

Facile Cleavage of Ethers in Ionic Liquid

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Various alkyl ethers were efficiently cleaved by treating them with pyridinium halides in ionic liquid, and the desired products were obtained in excellent yields.

The use of alkyl ethers as protecting groups for the hydroxy group is of fundamental importance in organic synthesis, and such protections are crucial in the preparation of many pharmaceutical agents and fine agrochemicals.¹ Alkyl ether cleavages are typically carried out under strong acidic conditions or by catalytic hydrogenolysis. Ether cleavages can also be realized through electron-transfer reactions,² or using photochemical, electrochemical, and enzymatic methods.³ However, there still exists a need to develop efficient and convenient methods for the removal of the alkyl ethers.

Ionic liquids have recently attracted much attention as reaction media for green chemical synthesis mainly due to their very low vapor pressure, excellent thermal stability and ease of handling.⁴ The use of ionic liquid as a solvent for nucleophilic displacement has been well studied.⁵ There have been a number of reports on the increased nucleophilicity of the nucleophiles in ionic liquids, thus facilitating various chemical transformations.⁶ Chi and co-workers have elegantly demonstrated that 1-butyl-3-methylimidazolium bromide (bmim)⁺Br[−] in (bmim)⁺[BF₄][−] in the presence of protic acids can cleave the ethers.^{6c} Johnson and co-workers have discovered that the novel 3-methylimidazolium bromohydrogenates(I) ionic liquid can cleave a range of methyl ethers.⁷ In a recent study carried out by Kemperman et al., chloroaluminate ionic liquid has been shown to be an excellent ether-cleaving agent.⁸

At the outset of this work, we aimed to develop a facile and efficient method for the cleavage of alkyl ethers. Pyridinium halide in an ionic liquid seems to be a good choice,⁹ because both a proton donor and a nucleophile are present in the same molecule. In the cleavage reaction, pyridinium cation can serve as a mild proton donor to protonate ether substrates, and the enhanced nucleophilicity of halide in an ionic liquid¹⁰ will then be utilized to cleave the protonated ethers. The availability, low cost and mild nature of pyridinium halides made this method especially appealing. Moreover, we envision that the use of the microwave irradiation¹¹ could further improve

Table 1. Debenzylation of Phenyl Benzyl Ethers^{a)}

Entry	Heating method ^{b)}	T/°C	Time	Yield ^{c)} /%
1	Thermal	115	10 h	95
2 ^{d)}	Thermal	115	7 h	97
3 ^{e)}	Thermal	115	7 h	<5
4 ^{d)}	Microwave	115	100 min	97
5	Microwave	200	20 min	93
6 ^{f)}	Microwave	200	15 min	93
7 ^{g)}	Microwave	200	40 min	93
8 ^{h)}	Microwave	200	25 min	97

a) Unless otherwise indicated, all the reactions were carried out on 0.5 mmol reaction scale of ether in 0.6 mL ionic liquid using 5 mmol of pyridinium chloride in (bmim)⁺[BF₄][−].

b) Microwave-assisted reactions were carried out in sealed vessels with a Biotage Initiator Microwave reactor; thermal refers to thermal heating, which was performed in an oil bath.

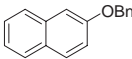
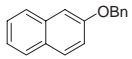
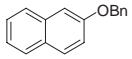
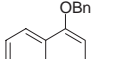
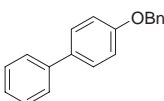
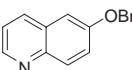
c) Isolated yield. d) (PyH)⁺Br[−] was used. e) Reaction was carried out in DMF and (PyH)⁺Br[−] was used. f) (Bmim)⁺[PF₆][−] was used. g) Equimolar amount of pyridinium chloride was used. h) Recovered ionic liquid was used.

the efficiency of the reactions. Since the dielectric properties of ionic liquids make them absorb microwave irradiation very efficiently, they are highly suitable for the microwave-assisted organic synthesis. Herein, we report that pyridinium halides in ionic liquids are effective reagents for the cleavage of various aryl and alkyl ethers.

We initially performed a feasibility study with phenyl benzyl ethers, and the results are summarized in Table 1. When a mixture of phenyl benzyl ether and ten molar amounts of pyridinium chloride in ionic liquid were heated in an oil bath for ten hours, the debenzylated product was isolated¹² in excellent yield (Entry 1). The reaction proceeded faster when pyridinium bromide was used (Entry 2). Ionic liquids are essential for the cleavage, and the reaction in normal solvents such as DMF, yielded only trace amount of dealkylated product (Entry 3). Microwave irradiation is more efficient than thermal heating. The rate of reaction was substantially improved when microwave irradiation was employed (Entries 4 and 5). In addition, the reaction worked equally well in the presence of different ionic liquids (Entry 6). We typically used ten molar amounts of pyridinium halide to expedite the reaction. It should be noted that the debenzylation also went to completion in the presence of only equimolar amount of pyridinium salt, although a longer reaction time was required (Entry 7). When we carried out reaction with the recovered ionic liquid,¹³ the reaction proceeded equally well (Entry 8).

The deprotections of various benzyl ethers are illustrated in Table 2. The efficiency of our method and the observed rate enhancement can be attributed to microwave effects.¹¹ The reaction under thermal heating in an ionic liquid at 200 °C only afforded a moderate yield of the desired product (Entry 1). However, the reaction under microwave irradiation at the same temperature was quantitative (Entry 2). In the absence of an ionic liquid, when pyridinium halide was used as both reagent and solvent, the reaction was less effective (Entry 3). Under the microwave irradiation conditions in an ionic liquid, the debenzylations of various substrates were typically completed

Table 2. Debenzylation of Aryl Benzyl Ethers^{a)}

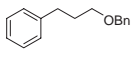
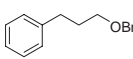
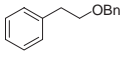
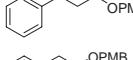
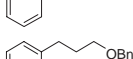
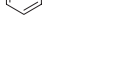
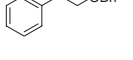
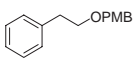
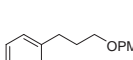
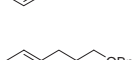
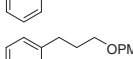
Entry	Substrate	<i>T</i> /°C	Time /min	Yield ^{b)} /%
1 ^{c)}		200	15	65
2		200	15	95
3 ^{d)}		200	15	36
4		200	15	96
5		200	20	91
6		180	25	92

a) Unless otherwise indicated, all the reactions were carried out on 0.5 mmol reaction scale of ether in 0.6 mL (bmim)⁺[BF₄][−] using 5 mmol of pyridinium chloride. All reactions were carried out under microwave irradiation conditions in sealed vessels with a Biotage Initiator Microwave reactor. b) Isolated yield. c) Reaction under thermal heating condition, and (PyH)⁺Br[−] was used. d) The reaction was run in the absence of an ionic liquid, and only (PyH)⁺Br[−] was used.

within half an hour, and the desired phenols were obtained in excellent yields (Entries 4 to 6).

We then investigated the cleavage of benzyl and *p*-methoxybenzyl (PMB) ethers which were derived from aliphatic alcohols (Table 3). The same reaction conditions using microwave irradiation led to the disappearance of the starting material, but surprisingly, none of the desired product was observed or isolated (Entry 1). Careful examination of the reaction progress revealed that the deprotected alcohol was formed initially. However, the desired alcohol disappeared upon further exposure under the reaction conditions, and the corresponding halide¹⁴ was obtained in the end. The formation of the halide is likely due to the protonation of the alcohol and subsequent nucleophilic displacement by halide. We reason that microwave irradiation may be too efficient in converting the alcohols into the halides. If milder reaction conditions are employed, the desired alcohols may be obtained. We therefore decided to use thermal heating to achieve selective dealkylations. When the reactions were carried out under thermal heating (115–120 °C), we were able to obtain the desired products with yields ranging from poor to good (Entries 2 to 5).¹⁵ To circumvent the formation of the undesired halide, we carried out the deblocking reactions in a mixture of ionic liquid/water (v/v = 1/1) with thermal heating.¹⁶ With this protocol,¹⁷ the desired aliphatic alcohols were isolated in excellent yields (Entries 6 to 9). We believe that the addition of water suppresses the undesired nucleophilic displacement of the alcohols by halides. If only water was used as the reaction medium, the dealkylation reactions did not proceed (Entries 10 and 11).

Table 3. Cleavage of Benzyl Ethers on Aliphatic Substrates^{a)}


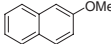
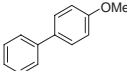
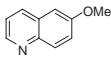
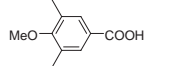
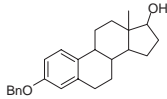
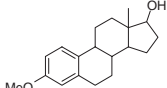
Entry	Substrate	<i>T</i> /°C	Condition ^{b)}	Time /h	Yield ^{c)} /%
1		200	Microwave/ (PyH) ⁺ Cl [−]	1	— ^{d)}
2		115	Thermal	25	63
3		115	Thermal	21	71
4		120	Thermal	19	33
5		120	Thermal	19	55
6		115	Thermal (IL/100% H ₂ O)	40	88
7		115	Thermal (IL/100% H ₂ O)	45	82
8		115	Thermal (IL/100% H ₂ O)	65	91
9		115	Thermal (IL/100% H ₂ O)	60	93
10		115	Thermal (H ₂ O)	90	— ^{e)}
11		115	Thermal (H ₂ O)	90	— ^{e)}

a) All the reactions were carried out on 0.5 mmol reaction scale of ether in 0.6 mL (bmim)⁺[BF₄][−] using 5 mmol of pyridinium bromide. b) The microwave-assisted reactions were carried out in sealed vessels with a Biotage Initiator Microwave reactor; thermal refers thermal heating. c) Isolated yield. d) Not determined, the desired product was almost undetectable. The corresponding halide was obtained in 24% yield. e) No desired product could be detected by TLC.

We next extended the scope of our method to further include methyl ether substrates and more complex structural scaffolds (Table 4). Demethylation of aromatic methyl ether substrates typically required longer reaction time than their benzyl ether counterparts. Excellent yields were obtained under microwave irradiation,¹⁸ and normally within one hour (Entries 1 to 4). 4-Methoxy-3,5-dimethyl benzoic acid is a useful intermediate for the preparation of dimethyl tyrosine analogues,¹⁹ the demethylation of which was almost quantitative (Entry 5). Remarkably, 17- β -estradiol 3-benzyl and methyl ethers underwent dealkylation reactions efficiently, affording the desired products in excellent yields (Entries 6 and 7).

In summary, we showed here that the pyridinium chloride or bromide in an ionic liquid effectively cleaved the alkyl ether protecting groups. The reported methods were applicable to both aromatic and aliphatic substrates, and the described procedures were efficient, mild and easy to manipulate. We anticipate that our methodology will find wide application for the cleavage of ether protective group in organic synthesis.

Table 4. Cleavage of Various Methyl Ethers^{a)}

Entry	Substrate	T/°C	Time/min	Yield ^{b)} /%
1		200	45	91
2		200	80	99
3		200	55	97
4		200	45	92
5		200	30	96
6		200	50	97
7		200	60	92

a) Deprotections of the steroid substrates were performed with 0.2 mmol of ether, while other substrates at 0.5 mmol scale, and 10 molar amounts of pyridinium chloride were used. The microwave reactions were carried out in sealed vessels using a Biotage Initiator Microwave Reactor. b) Isolated yield.

Supporting Information

Experimental procedures, data, and ¹H NMR spectra. This material is available free of charge on the web at <http://www.csj.jp/journals/bcsj/>.

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- A single example of demethylation of steroid in large excess of melting pyridinium chloride (200 °C) has been reported a few decades ago, see: J. C. Sheehan, R. A. Coderre, P. A. Cruickshank, *J. Am. Chem. Soc.* **1953**, 75, 6231.
- When pyridinium halides are dissolved in (bmim)⁺[BF₄]⁻ ionic liquid, (bmim)⁺X⁻ ion pairs are expected to be formed. We speculate that the size of (bmim)⁺ will make the halide anion relatively dissociated, resulting in higher concentration of available halide anions. Increased nucleophilicity of halides in ionic liquid is thus anticipated.
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- Benzyl chloride arose from the benzylic moiety of the substrate during the deprotection, which was easily separated from the desired phenol by flash chromatography.
- After extraction with diethyl ether, the ionic liquid containing pyridinium chloride was reused directly in the subsequent reaction.
- The formation of the corresponding chloride was confirmed by ¹H NMR and MS analysis.
- β-Elimination products were observed for the phenylethyl substrates.
- Chi and co-workers have reported that the addition of water could circumvent the formation of the undesired alkene when they performed fluorination of alkyl mesylates, See Ref. 6a.
- The Ionic liquid was recovered at the end of reaction and confirmed by ¹H NMR analysis.
- Methyl chloride was generated during the demethylation. Precaution should be taken when a large scale reaction is performed. We recommend that an open system be used for large scale reactions.
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