

A Convenient and Efficient Method for Demethylation of Aryl Methyl Ethers with Magnesium Iodide in Ionic Liquid

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Demethylation of aryl methyl ethers to the corresponding phenols are very important reactions in organic synthesis.^{1,2} A number of methods have been reported for the cleavage of highly stable aryl methyl ethers utilizing strong acids or bases such as aluminum chloride,³ boron tribromide,⁴ cerium chloride,⁵ alkaline thiolate,⁶ methyl magnesium iodide,⁷ and L-Selctride.⁸ However, all of these methods invariably suffered from one or more drawbacks such as harsh reaction conditions, long reaction times, difficulty of manipulation, use of exotic reagents, and low reaction yields. Furthermore, in the most of known methods for demethylation of aryl methyl ethers, use of large excess amounts of demethylating agents have been generally required. Thus, it is highly desirable to develop an improved convenient and efficient procedure for demethylation reactions of aryl methyl ethers.



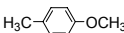
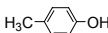
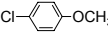

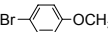



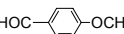
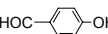
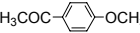
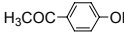


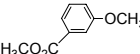
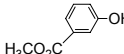
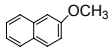

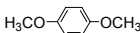

Magnesium iodide etherate, MgI₂(OEt)₂, freshly prepared *in situ* by treatment of magnesium solid with iodine in dry ethyl ether solution, has been utilized for the deprotection of aryl methyl ethers.⁹⁻¹¹ However, this method is ineffective for the deprotection of simple aryl methyl ethers and only applicable to the cleavage of activated phenolic *O*-methyl group present *ortho* to the carbonyl group. Moreover, MgI₂(OEt)₂ promoted demethylation reactions of 2-methoxy benzaldehyde derivatives have been always conducted in toxic organic solvents such as benzene, THF, and ethyl ether.

During the course of our search for the safe and practical reagent systems, we observed that readily available and non-toxic magnesium iodide in highly polar [BMIM]BF₄ medium can efficiently promoted the demethylation reactions of aryl methyl ethers. To the best of our knowledge, reports with combination of magnesium iodide and ionic liquid for the demethylation of aryl methyl ethers have not appeared so far.

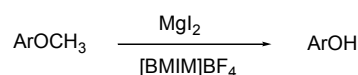
Herein, we wish to report a new efficient method for the demethylation of aryl methyl ethers utilizing combination of readily available and stable magnesium iodide with environmentally friendly ionic liquid under mild reaction conditions. Treatment of aryl methyl ethers with magnesium iodide (1.5 equiv.) in 1-butyl-3-methylimidazolium tetrafluoroborate, [BMIM]BF₄, ionic liquid at 50 °C for 4 - 7 h afforded demethylated

phenolic products in high yield. Change of ionic liquid medium from [BMIM]BF₄ to [BMIM]PF₆ at present reaction conditions produced much lower yields of desired demethylated products. In all of the cases examined, the demethylation reactions proceeded smoothly for removal of methyl group on the various aryl methyl ethers as shown in the Table 1. The generality of present method are exemplified in the successful demethylation reactions of substrates containing various sensitive functional groups including CHO, COCH₃, and COOCH₃. It is also note-

Table 1. Demethylation of aryl methyl ethers with MgI₂ in ionic liquid

Entry	Substrate	Product	Time (hr)	Yield (%) ^a
1			4	92
2			4	85
3			4	87
4			4	85
5			4	90
6			7	88
7			7	84
8			4	85
9			7	84
10			4	89
11			7	82

^aIsolated yield.



worthy that present method proved to be very effective for the demethylation of unactivated aryl methyl ethers which is hard to expect to in the other reported methods utilizing $\text{MgI}_2(\text{OEt})_2$. The high reactivity of magnesium iodide at present reaction conditions could possibly be explained by the enhancement of nucleophilicity of iodide as a result of increased charge separation in the transition state under $[\text{BMIM}]\text{BF}_4$. This result is analogous to the observations reported in halide induced nucleophilic substitution reactions in ionic liquid.^{12,13}

In conclusion, we have developed a new and efficient method for the demethylation of various types of aryl methyl ethers using readily available, stable, and easily handled magnesium iodide in $[\text{BMIM}]\text{BF}_4$ ionic liquid. Owing to its simplicity and mild reaction conditions the protocol reported herein may serve as a useful alternative to the existing methods for the deprotection of aryl methyl ethers to the corresponding phenolic derivatives.

Experimental Section

All solvents and reagents were of reagent grade. Merck pre-coated silica gel plates with fluorescent indicator (60 F₂₅₄) were used for analytical thin layer chromatography. Flash column chromatography was performed using Merck silica gel 60 (230-400 mesh ASTM). ¹H NMR spectra were recorded on a Varian Gemini 2000 (300 MHz) spectrometer in CDCl_3 .

A general synthetic procedure for demethylation of aryl methyl ethers is as follows.

To a solution of aryl methyl ether (1.0 mmol) in $[\text{bmim}]\text{BF}_4$ (2 mL) was added magnesium iodide (0.42 g, 1.5 mmol). The reaction mixture was stirred at 50 °C for 4 - 7 h. After addition of 5% aqueous sodium thiosulfate (10 mL), the product was

extracted with ether (2×10 mL), washed with brine (5 mL), and dried over MgSO_4 . The solvent was removed in vacuo and the crude mixture was purified by silica gel chromatography using ethyl ether:hexane (1:3) as eluent to give the desired phenolic product.

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References

1. Wuts, P. G. M.; Green, T. W. *Greens's Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons: New Jersey, 2007; p 370 and references therein.
2. Maercker, A. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 972.
3. Parker, K. A.; Petraitis, J. J. *Tetrahedron Lett.* **1981**, *22*, 397.
4. Miller, J. M.; So, K. H.; Clark, J. H. *Can. J. Chem.* **1979**, *57*, 1887.
5. Yadav, J. S.; Reddy, B. V. S.; Madan, C.; Hashim, S. R. *Chem. Lett.* **2000**, *29*, 738.
6. Dodge, J. A.; Stocksdale, M. G.; Fahey, K. J.; Jones, C. D. *J. Org. Chem.* **1995**, *60*, 739.
7. Mechoulam, R.; Gaoni, Y. A. *J. Am. Chem. Soc.* **1965**, *87*, 3273.
8. Majetich, G.; Zhang, Y.; Wheless, K. *Tetrahedron Lett.* **1994**, *35*, 8727.
9. Yamaguchi, S.; Sugiura, K.; Fukuoka, R.; Okazaki, K.; Takeuchi, M.; Kawase, Y. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3607.
10. Yamaguchi, S.; Nedachi, M.; Yokoyama, H.; Hirai, Y. *Tetrahedron Lett.* **1999**, *40*, 7363.
11. Snyder, S. A.; Tang, Z.-Y.; Gupta, R. *J. Am. Chem. Soc.* **2009**, *131*, 5744.
12. Lourenço, N. M. T.; Afonso, C. A. M. *Tetrahedron* **2003**, *59*, 789.
13. Judeh, Z. M. A.; Shen, H.-Y.; Chi, B. C.; Feng, L.-C.; Selvasothi, S. *Tetrahedron Lett.* **2002**, *43*, 9381.
14. Boovannahalli, S. K.; Kim, D. W.; Chi, D. Y. *J. Org. Chem.* **2004**, *69*, 3340.