Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 2824–2827
Tetrahedron Letters

Copper-catalyzed synthesis of 5-substituted 1*H*-tetrazoles via the [3+2] cycloaddition of nitriles and trimethylsilyl azide

Tienan Jin, Fukuzou Kitahara, Shin Kamijo, Yoshinori Yamamoto *

Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

Received 17 January 2008; revised 4 February 2008; accepted 21 February 2008
Available online 4 March 2008

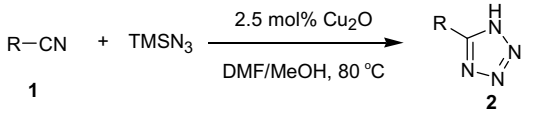
Abstract

The [3+2] cycloaddition between various nitriles and trimethylsilyl azide proceeds smoothly in the presence of a Cu^{I} catalyst in DMF/MeOH, to give the corresponding 5-substituted 1*H*-tetrazoles in good to high yields. The reaction most probably proceeds through the in situ formation of a copper azide species, followed by a successive [3+2] cycloaddition with the nitriles.

Keywords: 5-Substituted 1*H*-tetrazole; [3+2] Cycloaddition; Nitrile; Copper catalyst; Copper azide; Trimethylsilyl azide

Tetrazoles are regarded as biologically equivalent to the carboxylic acid group, and extensive work on the synthesis of tetrazoles has been carried out in the field of material sciences, pharmaceuticals, explosives, and photography.[1] The synthesis of 5-substituted 1*H*-tetrazoles from nitriles has received much attention recently, and new preparative methods have appeared.[2] Recently, Sharpless and co-workers reported an innovative and safe procedure for the preparation of 5-substituted 1*H*-tetrazoles from the corresponding nitriles and NaN_3 in the presence of a stoichiometric amount or 50 mol % of Zn(II) salts.[3] Later, Pizzo and co-workers reported an efficient method for the synthesis of tetrazoles by the reaction of nitriles with $TMSN_3$ using 50 mol % of TBAF as catalyst.[4] More recently, Lakshmi Kantam and co-workers efficiently synthesized tetrazoles by reaction of nitriles with NaN_3 using nanocrystalline ZnO or zinc hydroxyapatite as the catalyst at 120–130 °C.[5] The development of a *catalytic* synthetic method for tetrazoles still remains an active research area. In continuation of our interest in the development of efficient and environmentally friendly methods for the *catalytic* synthesis of nitrogen-containing heterocycles, such as tetrazoles and 1,2,3-triazoles, through 1,3-dipolar cycloaddition,[6] we report herein the synthesis of 5-substituted 1*H*-tetrazoles **2** by the copper-catalyzed [3+2] cycloaddition between the corresponding nitriles **1** and trimethylsilyl azide in MeOH/DMF (Eq. 1).

In the cycloaddition reaction between *p*-methoxybenzonitrile **1a** and $TMSN_3$, we investigated the effect of solvents and metal catalysts on the formation of tetrazole **2a** (Table 1). Among the solvents tested (using 2.5 mol % of Cu_2O), DMF gave a low yield of **2a** whereas the yield was dramatically improved using a 9:1 mixture of DMF and MeOH (entries 1 and 2).[6b,c] Other protic solvents such as ^{i}PrOH and H_2O were also effective (entries 3 and 4). We next investigated the effect of the metal catalysts. Among the copper catalysts tested, Cu_2O gave the best result at 80 °C (entry 2); CuBr exhibited high catalytic activity, although a higher reaction temperature was needed (entry 5). Other copper catalysts such as CuCl, CuI, $CuCl_2$, $CuBr_2$ and CuO gave lower yields of **2a** (entries 6–10). The reaction without a copper catalyst gave a low yield (entry 11). Other metal catalysts such as AuCl and $ZnBr_2$ were less effective (entries 12 and 13).



(1)

* Corresponding author. Tel.: +81 22 795 6581; fax: +81 22 795 6784.
E-mail address: yoshi@mail.tains.tohoku.ac.jp (Y. Yamamoto).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.02.115

Table 1
Effect of catalyst and solvent on the formation of tetrazole **2a** from **1a**[a]

Entry	Catalyst	Solvent (ratio)	Yield of **2a**[b] (%)
1	Cu_2O (2.5 mol %)	DMF	46
2	Cu_2O (2.5 mol %)	MeOH/DMF (1/9)	95 (84)[c]
3	Cu_2O (2.5 mol %)	^{i}PrOH/DMF (1/9)	77
4	Cu_2O (2.5 mol %)	H_2O/DMF (1/9)	86
5	CuBr	MeOH/DMF (1/9)	(85)
6	CuCl	MeOH/DMF (1/9)	(67)
7	CuI	MeOH/DMF (1/9)	69
8	$CuCl_2$	MeOH/DMF (1/9)	64
9	$CuBr_2$	MeOH/DMF (1/9)	72
10	CuO	MeOH/DMF (1/9)	78
11	None	MeOH/DMF (1/9)	34
12	AuCl	MeOH/DMF (1/9)	(16)
13	$ZnBr_2$	MeOH/DMF (1/9)	32

[a] The reaction of **1a** with $TMSN_3$ (1.5 equiv) was carried out in the presence of 5 mol % of catalyst at 100 °C for 24 h.
[b] ^{1}H NMR yield was determined by using dibromomethane as an internal standard. Isolated yield is shown in parentheses.
[c] 2.5 mol % of Cu_2O was used at 80 °C for 12 h.

The results of the [3+2] cycloaddition reaction of various nitriles **1** with $TMSN_3$ are summarized in Table 2.[7] The reactions of the arylnitriles **1a** and **1b**, bearing an electron-donating group at the *para*-position of the aromatic ring, with trimethylsilyl azide were carried out in a mixture of MeOH and DMF (1:9) at 80 °C in the presence of 2.5 mol % Cu_2O. The reactions were complete in 12 h affording the corresponding tetrazoles **2a** and **2b** in 84% and 79% yields, respectively (entries 1 and 2). The nitriles **1c** and **1d**, having an electron-withdrawing NO_2 group at the *para*- or *meta*-position, produced the corresponding tetrazoles **2c** and **2d** in excellent yields (entries 3 and 4). Nitrile **1e** containing an unprotected hydroxy group at the *para*-position also gave the product tetrazole **2e** in a high yield (entry 5). Other aryl nitriles such as 2-cyanonaphthalene **1f** also reacted without any problems to give the corresponding tetrazole **2f** in a high 92% yield (entry 6). The reaction of sterically hindered *ortho*-substituted aryl nitrile **1g** afforded the desired tetrazole **2g** in 50% yield, although

Table 2
Cu-catalyzed synthesis of 5-substituted 1*H*-tetrazoles **2**[a]

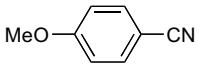
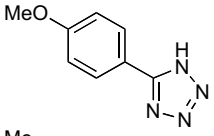
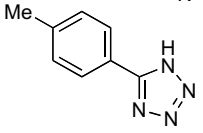
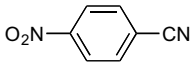
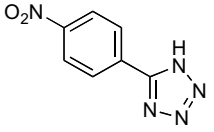
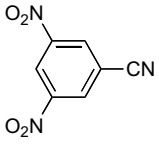
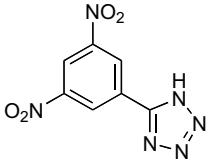
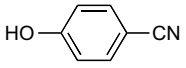
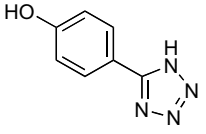
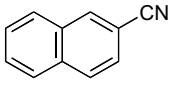
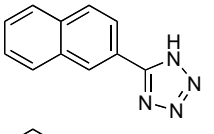
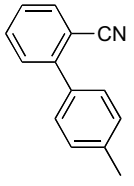
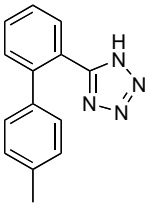
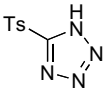
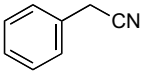
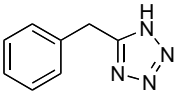
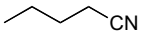
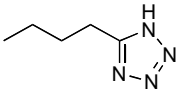
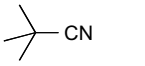
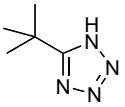
Entry	Substrate	**1**	Time (h)	Product	**2**	Yield[b] (%)	Mp (°C)
1		**1a**	12		**2a**	84	231–233
2		**1b**	12		**2b**	79	248–249
3		**1c**	12		**2c**	96	219–220
4		**1d**	12		**2d**	91	178–179
5		**1e**	12		**2e**	87	234–235
6		**1f**	12		**2f**	92	205–206
7		**1g**	24		**2g**	50[c]	149–151

Table 2 (*continued*)

Entry	Substrate	1	Time (h)	Product	2	Yield[b] (%)	Mp (°C)
8	Ts–CN	**1h**	12		**2h**	77	133–135
9		**1i**	24		**2i**	66	123–124
10		**1j**	24		**2j**	55	40–42
11		**1k**	24		**2k**	36	—

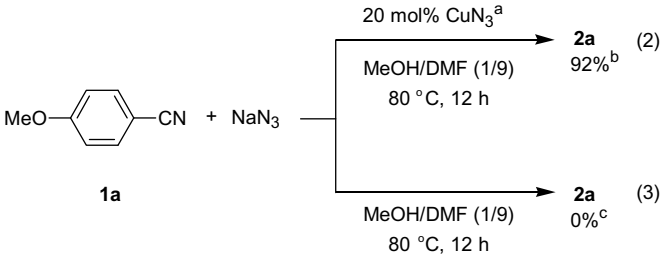
[a] Unless otherwise noted, the reaction of nitriles **1** with $TMSN_3$ (1.5 equiv) was conducted in MeOH/DMF (1:9, 0.5 M) in the presence of 2.5 mol % of Cu_2O at 80 °C for the time shown in Table 2.

[b] Isolated yield.

[c] The reaction was carried out in the presence of 10 mol % of Cu_2O at 120 °C.

a prolonged reaction time, higher temperature and larger amount of catalyst were required (entry 7). The above results indicate that the tetrazole-forming reaction tolerates a wide range of functional groups and the [3+2] cycloaddition proceeds well irrespective of the position and electronic nature of the substituents on the aromatic ring. The tosyl nitrile **1h**, which has a heteroatom directly linked to CN, reacted smoothly with $TMSN_3$, giving the corresponding tetrazole **2h** in 77% yield (entry 8). Next we investigated the reactivity of the alkyl nitriles **1i–k**. The reaction of benzylnitrile **1i**, valeronitrile **1j** and sterically bulky pivalonitrile **1k** furnished the desired tetrazoles **2i–k** in good to moderate yields, although longer reaction times were needed (entries 9–11).

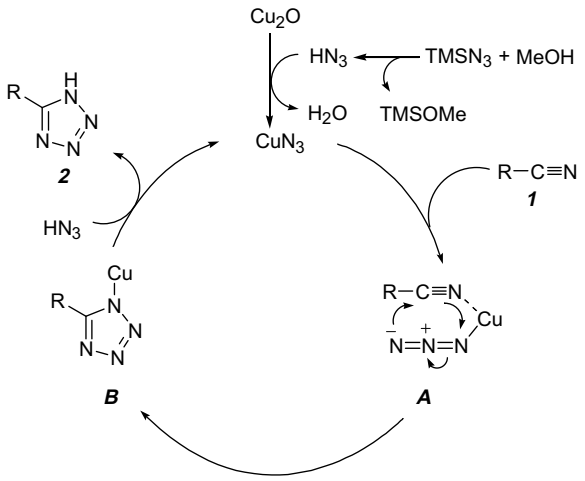
A plausible mechanism is shown in Scheme 1. Initially, Cu_2O reacts with HN_3 to produce the CuN_3 catalytic species; HN_3 is formed in situ via the reaction of $TMSN_3$ with MeOH.[8] The [3+2] cycloaddition between the C–N bond of nitrile **1** and CuN_3 takes place readily to form the intermediate **B**; precoordination of the nitrogen atom of the CN group of **1** with copper azide to form complex **A** would accelerate this cyclization step. Protonolysis of the intermediate **B** by HN_3 affords the 5-substituted 1*H*-tetrazole **2** and copper azide catalyst.



[a] CuN_3 was prepared insitu by mixing NaN_3 with CuI in DMF at rt for 30 min.

[b] ^1H NMR yield was determined using dibromomethane as an internal standard.

[c] **1a** was recovered in 89% NMR yield.



Scheme 1. A plausible mechanism for the formation of tetrazoles **2**.

To obtain support for the proposed mechanism, the following experiments were carried out. The reaction of **1a** (1 equiv) with NaN_3 (1.5 equiv) in the presence of 20 mol % of CuN_3, which was generated in situ from NaN_3 (0.2 equiv) and CuI (0.2 equiv),[9] in MeOH/DMF (1/9) gave the corresponding tetrazole **2a** in 92% NMR yield (Eq. 2). On the other hand, the reaction of **1a** with NaN_3 in MeOH/DMF (1/9) did not proceed at all in the absence of the in situ generated CuN_3 catalyst, and the starting material **1a** was recovered in 89% NMR yield (Eq. 3). These results clearly indicate that, (1) CuN_3 is a key catalytic species which enables the [3+2] cycloaddition with **1a** to produce **B**, (2) the reaction of **B** with NaN_3 produces CuN_3 together with the sodium tetrazole salt which

undergoes protonolysis with MeOH to give **2a**, and (3) the [3+2] cycloaddition of **1a** with NaN_3 does not take place.

We are now in a position to synthesize 5-substituted tetrazoles **2** with a wide range of substituents in good to high yields through the efficient and convenient copper-catalyzed cycloaddition reaction between nitriles **1** and trimethylsilyl azide. The reaction most likely proceeds through the in situ formation of a copper azide catalytic species, followed by a successive [3+2] cycloaddition with the nitrile.

Acknowledgement

We thank the faculty members in the Instrumental Analysis Center at Tohoku University for the measurements of NMR spectra, mass spectra, and elemental analysis.

References and notes

1. (a) Meier, H. R.; Heimgarther, H. In *Methoden der Organischen Chemie (Houben-Weyl)*; Schumann, E., Ed.; Georg Thieme: Stuttgart, 1994; Vol. E8d, p 664; (b) Bulter, R. N. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 5, p 791; (c) Singh, H.; Chawla, A. S.; Kapoor, V. K.; Paul, D.; Malhotra, R. K. *Prog. Med. Chem.* **1980**, *17*, 151; (d) Ostrovskii, V. A.; Pevznert, M. S.; Kofmna, T. P.; Shcherbinin, M. B.; Tselinskii, I. V. *Targets Heterocycl. Syst.* **1999**, *3*, 467; (e) Koldobskii, G. I.; Ostrovskii, V. A. *Usp. Khim.* **1994**, *63*, 847.
2. (a) Duncia, J. V.; Pierce, M. E.; Santella, J. B., III. *J. Org. Chem.* **1991**, *56*, 2395; (b) Huff, B. E.; Staszak, M. A. *Tetrahedron Lett.* **1993**, *34*, 8011; (c) Wittenberger, S. J.; Donner, B. G. *J. Org. Chem.* **1993**, *58*, 4139; (d) Koguro, K.; Oga, T.; Mitsui, S.; Orita, R. *Synthesis* **1998**, 910; (e) Curran, D. P.; Hadida, S.; Kim, S.-Y. *Tetrahedron* **1999**, *55*, 8997.
3. (a) Demko, Z. P.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 7945; (b) Demko, Z. P.; Sharpless, K. B. *Org. Lett.* **2002**, *4*, 2525; (c) Himo, F.; Demko, Z. P.; Noodleman, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **2002**, *124*, 12210; (d) Himo, F.; Demko, Z. P.; Noodleman, L.; Sharpless, K. B. . *J. Am. Chem. Soc.* **2003**, *125*, 9983.
4. Amantini, D.; Beleggia, R.; Fringuelli, F.; Pizzo, F.; Vaccoro, L. *J. Org. Chem.* **2004**, *69*, 2896.
5. (a) Lakshmi Kantam, M.; Shiva Kumar, K. B.; Sridhar, C. *Adv. Synth. Catal.* **2005**, *347*, 1212; (b) LakshmiKantam, M.; Balasubrahmanyam, V.; Shiva Kumar, K. B. *Synth. Commun.* **2006**, *36*, 1809; (c) LakshmiKantam, M.; Shiva Kumar, K. B.; Phani Raja, K. *J. Mol. Catal. A: Chem.* **2006**, *247*, 186.
6. (a) Kamijo, S.; Huo, Z.; Jin, T.; Kanazawa, C.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 6389; (b) Jin, T.; Kamijo, S.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 9435; (c) Jin, T.; Kamijo, S.; Yamamoto, Y. *Eur. J. Org. Chem.* **2004**, 3789; (d) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 2386; (e) Kamijo, S.; Jin, T.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 689; (f) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7786; (g) Kamijo, S.; Jin, T.; Huo, Z.; Gyong, Y.-S.; Yamamoto, Y. *Mol. Diversity* **2003**, *6*, 181; (h) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *Tetrahedron Lett.* **2002**, *43*, 9707; (i) Kamijo, S.; Jin, T.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 7413.
7. The procedure for the synthesis of the tetrazole **2a** is representative. Trimethylsilyl azide (0.1 ml, 0.75 mmol) was added to a DMF and MeOH solution (1 ml, 9:1, 0.5 M) of Cu_2O (1.8 mg, 0.0125 mmol) and *p*-methoxybenzonitrile **1a** (66.6 mg, 0.5 mmol) in a pressure vial. The reaction mixture was stirred at room temperature for 10 min then heated at 80 °C for 12 h. After consumption of **1a**, the reaction mixture was cooled to room temperature and extracted with ethyl acetate. The organic layer was washed with 1 N HCl, dried with anhydrous Na_2SO_4, and concentrated. To the residue was added 0.25 N NaOH and the resulting mixture was stirred for 30 min at room temperature. The mixture was washed with ethyl acetate, and then concd HCl was added until the pH value of the water layer became 1. The aqueous layer was extracted with ethyl acetate (×3) and the combined organic layers were washed with 1 N HCl. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The tetrazole **2a** was obtained in 84% yield as a white solid (73.7 mg), mp = 231–233 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.83 (3H, s), 7.14 (2H, d, $J = 9.0$ Hz), 7.96 (2H, d, $J = 9.0$ Hz); ^{13}C NMR (100 MHz, DMSO-d_6): 55.41, 114.74, 116.20, 128.50, 154.64, 161.30; IR (KBr) 3200–3300 (br), 1298, 1184, 1035, 750 cm^{-1}; Anal. Calcd for $C_8H_8N_4O$: C, 54.53; H, 4.58; N, 31.81. Found: C, 54.60; H, 4.83; N, 32.06. HRMS (EI) calcd for $C_8H_7N_4O$ ([M−H]$^-$) 175.0625. Found 175.0622. All the 5-substituted tetrazole products **2** are known compounds and the spectral data and melting points are identical to those reported in the literatures.
8. It was reported that trimethylsilyl azide is a convenient source of hydrazoic acid in methanol, see: (a) Bienayme, H.; Bouzid, K. *Tetrahedron Lett.* **1998**, *39*, 2735; (b) Nixey, T.; Kelly, M.; Semin, D.; Hulme, C. *Tetrahedron Lett.* **2002**, *43*, 3681.
9. Yamamoto, Y.; Asao, N. *J. Org. Chem.* **1990**, *55*, 5303.