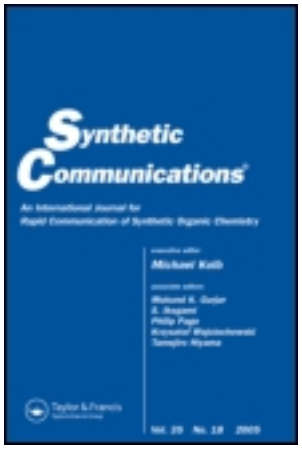


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# EFFICIENT METHOD FOR DEMETHYLATION OF ARYL METHYL ETHER USING ALIQUAT-336

**Suresh B. Waghmode,[1] Ganesh Mahale,[1] Viraj P. Patil,[1] Kartik Renalson,[2] and Dharmendra Singh[2]**

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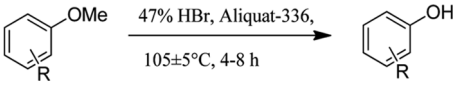
[2]*IPCA Laboratories, Kandivali Industrial Estate Charkop, Kandivali West, Mumbai, India*

## GRAPHICAL ABSTRACT




**Abstract** *A rapid method for selective cleavage of aryl methylethers can be achieved in the presence of a protic acid and a catalytic amount of phase-transfer catalyst (Aliquat-336). Aliquat-336 accelerates the rate of reaction and affords the corresponding phenols in excellent to good yields on a wide variety of substrates.*

*[Supplementary materials are available for this article. Go to the publisher's online edition of* Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

**Keywords** Aliquat-336; aryl methyl ethers; demethylation; hydrobromic acid; PTC

## INTRODUCTION

Phenolic hydroxyl groups are often found in a large number of natural products and biologically important substrates.[1] The protection of phenolic group is needed because of its high reactivity toward other reagents during synthesis. Methylation is one of the most commonly used methods for the protection of the phenolic group. The aryl ether cleavage remains an integral functional group transformation, primarily as a deprotection step to unmask a hydroxyl group. The demethylation of phenolic ether extends to both academic and commercial pursuits including natural product, pharmaceutical, and fine chemical synthesis.[1] Use of the methyl ether functionality to protect hydroxyl group has been limited by the lack of effective and selective demethylation reagents. Although methods for demethylation of aryl methyl ethers are available, these employ harsh reaction conditions or special neuclophilic thiolates,[2] ionic liquids,[3] Lewis acid,[4] strong acids[5] or bases,[6] alkali metals,[7] or oxidizing[8] or reducing[9] reagents. These reactions often suffer from undesired

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reactions and side products, foul smell, high cost of reagents, and poor reaction yields. Ionic liquid (3-methylimidazolium bromohydrogenate [bmim][$BF_4$]–HBr) was used along with 47% aqueous HBr,[3a] but the time required to complete the reaction was very high. In this reaction nucleophilic displacement of the alkyl group was enhanced by the addition of ionic liquids. Thus, it is necessary to develop a novel and efficient procedure for selective cleavage of aryl methylethers in the presence of different functional groups with cheap, commercially available reagents under feasible conditions in a short reaction time. Keeping in mind these objectives, we thought that Aliquat-336 will be one of the ideal choices to promote the selective cleavage of aryl methyl ethers.

Aliquat-336 (methyltrioctylammonium chloride) is also known as Starks's catalyst.[10] Aliquat-336 has various applications in organic synthesis such as benzylation[11] and hydrogenation of arenes,[12] versatile and as an affordable cation source for hydrophobic ionic liquids.[13] In continuation of our interest in the development of new organic synthetic methodologies,[14] we report herein a rapid, simple, and efficient method for the deprotection of aryl methyl ethers using the commercially available and environmentally friendly Aliquat-336 as a promoter in the presence of protic acid to the corresponding phenol in a short reaction time.



## RESULTS AND DISCUSSION

We primarily focused on aqueous HBr and searched for the phase-transfer catalyst (PTC) that accelerates the rate of demethylation reaction with minimum side reaction products. To achieve maximum conversion, we investigated the effect of PTC [viz., tetra-*n*-butylammonium iodide (TBAI), tetra-*n*-butylammonium bromide (TBAB), and Aliquat-336] on the demethylation of 2-methoxynaphthalene as a model reaction by keeping other parameters constant [protic acid (HBr 47%, 4.5 mmol equiv.), temperature ($105 \pm 5\,^{\circ}C$), time (2 h), and amount of promoter (10 wt.% of substrate)], and results are shown in Table 1. Under these reaction conditions 47% HBr alone (without PTC) gave 49% conversion in 2 h (Table 1; entry 1). The demethylation of 2-methoxynaphthalene reported by Chi et al. with concentrated HBr (47%) using 5 mmol equiv. in ionic liquid [bmim]$BF_4$ was 98% within 7 h.[3a] Tetra-*n*-butylammoniumiodide (TBAI) and tetra-*n*-butylammonium bromide (TBAB) gave slight improvement in conversion (55 and 57%, respectively; Table 1, entries 2 and 3). We presume that these differences are due to the homogeneity of the reaction

**Table 1.** Effect of promoters on demethylation of 2-methoxynaphthalene

| Entry | PTC | Conversion (%)[a] |
|---|---|---|
| 1 | No PTC | 49 |
| 2 | TBAB | 57 |
| 3 | TBAI | 55 |
| 4 | Aliquat-336 | 98 |

*Note*. Reaction conditions: 2-methoxy naphthalene (20 mmol); 47% HBr (4.5 mmol equiv.); PTC (10 wt.% of substrate); temp. $= 105 \pm 5\,^{\circ}C$; time = 2 h.
[a]Conversion based on GC analysis.

mass as a result of the addition of PTC. When reaction carried out with Aliquat-336, conversion significantly increased to 98% in 2 h. This study emphasize that there is substantial improvement in the rate of demethylation of 2-methoxynaphthalene due to the addition of PTC (Aliquat-336). To find the suitable reaction temperature for demethylation, reactions were carried out at different temperatures, and results are shown in Table 2. At room temperature only 13% conversion was observed and was found to increase with temperature. Maximum conversion was achieved at $105 \pm 5\,^{\circ}C$ in 2 h. The reaction time was optimized by monitoring the reaction at 30-min time intervals from 0 to 2 h. Demethylation increases with time and complete conversion was achieved in 2 h (Table 3). To find out the optimum amount of the protic acid for demethylation, the reaction was carried out with different concentrations (0.5 to 9.2 mmol equiv. of substrate) and results are shown in Fig. 1. Demethylation increases with increase in equiv. of HBr up to 4.5 mmol equiv. and decreased thereafter with increase in concentration. This is due to the unwanted side reaction products. To achieve maximum conversion optimization, the amount of PTC was varied from 0 to 20 wt.% of substrate, and results are shown in Fig. 1. Demethylation increases with amount of PTC; maximum conversion (98%) was achieved at 10% Aliquat-336. With further increase in concentration, decreased conversion was observed. This is due to the undesired side reactions. To establish general applicability at the optimized reaction conditions, various substituted aryl methyl ethers were subjected to demethylation in the presence of Aliquat-336, and results are shown in Table 4. Substitution on the aromatic ring plays an important role in the rate of the reaction. A variety of functional groups including OH, Cl, Br, $CH_3$, CN, $NH_2$, COOH, and $NO_2$ could tolerate the optimized reaction conditions. Electronic and steric effects affect the rate of reaction. The presence of electron-withdrawing groups at *ortho* and *para* positions accelerate the reaction, whereas electron-donating groups retard the rate of reaction. Anisole and ethoxybenzene required 5 and 7 h for deprotection of methyl and ethyl groups, respectively (Table 4; entries 1 and 2). While methoxy group incorporation in the anisole mono demethylation takes place selectively in 6 h (entry 3), both methyl group cleaved in 12 h. By introducing the methoxy group at the *ortho* position of anisole, the rate of demethylation was retarded. The deprotection of 1-ethoxy-2-methoxybenzene took 9 h (entry 5); first selectively demethylation was observed over deethoxylation. Substitution at *ortho* and *para* positions seem to be electronically equivalent as similar results were obtained. The complete demethylation of 1,4-dimethoxybenzene require 12 h and gave 85% yield (entry 7). Amine

**Table 2.** Effect of temperature on rate of reaction

| Entry | Temperature ($\pm 5\,^{\circ}C$) | Conversion (%)[a] |
|---|---|---|
| 1 | 30 | 13 |
| 2 | 50 | 32 |
| 3 | 75 | 66 |
| 4 | 105 | 98 |

*Note*. Reaction conditions: 2-methoxy naphthalene (20 mmol); 47% HBr (4.5 mmol equiv.); Aliquat-336 (10 wt.% of substrate); time = 2 h.
[a]Conversion based on GC analysis.

**Table 3.** Effect of time on demethylation of 2-methoxynaphthalene

| Entry | Time (h) | Conversion (%) |
|---|---|---|
| 1 | 0.5 | 44 |
| 2 | 1.0 | 80 |
| 3 | 1.5 | 93 |
| 4 | 2.0 | 98 |

*Note*. Reaction conditions: 2-methoxynaphthalene (20 mmol); 47% HBr (4.5 mmol equiv.); Aliquat-336 (10 wt.% of substrate); temp. = 105 ± 5 °C.



substituted at *ortho* and *para* positions slightly lowers rate of deprotection of the methyl group (entries 8 and 9). The presence of a carboxylic group at *ortho* and *para* position with respect to methoxy enhances the rate of reaction (entries 10 and 11). The cyano group at *meta* and *para* positions gave 90 and 92% yields in 6.5 and 6 h, respectively (entries 12 and 13). The nitro group at *ortho* and *para* positions accelerates the rate of reaction (entries 14 and 15). Demethylation of hetercyclic compounds was carried out with good yield (entry 16). More substituted compounds were also underwent demethylation of methyl (entries 17 and 18).

Further we have extended this methodology for the synthesis of a class of pharmaceutically important drug molecules, flavonoids. Flavones are naturally occurring phenolic compounds that show biological and pharmacological activity coupled with low toxicity.[15] These compounds are widely distributed in the plant kingdom and ingested daily by humans. Therefore, their use as potential therapeutic compounds against a variety of diseases is of prime interest.[16] A variety of biological activities

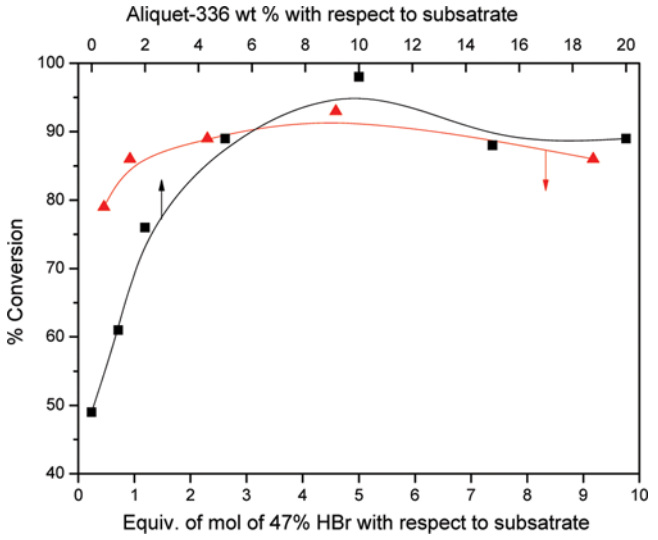
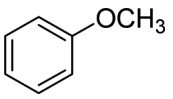
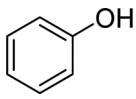
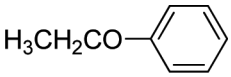
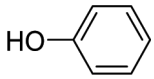
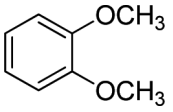
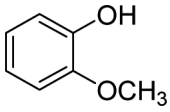
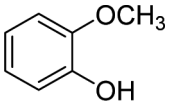
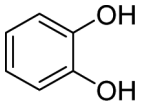
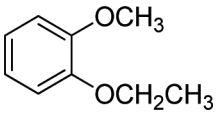
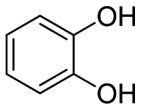
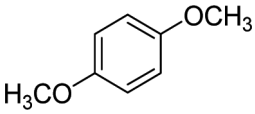
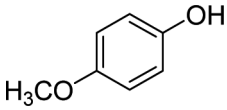
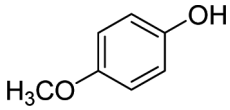
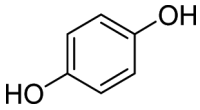
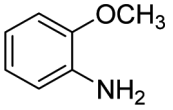
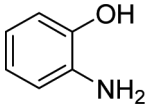
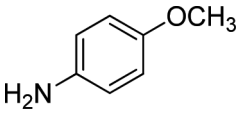
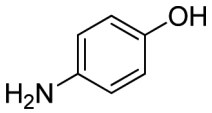
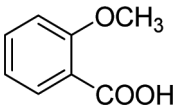
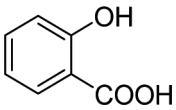
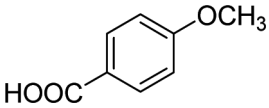
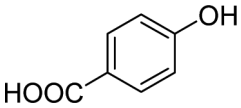
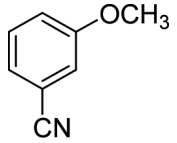
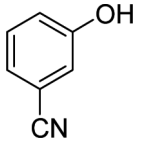


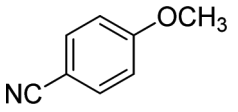
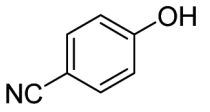
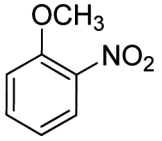
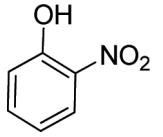
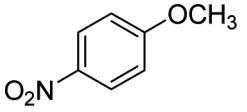
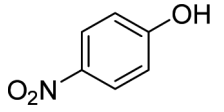
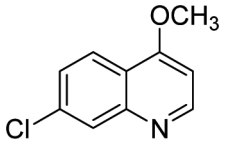
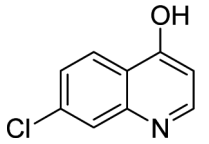
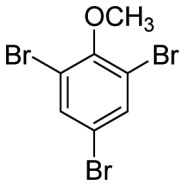
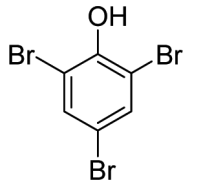
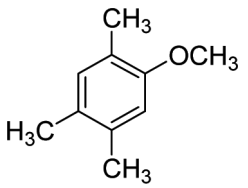
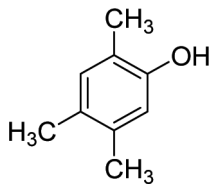
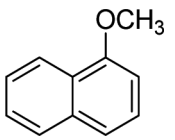
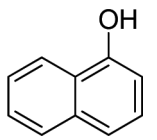
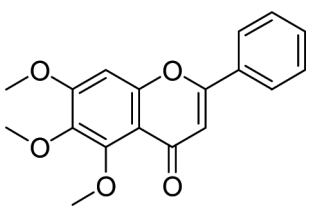
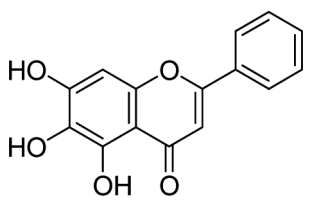

**Figure 1.** Effect of percentage of Aliquet-336 and HBr on demethylation of 2-methoxynaphthalene. Reaction conditions: 2-methoxynaphthalene (20 mmol); Aliquat-336 (10 wt.% of substrate variable); 105 ± 5 °C, 47% HBr (4.5 mmol equiv.); time = 2 h; and conversion based on GC analysis. (Figure is provided in color online.)

**Table 4.** Reaction of different substrates with optimized conditions[a]

| Entry | Substrate | Product | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  | 5 | 96 |
| 2 |  |  | 7.5 | 90 |
| 3 |  |  | 6 | 68 |
| 4 |  |  | 6 | 78 |
| 5 |  |  | 9 | 72 |
| 6 |  |  | 5 | 62 |
| 7 |  |  | 7 | 85 |
| 8 |  |  | 6.5 | 72 |
| 9 |  |  | 6 | 80 |
| 10 |  |  | 4 | 78 |
| 11 |  |  | 4.5 | 84 |
| 12 |  |  | 6.5 | 90 |

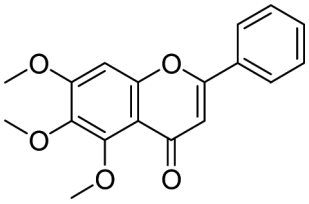
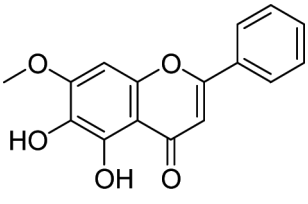
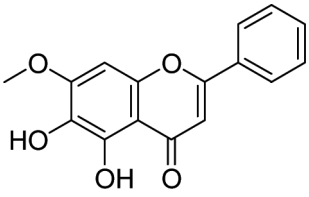
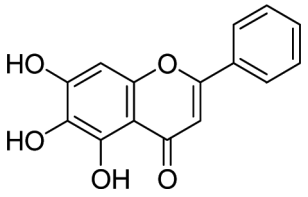
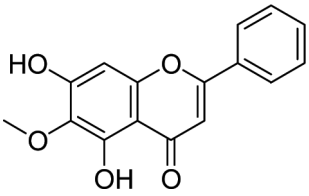
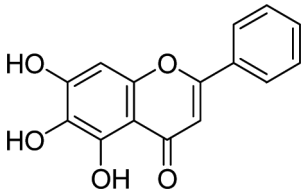
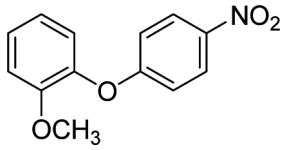
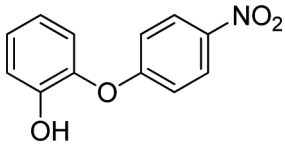
(*Continued*)

**Table 4.** Continued

| Entry | Substrate | Product | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 13 |  |  | 6 | 92 |
| 14 |  |  | 4.5 | 92 |
| 15 |  |  | 3.5 | 97 |
| 16 |  |  | 4 | 85 |
| 17 |  |  | 5 | 95 |
| 18 |  |  | 8 | 75 |
| 19 |  |  | 3.5 | 90 |
| 20 |  |  | 15 | 76 |

(*Continued*)

**Table 4.** Continued

| Entry | Substrate | Product | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 21 |  |  | 7 | 85 |
| 22 |  |  | 8 | 80 |
| 23 |  |  | 7 | 84 |
| 24 |  |  | 4.5 | 85 |

[a]Reaction conditions: Aryl methyl ether (10 mmol); 47% HBr (4.5 mmol equiv. of substrate); Aliquat-336 (10 wt.% of substrate); temp. = 105 ± 5 °C.
[b]Isolated yields.

have been attributed to baicalein (5,6,7-trihydroxyflavone). Synthesis of baicalein, (an active ingredient of Indian medicinal plant oroxyliumindicum) from flavones required more than 50 h for complete demethylation,[17] whereas use of Aliquat-336 reduces reaction time to 15 h (entry 20). Selective didemethylation of trimethoxyflevones was observed at the 5,6-position in 7 h with 85% yield (neglectein; entry 21).[18] 5,6-Diydroxy,7-methoxyflavones and 5,7-diydroxy 6-methoxyflavones gave the corresponding hydroxyl compound, 5,6,7-trihydroxyflavones (entries 22 and 23).

## CONCLUSIONS

In summary, we have successfully used Aliquat-336 in catalytic amounts as a PTC and developed a rapid and efficient procedure for cleavage of aryl methyl ether in the presence of other functional groups. This method offers several advantages such as rapidity, cleanliness, excellent to good yields, and low cost PTC.

## EXPERIMENTAL

Aliquat-336 (10 wt.% of substrate) was added in a single lot to a stirred solution of aryl methyl ether (20 mmol) and aqueous HBr (47%, 4.5 mmol equiv. of substrate). The resulting reaction mixture was heated at $105 \pm 5\,^{\circ}C$, and the progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, it was cooled to room temperature and quenched by adding water (25 ml). The resulting reaction mass was extracted with $3 \times 30$ ml ethyl acetate. The ethyl acetate layer washed twice with 20 ml of water, dried over anhydrous $Na_2SO_4$, and evaporated under reduced pressure. The crude product was purified by silica-gel column chromatography using ethyl acetate/hexane system.



## SPECTRAL DATA

### 5,6,7-Trihydroxy-2-phenyl-4h-chromen-4-one Flavones (Baicalein; Entry 20)

Yellow solid, yield: 4.32 g (80%). $^1$HNMR (400 MHz, DMSO-$d_6$): $\delta = 12.67$ (1H, s), 10.6 (1H, s), 8.84 (1H s), 8.08–8.06 (2H d, $J = 8.0$ Hz), 7.62–7.55 (3H, m), 6.94 (1H, s), 6.63 (1H, s). $^{13}$C NMR (DMSO, 100 MHz) δ: 94.5, 104.7, 104.9, 126.7, 126.7, 129.6, 129.6, 129.8, 131.4, 132.4, 147.4, 150.3, 154.1, 163.4, 182.6. IR (KBr): 3414, 3091, 1656, 1620, 1300, 1087 $cm^{-1}$; MS (EI) $m/z$ 270 ($M^+$).

### 5,6-Dihydroxy-7-methoxy-2-phenyl-4h-chromen-4-one (Neglectein; Entry 21)

Yellow solid, yield 4.83 g (85%). $^1$H NMR (400 MHz, DMSO): $\delta = 12.51$ (s, 1H), 8.8 (s, 1H), 8.11–8.09 (m, 2H), 7.62–7.58 (m, 3H), 7.00 (s, 1H), 6.97 (s, 1H), 3.93 (s, 3H). $^{13}$C NMR (DMSO, 100 MHz) δ: 56.8, 91.8, 105.2, 105.8, 105.8, 126.8, 126.8, 130.5, 131.3, 132.4, 146.5, 150.3, 155.1, 155.1, 163.6, 182.6; IR (KBr): 3448, 3101, 1665, 1608, 1328, 1080, 956 $cm^{-1}$; MS (ESI) $m/z$ 283($M^+$).

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18. Note: In most of the references reported the end products are methoxy compounds as a result of didemethylation of 5,6,7-trimethoxyflavones, but actually we found the 7-methoxy analog, that is, neglectein (Kiem, P. V.; Minh, C. V.; Huong, H. T.; Lee, J. J.; Lee, I. S.; Kim, Y. H. *Arch Pharm Res.* **2005**, *28*, 1345). We are further characterizing the data and communicating results separately.