An Efficient Lutidine-assisted Etherification of Phenols with Alkyl Chloride in Water

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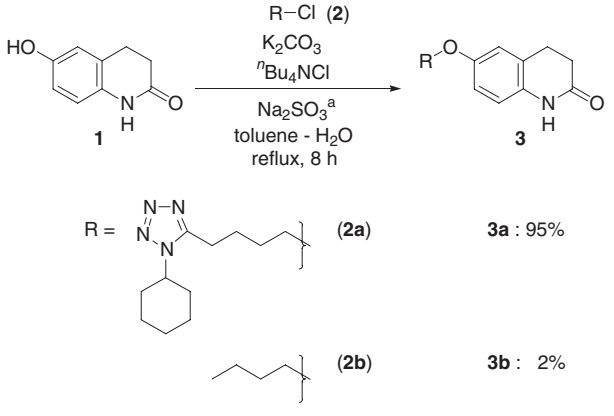
An efficient etherification of phenol derivatives with alkyl chloride in water was achieved. The reactivity of the ether bond forming reaction was activated by addition of 2,6-lutidine.

Preparation of alkyl phenyl ether is one of the important synthetic methods and various protocols have been reported.[1] Among them, etherification of phenols and alkyl halides is more familiar than that of alkyl alcohols and phenylhalides.[2] In the former mode of the reactions, the phase-transfer catalyst technique is useful, since water, an environmentally friendly solvent, and alkyl chlorides as an alkylating agent could be used.[3] The advantage using alkyl chloride is its stability, although it has a less reactivity compared to other agents.[4] Herein, we disclose the results of our study; the reaction of phenols with alkyl chloride in water, activating the reaction by addition of a base such as 2,6-lutidine.[5]

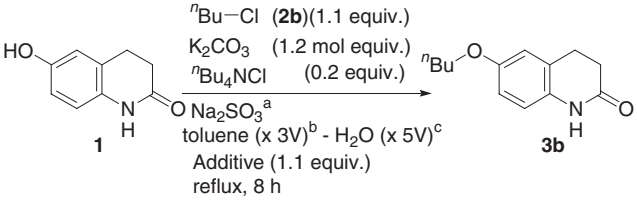
In the course of our research, we found that the etherification of 3,4-dihydro-6-hydroxy-2(1*H*)-quinolinone (**1**) with alkyl chloride derivative (**2a**) proceeded efficiently under the phase-transfer catalyst condition in toluene–water,[6] however the reaction of **1** with 1-chlorobutane (**2b**) did not proceed in a satisfactory yield under the same conditions (Scheme 1). We supposed that the tetrazole moiety of **2a** activated the reaction by the neighboring group participation. Thus, we planned to use an additive having an electron-donating property instead of tetrazole group in the reaction system. (Table 1) As a result, addition of the bases, which have a carbon–nitrogen double bond, were effective for the activation (Table 1, Entries 2–6). On the basis of this finding, we selected 2,6-lutidine as an additive for the following study, because it was inexpensive and suitable for scale-up studies owing to less odor.

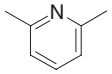
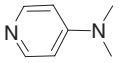
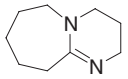
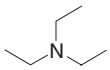


(a) Sodium bisulfate was added to the reaction system for the prevention of coloring due to the air oxidation of **1**.

Scheme 1. Etherification reaction of **1** with alkyl chloride.

Table 1. Screening of the additive



Entry	Additive	Yield / %[d]
1	none	2
2		34
3		35
4		39
5		42
6		44
7		2
8		15[e]

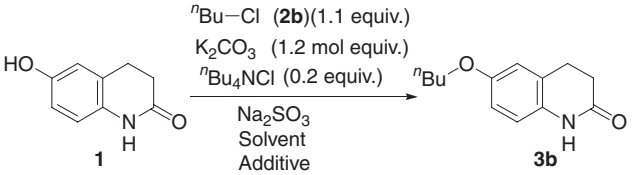
[a]0.06 equiv. of Na_2SO_3 were used. [b]Three-fold volume of water to the weight of **1** was used. [c]Five-fold volume of water to the weight of **1** was used. [d]Isolated yield. [e]0.4 equiv. of $^nBu_4NCl$ were used.

We established the reaction in high yield using 1.1 equiv. of 2,6-lutidine in water, after several optimization trials of the reaction condition (Table 2, Entries 7, 8). We found that the reaction has following characteristics: (1) 2,6-Lutidine does not perform deprotonation of the hydroxy group (Table 2, Entry 3). (2) 2,6-Lutidine has a catalytic activity (Table 2, Entries 2, 5). (3) Water is a superior solvent rather than a co-solvent for toluene in this reaction (Table 2, Entries 2, 7).

We next tried to extend the reaction to several phenols, and the results are summarized in Table 3. The etherification of several phenols having both electron-donating and electron-withdrawing groups were enhanced by addition of 2,6-lutidine (Table 3, Entries 1–8). Thus, this procedure is effective for the preparation of phenol ethers. Furthermore, this reaction is applicable for not only phenols but also naphthols (Table 3, Entry 9).

Typical experimental procedure is as follows (Table 3,

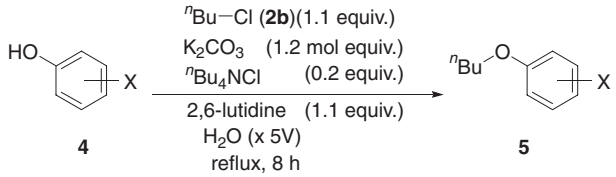
Table 2. Optimization trials of the reaction conditions

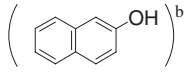


Entry	K_2CO_3 / mol equiv.	2,6-Lutidine / equiv.	$^nBu_4NCl$ / equiv.	Solvent	Yield / %[a]
1	1.2	0	0.2	H_2O–toluene[b]	2
2	1.2	1.1	0.2	H_2O–toluene[b]	35
3	0	2.3	0.2	H_2O–toluene[b]	1
4	1.2	1.1	0	H_2O–toluene[b]	2
5	1.2	0.2	0.2	H_2O–toluene[b]	21
6	1.2	1.1	0.4	H_2O–toluene[b]	70
7	1.2	1.1	0.2	H_2O[c]	84
8	1.2	1.1	0.4	H_2O[c]	89

[a]Isolated yield. [b]The co-solvent of five-fold volume of water and three-fold volume of toluene to the weight of **1** was used. [c]Five-fold volume of water to the weight of **1** was used.

Table 3. Etherification reaction of phenol derivatives with butyl chloride



Entry	X	Yield / %[a] : 2,6-Lutidine 1.1 equiv.	0 equiv.
1	H	93	77
2	*o*-OMe	97	92
3	*p*-OMe	94	88
4	*p*-Me	92	75
5	*p*-NHAc	84	20
6	*p*-Cl	74	48
7	*p*-CN	46	13
8	*p*-NO_2	28	16
9		97	78

[a]Isolated yield. [b]Instead of phenols, 2-naphthol was used.

Entry 1): The suspension of phenol (1.00 g, 10.6 mmol), 1-chlorobutane (1.22 mL, 11.7 mmol), potassium carbonate (1.76 g, 12.8 mmol), tetra-*n*-butylammonium chloride (0.59 g, 2.1 mmol), and 2,6-lutidine (1.36 mL, 11.7 mmol) in water was refluxed for 8 h. The reaction mixture was diluted with aq NaOH, and extracted with 3 times of dichloromethane. The combined organic layer was washed with aq NaOH, water, 2M aq HCl, water, and saturated aq $NaHCO_3$. After drying with anhydrous magnesium sulfate, the filtrate was concentrated in the reduced pressure to give 1.48 g (93%) of *n*-butyl phenyl ether as colorless oil.

In summary, we have developed the 2,6-lutidine-assisted etherification of phenol derivatives with alkyl chloride. The reaction proceeded in good yield in water. Further studies of the reaction including the investigation on the reaction mechanism are on-going.[7]

References and Notes

1 R. C. Larock, in "Comprehensive Organic Transformations," 2nd ed., John Wiley & Sons, Inc., New York (1999), p 889.

2 For examples, see: a) T. Nobori, S. Fujiyoshi, I. Hara, T. Hayashi, A. Shibahara, K. Funaki, K. Mizutani, and S. Kiyono, Presented at the 81st Annual Meeting of the Chemical Sociaty of Japan, Tokyo, March 2002, Abstr., No. 1F9-27. b) T. Nobori, S. Fujiyoshi, I. Hara, T. Hayashi, A. Shibahara, K. Funaki, K. Mizutani, and S. Kiyono WO01, 81274 (2001). c) H. K. Yoo, D. M. Davis, Z. Chen, L. Echegoyen, and G. W. Gokel, *Tetrahedronn Lett.*, **31**, 55 (1990). d) M. R. V. Sahyun and D. J. Cram, *Org. Synth.*, Coll. Vol. **V**, 926 (1973).

3 For examples, see: a) J. J. V. Eynde and I. Mailleux, *Synth. Commun.*, **31**, 1 (2001). b) H. H. Freedman and R. A. Dubois, *Tetrahedron Lett.*, **38**, 3251 (1975). c) A. McKillop, J.-C. Fiaud, and R. P. Hug, *Tetrahedron*, **30**, 1379 (1974).

4 The order of reactivity of the alkylating agents was reported as R-I > R-OMs > R-Br ≫ R-Cl; see: G. Gelbard, *Synthesis*, **1977**, 113.

5 The similar enhancement of the methylation reactions of phenols using dimethylcarbonate (DMC) as an alkylating agent, 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU), and tetra-*n*-butyl-ammonium iodide, was reported. However the reaction was necessary to use an excess amount of DMC as a solvent, see: W. Shieh, S. Dell, and O. Repič, *Org. Lett.*, **3**, 4279 (2001).

6 S. Aki, M. Kurimura, T. Nishi, M. Tominaga, J. Minamikawa, A. Yamamoto, and N. Fukuyama, Jpn. Kokai Tokkyo Koho JP2001, 213,877; *Chem. Abstr.*, **135**, 137510s (2002).

7 The reaction using *N*-*n*-butylpyridinium chloride as the alkylating agent did not proceed. Although we do not have certain evidence to explain the mechanism on etherification accelerated by 2,6-lutidine, we speculate it as follows: 1) The intermolecular interaction between 2,6-lutidine and 1-chlorobutane accelerates at the C–Cl bond cleavage step without forming the corresponding pyridinium salt. 2) The formation of 2,6-lutidine salt with phenols increases the solubility of the phenols in water to enhance the initial formation of potassium phenoxide derivatives of the phenols with the potassium carbonate. In addition, 2,6-lutidine accelerates the phase-transfer of tetra-*n*-butylammonium phenoxide derivatives, which form in the following step, from a water phase to an organic phase.

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