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Simple and efficient copper-catalyzed cascade synthesis of naphthols containing multifunctional groups under mild conditions†

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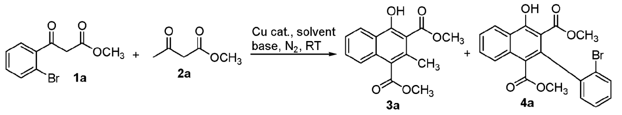
Received 24th May 2010, Accepted 31st August 2010
DOI: 10.1039/c0cc01544j

A simple and efficient copper-catalyzed method for synthesis of naphthols containing multifunctional groups has been developed under mild conditions (room temperature to 60 °C), and it can tolerate various functional groups.

The demand for functionalized aromatic compounds is growing rapidly in many research fields.[1] In the aromatic compounds, naphthalene derivatives show wide applications in academic lab and industry,[2,3] and they often occur as the basic skeletons of natural products and pharmaceuticals.[4] Therefore, it is very desired to develop practical and efficient methods for the synthesis of naphthalenes with various functional groups.[5] In the previous methods, aromatic electrophilic substitution is a common strategy, however, it is often difficult to control substitution sites regioselectively with this reaction. The direct construction of naphthalene rings presents a potential advantage from monocyclic precursors in which substituents are arranged at predetermined positions.[6] Recently, copper-catalyzed coupling reactions have made great progress,[7] and the cross-coupling strategy has been used to make heterocycles.[8] In continuation of our endeavors to develop copper-catalyzed coupling reactions,[9] herein, we report a simple and efficient copper-catalyzed synthesis of naphthols containing multifunctional groups under mild conditions.

Initially, methyl 3-(2-bromophenyl)-3-oxopropanoate (**1a**) and methyl 3-oxobutanoate (**2a**) were chosen as the model substrates to optimize reaction conditions including the catalysts, bases and solvents under nitrogen atmosphere. As shown in Table 1, seven copper catalysts (0.1 equiv.) were tested at room temperature by using 2 equiv. of Cs_2CO_3 as the base (relative to amount of **1a**) in DMF (entries 1–7), CuCl showed the highest activity, and the target product (**3a**) was obtained in 90% yield with trace amounts of dimer (**4a**) from **1a** appearing (entry 3). The reaction could not be carried out in the absence of copper catalyst (entry 8). The effect of bases was investigated (compare entries 3, 9 and 10), and the results showed that Cs_2CO_3 was the best choice (entry 3). We attempted various solvents (compare entries 3, 11–13), and DMF provided the highest yield. When CuCl was reduced to 5 mol% from 10 mol% in entry 3, a 60% yield was provided, and the cascade reaction also gave higher yield (73%) as time elongated (entry 14). The yield decreased because of hydrolysis of a small amount of ester bonds in **2a** and **3a** when temperature was raised to 60 °C (entry 15). Interestingly, the reaction did not need an additional ligand or additive, and the result implies that the substrates (methyl 3-(2-bromophenyl)-3-oxopropanoate and methyl 3-oxobutanoate) containing β-keto ester group can act as ligands (see reaction mechanism in Scheme 2), and similar copper-catalyst ligands, β-diketone[10] and β-keto ester,[11] were reported in the previous researches.

Table 1 Copper-catalyzed cascade synthesis of dimethyl 4-hydroxy-2-methylnaphthalene-1,3-dicarboxylate (**3a**) *via* coupling of methyl 3-(2-bromophenyl)-3-oxopropanoate (**1a**) with methyl 3-oxobutanoate (**2a**): optimization of conditions[a]



Entry	Cu Cat.	Base	Solvent	Yield of **3a**[b] (%)	Yield of **4a**[b] (%)
1	CuI	Cs_2CO_3	DMF	82	Trace
2	CuBr	Cs_2CO_3	DMF	80	Trace
3	**CuCl**	$\mathbf{Cs_2CO_3}$	**DMF**	**90**	**Trace**
4	Cu_2O	Cs_2CO_3	DMF	16	Trace
5	CuO	Cs_2CO_3	DMF	5	0
6	$Cu(OAc)_2$	Cs_2CO_3	DMF	30	Trace
7	Cu	Cs_2CO_3	DMF	5	0
8	—	Cs_2CO_3	DMF	Trace	0
9	CuCl	K_2CO_3	DMF	82	Trace
10	CuCl	K_3PO_4	DMF	69	Trace
11	CuCl	Cs_2CO_3	DMSO	63	Trace
12	CuCl	Cs_2CO_3	Dioxane	5	0
13	CuCl	Cs_2CO_3	THF	7	0
14[c]	CuCl	Cs_2CO_3	DMF	60 (73[d])	Trace
15[e]	CuCl	Cs_2CO_3	DMF	62	Trace

[a] Reaction condition: methyl 3-(2-bromophenyl)-3-oxopropanoate (**1a**) (0.5 mmol), methyl 3-oxobutanoate (**2a**) (0.6 mmol), catalyst (0.05 mmol), base (1 mmol), solvent (2 mL), room temperature (~25 °C) under nitrogen atmosphere, reaction time (1 h). [b] Isolated yield. [c] 0.025 mol of CuCl was used. [d] Reaction time (4 h). [e] Reaction temperature (60 °C).

The scope of copper-catalyzed cascade synthesis of naphthol derivatives was investigated under the optimized condition (10 mol% CuCl as the catalyst, 2 equiv. of Cs_2CO_3 as the base, DMF as the solvent). As shown in Table 2, most of the substrates examined provided moderate to good yields under very mild conditions. For the substituted methyl 3-(2-bromophenyl)-3-oxopropanoates (entries 1–17) and 3-(2-bromo-5-chlorophenyl)-3-oxopropanenitrile (entries 18–20), the reactions were carried out at room temperature (~25 °C) (except entry 6). Methyl 3-(2-chlorophenyl)-3-oxopropanoate

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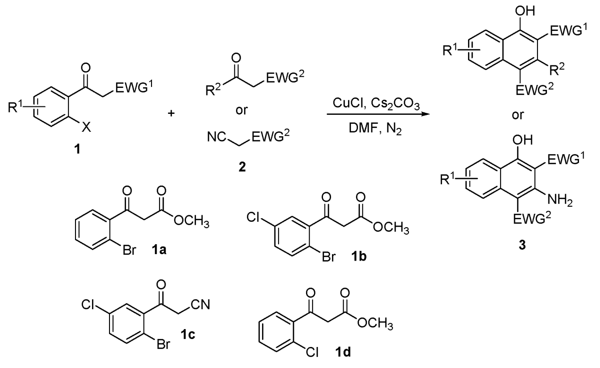
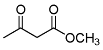
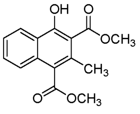
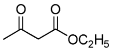
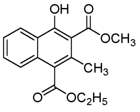
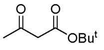
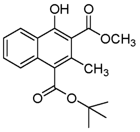
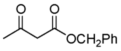
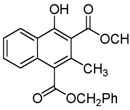
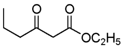
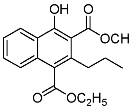
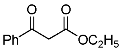
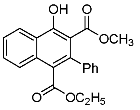
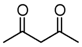
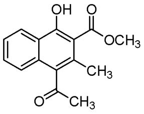
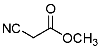
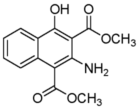
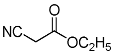
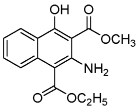
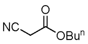
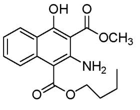
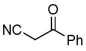
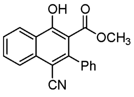
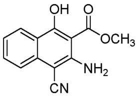
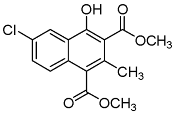
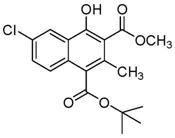
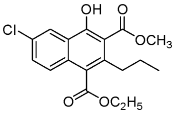
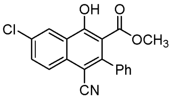
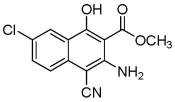
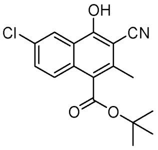
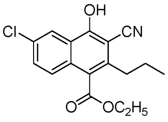
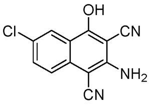
† Electronic supplementary information (ESI) available: General procedure for synthesis of compounds **3a–t**, characterization data for compounds **3a–t**, and ^1H and ^{13}C NMR spectra of compounds **3a–t**. See DOI: 10.1039/c0cc01544j

Table 2 Copper-catalyzed synthesis of naphthol derivatives[a]



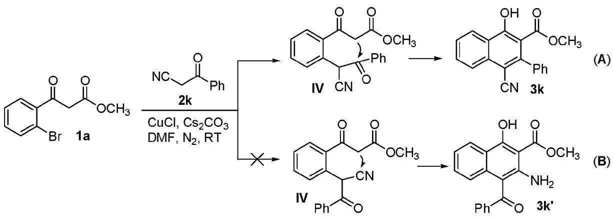
Entry	1	2	Time/h	3	Yield[b] (%)
1	**1a**	 **2a**	1	 **3a**	90
2	**1a**	 **2b**	1	 **3b**	66
3	**1a**	 **2c**	1	 **3c**	75
4	**1a**	 **2d**	1	 **3d**	95
5	**1a**	 **2e**	1	 **3e**	68
6	**1a**	 **2f**	8	 **3f**	90
7	**1a**	 **2g**	4	 **3g**	95
8	**1a**	 **2h**	2	 **3h**	61
9	**1a**	 **2i**	2	 **3i**	66
10	**1a**	 **2j**	8	 **3j**	64
11	**1a**	 **2k**	6	 **3k**	63
12	**1a**	 **2l**	8	 **3l**	83
13	**1b**	**2a**	1	 **3m**	84
14	**1b**	**2c**	1	 **3n**	68
15	**1b**	**2e**	1	 **3o**	74
16	**1b**	**2k**	6	 **3p**	62
17	**1b**	**2l**	2	 **3q**	68
18	**1c**	**2c**	5	 **3r**	58
19	**1c**	**2e**	5	 **3s**	55
20	**1c**	**2l**	5	 **3t**	77
21	**1d**	**2a**	12	**3a**	52
22	**1d**	**2i**	12	**3i**	58
23	**1d**	**2j**	12	**3j**	41

[a] Reaction condition: under nitrogen atmosphere, **1** (0.5 mmol), **2** (0.6 mmol), catalyst (0.05 mmol), base (1 mmol), DMF (2 mL), reaction temperature (~25 °C for entries 1–5 and 7–20, 40 °C for entry 6, 60 °C for entries 21–23). [b] Isolated yield.

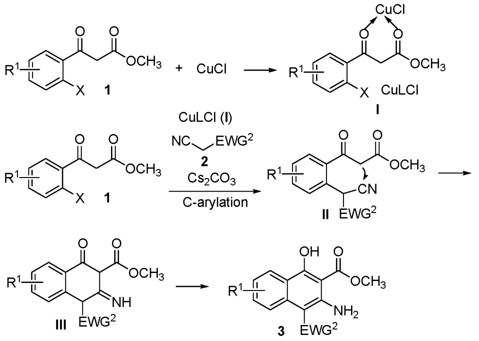
(**1d**) did not work at this temperature, fortunately, it also afforded the corresponding target products in the reasonable yields when the temperature was raised to 60 °C (entries 21–23). In fact, aryl chlorides were very weak substrates in the previous copper-catalyzed Ullmann-type couplings.[7] For β-keto esters, ethyl 3-oxo-3-phenylpropanoate showed slightly weaker reactivity than the others, so the reaction needed higher temperature (40 °C) (entry 6). Reaction of acetylacetone with methyl 3-(2-bromophenyl)-3-oxopropanoate (**1a**) gave the target product (**3g**) in an excellent yield (95%) (entry 7). Alkyl 2-cyanoacetates, 3-oxo-3-phenylpropanenitrile and malononitrile also showed higher reaction activity (entries 8–12). Interestingly, reaction of substituted methyl 3-(2-bromophenyl)-3-oxopropanoate (**1a**) with 3-oxo-3-phenylpropanenitrile (**2k**) afforded product **3k** not **3k′**, and the result exhibited that nucleophilic attack of α-C of β-keto ester in intermediate **IV** selectively occurred on the carbonyl rather than on the cyano group as shown in Scheme 1, which is attributed in higher electrophilicity of carbonyl than cyano in 3-oxo-3-phenylpropanenitrile.

We attempted the reaction of 3-(2-bromo-5-chlorophenyl)-3-oxopropanenitrile (**1c**) with malononitrile (**2l**) without the addition of an extra ligand, the copper-catalyzed cascade reaction provided the corresponding target product (**3t**) in 77% yield (entry 20), and the result indicated that **1c** or/and **2l** could act as ligand(s). The nitrile as a ligand was reported in the previous research.[12] The copper-catalyzed cascade synthesis of naphthol derivatives above could tolerate various functional groups including ester (entries 1–19, 21–23), carbonyl (entry 7), C–Cl bond (entries 13–20), and cyano group (entries 11, 12, 16–20) in the substrates.

A possible mechanism for synthesis of naphthol derivatives was proposed in Scheme 2 according to the results above (herein, reaction of substituted methyl 3-(2-halophenyl)-3-oxopropanoate (**1**) with the substrate (**2**) containing cyano group was chosen as an example). Coordination of β-keto ester (**1**) with CuCl forms complex CuLCl (**I**), so part of β-keto ester acts as the ligand.[10,11] Coupling of the free substrate (**1**) with **2** under catalysis of CuLCl provides *C*-arylation product (**II**). Intramolecular nucleophilic addition of α-C–H to CN in **II** gives intermediate **III**, and isomerization of **III** provides the desired target product (**3**).



Scheme 1 Reaction mechanism of substituted methyl 3-(2-bromophenyl)-3-oxopropanoate (**1a**) with 3-oxo-3-phenylpropanenitrile (**2k**).



Scheme 2 Possible mechanism for synthesis of naphthol derivatives.

In summary, we have developed a simple and highly efficient copper-catalyzed method for synthesis of naphthols containing multifunctional groups under mild conditions. The protocol uses readily available substrates as the starting materials, and the target products containing various substituents, such as hydroxyl, amino, ester, cyano, and carbonyl groups, were obtained in moderate to good yields. The present method can tolerate various functional groups, and shows economical and practical advantages over the previous methods, so it will provide opportunity for construction of diverse and useful molecules in organic chemistry and medicinal chemistry.

Financial support was provided by the National Natural Science Foundation of China (Grant No. 20972083), Chinese 863 Project (Grant No. 2007AA02Z160) and the Key Subject Foundation from Beijing Department of Education (XK100030514).

Notes and references

1 For a comprehensive review, see: *Modern Arene Chemistry*, ed. D. Astruc, Wiley-VCH, Weinheim, 2002.
2 R. T. Mason, M. Talukder and C. R. Kates, in *Kirk-Othmer Encyclopedia of Chemical Technology*, ed. R. E. Kirk, Wiley, New York, 4th ed., 1995, vol. 16, pp. 963–1017.
3 (*a*) P. E. Georghiou, Z. Li, M. Ashram, S. Chowdhury, S. Mizyed, A. H. Tran, H. Al-Saraierh and D. O. Miller, *Synlett*, 2005, 879; (*b*) M. Medarde, A. B. S. Maya and C. Pérez-Melero, *J. Enzyme Inhib. Med. Chem.*, 2004, **19**, 521.
4 (*a*) T. Kometani, Y. Takeuchi and E. Yoshii, *J. Org. Chem.*, 1983, **48**, 2630; (*b*) W. Lester, *Annu. Rev. Microbiol.*, 1972, **26**, 85; (*c*) K. L. Rinehart, Jr, *Acc. Chem. Res.*, 1972, **5**, 57.
5 (*a*) C. B. de Koning, A. L. Rousseau and W. A. L. van Otterlo, *Tetrahedron*, 2003, **59**, 7; (*b*) M. Brasholz, S. Sörgel, C. Azap and H.-U. Reiβig, *Eur. J. Org. Chem.*, 2007, 3801; (*c*) K. Tsubaki, *Org. Biomol. Chem.*, 2007, **5**, 2179.
6 G. Chai, Z. Lu, C. Fu and S. Ma, *Chem.–Eur. J.*, 2009, **15**, 11083.
7 For recent reviews on copper-catalyzed cross couplings, see: (*a*) D. Ma and Q. Cai, *Acc. Chem. Res.*, 2008, **41**, 1450; (*b*) K. Kunz, U. Scholz and D. Ganzer, *Synlett*, 2003, 2428; (*c*) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400; (*d*) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337; (*e*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054; (*f*) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6954 and references cited therein.
8 (*a*) R. Martin, M. R. Rivero and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2006, **45**, 7079; (*b*) G. Evindar and R. A. Batey, *J. Org. Chem.*, 2006, **71**, 1802; (*c*) F. Bonnaterre, M. Bois-Choussy and J. Zhu, *Org. Lett.*, 2006, **8**, 4351; (*d*) B. Zou, Q. Yuan and D. Ma, *Angew. Chem., Int. Ed.*, 2007, **46**, 2598.
9 Selected papers for copper-catalyzed cross couplings, see: (*a*) D. Jiang, H. Fu, Y. Jiang and Y. Zhao, *J. Org. Chem.*, 2007, **72**, 672; (*b*) H. Rao, Y. Jin, H. Fu, Y. Jiang and Y. Zhao, *Chem.–Eur. J.*, 2006, **12**, 3636; (*c*) H. Rao, H. Fu, Y. Jiang and Y. Zhao, *Angew. Chem., Int. Ed.*, 2009, **48**, 1114; (*d*) X. Liu, H. Fu, Y. Jiang and Y. Zhao, *Angew. Chem., Int. Ed.*, 2009, **48**, 348.
10 S. Shafir and S. L. Buchwald, *J. Am. Chem. Soc.*, 2006, **128**, 8742.
11 X. Lv and W. Bao, *J. Org. Chem.*, 2007, **72**, 3863.
12 R. Zhu, L. Xing, X. Wang, C. Cheng, D. Su and Y. Hu, *Adv. Synth. Catal.*, 2008, **350**, 1253.