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Application of Ionic Liquid Halide Nucleophilicity for the Cleavage of Ethers: A Green Protocol for the Regeneration of Phenols from Ethers

Shanthaveerappa K. Boovanahalli, Dong Wook Kim, and Dae Yoon Chi*

Department of Chemistry, Inha University, 253 Yonghyundong Namgu, Inchon 402-751, Korea

dychi@inha.ac.kr

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We have used the high nucleophilicity of bromide ion in the form of the ionic liquid, 1-*n*-butyl-3-methylimidazolium bromide ([bmim][Br]), for the nucleophilic displacement of an alkyl group to regenerate a phenol from the corresponding aryl alkyl ether. Using 2-methoxynaphthalene (**1**) as a model compound, we found that the combination of ionic liquid [bmim][Br] and *p*-toluenesulfonic acid with warming effected demethylation in 14 h, affording the desired product 2-naphthol (**2**) in good yield (97%). Various other protic acids (MsOH, hydrochloric acid (35%), dilute sulfuric acid (50%)) could be used as a proton source in this demethylation reaction. Under the same conditions, cleavage of alkyl alkyl ether 2-(3-methoxypropyl)naphthalene yielded mixture of corresponding 2-(3-bromopropyl)naphthalene and 2-(3-hydroxypropyl)naphthalene. Dealkylation of various aryl alkyl ethers could also be achieved using significantly reduced (i.e., stoichiometric) amounts of concentrated hydrobromic acid (47%) in the ionic liquid. Both procedures afforded the desired products in moderate to good yield; however, cleavage of aryl alkyl cyclic ether, 2,3-dihydrobenzofuran, resulted in low yield of the desired product *o*-2-bromoethylphenol. The convenience of this method for ether cleavage and its effectiveness using only a moderate excess of hydrobromic acid make it attractive as a green chemical method.

Introduction

The cleavage of ethers is a nearly ubiquitous transformation in organic synthesis for the production of many of pharmaceuticals and other fine chemicals.[1] Although a variety of reagents is capable of cleaving ethers, most conventional methods involve harsh reagents and/or drastic conditions.[2] Consequently, methods that effect ether cleavage under milder conditions have been the focus of much attention.

Nucleophilic substitution reactions are solvent dependent, and the outcome of these reactions in terms of both equilibrium and rate can be altered by the microenvironment created by the solvent.[3] In our recent reports, we have successfully developed novel methodologies for various nucleophilic substitution reactions performed in the presence of ionic liquids, and the results we have obtained are superior compared with those of earlier reported methods.[4]

Ionic liquids (Figure 1) are a fascinating group of chemicals, composed of anions and cations, either of which may interact with solutes and therefore significantly affect the outcome of reactions. Numerous nucleophilic displacement reactions have been reported in these new media.[5] In this respect, ionic liquids are attracting growing interest as alternative reaction media.[6] Their properties, low vapor pressure, recyclability, high thermal stability, and ease of handling, and the fact that ionic liquids can often act as catalysts as well as reaction media, make these systems very attractive for developing environmentally benign chemical processes.

Ford et al.[7] reported that the relative nucleophilicities of Cl^-, Br^-, and I^- in triethylhexylammonium triethyl-

* Phone: +82-32-860-7686. Fax: +82-32-867-5604.

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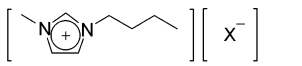


[bmim][X] {X = BF_4, PF_6, OTf, NTf_2, OAc, Br}

FIGURE 1. Ionic liquids.

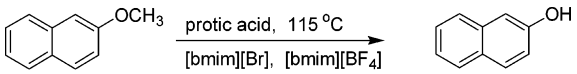
hexylboride ionic liquid were in agreement with the known gas-phase nucleophilicities of the halide ions.[8] Recently, a few investigations on the nucleophilicity of an ionic liquid anion itself such as chloride, bromide, and iodide salts of the 1-*n*-butyl-3-methylimidazolium cation, i.e., [bmim][X] (X = Cl^-, Br^-, and I^-), have also been reported. In these studies, the nucleophilicities of Cl^- and I^-, compared with Br^-, were found to be approximately constant; iodide showed a little variation, but chloride showed more.[9]

It is well-known that a strong bond is present between the halide anions and the complex $[bmim]^+$ cation;[10] this "hydrogen bond" is formed via the hydrogen atom on a carbon α to a quaternary nitrogen.[11] Moreover, there have been speculations on the effect of this ionic liquid hydrogen bonding on organic reactions.[12,13] Thus, we anticipated that the dissociation of the $[bmim]^+$ cation from the halide counterion, in reaction media in the presence of substrate, would give rise to a high concentration of available halide ion, which might effectively catalyze certain reactions. In view of these considerations, we have explored the cleavage of ethers by utilizing as a catalyst the enhanced halide anion nucleophilicity of the ionic salt [bmim][Br] in ionic liquid [bmim]-$[BF_4]$ as a solvent media.

Recently, Kemperman et al. reported the use of chloroaluminate ionic liquids for the cleavage of aromatic methyl ethers.[14] Acylative cleavage of ethers using 1-ethyl-3-methylimidazolium halogenoaluminate ionic liquids has also been reported,[15] as has cleavage of ether using anhydrous hydrobromic acid in 1-methylimidazole.[16] However, to our knowledge, there has been no report on the dealkylation of ethers using the enhanced halide nucleophilicity of an ionic liquid anion in the presence of a proton source in ionic liquid media.

Herein, we report the application of the enhanced nucleophilicity of the ionic liquid salt [bmim][Br] for the nucleophilic displacement of the alkyl group in aryl−alkyl, alkyl−alkyl, and aryl−alkyl cyclic ethers to obtain the corresponding phenol or alcohol in an ionic liquid as the medium and in the presence of a proton source. We also report the regeneration of the phenol in this system using only stoichiometric amounts of concentrated hydrobromic acid in the ionic liquid, a procedure that could be used to significantly reduce the amount of concentrated hydrobromic acid used in such conversions, as typically performed by conventional methods.

TABLE 1. Demethylation of 2-Methoxynaphthalene with Various Protic Acids in [Bmim][BF_4][a]



1 **2**

entry	protic acid	equiv	[bmim][Br] (equiv)	time (h)	yield (%)[b]
1	HBr (47%)	5		7	96
2	HBr (47%)	2		9	97
3	HBr (47%)	1		32	94
4			3	22	
5	*p*-TsOH	3		22	30
6	*p*-TsOH	2	2	22	97
7	*p*-TsOH	3	3	14	97
8	MsOH	3		22	27
9	MsOH	3	3	14	97
10	AcOH	3		22	
11	AcOH	3	3	22	
12	HCl (35%)	3		22	25
13	HCl (35%)	3	3	22	93
14	H_2SO_4 (50%)	3		22	29
15	H_2SO_4 (50%)	3	3	22	93
16	H_2O	3	3	22	

[a] All reactions were carried out on a 1.0 mmol reaction scale of 2-methoxynaphthalene **1** in 1.0 mL of [bmim][BF_4] at 115 °C. [b] Isolated yield.

Results and Discussion

To investigate the relative nucleophilic reactivity of various ionic liquid salts, we carried out the demethylation of 2-methoxynaphthalene (**1**) in the ionic liquid [bmim][BF_4] in the presence of various protic acids. Table 1 illustrates the nucleophilic demethylation of this compound with the Brönsted acids, concentrated hydrobromic acid (47%), *p*-toluenesulfonic acid (*p*-TsOH), methanesulfonic acid (MsOH), acetic acid, concentrated hydrochloric acid (35%), and dilute sulfuric acid (50%), as well as a combination of these protic acids as proton donors with [bmim][Br] as a nucleophile source; initial investigations were done using [bmim][BF_4] as the reaction medium. Reactions were performed on a 1 mmol reaction scale of methyl ether **1**, along with protic acid alone, and with the combination of protic acid and ionic liquid [bmim][Br] on different mmol scales in 1 mL of [bmim]-$[BF_4]$.

The reaction with concentrated hydrobromic acid alone with 5 or 2 mmol equiv in [bmim][BF_4] was completed in 7 and 9 h, respectively, affording 2-naphthol **2** in excellent yields (96 and 97%, entries 1 and 2, respectively). The same reaction with a lower mole ratio (1.1 mmol equiv) also furnished the desired product in good yield but was significantly slower and required longer reaction times (32 h, 94%, entry 3). This difference can

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be attributed to the catalytic influence of bromide ion concentration on the rate of ether cleavage, and it suggests that a minimum of ca. 2 equiv of hydrobromic acid is required for achieving an optimal conversion rate.

Use of other protic acids such as *p*-TsOH, MsOH, hydrochloric acid, and sulfuric acid alone resulted in poor conversion (30, 27, 25, and 29%, entries 5, 8, 12, and 14, respectively); moreover, the reaction using acetic acid did not proceeded at all (entry 10). We presume that these differences are due to the lower nucleophilicity of the counterions of these acids relative to hydrobromic acid. However, the efficiency of *p*-TsOH, MsOH, concentrated hydrochloric acid (35%), and dilute sulfuric acid (50%) in cleaving the methyl ether was significantly increased when these were employed together with the ionic liquid [bmim][Br] as a source of additional nucleophile.

The reaction using the combination of *p*-TsOH as proton donor on a 2 mmol scale in conjunction with [bmim][Br] on a 2 mmol scale as a nucleophile source was complete in 22 h, furnishing the desired product 2-naphthol **2** in very good yield (97%, entry 6). Consequently, the duration of reaction could be reduced further by employing *p*-TsOH and [bmim][Br], each on a 3 mmol scale, complete conversion being achieved within 14 h (97%, entry 7). As expected, similar results were obtained using the combination of ionic liquid [bmim][Br] along with protic acids, MsOH, concentrated hydrochloric acid (35%) and dilute sulfuric acid (50%), each on a 3 mmol ratio, giving the desired product in 14, 22, and 22 h, respectively, in good yields (97, 93, and 93%, entries 9, 13, and 15, respectively). However, under the same conditions, the reaction using acetic acid and water as a proton source along with [bmim][Br] as nucleophile did not proceed at all, even after 22 h (entries 11 and 16). Accordingly, it was found that [bmim][Br] alone also is not sufficiently effective for dealkylation of the ether, with no detectable transformation being noted when the reaction was performed with this reagent alone in [bmim]-[BF_4], despite heating for 22 h (entry 4).

From these results, it is evident that both an efficient nucleophile as well as an effective proton source are required to achieve a smooth transformation of ether to phenol, with the reaction failing when either of the two components is omitted. Notably, hydrobromic acid exhibits dual character, being a proton donor as well as an effective nucleophile in the ionic liquid.

The initial reaction is obviously formation of the protonated ether. Cleavage then involves nucleophilic attack by the halide ion on the alkyl carbon adjacent to this protonated ether. In the cases where *p*-TsOH donates a proton, the ionic liquid [bmim][Br] acts as a halide nucleophile source, with the resulting ionic liquid stabilized as $[bmim]^+[OTs]^-$.

As with organic solvents, all ionic liquids will not be suitable for a particular reaction, and any one ionic liquid will not always be best for every reaction. However, by varying the structure of the ionic liquid, one can optimize both the rates and the selectivity for each reaction. As a further study of the reactions shown in entry 2 and 7 in Table 1 and to establish the generality of reaction media, we have performed demethylation of 2-methoxynaphthalene **1** employing various other ionic liquids such as [bmim][PF_6], [bmim][NTf_2], [bmim][OTf], [bmim][OAc], and solvents such as 1,2-dichloroethane, benzene, acetonitrile (Table 2).

TABLE 2. Conversion of 2-Methoxynaphthalene to 2-Naphthol in Various Ionic Liquids and Solvents[a]

entry	[bmim][X] or solvent	protic acid (equiv)	[bmim][Br] (equiv)	time (h)	yield (%)[b]
1	[bmim][PF_6]	HBr (47%) (2)		12	90
2	[bmim][NTf_2]	HBr (47%) (2)		16	92
3	[bmim][OTf]	HBr (47%) (2)		12	95
4	[bmim][OAc]	HBr (47%) (2)		22	37
5	$ClCH_2CH_2Cl$	HBr (47%) (2)		48	37
6	benzene	HBr (47%) (2)		48	34
7	CH_3CN	HBr (47%) (2)		48	19
8	H_2O	HBr (47%) (2)		48	35
9	[bmim][PF_6]	*p*-TsOH (3)	3	20	90
10	[bmim][NTf_2]	*p*-TsOH (3)	3	16	93
11	[bmim][OTf]	*p*-TsOH (3)	3	22	93
12	[bmim][OAc]	*p*-TsOH (3)	3	22	–

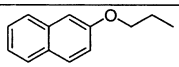
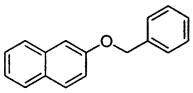
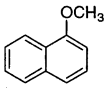
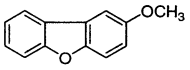
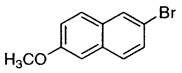
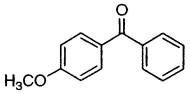
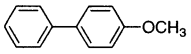
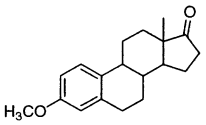
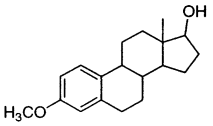
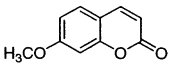
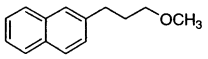
[a] All reactions were carried out on a 1.0 mmol reaction scale of 2-methoxynaphthalene **1** in 1.0 mL of ionic liquid or solvent at 115 °C. [b] Isolated yield.

A comparison of entries 3 and 4 in Table 2 demonstrates that demethylation in the ionic liquid [bmim][OTf] not only proceeded remarkably faster but also provided 2-naphthol **2** in higher yield (95%) (12 h, entry 3). In contrast to this, the same reaction in [bmim][OAc] converted only 37% of 2-methoxynaphthalene **1** to 2-naphthol **2** in 22 h (entry 4). It is noteworthy that both the ionic liquids [bmim][PF_6] and [bmim][NTf_2] were also found to be equally good for this conversion, affording the desired product 2-naphthol **2** in good yield (90 and 92% in 12 and 16 h, entries 1 and 2, respectively). Interestingly, by employing ionic liquids [bmim][PF_6], [bmim][NTf_2], and [bmim][OTf] as reaction media in the presence of [bmim][Br] and *p*-TsOH, the expected product, 2-naphthol **2**, was also obtained in good yield (90, 93, and 93%, respectively; 20, 16, and 22 h, entries 9−11, respectively), whereas the same reaction in [bmim][OAc] did not proceed at all, even after 22 h (entry 12). All four solvents, 1,2-dichloroethane, benzene, acetonitrile, and water, afforded the desired compound in low yield, despite having the reaction heated for 48 h (entries 5−8, yields of 37, 34, 19, and 35%, respectively), indicating that the specific ionic liquid used plays a pivotal role in providing the enhanced nucleophilicity of HBr in this displacement reaction, and that certain solvents can moderate the effectiveness of the ether cleavage reagent.

These results reveal that the ionic liquids [bmim][PF_6], [bmim][NTf_2], and [bmim][OTf] enhance the reactivity of HBr, as does the combination of [bmim][Br] and *p*-TsOH, resulting in the facile demethylation of 2-methoxynaphthalene **1**. Thus, considerable selectivity in ether cleavage can also be achieved by using [bmim][PF_6], [bmim][NTf_2], and [bmim][OTf] as a solvent medium. On the other hand, a significant decline in yield or no reaction is noted when using [bmim][OAc], indicating that this ionic liquid diminishes not only the activity of HBr but also the combination of [bmim][Br] and *p*-TsOH, thereby giving poor conversion.

To enlarge the scope of both of these dealkylation methods, we have subjected a series of aryl methyl ethers, as well as aryl benzyl and propyl ethers, to the same conditions as done for entries 2 and 7 in Table 1; the results are shown in Table 3. Interestingly, entries 1 and

TABLE 3. Cleavage of Various Ethers in [Bmim][BF_4][a]

entry	Substrate	method A[a] time (h)	method A[a] yield (%)[c]	method B[b] time (h)	method B[b] yield (%)[c]
1		13	95	20	91
2		4	93	4	90
3		12	89	20	89
4		5	94	10	95
5		10	95	12	92
6		13	93	13	91
7		20	94	20	95
8		5	86	5	85
9		5	87	5	87
10		13	75	13	80
11[d]		12	46	12	47
12[e]		13	40	13	40

[a] All reactions were carried out on a 1.0 mmol reaction scale of ether in 1.0 mL of [bmim][BF_4] at 115 °C using a 2.0 mmol ratio of concentrated hydrobromic acid (47%). [b] All reactions were carried out on a 1.0 mmol reaction scale of ether in 1.0 mL of [bmim][BF_4] at 115 °C using a combination of *p*-TsOH and [bmim][Br] each in a 3.0 mmol ratio. [c] Isolated yield. [d] 2-(3-Bromopropyl)naphthalene was also obtained in 45 and 46% yield for method A and method B, respectively. [e] 2-(2-Bromoethyl)phenol was obtained, and starting material was recovered.

2 show that both of the dealkylation procedures are widely applicable, besides 2-methoxynaphthalene (entries 2 and 7 in Table 1), 2-*n*-propoxynaphthalene (13 h, 95% and 20 h, 91%, entry 1) and 2-benzyloxynaphthalene (4 h, 93% and 4 h, 90%, entry 2) can also be cleaved efficiently in good yield. In entry 3, demethylation of 1-methoxynaphthalene with concentrated hydrobromic acid in [bmim][BF_4] yielded the desired product 1-naphthol in 12 h (89%)]. The same reaction using a combination of [bmim][Br] and *p*-TsOH in [bmim][BF_4] was accomplished in identical yield (89%), but it required longer reaction time (20 h). Similarly, in the demethylation of 2-methoxydibenzofuran (entry 4), complete transformation was achieved in 5 h (94%) with concentrated hydrobromic acid in [bmim][BF_4], whereas the combination of [bmim][Br] and *p*-TsOH in [bmim][BF_4] afforded the expected product in 10 h in good yield (95%). Furthermore, in entries 5−7, demethylation of 2-bromo-6-methoxynaphthalene (10 h, 95% and 12 h, 92%), 4-methoxybenzophenone (13 h, 93% and 13 h, 91%), and 4-methoxybiphenyl (20 h, 94% and 20 h, 95%), respectively, gave identical results with both procedures.

A few steroids and coumarins are known to be sensitive to high concentrations of protic and Lewis acids at higher temperatures. Therefore, methods for the efficient demethylation of these methoxy aromatic compounds would be useful. Remarkably, estrone-3-methyl ether and 17β-estradiol-3-methyl ether underwent demethylation with both the procedures in 5 h, providing the desired products estrone (entry 8, 86 and 85%, respectively) and β-estradiol (entry 9, 87 and 87%, respectively) in good yields. Consequently, virtually complete demethylation of 7-methoxycoumarin was accomplished in 13 h, under both the conditions, giving 7-hydroxycoumarin in moderate yield (entry 10, 75 and 80%, respectively).[17]

We have also investigated the reactivity of an alkyl alkyl ether and an aryl alkyl cyclic ether toward both the reagents. 2-(3-Methoxypropyl)naphthalene gave a mixture of 2-(3-bromopropyl)naphthalene and 2-(3-hydroxypropyl)naphthalene under both procedures, in 12 h (45, 46% and 46, 47%, entry 11). Informatively, 2,3-dihydrobenzofuran underwent ring cleavage to give corresponding *o*-2-bromoethylphenol with both the procedures, but in low yield (40 and 40%, entry 12). Unfortunately, with this reactant, we were unable to effect an improvement in yield even upon prolonged heating, with byproducts being formed in preference to additional product. It is evident from these results that both the procedures for the dealkylation of ethers furnished the desired products in good to excellent yield.

Conclusion

From the results described in this report, it is apparent that one can often anticipate the conditions required to achieve a particular conversion efficiently and effectively by making use of an ionic liquid having a suitable combination of cation and anion. Here, we have demonstrated one useful application of enhanced halide anion nucleophilicity, in the form of ionic liquid [bmim][Br], in conjunction with a proton source for the regeneration of phenols from various ethers. In this work, the halide anion of the ionic liquid [bmim][Br] exhibits a pivotal role as an efficient nucleophile acting in the presence of an effective proton donor to achieve this important and general transformation. There are some limitations, as cleavage of an alkyl alkyl ether under the same conditions resulted in the mixture of corresponding alcohol and haloalkane, and efforts to cleave an aryl alkyl cyclic ether,

(17) Moderate isolated yield can be attributed to the poor solubility of 7-hydroxycoumarin in ether at room temperature; hence, product was isolated with warm ether.

2,3-dihydrobenzofuran, resulted in a low yield of the desired product, *o*-2-bromoethylphenol, by both procedures.

Cleavage of aryl alkyl and alkyl alkyl ethers depends on three factors: halide anion nucleophilicity, proton source, and temperature. Among the proton sources employed, *p*-TsOH was found to be preferable in terms of yield and ease of handling; moreover, sulfonate ion is a very weak base and thus is a very good leaving group. Other proton sources (MsOH, concentrated hydrochloric acid (35%), dilute sulfuric acid (50%)) in the presence of [bmim][Br] also afforded the desired products in good yield. However, the use of acetic acid and water as a proton source under the same conditions did not proceed at all. Out of the several ionic liquids employed as reaction media, [bmim][BF_4] most reliably enhanced the reactivity of the combination of [bmim][Br] and *p*-TsOH, furnishing the desired products in high yield.

Our alternative approach for the facile cleavage of ethers offers a promising tool, as it involves only near stoichiometric amounts of hydrobromic acid, which is significantly less than the amount of this acid typically used in conventional ether cleavage methods. Thus, the use of ionic liquids as reaction media for this transformation avoids the use of excessive amounts of hydrobromic acid in acetic acid or acetic anhydride, by functioning in a dual role, as the solvent as well as the catalyst. Moreover, the products can be obtained in good yield by a simple isolation procedure. The scope and generality of both of the procedures are illustrated with some oxygen-containing heterocyclic aromatic compounds. We have also demonstrated that both methods are widely applicable: besides methyl ethers, benzyl and propyl ethers can also be cleaved efficiently. Both the procedures are expected to contribute significantly to the development of green chemistry strategies for the regeneration of phenols from ethers.

Experimental Section

Typical Procedure for Cleavage of Ether: Method A. Ether (1 mmol) and concentrated hydrobromic acid (47%, 2 mmol) in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (1.0 mL) were stirred at 115 °C for an appropriate time (see Table 3). The reaction time was determined by TLC analysis. The reaction mixture was extracted with diethyl ether (4 × 10 mL). The combined ether extracts were concentrated under reduced pressure, and the resulting product was purified by flash column chromatography (10% EtOAc/hexane) to furnish phenol. The products were characterized by comparison of their ^{1}H NMR, ^{13}C NMR, and TLC data with authentic samples. The spectral data of all products were identical with those of authentic samples.

Method B. Ether (1 mmol), 1-*n*-butyl-3-methylimidazolium bromide (657 mg, 3 mmol), and *p*-TsOH (3 mmol) in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (1.0 mL) were stirred at 115 °C for an appropriate time (see Table 3). The reaction mixture was worked up as in method A to obtain the phenol product.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectral data of compounds in this manuscript. This material is available free of charge via the Internet at http://pubs.acs.org.

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