Copper-Mediated Addition of Ethanolamine Affording 2-Hydroxymethyl Naphtho[2,1-*d*]oxazoles from 2-Naphthols

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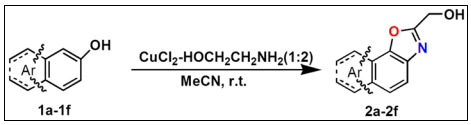
Received January 13, 2012
DOI 10.1002/jhet.1666
Published online 00 Month 2013 in Wiley Online Library (wileyonlinelibrary.com).



A new and mild synthetic approach was presented for the synthesis of naphtho[2,1-*d*]oxazoles. In the presence of copper (II)-ethanolamine, 2-hydroxymethyl naphtho[2,1-*d*]oxazoles were one-pot synthesized in moderate to good yields through copper-mediated oxidation of 2-naphthols followed with the addition of ethanolamine in acetonitrile.

J. Heterocyclic Chem., **00,** 00 (2013).

INTRODUCTION

Aryloxazoles are often found in naturally occurring compounds that exhibit multiple and strong biological activities, such as inhibitors of immune complex [1], bacteriostatic agents [2], and cysteine protease inhibiters [3]. These compounds have been studied for extensively ever since Fisher *et al*. synthesized 2-methylnaphthoxaz-ole in 1906 [4]. Many useful synthetic approaches have been developed, including the oxidation of 6-hydroxyindole with primary amines [5], the reaction of α-nitroso-β-naphthol with a pyridinium betaine to give oxazoles [6], the reactions of quinone monoximes with alkyl halides [7], the coupling of aminonaphthols with carboxylic acid derivatives [8], photolysis of naphthoxazinone to afford 2-phylnaphthoxazole [9], or photochemical synthesis from 5-(phenyl/heteroarylenthenyl)oxazoles [10]. However, copper-mediated synthesis of naphthoxazole has not been reported so far. Copper is an important oxidation catalysts element for laboratory and industrial use. Another, copper-containing oxidases play a crucial role in metalloproteins bio-oxidation catalytic reactions.

Herein, we disclose a new synthetic route for oxidation of 2-naphthols **1a–1f** by the $CuCl_2$-ethanolamine complex, then with an addition of ethanolamine to generate corresponding 2-hydroxymethyl naphtho[2,1-*d*]oxazoles **2a–2f**. The interest of the reaction focuses on using ethanolamine from copper-amine complex as a nucleophile to take part in the cyclization of 2-naphthols (Scheme 1).

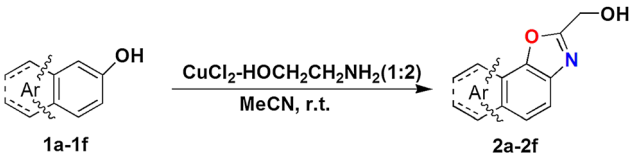
RESULTS AND DISCUSSION

We took the synthesis of **2a** as a sample. The initial experiment was carried out by oxidation of 2-naphthol **1a** under $CuCl_2$-ethanolamine complex in DMF. An annulated naphthoxazole **2a** resulted from the substrate, but the yield was poor with only 16%. In order to enhance the yield, the reaction conditions were optimized by changing the solvent, temperature, and reaction atmosphere. The results were summarized in Table 1. It was found that solvents played a significant role in improving the yields (Table 1, entries 1–6). As seen from Table 1, the yield was as high as 57% with acetonitrile. Additionally, we screened the impact of temperature and reaction atmosphere on the yields. The highest yield of 52% was obtained at 60 °C and the reaction time was shorten to 10 h (Table 1, entry 8). At the temperature of 90 °C, the low yield was observed. To elucidate if oxygen is necessary to the reaction, the experiment was performed under N_2, no desired product was found (Table 1, entry 9), but the reaction yield was not improved under O_2 atmosphere compared with under air, it showed that the quantity of O_2 in air was enough for the reaction. (Table 1, entry 10).

The optimal condition for these reactions was the copper-amine complex formed by two equiv of $CuCl_2$ with four equiv of ethanolamine in 10–15 mL acetonitrile, stirred for 10–15 h at 60 °C in air. Under this optimization, the substrate scope was investigated in detail. We found that 1-naphthol **1g** was oxidized to provide *para*-1, 4-naphthoquin-one **2g** rather than corresponding naphthoxazole(Table 2, entry 7). However, when substrates were 2-naphthols **1a–1f**, 2-hydroxymethyl naphtho[2,1-***d***]oxazoles **2a–2f** were obtained in moderate to good yield, which are shown in Table 2.

It is well known that there are two isomeric structures of naphthoxazole, one is N atom at *C*-1 and O atom at *C*-2 position of naphthyl ring that is formulated as naphtho [1,2-*d*]oxazole [11], another enantiomer is naphtho[2,1-*d*] oxazole [12]. In this paper, we obtained X-ray crystallography of compound **2a** [13], the structure of naphthoxazole is the latter. An ORTEP drawing of the cation with the atomic numbering scheme is depicted in Figure 1. In this

Scheme 1



structure, N atom locates at β-position and oxygen atom at α-position in naphthyl cycle.

During the course of reaction, a red intermediate was found by thin-layer chromatography (TLC), which was confirmed to be *ortho*-1,2-naphthoquinone. Therefore, we deduced the possible reaction mechanism as following: 2-naphthol reactant was firstly oxidized to radical (i) by $CuCl_2$-ethanolamine complex and oxygen; this radical was also occurred oxidant reaction to form intermediate 1, 2-naphthoquinone (ii). Then, ethanolamine as a nucleophile reacted with naphthoquinone (ii) to provide enamine (iii), followed by intramolecular rearrange to obtain (iv). Finally, compound (iv) was annulated to form 2-hydroxymethyl naphtho[2,1-*d*]oxazoles through oxidative cyclization. The plausible mechanism of this reaction is outlined in the succeeding text (Scheme 2).

In summary, we have developed a new methodology for the synthesis of 2-hydroxymethyl naphtho[2,1-*d*]oxazoles by copper-mediated oxidation and the addition of ethanolamine from 2-naphthol and derivatives. The reaction utilizes readily available starting materials and extends those previously reported for the synthesis of naphthoxazoles.

EXPERIMENTAL

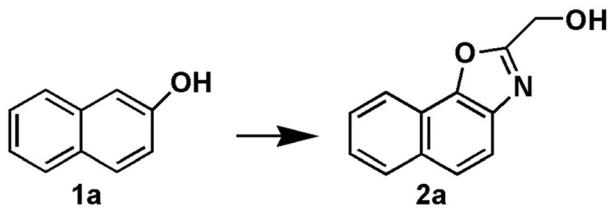
Microanalysis (C, H, and N) was carried out with a Perkin-Elmer 240Q elemental analyzer (PerkinElmer Inc., Waltham, MA). Fast atom bombardment (FAB) mass spectra were recorded on a VG ZAB-HS spectrometer (VG Scientific Ltd, Cornwall, England) in a 3-nitrobenzyl alcohol matrix. Electrospray mass spectra were recorded on a LCQ system (Finnigan MAT, USA) using methanol as mobile phase. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian-300 spectrometer (Varian Medical Systems Inc. Palo Alto, CA). All chemical shifts were given relative to tetramethylsilane. Infrared spectra were taken on a Galaxy series FTIR 7000 (Thermo Nicolet, USA) in potassium bromide pellets.

Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures. Reactions were monitored by TLC. All yields reported refer to isolated material. Column chromatography purifications were carried out using silica gel (100–200mesh).

General experimental procedure for the synthesis of 2-hydroxymethyl naphtho[2,1-*d*]oxazole. To a stirred solution of $CuCl_2$ (0.350 g, 2 mmols) and ethanolamine (0.240 g, 4 mmols) in 15 mL MeCN were added 2-naphthols **1** (0.5 mmol) at 60 °C. The mixture was stirred for 15 h, the reaction was quenched with 5% $NH_3 \cdot H_2O$, and the mixture was extracted with EtOAc. The organic extract was washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated and purification by silica gel chromatography (EtOAc-petroleum ether 1:2), and the solid of naphtho[2,1-*d*]-oxazole was obtained.

Table 1

Optimization of reaction condition.[a]

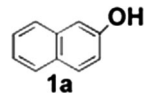
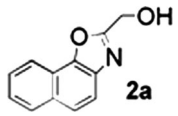
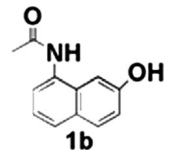
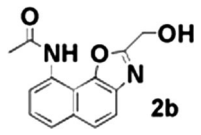
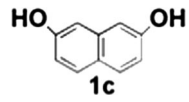
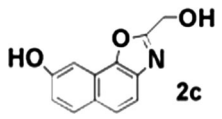
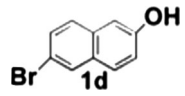
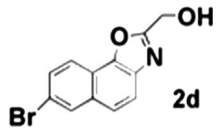
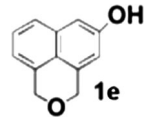
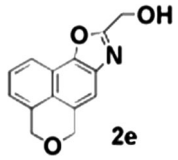
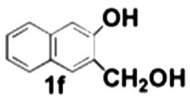
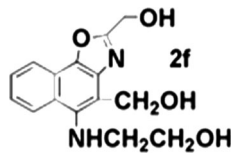
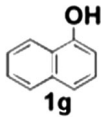
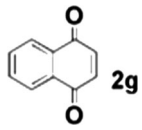


Entry	Solvent	Reaction atmosphere	Temp (°C)	Time (h)	Yield[b] (%)
1	DMSO	in air	25	72	—
2	CH_3COOH	in air	25	72	—
3	DMF	in air	25	48	16
4	THF	in air	25	48	23
5	Acetone	in air	25	20	30
6	CH_3CN	in air	5	72	40
7	CH_3CN	in air	25	20	57
8	CH_3CN	in air	60	10	52
9	CH_3CN	in N_2	60	72	—
10	CH_3CN	in O_2	60	10	43

[a]Unless otherwise specified, all the reactions were carried out in presence of 1 mmol of **1a**, 2 mmol of $CuCl_2$, 4 mmol of ethanolamine in 10–15 mL of solvent.
[b]Isolated yield after column chromatography.

Table 2

Copper-catalyzed synthesis of naphthoxazoles.[a]

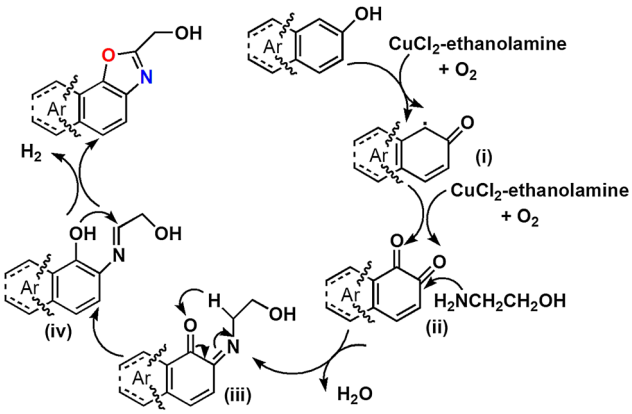
Entry	Reactants	Products	Yield[b] (%)
1	 1a	 2a	57
2	 1b	 2b	62
3	 1c	 2c	44
4	 1d	 2d	68
5	 1e	 2e	76
6	 1f	 2f	40
7	 1g	 2g	92

[a]Reagents and conditions: 2 mmol $CuCl_2$ and 4 mmol ethanolamine to form copper-amine complex in 10–15 mL MeCN, heated at 60 °C in air.
[b]Isolated yield after column chromatography.

2-Hydroxymethyl naphtho[2,1-d]oxazole (2a). This compound was obtained as colorless needle crystal. ^{1}H NMR (300 MHz, Acetone-d_6) δ: 4.95(d, J = 5.4 Hz, 2H), 7.58 (t, J = 7.5 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.87 (d, J = 8.7 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 8.21 (dd, J = 8.1Hz, 0.6 Hz, 1H). ^{13}C NMR (75 MHz, Acetone-d_6) δ: 58.0, 119.4, 120.6, 121.2, 126.0, 126.6, 127.9, 129.6, 132.6, 138.4, 147.2, 166.0 ppm. FAB-MS: m/z = 200 (100 $[M+H]^+$), 182 (36 $[M-OH]^+$). IR (KBr): 3254, 1599, 1270, 1084, 801 cm^{-1}. *Anal*. Calcd for $C_{12}H_9NO_2$ (199): C, 72.35%; H, 4.55%; N, 7.03%. Found: C 72.28%; H 4.63%; N 7.01%.

9-Acetylamino-2-hydroxymethyl naphtho[2,1-d]oxazole (2b). This compound was obtained as white solid. ^{1}H NMR (300 MHz, Acetone-d_6) δ: 2.23 (s, 3H), 4.81 (d, J = 3.0, 2H), 5.97 (t, J = 6.0 Hz, 1H), 7.57 (t, J = 8.1 Hz, 1H), 7.67 (d, J = 7.2 Hz, 1H), 7,86 (d, J = 8.7 Hz, 1H), 7.96 (t, J = 8.4 Hz, 1H), 9.97 (s, 1H). ^{13}C NMR (75 MHz, Acetone-d_6) δ: 23.45, 56.50, 116.89, 118.78, 123.87, 125.54, 125.58, 126.14, 130.92, 132.31, 137.95, 144.61, 165.10, 169.44 ppm. ESI-MS: m/z = 256.9 ($[M+H]^-$). IR (KBr): 3270, 1662, 1554, 1399, 1281, 1142, 1089, 816, 693 cm^{-1}. *Anal*. Calcd for $C_{14}H_{12}N_2O_3$ (256): C, 65.62%; H, 4.72%; N, 10.93%. Found: C 65.99%; H 4.72%; N 10.62%.

Scheme 2 Proposed mechanism for the formation of naphthoxazole **2**.



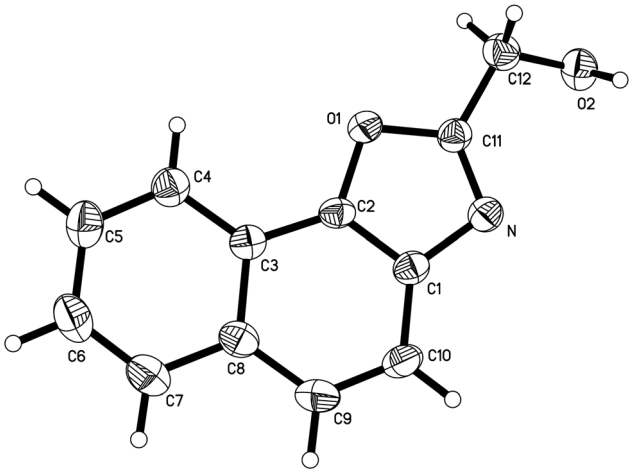


Figure 1. An ORTEP drawing of 2a. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

2-Hydroxymethyl-8-hydroxyl naphtho[2,1-d]oxazole (2c). This compound was obtained as pale white solid. ^{1}H NMR (300 MHz, Acetone-d_6) δ: 4.75 (s, 2H), 7.10 (dd, J = 9.0, 2.4 Hz, 1H), 7.34 (s, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.92 (d, J = 8.7 Hz, 1H), 10.16 (s, 1H). ^{13}C NMR (75 MHz, Acetone-d_6) δ: 59.9, 104.3, 117.9, 120.4, 124.4, 127.6, 129.1, 133.3, 140.6, 148.4, 159.2, 167.4 ppm. ESI-MS: m/z = 214 ([M − H]$^-$). IR (KBr): 3262, 3105, 2827, 1649, 1599, 1451, 1221, 1044 cm^{-1}. *Anal.* Calcd for $C_{12}H_9NO_3$ (215): C, 66.97%; H, 4.22%; N, 6.51%. Found: C 66.00%; H 4.24%; N 6.50%.

7-Bromo-2-hydroxymethyl naphtho[2,1-d]oxazole (2d). This compound was obtained as off white solid. ^{1}H NMR (300 MHz, Acetone-d_6) δ: 4.61 (s, 2H), 6.88 (d, J = 9.0 Hz, 1H), 6.91 (s, 2H), 7.26 (d, J = 9.0 Hz, 1H), 7.36 (s, 1H). ^{13}C NMR (75 MHz, Acetone-d_6) δ: 56.5, 118.2, 118.8, 119.9, 121.9, 124.5, 130.2, 130.7, 132.3, 137.5, 145.5, 165.6 ppm. FAB-MS: m/z = 278 ([M + H]$^+$). IR (KBr): 3256, 2922, 2852, 1587, 1359, 1157, 1042 cm^{-1}. *Anal.* Calcd for $C_{12}H_8NBrO_2$ (278): C, 51.83%; H, 2.90%; N, 5.04%. Found: C 51.90%; H 3.04%; N 4.92%.

5,6-Oxodimethylene-2-hydroxymethyl naphtho[2,1-d]oxazole (2e). This compound was obtained as yellow solid. ^{1}H NMR (300 MHz, Acetone-d_6) δ: 4.91 (s, 2H), 5.06 (s, 2H), 5.10 (s, 2H), 7.34 (d, J = 6.6 Hz, 1H), 7.55 (s, 1H), 7.64 (t, J = 8.1 Hz, 1H), 8.06 (d, J = 8.1 Hz, 1H). ^{13}C NMR (75 MHz, Acetone-d_6) δ: 56.5, 68.2, 68.6, 112.8, 118.1, 119.1, 120.3, 124.4, 126.9, 129.9, 134.1, 136.5, 144.5, 165.2 ppm. ESI-MS: m/z = 240 ([M − H]$^-$). IR (KBr): 3214, 2946, 2830, 1564, 1448, 1365, 1176, 1111, 1046 cm^{-1}. *Anal.* Calcd for $C_{14}H_{11}NO_3$ (241): C, 69.70%; H, 4.60%; N, 5.81%. Found: C 69.55%; H 4.60%; N 5.60%.

5-Hydroxyethyamino-2,4-dihydroxymethyl naphtho[2,1-d] oxazole (2f). This compound was obtained as yellow solid. ^{1}H NMR (300 MHz, Acetone-d_6) δ: 3.43 (t, J = 4.8 Hz, 1H), 3.73 (t, J = 4.8 Hz, 1H), 4.87 (s, 2H), 5.12 (s, 2H), 7.52 (t, J = 7.5 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 8.35 (d, J = 9.0 Hz, 2H). ^{13}C NMR (75 MHz, Acetone-d_6) δ: 53.3, 55.5, 57.1, 61.3, 115.7, 121.9, 122.6, 124.4, 125.2, 126.7, 126.9, 130.8, 143.8, 147.8, 163.4 ppm. FAB-MS: m/z = 288 ([M]$^+$). IR (KBr): 3315, 3074, 2907, 2854, 1638, 1589, 1401, 1339, 1215, 1083 cm^{-1}.

Acknowledgment. We thank Guangdong Province Department of Education (Nos. 1057310015) for providing funds for this project. We also thank Yong Chen (Guangdong Institute of Analysis) for the help with the NMR spectrometers.

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[13] Note: Crystallographic data (excluding structure factors) for the structures reported in this work have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication No. CCDC-839716. Copies of the data can be obtained free of charge on application *via* www.ccdc.cam.ac.uk/data_request/cif or email (deposit@ccdc.cam.ac.uk).