

## Efficient Cleavage of Alkyl Aryl Ethers Using an Ionic Liquid under Microwave Irradiation

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A highly reliable dealkylation protocol of alkyl aryl ethers, whose alkyl groups are longer than methyl group, has been developed. We report that various ethyl, *n*-propyl, and benzyl aryl ethers are successfully cleaved using an ionic liquid, 1-*n*-butyl-3-methylimidazolium bromide, [bmim][Br], under microwave irradiation. Despite many characteristics such as lower cost and less toxicity of the alkylating agents, and greater hydrophobicity of the products, longer alkyl ethers have been significantly less exploited than methyl ethers, probably due to more difficulty in the deprotection step. Since it has the same advantages as the demethylation method developed by this group including mild conditions, short reaction time, and small use of the ionic liquids, the dealkylation protocol can greatly encourage the broader use of longer alkyl groups in the protection of phenolic groups. As with our previous study of demethylation using [bmim][Br], the microwave irradiation is crucial for the deprotection of longer alkyl aryl ethers. Unlike the conventional heating, which causes either low conversion or decomposition, the microwave irradiation seems to more effectively provide energy to cleave the ether bonds and therefore suppresses the undesired reactions.

**Key Words :** Dealkylation, Debenzylation, Ionic liquid, [bmim][Br], Microwave irradiation

### Introduction

Phenolic functional groups are widely found in a great number of natural and non-natural products including pharmaceutically interesting agents, biologically important substances, and other industrial chemicals. Synthetic process of any phenol containing compounds often requires temporary masking the phenol functionality during a series of synthetic transformations to prevent its involvement in many undesired reactions such as oxidation and nucleophilic substitution.<sup>1</sup> Among a variety of protective groups developed are ethers which are most commonly used due to their durability and comparability under various reaction conditions. After serving the purpose, these alkyl ethereal protective groups are cleaved usually in an S<sub>N</sub>2 manner either by anions aided by strong acids<sup>2</sup> such as BBr<sub>3</sub>, HBr, and TMSI or by more potent nucleophiles such as thiolates without acid activation.<sup>3</sup> However, the dealkylation conditions are often very harsh, which necessitates excess reagents at an elevated temperature, affecting other functional groups in the molecules. Therefore, there are incessant needs for more efficient and milder dealkylation methods. Although there are many possible candidates for the ether protection of phenolic groups, methyl group is most frequently chosen, probably because it is the simplest alkyl group and its deprotection methods are relatively more studied than other longer alkyl groups.<sup>1</sup> The choice of methylating agent in the preparation of the methyl ethers seems limited to iodomethane<sup>4</sup> and dimethyl sulfate<sup>5</sup> because other reagents such as chloro- and bromo-methane, and methyl triflate are more difficult to handle. Despite the reliable reactivity, both iodo-

methane (CH<sub>3</sub>I = 142) and dimethyl sulfate ((CH<sub>3</sub>)<sub>2</sub>SO<sub>4</sub> = 126) are not very attractive reagents in terms of material balances because only a small fraction (CH<sub>3</sub> = 15) of their molecular weights is transferred to the substrate phenols. Furthermore, although dimethyl sulfate is considered a cheaper alternative to iodomethane, especially for industrial applications, the infamous toxicity and environmental awareness have discouraged its wider usage. Most of alkylating reagents are considered highly carcinogenic and those reagents with lower boiling points than ambient temperature are often avoided because they require additional precautions.<sup>6</sup> Compared to iodomethane, longer alkyl halides such as bromoethane and bromopropane have similar to higher boiling points, so that their handling should not be quite different from the methylation protocol with iodomethane. Their lower reactivity does not seem to cause any problems as they still show clean conversions in the alkylation of phenolic groups. To the contrary, their lower reactivity is favored considering the safety and health issue in dealing with alkylating reagents. Moreover, the above mentioned longer alkyl halides are cheaper and have lower molecular weights than the corresponding alkyl iodides so their uses are economically more viable. In addition, longer alkyl groups can endow the intermediate substrates with greater hydrophobicity than smaller methyl group, thereby enabling to tweak their properties such as solubility, boiling points, viscosity, etc. However, despite the efficient preparation of ethyl and *n*-propyl aryl ethers, one can imagine that the removal of longer alkyl groups would be problematic because the reaction involves an S<sub>N</sub>2 reaction at the secondary carbon. Therefore, we envisaged that an efficient deprotection protocol for longer

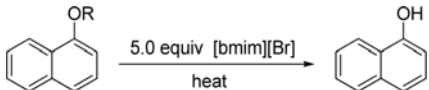
alkyl protecting groups such as ethyl and *n*-propyl would greatly encourage their usage in the phenolic group protection.

We previously reported that methyl aryl ethers can be cleaved using an ionic liquid, [bmim][Br] under microwave irradiation.<sup>7</sup> While ionic liquids are generally utilized as green reaction media substituting for the traditional polar organic solvents,<sup>8</sup> we explored that the nucleophilic counter anions of ionic liquids can take part in S<sub>N</sub>2 reactions. We demonstrated that [bmim][Br] plays dual roles as a cleaving reagent and solvent, and does not require any other activating reagents or solvents. In this reaction, microwave irradiation was found to be crucial. As a continuing work in this area, herein, we wish to report that the developed protocol can be further extended to other longer alkyl protecting groups such as ethyl and *n*-propyl groups. Benzyl protecting group can be also cleanly cleaved under the developed reaction protocol.

## Results and Discussion

It has been reported that counter anions of some ionic liquids such as chloride, bromide, and iodide have nucleophilicity<sup>9</sup> and there are a few instances, where ionic liquids were applied in the dealkylation of alkyl aryl ethers. Pyridinium halides have long been used for dealkylation of alkyl aryl ethers at their melting point temperature.<sup>10</sup> More recently, [bmim][Br] combined with [bmim][BF<sub>4</sub>] has been employed for cleaving alkyl aryl ethers.<sup>11</sup> However, in both cases, nucleophilic halides can function to cleave the alkyl aryl ethers only when the ethers are activated by proton sources. In our earlier study, we showed that nucleophilicity of halides of ionic liquids can be enhanced by microwave irradiation and thereby no other activating reagent was necessary when cleaving methyl aryl ethers.<sup>7</sup> With the demethylation protocol developed in our laboratory, we set out the

**Table 1.** Comparison of dealkylation reactions between conventional heating and microwave irradiation<sup>a</sup>



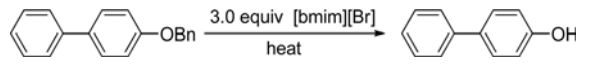
Entry	R	Temp	Time	Conversion <sup>b</sup>	Yield <sup>b</sup>
1	Me	160 °C	16 h	5%	5%
2	Me	210 °C	16 h	45%	32%
3 <sup>c</sup>	Me	200-220 °C (MW)	30 min	> 99%	93%
4	Et	160 °C	16 h	0%	0%
5	Et	210 °C	16 h	5%	5%
6 <sup>c</sup>	Et	200-220 °C (MW)	30 min	> 99%	97%
7	<i>n</i> -Pr	160 °C	16 h	0%	0%
8	<i>n</i> -Pr	210 °C	16 h	4%	4%
9 <sup>c</sup>	<i>n</i> -Pr	200-220 °C (MW)	30 min	> 99%	94%

<sup>a</sup>Reaction was carried out on a 1 mmol scale of 1-alkoxynaphthalene. <sup>b</sup>Conversion and yield were determined by GC. <sup>c</sup>Microwave reaction mode was power control with 20 W and the reaction temperature was in the range of 200-220 °C.

dealkylation reactions of longer alkyl ethers using ionic liquids as a sole reagent (Table 1). 1-Methoxy, 1-ethoxy, and 1-propoxy naphthalenes were treated with 5.0 equivalent of [bmim][Br] in the absence of any other reagent or solvent under both conventional heating and microwave irradiation. While demethylation occurred partially at the elevated temperature as high as 210 °C in the oil bath, deethylation and depropylation were barely proceeded under the similar reaction conditions, clearly indicating that ethyl and *n*-propyl groups are less reactive towards the S<sub>N</sub>2 type cleavage reactions. However, the microwave irradiation greatly accelerated the dealkylation process giving more than 90% of 1-naphthol with almost full conversion. The results strongly suggest that microwave irradiation is crucial for the effective cleavage reactions.

We, then, turned our attention to benzyl protecting group. Along with methyl protecting group, benzyl is also often used for the protection of phenolic functional groups.<sup>1</sup> Cleaving benzyl group is usually carried out under hydrogen atmosphere with palladium catalysts. While it can provide with great advantages such as easy recovery of the debenzylated product by simple filtration, the use of costly catalyst and the fire safety issue in dealing with palladium and hydrogen make the hydrogenative cleavage protocol less attractive, thus found in rather limited applications. Similarly to the other dealkylation reactions, debenzylation can also be achieved by nucleophilic substitution reactions, where strong acids are mostly involved. Due to the enhanced reactivity towards nucleophiles, we thought that benzyl protecting group can be more readily cleaved than ethyl or *n*-propyl group under our developed conditions. Accordingly, we examined the debenzylation with 4-benzyloxy(biphenyl) under conventional heating and microwave irradiation respectively (Table 2). As expected, debenzylation occurred at the lower temperature of 160 °C in heating oil, but the full conversion was not obtained even after a prolonged reaction time. Elevation of the reaction temperature did not help since more decomposition was observed under the conditions; a longer reaction time at the higher temperature led to the

**Table 2.** Comparison of debenzylation reactions between conventional heating and microwave irradiation<sup>a</sup>



Entry	Temp	Time	Conversion <sup>b</sup>	Yield <sup>b</sup>
1	160 °C	2 h	2%	2%
2	160 °C	16 h	37%	23%
3	210 °C	6 h	20%	8%
4	210 °C	10 h	31%	14%
5	210 °C	16 h	> 99%	0%
6 <sup>c</sup>	200-220 °C (MW)	10 min	> 99%	72%
7 <sup>c</sup>	200-220 °C (MW)	2.5 min	> 99%	94%


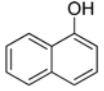
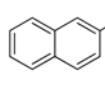
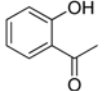
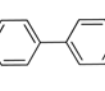
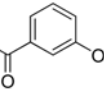
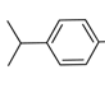
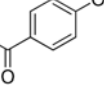
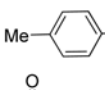
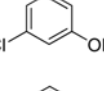
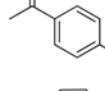
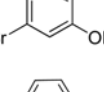
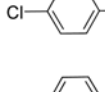
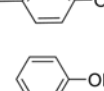
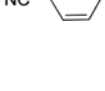
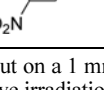
<sup>a</sup>Reaction was carried out on a 1 mmol scale of 4-(benzyloxy)biphenyl. <sup>b</sup>Conversion and yield were determined by GC. <sup>c</sup>Microwave reaction mode was power control with 20 W and the reaction temperature was in the range of 200-220 °C.

complete decomposition of the material (Table 2, entry 5). In great contrast to the conventional heating, we were able to shorten the reaction time by using microwave irradiation, thus avoiding the undesired side reaction pathways. Indeed, when the reaction was quenched after 10 min of irradiation, we found that no starting material remained and 4-phenyl phenol was obtained in 72% yield. From further experiments, we realized that the reaction can be completed by the irradiation duration as short as 2.5 min, meanwhile the decomposition was significantly suppressed, and the desired product was obtained in 94% yield. In addition, keeping the microwave irradiation power at 20 W for a short time was more efficient than lowering the microwave irradiation power at 15-10 W for a longer time.

Before we applied the microwave irradiated cleavage protocol to a broader range of substrates, we further elaborated the details on microwave usage. The single-mode microwave reactor releases the focused and planar polarized microwaves in a well-defined distribution manner and thus, heating the reaction mixture can be achieved uniformly and efficiently.<sup>12</sup> The single-mode microwave reactors are certainly preferred in research area over the multi-mode microwave ovens. For microwave heating, most microwave reactors provide two types of irradiation modes, temperature control

mode and power control mode. The temperature control mode keeps the set point of reaction temperature by fluctuating microwave irradiation power whereas the power control mode provides the reactants with the consistent power while cooling the reaction vessel by air-flow to prevent from overheating. In the previous work, we figured out that the power control mode is more effective and the consistent, low power irradiation with cooling is the key to obtain the desired demethylated product in maximum yields. Stronger power and longer reaction time led to the decomposition of the materials in the reaction vessels yielding more tar materials. The same experimental results were observed in deethylation, depropylation, and debenzylolation. Therefore, it was very important to keep the microwave power under 30 W with air cooling and not to let the reaction vessel stand for the longer time than required for completion. The reaction temperature was measured in a range of 200-220 °C. Under these optimized conditions, 3.0 equivalent of ionic liquid [bmim][Br] were enough to complete the dealkylation reaction of a variety of ethyl, *n*-propyl, and benzyl protected phenols. In brief, a typical reaction protocol optimized is following: use of 3.0 equivalents of [bmim][Br] and 20 W power control mode irradiation with the reaction temperature kept below 220 °C by air cooling throughout the reac-

**Table 3.** Deethylation and depropylation reactions of various alkyl aryl ethers using [bmim][Br] under microwave irradiation<sup>a</sup>

									
Entry	R	Product (ArOH)	Time (min)	Yield (%) <sup>b</sup>	Entry	R	Product (ArOH)	Time (min)	Yield (%) <sup>b</sup>
1	Et		30	97	9	<i>n</i> -Pr		30	94
2 <sup>c</sup>	Et		30	99	10	<i>n</i> -Pr		30	99
3	Et		30	99	11	<i>n</i> -Pr		30	96
4	Et		30	99	12	<i>n</i> -Pr		40	85
5	Et		40	99	13	<i>n</i> -Pr		30	81
6	Et		30	98	14	<i>n</i> -Pr		30	78
7	Et		30	99	15	<i>n</i> -Pr		30	96
8	Et		25	94					

<sup>a</sup>All reactions were carried out on a 1 mmol scale of alkyl aryl ether using 3.0 equiv of [bmim][Br]. <sup>b</sup>Isolated yields of > 95% purity as determined by GC and <sup>1</sup>H-NMR. <sup>c</sup>Microwave irradiation power was 15 W.

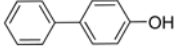
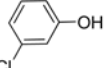
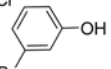
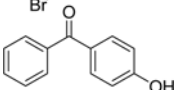
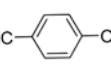
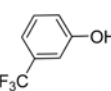
tion. The dealkylation reaction time can vary from several minutes to 40 minutes depending on the protecting groups and the substituents of the protected phenolic substrates. Table 3 summarized the deethylation and depropylation reactions of the substrates of various functional group substituents. Deethylation generally showed a slightly better reactivity and selectivity than depropylation. Clean conversions to the corresponding phenols with no noticeable side-products were observed for the deethylation reactions. Regardless of electronic effect of substituents such as electron releasing and electron withdrawing, most substrates required the similar microwave power and irradiation time. We presumed that substrates with electron withdrawing substituents might need a shorter reaction time or a weaker irradiation power as the reaction would proceed in an S<sub>N</sub>2 manner, but such substituent influence was observed only in the case of nitro substituted ethoxy phenol in a little extent (Table 3, entry 8); 1-ethoxy-3-nitrobenzene needed slightly shorter reaction time as 25 min while others needed 30-40 min. This suggests that comparable and high activation energies are necessary for the nucleophilic substitutions. Both 1-ethoxynaphthalene and 2-propoxynaphthalene were converted into the corresponding naphthols in excellent yields (Table 3, entries 1 and 9). As the deethylation is very effective under the reaction conditions, deethylation of all the acetylated ethoxybenzenes occurred equally well irrespective of the substituent positions at *ortho*, *meta*, and *para* (Table 3, entries 2-4). Halogen groups were fairly compatible with the reaction conditions; most of chloro- and bromo- substituents remained intact during the deethylation (Table 3, entries 5, 6, and 14<sup>13</sup>). In some *n*-propyl protected phenolic substrates such as entries 12 and 13, full conversions were achieved

after a longer reaction time, but tar materials were observed, lowering the product isolation yields. In these cases, the best yields were obtained upon ca. 90% conversion. The other substituents such as phenyl, isopropyl and cyano group were also compatible under the reaction conditions, showing clean conversion to the corresponding phenols.

As we noticed in the test reaction of 4-benzyloxy(bi-phenyl), debenzoylation was much more efficient than other dealkylations. When the same reaction protocol, that is, three equivalent of [bmim][Br] under 20 W microwave irradiation, was applied, much shorter time was required for the completion, implying that the better reactivity of benzyl group towards nucleophilic substitution reactions (Table 4). A time range of 2.5-10 minutes was enough for the completion of debenzoylation, whereas 20-40 minutes was needed for demethylation, deethylation and depropylation. Similarly to dealkylation, electronic effect was not very critical. All the substrates with electron releasing or electron withdrawing substituents were converted into the corresponding phenols with excellent yields.

In conclusion, we successfully broadened the scope of the microwave-assisted dealkylation protocol with ionic liquid [bmim][Br] to the dealkylation of ethyl-, *n*-propyl-, and benzyl protected phenolic compounds. The presented protocol employs ionic liquid [bmim][Br] as a sole reagent. It does not need any other additional agents such as strong acids to activate the ether bond towards nucleophilic cleavage. The ionic liquid, [bmim][Br], is effective enough not only to cleave the protecting group but also to dissolve most of the substrates, and thus, additional solvents are not necessary. Low power microwave irradiation with consistent air cooling in a short time was proved to be very effective for the cleavage process, improving the reaction conversions and yields. The conventional heating using hot oil bath shows low conversions even for a prolonged time and the prolonged reaction time often causes the decomposition of the materials. Such disadvantage of the conventional heating method can be superbly overcome by incorporating the microwave irradiation technique. By demonstrating that this highly efficient protocol can be utilized in cleaving various kinds of alkyl aryl ethers including ethyl, *n*-propyl, benzyl groups, we are able to provide researchers in this area with more choices in the selection of protection groups.

**Table 4.** Debenzoylation reactions of various benzyl aryl ethers using [bmim][Br] under microwave irradiation<sup>a</sup>

Entry	Product (ArOH)	Time (min)	Yield (%) <sup>b</sup>
1		2.5	99
2		5	99
3		10	99
4		5	96
5		10	97
6		5	98

<sup>a</sup>All reactions were carried out on a 1 mmol scale of benzyl aryl ether using 3.0 equiv of [bmim][Br]. <sup>b</sup>Isolated yields of >95% purity as determined by GC and <sup>1</sup>H-NMR.

## Experimental Section

**Representative Procedure.** To a microwave tube was added alkyl aryl ether (1.0 mmol) and 1-*n*-butyl-3-methyl imidazolium bromide (0.65 g, 3.0 mmol). The reaction tube was flushed with argon and then was irradiated at 20 W for the designated time period with air-flow cooling to prevent overheating (power control mode). After cooled to room temperature, the reaction mixture was acidified with 1 N HCl solution and extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with water and brine, and dried over anhydrous MgSO<sub>4</sub> and the solvent was evaporated under vacuum. Purification of the crude product

by column chromatography (ethyl acetate in *n*-hexane) afforded the desired product.

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- In case of 1-chloro-4-propoxybenzene (Table 3, entry 14), ca. 8% phenol, which appears to be derived from dechlorination, was detected by GC-MS analysis.