9H_9N_3$ [M^+] 159.0791; found 159.0791.

[1] Reviews on 1,2,3-triazoles, see: [1a] H. Dehne, in *Methoden der Organischen Chemie (Houben-Weyl)* (E. Schumann, Ed.), Thieme: Stuttgart, **1994**, vol. E8d, p. 305−405. [1b] H. Wamhoff, in *Comprehensive Heterocyclic Chemistry* (A. R. Katritzky, C. W. Rees, Eds.), Pergamon: Oxford, **1984**, vol. 5, p. 669−732.

[2] [2a] G. L'Abbé, *Chem. Rev.* **1969**, *69*, 345−363. [2b] L. Garanti, G. Molteni, *Tetrahedron Lett.* **2003**, *44*, 1133−1135. [2c] A. R. Katritzky, S. K. Singh, *J. Org. Chem.* **2002**, *67*, 9077−9079. [2d] H. Suzuki, C. Nakaya, Y. Matano, *Tetrahedron Lett.* **1993**, *34*, 1055−1056.

[3] Cu-catalyzed synthesis of 1,2,3-triazoles, see: [3a] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596−2599. [3b] C. W. Tornøe, C. Christensen, M. Medal, *J. Org. Chem.* **2002**, *67*, 3057−3064. [3c] F. Fazio, M. C. Bryan, O. Blixt, J. C. Paulson, C.-H. Wong, *J. Am. Chem. Soc.* **2002**, *124*, 14397−14402. [3d] Q. Wang, R. C. Chan, R. Hilgraf, V. V. Fokin, K. B. Sharpless, M. G. Finn, *J. Am. Chem. Soc.* **2003**, *125*, 3192−3193. [3e] S. Löber, P. Rodriguez-Loaiza, P. Gmeiner, *Org. Lett.* **2003**, *5*, 1753−1755. [3f] F. Pérez-Balderas, M. Ortega-Munoz, J. Morales-Sanfrutos, F. Hernández-Mateo, F. G. Calvo-Flores, J. A. Calvo-Asin, J. Isac-Garcia, F. Santoyo-González, *Org. Lett.* **2003**, *5*, 1951−1954.

[4] [4a] S. Komeda, M. Lutz, A. L. Spek, Y. Yamanaka, T. Sato, M. Chikuma, J. Reedijk, *J. Am. Chem. Soc.* **2002**, *124*, 4738−4746. [4b] K. Nomiya, K. Tsuda, N. C. Kasuga, *J. Chem. Soc., Dalton Trans.* **1998**, *10*, 1653−1659. [4c] M. J. Fray, D. J. Bull, C. L. Carr, E. C. L. Gautier, C. E. Mowbray, A. Stobie, *J. Med. Chem.* **2001**, *44*, 1951−1962. [4d] M. Kume, T. Kubota, Y. Kimura, H. Nakashimizu, K. Motokawa, M. Nakano, *J. Antibiotics* **1993**, *46*, 177−192. [4e] M. Arimoto, S. Yokohama, M. Sudou, Y. Ichikawa, T. Hayano, H. Tagawa, M. Furukawa, *J. Antibiotics* **1988**, *41*, 1795−1811. [4f] S. K. Nimkar, S. Mabic, A. H. Anderson, S. L. Palmer, T. H. Graham, M. de Jonge, L. Hazelwood, S. J. Hislop, Jr., N. Castagnoli, *J. Med. Chem.* **1999**, *42*, 1828−1835. [4g] G. Cristalli, A. Eleuteri, R. Volpini, S. Vittori, E. Camaioni, G. Lupidi, *J. Med. Chem.* **1994**, *37*, 201−205.

[5] [5a] F. P. Woerner, H. Reimlinger, *Chem. Ber.* **1970**, *103*, 1908−1917. [5b] M. Journet, D. Cai, J. J. Kowal, R. D. Larsen, *Tetrahedron Lett.* **2001**, *42*, 9117−9118.

[6] [6a] O. Dimroth, G. Fester, *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 2219−2223. [6b] J. C. Sheehan, C. A. Robinson, *J. Am. Chem. Soc.* **1949**, *71*, 1436−1440. [6c] L. W. Hartzel, F. R. Benson, *J. Am. Chem. Soc.* **1954**, *76*, 667−670.

[7] [7a] L. Birkhofer, A. Ritter, *Angew. Chem.* **1965**, *77*, 414−426. [7b] L. Birkhofer, P. Wegner, *Chem. Ber.* **1967**, *100*, 3485−3494. [7c] K. Banert, *Chem. Ber.* **1989**, *122*, 911−918.

[8] [8a] S. Kamijo, T. Jin, Z. Huo, Y. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 7786−7787. [8b] S. Kamijo, T. Jin, Y. Yamamoto, *Tetrahedron Lett.* **2004**, *45*, 689−691. [8c] S. Kamijo, T. Jin, Z. Huo, Y. Yamamoto, *Tetrahedron Lett.* **2002**, *43*, 9707−9710.

[9] It was reported that trimethylsilyl azide was a convenient source for hydrazoic acid in methanol. [9a] H. Bienaymé, K. Bouzid, *Tetrahedron Lett.* **1998**, *39*, 2735−2738. [9b] T. Nixey, M. Kelly, D. Semin, C. Hulme, *Tetrahedron Lett.* **2002**, *43*, 3681−3684.

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