



Note

A recyclable copper catalysis in quinoxaline synthesis from α -hydroxyketones and *o*-phenylenediamines

Chan Sik Cho*, Wen Xiu Ren

Department of Applied Chemistry, Kyungpook National University, Daegu 702-701, Republic of Korea

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ABSTRACT

o-Phenylenediamines react with α -hydroxyketones in toluene at 100 °C in the presence of a catalytic amount of a copper catalyst along with MS 4A under O₂ atmosphere to afford the corresponding quinoxalines in high yields. The catalytic system could be easily recovered and reused several times without any loss of catalytic activity.

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1. Introduction

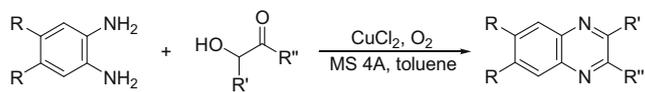
Transition metal-catalyzed in situ oxidation of alcohols to carbonyl compounds followed by condensation (oxidative cyclization) frequently provides a convenient synthetic route for N-heterocycles. Several synthetic methods for N-heterocycles have been exemplified with such a transition metal-catalyzed oxidative cyclization. As the part of our ongoing studies on transition metal-catalyzed carbon–carbon bond forming reactions using alcohols as an electrophile, we recently disclosed on ruthenium- and palladium-catalyzed coupling processes between ketones (or secondary alcohols) and primary alcohols [1–10]. This type of carbon–carbon bond forming reaction could be applied to the synthesis of quinolines via transition metal-catalyzed oxidative cyclization of 2-aminobenzyl alcohol with ketones and secondary alcohols [11–19]. Recently, we developed an economical reusable catalytic system, CuCl₂ combined with molecular sieve 4A (MS 4A) for this oxidative cyclization [20]. It is also reported by us that vicinal-diols are oxidatively cyclized with *o*-phenylenediamines in the presence of a ruthenium catalyst to afford quinoxalines [21]. α -Hydroxyketones were also found to undergo an oxidative cyclization with *o*-phenylenediamines in the presence of a transition metal catalyst to afford quinoxalines [22–26]. Under these circumstances, the present work was disclosed during the course of the application of the recyclable copper catalytic system (CuCl₂/MS 4A) for

the quinoline synthesis to the reaction of *o*-phenylenediamines with α -hydroxyketones. Herein we describe a recyclable copper-catalyzed oxidative cyclization of α -hydroxyketones with *o*-phenylenediamines leading to quinoxalines (Scheme 1) [27,28].

2. Results and discussion

Initial attempts for the oxidative cyclization of 2-hydroxyacetophenone (**2a**) with *o*-phenylenediamine (**1a**) were carried out under several conditions and the results are listed in Table 1. We recently reported that **1a** reacts with **2a** in toluene at 100 °C for 3 h in the presence of a catalytic amount of CuCl₂ under an atmosphere of air afforded 2-phenylquinoxaline (**3a**) in 94% yield [26]. When the reaction was carried out with further addition of molecular sieve 4A (MS 4A) as a recyclable medium to the copper catalytic system, **3a** was obtained in 80% isolated yield (entry 1) and the copper catalytic system could be easily recovered by simple filtration from the reaction mixture. No Cu in the filtrate was observed by ICP-AES (inductively coupled plasma-atomic emission spectroscopy) determination. However, although the recovered CuCl₂/MS 4A could be reused several times, the catalytic activity during second to fourth runs was lower than that of first run. Performing the reaction for a longer reaction time (10 h) gave an increased yield of **3a** and the recovered CuCl₂/MS 4A could be reused three times without any loss of catalytic activity (entry 2). A slightly increased yield of **3a** was observed with a higher molar

* Corresponding author. Tel.: +82 53 950 5586; fax: +82 53 950 6594.
E-mail address: cscho@knu.ac.kr (C.S. Cho).



Scheme 1.

Table 1
Copper-catalyzed reaction of **1a** with **2a** under several conditions^a

Entry	[2a]/[1a]	Atmosphere	Time (h)	Isolated yield (%)					
				1	2	3	4	5	6
1	1.0	Air	3	80	67	63	66		
2	1.0	Air	10	91	86	84	85		
3	1.1	Air	10	95	95	90	90	89	88
4	1.1	O ₂	3	90	91	88	86	84	87
5 ^b	1.1	O ₂	3	41	38	40	43		
6	1.1	O ₂	10	95	95	96	95	94	93

^a All reactions were carried out with **1a** (0.5 mmol), CuCl₂ (0.05 mmol) and MS 4A (0.3 g) in toluene (5 mL) at 100 °C.

^b In the absence of CuCl₂.

ratio of **2a** to **1a** and the recovered CuCl₂/MS 4A could be reused five times without any loss of catalytic activity (entry 3). Furthermore, performing the reaction under O₂ atmosphere resulted in a higher catalytic activity compared with that under air atmosphere (entries 1 and 4) and the presence of CuCl₂ was essential for the effective formation of **3a** (entry 5). As a result, the best result in terms of both yield and catalytic activity of recovered CuCl₂/MS 4A was accomplished by the standard set of reaction conditions shown in entry 6 of Table 1.

After the reaction conditions have been established, various α -hydroxyketones **2** were subjected to the reaction with *o*-phenylenediamines **1** in order to investigate the reaction scope and several representative results are summarized in Table 2. With α -hydroxyketones (**2a–i**) having aryl group attached to carbonyl carbon, the corresponding quinoxalines (**3a–i**) were formed in the range of 84–95% yields without any identifiable side products. The position and electronic nature of the substituent on the aromatic ring had no relevance to the quinoxaline yield. As is the case for the reaction of **1a** with **2a**, the copper combined with MS 4A as recyclable medium also could be recovered and reused three times without any loss of catalytic activity. 2-Hydroxy-2'-acetonephthone (**2j**) was also oxidatively cyclized with **1a** to give 2-(2-naphthyl)quinoxaline in 84% yield and exhibited similar recycling potential. Although the reaction proceeds with α -hydroxyketones **2k** having a heteroaryl group attached to carbonyl carbon, the product yield was lower than that when α -hydroxyketones (**2a–j**) having aryl group attached to carbonyl carbon were employed. Lower reaction rate and yield were observed with α -hydroxyketone **2l** which has an alkyl group attached to carbonyl carbon. From the reaction between **1a** and cyclic α -hydroxyketone **2m**, 6,7,8,9-tetrahydrophenazine (**3m**) was also produced in 63% yield. Similar treatment of α -hydroxyketones (**2n** and **2o**), which have an alkyl group attached to α -carbon with **1a** under the employed conditions afforded the corresponding 3-alkyl substituted quinoxalines (**3n** and **3o**). The reaction of dimethyl-1,2-phenylenediamine (**1b**) with **2a** also proceeds to give 6,7-dimethyl-2-phenylquinoxaline (**3p**) with similar yield and recycling potential.

Table 2
Recyclable copper-catalyzed synthesis of quinoxalines **3** from **1** and **2**^a

1	α -Hydroxyketones 2	Quinoxalines 3	Yield (%)		
			1	2	3
1a					
	2a R = Ph	3a R = Ph	95	95	96
	2b R = 4-MeC ₆ H ₄	3b R = 4-MeC ₆ H ₄	88	85	85
	2c R = 3-MeC ₆ H ₄	3c R = 3-MeC ₆ H ₄	88	84	84
	2d R = 2-MeC ₆ H ₄	3d R = 2-MeC ₆ H ₄	88	86	85
	2e R = 4-MeOC ₆ H ₄	3e R = 4-MeOC ₆ H ₄	89	83	83
	2f R = 3-MeOC ₆ H ₄	3f R = 3-MeOC ₆ H ₄	87	83	83
	2g R = 2-MeOC ₆ H ₄	3g R = 2-MeOC ₆ H ₄	84	81	82
	2h R = 4-FC ₆ H ₄	3h R = 4-FC ₆ H ₄	88	84	84
	2i R = 3-CF ₃ C ₆ H ₄	3i R = 3-CF ₃ C ₆ H ₄	89	90	90
	2j R = 2-naphthyl	3j R = 2-naphthyl	84	83	85
2k R = 2-thienyl	3k R = 2-thienyl	77	73	72	
			58	57	56
2l	3l				
			63	61	60
2m	3m				
			87	87	87
2n	3n				
			62	60	59
2o	3o				
1b	2a		88	86	84
		3p			

^a All reactions were carried out with **1** (0.5 mmol), **2** (0.55 mmol), CuCl₂ (0.05 mmol) and MS 4A (0.3 g) in toluene (5 mL) at 100 °C for 10 h under O₂ atmosphere.

3. Conclusion

In summary, we have shown that α -hydroxyketones undergo an oxidative cyclization with *o*-phenylenediamines in the presence of a copper catalyst combined with MS 4A under O₂ atmosphere to give quinoxalines in high yields. The copper catalyst combined with MS 4A could be easily recovered by a simple filtration and reused several times without any loss of catalytic activity. The present reaction provides a cheaper catalytic method for quinoxalines compared with known catalytic routes and further study of synthetic applications using the present recyclable copper catalytic system is currently under investigation.

4. Experimental

¹H and ¹³C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using TMS as an internal standard. ICP-AES was measured on a Thermo Jarrell Ash IRIS/AP. The isolation of pure products was carried out via thin layer chromatography (silica gel 60 GF₂₅₄, Merck). Except for 1-hydroxyhexan-2-one (**2l**), which was prepared by selective oxidation of diols [29], all α -hydroxyketones were synthesized by direct α -hydroxylation of

ketones with [bis(trifluoroacetoxy)iodo]benzene and trifluoroacetic acid [30] as well as α -bromination of ketones followed by hydroxylation [31,32]. Commercially available organic and inorganic compounds were used without further purification.

4.1. Typical procedure for copper-catalyzed synthesis of quinoxalines from *o*-phenylenediamines and α -hydroxyketones

To an organic reactor (Radleys Discovery Technologies) were added *o*-phenylenediamine (0.054 g, 0.5 mmol), 2-hydroxyacetophenone (0.075 g, 0.55 mmol), CuCl₂ (0.007 g, 0.05 mmol), MS 4A (0.3 g) and dry toluene (5 mL). After the system was flushed with O₂ from a balloon connected to the organic reactor, the reaction mixture was allowed to react at 100 °C for 10 h. The reaction mixture cooled to room temperature was filtered through a filter paper, washed with ethyl acetate, dried under vacuo and subjected to a second run by charging the reactor with **1a**, **2a**, toluene and O₂ substitution. Removal of the solvent from the filtrate left an oil, which was purified by thin layer chromatography (silica gel, ethyl acetate–hexane = 1/5) to give 2-phenylquinoxaline (**3a**) (0.098 g, 95%). Except for **3i** and **3o**, which were characterized spectroscopically as shown below, all quinoxalines exhibited characteristics identical to those previously synthesized by our recent reports [21,26].

4.1.1. 2-(3-Trifluoromethylphenyl)quinoxaline (**3i**)

Solid, m.p. 115 °C (from hexane–chloroform); ¹H NMR (CDCl₃) δ 7.67 (t, *J* = 7.8 Hz, 1H), 7.74–7.82 (m, 3H), 8.12–8.17 (m, 2H), 8.36 (d, *J* = 7.8 Hz, 1H), 8.50 (s, 1H), 9.32 (s, 1H); ¹³C NMR (CDCl₃) δ 124.39 (q, *J* = 270.8 Hz), 124.81 (q, *J* = 3.9 Hz), 127.09 (q, *J* = 3.6 Hz), 129.40, 129.81, 129.90, 130.28, 130.74, 130.79, 132.09 (q, *J* = 32.24 Hz), 137.73, 142.08, 142.37, 142.94, 150.28. Anal. Calc. for C₁₅H₉F₃N₂: C, 65.69; H, 3.31; N, 10.21. Found: C, 65.48; H, 3.25; N, 10.18.

4.1.2. 2-Butyl-3-phenylquinoxaline (**3o**)

Solid, m.p. 39–41 °C (from hexane–chloroform); ¹H NMR (CDCl₃) δ 0.84 (t, *J* = 7.5 Hz, 3H), 1.27–1.36 (m, 2H), 1.68–1.76 (m, 2H), 3.04 (t, *J* = 7.8 Hz, 2H), 7.48–7.54 (m, 3H), 7.60–7.62 (m, 2H), 7.67–7.75 (m, 2H), 8.07–8.12 (m, 2H); ¹³C NMR (CDCl₃) δ 13.96, 22.73, 31.30, 35.94, 128.66, 128.68, 128.95, 129.00, 129.30, 129.36, 129.75, 139.36, 140.87, 141.62, 155.22, 156.49. Anal. Calc. for C₁₈H₁₈N₂: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.22; H, 7.02; N, 10.48.

4.2. ICP-AES measurement

To an organic reactor (Radleys Discovery Technologies) were added *o*-phenylenediamine (0.054 g, 0.5 mmol), 2-hydroxyacetophenone (0.068 g, 0.5 mmol), CuCl₂ (0.007 g, 0.05 mmol), MS 4A

(0.3 g) and dry toluene (5 mL). After the system was connected to an air balloon, the reaction mixture was allowed to react at 100 °C for 3 h. The reaction mixture cooled to room temperature was filtered through a filter paper and washed with ethyl acetate. After the filtrate was evaporated under reduced pressure, the residue was dissolved in chloroform (30 mL) and poured into a separatory funnel containing 5% HCl aqueous solution (200 mL). The aqueous phase was subjected to ICP-AES measurement.

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