

Copper-Catalyzed Synthesis of Quinoxalines with *o*-Phenylenediamine and Terminal Alkyne in the Presence of Bases

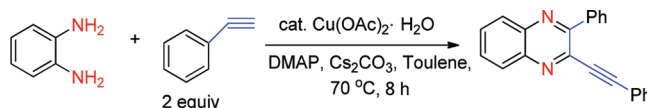
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ABSTRACT



A novel way of synthesizing quinoxalines efficiently through cyclization of *o*-phenylenediamine and terminal alkyne by Cu(II) and bases is developed. This reaction proceeds smoothly to give the products in moderate to good yields.

Quinoxalines play an important role in the area of nitrogen-containing heterocycles as they are useful intermediates of other organic cyclic compounds¹ and are useful dyes.² In addition, their derivatives possess significant biological activities including antiviral, antibacterial, and anti-inflammatory.³ The quinoxalines are also well-known in the pharmacological industry.⁴ During the last decades, many methods have been developed for the

preparation of quinoxalines.⁵ Most of them utilized *o*-phenylenediamine and alkyne, which is oxidized to diketone (Scheme 1).⁶ Numerous oxidants and catalytic systems for this process have been reported: DMSO/PdX₂,⁷ PdCl₂/CuCl₂/PEG,⁸ KMnO₄/NaHCO₃,⁹ SO₃/dioxane,¹⁰ I₂/DMSO,¹¹ O₂/Cu,¹² and Ga(OTf)₃.¹³ Although they are efficient methods for quinoxalines, most of them make use of elevated temperature, prolonged reaction time, toxic oxidants, and functionalized substrates. Here we developed a novel method to synthesize quinoxalines with *o*-phenylenediamine and phenylacetylene catalyzed by Cu(OAc)₂·H₂O in the presence of bases.

(1) Dailey, S.; Feast, J. W.; Peace, R. J.; Sage, I. C.; Till, S.; Wood, E. L. *J. Mater. Chem.* **2001**, *11*, 2238.

(2) (a) Brock, E. D.; Lewis, D. M.; Yousaf, T. I.; Harper, H. H. The Procter and Gamble Co. WO9951688, 1999. (b) Sonawane, N. D.; Rangnekar, D. W. *J. Heterocycl. Chem.* **2002**, *39*, 303.

(3) (a) Schutz, H. *Benzodiazepines*; Springer: Heidelberg, 1982. (b) Landquist, J. K. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 1, pp 166–170. (c) Seitz, L. E.; Suling, W. J.; Reynolds, R. C. *J. Med. Chem.* **2002**, *45*, 5604. (d) Kim, Y. B.; Kim, Y. H.; Park, J. Y.; Kim, S. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 541. (e) He, W.; Meyers, M. R.; Hanney, B.; Spada, A.; Blider, G.; Galzeinski, H.; Amin, D.; Needle, S.; Page, K.; Jayyosi, Z.; Perrone, H. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3097.

(4) Lindsley, C. W.; Zhao, Z.; Leister, W. H.; Robinson, R. G.; Barnett, S. F.; Defeo-Jones, D.; Jones, R. E.; Hartman, G. D.; Huff, J. R.; Huber, H. E.; Duggan, M. E. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 761.

(5) (a) Porter, A. E. A. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; p 157. (b) Woo, G. H. C.; Snyder, J. K.; Wan, Z. K. *Prog. Heterocycl. Chem.* **2002**, *14*, 279.

(6) (a) Katritzky, A. R.; Zhang, D.; Kirichenko, K. *J. Org. Chem.* **2005**, *70*, 3271. (b) Merkul, E.; Dohe, J.; Gers, C.; Rominger, F.; Muller, T. J. *J. Angew. Chem., Int. Ed.* **2011**, *50*, 2966.

(7) Mousset, C.; Provot, O.; Hamze, A.; Brion, J.-D.; Alami, M. *Tetrahedron* **2008**, *64*, 4287.

(8) Chandrasekhar, S.; Kesava Reddy, N.; Praveen Kumar, V. *Tetrahedron Lett.* **2010**, *51*, 3623.

(9) Deng, X.; Mani, N. S. *Org. Lett.* **2006**, *8*, 269.

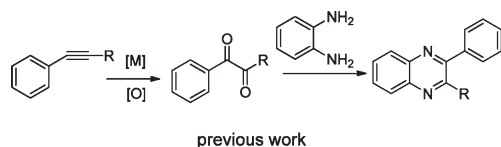
(10) Rogatchov, V. O.; Filimonov, V. D.; Yusubov, M. S. *Synthesis* **2001**, 1001.

(11) Bhosale, R. S.; Sarda, S. R.; Ardhapure, S. S.; Jadhav, W. N.; Bhusare, S. R.; Pawar, R. P. *Tetrahedron Lett.* **2005**, *46*, 7183.

(12) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28.

(13) Cai, J.; Zou, J. P.; Pan, X. Q.; Zhang, W. *Tetrahedron Lett.* **2008**, *49*, 7386.

Scheme 1



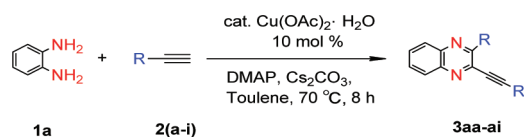
Treatment of a toluene solution of *o*-phenylenediamine **1a** (0.25 mmol) with phenylacetylene **2a** (1 mmol) in the presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (10 mol %), based on the molar amount of **1a**, Cs_2CO_3 (0.75 mmol), and 4-dimethylaminopyridine (DMAP, 0.75 mmol) at 70 °C for 8 h gave the corresponding quinoxaline **3a** in a yield of 86%. Three

Table 1. Screening of Reaction Conditions for Synthesis of Quinoxalines with **1a** and **2a**^a

entry	catalyst	base	yield ^b (%)
1	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	Cs_2CO_3	42
2	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	DMAP + Cs_2CO_3	86
3	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	$\text{Et}_3\text{N} + \text{Cs}_2\text{CO}_3$	64
4	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	TMDEA + Cs_2CO_3	55
5	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	pyridine + Cs_2CO_3	59
6	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	DMAP	0
7	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	DMAP + Na_2CO_3	52
8	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	DMAP + KOH	46
9	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	DMAP + K_3PO_4	35
10	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	DMAP + Cs_2CO_3	79 ^c
11	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}^d$	DMAP + Cs_2CO_3	86 ^e
12	CuCl_2	DMAP + Cs_2CO_3	43
13	$\text{Cu}(\text{PPh}_3)_3\text{Br}$	DMAP + Cs_2CO_3	34 ^f

^a All of the reactions were carried out in tubes using 0.25 mmol of **1a**, 1 mmol of **2a**, 10 mol % of catalyst, and 3 equiv of each base in the solvent at 70 °C for 8 h. ^b Isolated yields. ^c For 24 h. ^d 20 mol % catalyst. ^e The reaction was carried out at 100 °C. ^f Protected by N_2 .

equivalents of DMAP was employed in this reaction to get the best yield. Pyridine, Et_3N , and tetramethylethylenediamine (TMEDA) were tested (Table 1, entries 1–5), but the yields did not increase evidently. However, this reaction did not work in the absence of inorganic base. Among various inorganic bases tested, Na_2CO_3 , KOH, and K_3PO_4 were all effective, albeit affording the products with diminished yields, and Cs_2CO_3 turned out to be the best one (Table 1, entries 6–9). The screening experiments also showed that increasing the amount of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ did not enhance the yield and even prolonged the reaction time to 24 h (Table 1, entry 10). The effects of different copper sources were also examined, and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ showed the highest activity (Table 1, entries 11–13). Other catalysts such as FeCl_3 and AlCl_3 were found to be

Table 2. Reactions of *o*-Phenylenediamine **1a** with Various Terminal Alkynes^a

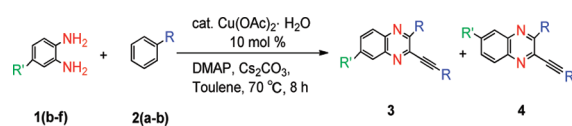
entry	alkyne	product	yield ^b
1	2a	3aa	86
2	2b	3ab	49
3	2c	3ac	42
4	2d	3ad	79
5	2e	3ae	99
6	2f	3af	trace
7	2g	3ag	54
8	2h	3ah	52
9	2i	3ai	80

^a All of the reactions were carried out in sealed tubes using 0.25 mmol of **1**, 1 mmol of **2**, 10 mol % of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, and 3 equiv of each base in toluene at 70 °C for 8 h. ^b Isolated yields.

essentially ineffective in this reaction. When the reaction was conducted at a lower temperature, it proceeded smoothly with a lower yield, and a higher reaction temperature did not increase the yield (Table 1, entry 11). Further inspection of the reaction conditions reveals that the reaction proceeded efficiently in solvents such as CH_3CN , THF, benzene, 1,4-dioxane, and ethyl alcohol, whereas they were less efficient compared with toluene.

To investigate the scope of the reaction, a variety of different substituted *o*-phenylenediamines and phenylacetylenes were subjected to the standard reaction conditions. The corresponding quinoxalines were obtained in moderate to good yields as shown in Table 2. First, a variety of

Table 3. Reactions of Substituted *o*-Phenylenediamine with Terminal Alkynes^a



entry	R'	R	product	yield ^b
1	OCH ₃ (1b)	H (2a)	 3ba	87
2	CH ₃ (1c)	CH ₃ (2b)	 3cb:4cb = 2.0 : 1	89
3	Br (1d)	CH ₃ (2b)	 3db:4db = 1.2 : 1	31
4	Cl (1e)	CH ₃ (2b)	 3eb:4eb = 1.3 : 1	30
5	NO ₂ (1f)	H (2a)	N.R.	N.R.

^a All of the reactions were carried out in sealed tubes using: 0.25 mmol of **1**, 1 mmol of **2**, 10 mol % of Cu(OAc)₂·H₂O, and 3 equiv of each base in toluene at 70 °C for 8 h. ^b Isolated yields.

aromatic alkynes were efficient, although those ones bearing electron-rich groups generated the products with moderate yields (Table 2, entries 1–7). This reaction was not limited to aromatic alkynes; aliphatic alkynes were also tested, and it turned out that they could react with **1a** to give quinoxalines smoothly (Table 2, entries 8 and 9).

Next, the reaction scope of *o*-phenylenediamine was studied (Table 3). Those compounds bearing an electron-donating group formed the products in good yields. The chloro and bromo moieties on *o*-phenylenediamine were all well tolerated under these reaction conditions but afforded the target products with lower yields (Table 3, entries 1–5). Notably, regioselectivities were observed in this transformation. Substrates substituted by CH₃, Cl, or Br groups gave a mixture of regioisomers. The combined yields ranged from 30 to 89%, and the ratio of isomers varies from 2.0:1 to 1.2:1. Confirmed by ¹H NMR, ¹³C NMR, HMBC, and HRMS, reaction involving 4-methylbenzene-1,2-diamine can be highly regioselective with **3ba** as product. Thus, we assume the favorable isomer would be **3**.

All products displayed spectroscopic data in agreement with the expected quinoxaline, and the structure was further confirmed by X-ray data (Figure 1).

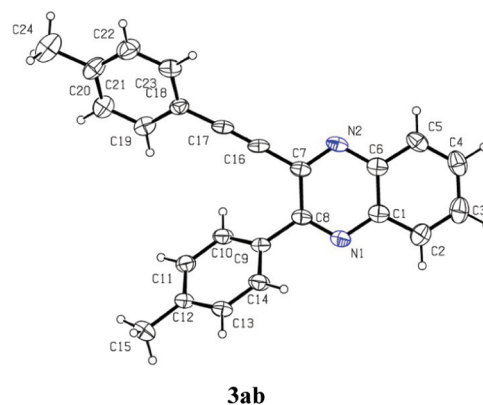
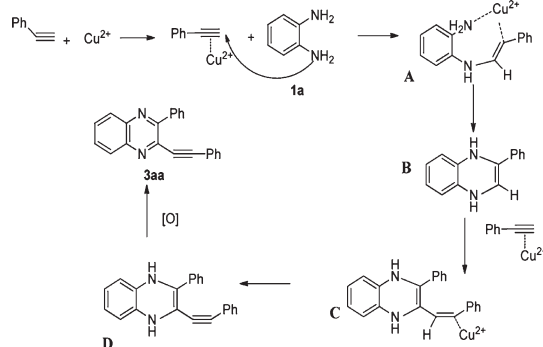


Figure 1. X-ray structure of **3ab**.

We also explored the mechanism of the reaction. When the product of homocoupling of **2a** was used as a substrate, **3a** was not observed. Unactivated alkyne such as diphenylacetylene did not react either. On the basis of the experiments mentioned above, a plausible mechanism was proposed as shown in Scheme 2. The proposed initiated complex **A** would lose H⁺ and Cu²⁺ to give **B**, which was attacked by a second equivalent of alkyne to form **C** after losing another H⁺ and Cu²⁺, and a precursor of quinoxaline **D** was obtained. Next, **D** could be easily aromatized to the target compound quinoxaline **3aa** by air.¹⁴ We will focus on the systematic investigation in future studies.

Scheme 2. Proposed Mechanism



In conclusion, we have developed a copper-catalyzed method for synthesis of quinoxaline by using *o*-phenylenediamine and terminal alkyne. This method uses simple available substrates and can proceed successfully with a one-step synthetic procedure, and the reaction conditions were relatively mild.

(14) (a) Zhou, L.; Shi, Y.; Xiao, Q.; Liu, Y. z.; Ye, F.; Zhang, Y.; Wang, J. B. *Org. Lett.* **2011**, *13*, 968. (b) Tetsuya Hamada, Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833. (c) Xiao, Q.; Xia, Y.; Li, H.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1114.

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Supporting Information Available. Experimental details, spectra, and X-ray data (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.