

An efficient method for demethylation of aryl methyl ethers

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Abstract

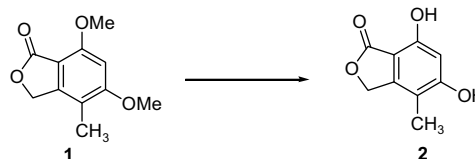
A new efficient method for demethylation of aryl methyl ethers using iodocyclohexane in DMF under reflux condition is described. © 2008 Elsevier Ltd. All rights reserved.

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The phenolic hydroxyl group can be found in a large number of natural products and biologically important substances. The protection of the phenol moiety is often mandatory during the synthesis of any phenol-containing product as a result of its high sensitivity toward other reagents. Methylation of phenolic hydroxyl groups is one of the most commonly used means for the protection of the functionality in organic synthesis.¹ The highly stable protected methyl ether form can be tolerated to a variety of reagents and experimental conditions. On the other hand, its high stability creates a problem for removing the protecting group. Although a variety of cleavage methods are available,¹ generally Harsh reaction conditions such as using strong acids² or bases,³ alkali metals,⁴ or oxidizing⁵ or reducing⁶ reagents are employed and thus often result in undesired reactions and products and low reaction yields. In this Letter, we report a new method for demethylation of aryl methyl ethers under relatively mild reaction conditions in high efficiency. We have found that the demethylation of aryl methyl ethers can be achieved by

the treatment of iodocyclohexane in DMF under reflux in high yields (88–95%) with short reaction times (2.5–14 h).

In our ongoing medicinal chemistry program, a key intermediate phenol **2** is needed for the synthesis of the derivatives of mycophenolic acid, an immunosuppressive agent (Scheme 1).⁷ Canonica's approach to demethylation of 5,7-dimethoxy-4-methylphthalide **1** was attractive to us because of operational simplicity and readily available reagents.^{7c,d} They prepared this intermediate from **1** (Scheme 1, condition A) in 70% yield by using BBr₃ as the demethylation agent at rt, but requiring very long reaction time (8d).^{7c,d} In order to shorten the reaction time, they also used a very Harsh reaction condition (condition B): hydroiodic acid (57% aq) in the presence of phosphorus



Condition A: BBr₃, rt, 8d, 70% yield

Condition B: 57% HI, anhy P, Ac₂O, reflux, 12 h, 49% yield

Scheme 1. Canonica's approach to demethylation of 5,7-dimethoxy-4-methylphthalide **1**.

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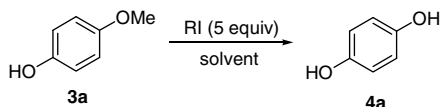
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under reflux in acetic anhydride for 12 h to remove these methyl groups. Disappointedly, only 49% yield was obtained.^{7d}

To seek a more efficient and mild method to remove the methyl group of aryl methyl ethers, we initiated a study in this endeavor. In Canonica's approach (Scheme 1, condition B), highly concentrated HI was employed.^{7d} The low reaction yield might result from the Harsh reaction conditions. We envisioned that a mild reaction condition, which enabled to slowly generate HI from a HI source, could lead to an efficient demethylation of aryl methyl ethers in high reaction yields while minimizing side reactions.

It is known that HI can be produced in situ from iodoalkanes via an elimination process.⁸ Accordingly, a model reaction of 4-methoxyphenol **3a** with an iodoalkane in DMF was performed. The results of the investigation are summarized in Table 1. The efficiency of deprotection of the methyl ether group varied significantly with respect to iodoalkanes employed (entries 1–5). Among them, iodocyclohexane was identified to be the best one for the reaction (entry 5). In this instance, the process proceeded smoothly (3 h) to afford the desired product **4a** in 93% yield in DMF under reflux and argon conditions. Probing solvents effect revealed that the cleavage efficiency was highly solvent dependent (entries 5 and 8–10). No reaction occurred with DMSO and pyridine. The use of *N*-methylpyrrolidinone (NMP) gave rise to **4a** in good yield (81%), whereas a better reaction yield (93%) was achieved in DMF. These results indicate that the basicity of the solvents plays a critical role in reaction efficiency. On the one hand, the solvent should be basic enough to facilitate the generation of HI from iodoalkanes via an elimination reaction. On the other hand, the solvent basicity should be weak to minimize the neutralization effect of HI since the strongly HI acid is essential for demethylation. Therefore,

Table 1
Optimization of reaction conditions for demethylation of 4-methoxyphenol **4a**^a



Entry	RI	Solvent	<i>T</i> (°C)	<i>t</i> (h)	Yield ^b (%)
1	EtI	DMF	80	3	NR ^c
2	2-Iodopropane	DMF	100	14	24
3	1-Iodobutane	DMF	Reflux	3	26
4	1-Iodopentane	DMF	Reflux	3	22
5	Iodocyclohexane	DMF	Reflux	3	93
6	Iodocyclohexane ^d	DMF	Reflux	3	57
7	Iodocyclohexane ^c	DMF	Reflux	3	81
8	Iodocyclohexane	DMSO	Reflux	2	NR ^c
9	Iodocyclohexane	NMP	Reflux	2	81
10	Iodocyclohexane	Pyridine	Reflux	2	NR ^c

^a Unless specified, see Ref. 8 for detailed reaction procedure.

^b Isolated yield.

^c No reaction.

^d 3.0 equiv used.

^e 4.0 equiv used.

the above studies prompted us to select the use of iodocyclohexane (5.0 equiv) in DMF under reflux to probe the scope of the demethylation reaction.

The new methodology proves to be a general strategy for demethylation of aryl methyl ethers (Table 2).⁹ Under the relatively mild reaction conditions, the methyl group

Table 2
Iodocyclohexane/DMF facilitated demethylation of aryl methyl ethers^a

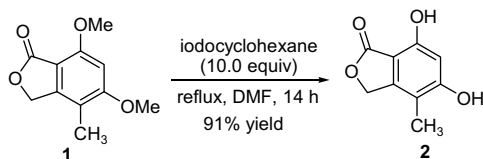
Entry	Compound 3	Product	<i>t</i> (h)	Yield ^b (%)
1		4a	3	93
2		4b	4	91
3		4c	5	88
4		4d	8	91
5 ^c		4e	3.5	91
6		4f	3	95
7 ^c		4g	3	92
8		4h	5	90
9		4i	3	91
10		4j	3	89
11		4k	2.5	44 ^d

^a Unless specified, see typical experimental procedure in Ref. 8.

^b Isolated yield.

^c 10.0 equiv iodocyclohexane used.

^d In addition, mono-demethylation product was also obtained in 43% yield.



Scheme 2. Efficient demethylation of 5,7-dimethoxy-4-methylphthalide **1** by iodocyclohexane/DMF.

can be readily cleaved to afford clean phenol-derived products **4** in short reaction times (2.5–8 h) and in high yields. The versatile by-products cyclohexene, and the remaining HI and iodocyclohexane can be conveniently removed by evaporation. A variety of functional groups including OH (entry 1), COOH (entries 5 and 6) and lactone (Scheme 2) can be tolerated to the reaction conditions. It appears that the electronic and steric effect has limited effect on the process. The substrates bearing electron-donating (entries 1–3), withdrawing (entries 4–6), a combination (entry 7), and neutral (entry 8) groups can efficiently participate in the reaction. The same trend is observed in terms of steric effect (entries 2 and 6). We also demonstrated that the protocol could be applied for fused aromatic systems (entries 9–11). It is noteworthy that the substrates possessing multiple methoxy groups can be removed at the same time (entry 7). However, 10.0 equiv of iodocyclohexane is required. The use of 5.0 equiv resulted in a mixture of mono- and bis-demethylation product (entry 11).

Finally, we applied the method for the demethylation of compound **1** (Scheme 2). Under the standard reaction conditions, the two methyl groups could be cleanly removed with 10.0 equiv of iodocyclohexane to give desired product **2** in 91% yield without further purification.⁹ Notably, the method described here is more efficient than that of Canonica et al. reported.^{7c,d}

In summary, a new, efficient demethylation of aryl methyl ethers using iodocyclohexane as HI source in DMF has been developed. It has demonstrated that the methyl group can be effectively removed in high yields within short reaction times under relatively mild reaction conditions. The strategy affords a new alternative approach to the cleavage of methyl ethers, a widely used protecting group for phenols.

Acknowledgments

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- Typical procedure for demethylation: 5,7-Dimethoxy-4-methylphthalide 1* (208 mg, 1.0 mmol) was dissolved in DMF (2.0 mL) in a round-bottomed flask and iodocyclohexane (1.3 mL, 10.0 mmol) was added. The reaction system was equipped with reflux condenser under argon. The reaction mixture was refluxed for 14 h, cooled, poured into water (20 mL) and extracted with EtOAc (20 mL × 3). The organic layer was washed with saturated aq NaHSO₃ and brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated and dried in vacuum to afford 5,7-dihydroxy-4-methylphthalide (164 mg, 91% yield).