A Facile and Green Protocol for Nucleophilic Substitution Reactions of Sulfonate Esters by Recyclable Ionic Liquids [bmim][X]

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Abstract: Ionic liquids [bmim][X] (X = Cl, Br, I, OAc, SCN) are highly efficient reagents for nucleophilic substitution reactions of sulfonate esters derived from primary and secondary alcohols. The counter anions (X^-) of the ionic liquids, [bmim][X], effectively replace the sufonates affording the corresponding substitution products such as alkyl halides, acetates, and thiocyanides in excellent yields. The newly developed protocol is very environmentally attractive because the reactions use stoichiometric amounts of ionic liquids as sole reagents in most cases and do not require additional solvents, any other activating reagents, non-conventional equipment, or special precautions. Moreover, these ionic liquids can be readily recycled without loss of reactivity, making the whole process 'greener'.

Key words: ionic liquids, nucleophilic substitution, halogenation, recyclability, green chemistry

Ionic liquids (ILs) have attracted intense interest from synthetic chemists both in academia and industry due to their wide applications as attractive alternative organic reaction media for environmentally friendly green chemical processes (Figure 1).[1] The useful characteristics of ILs as 'green solvents' include low vapor pressure, high thermal stability, non-flammability,[2] recyclability,[3] and good solubility for many organic and inorganic compounds.[4] The ease of modifying ILs, i.e., flexible combination of positive and negative ions, is an additional advantageous property that allows ILs to be tailored for specific reactions and work-up processes.[5] Indeed, there are a plethora of examples that demonstrate that the incorporation of suitable ILs as reaction media results in an improvement in reaction rates and selectivities.[6] A variety of organic reactions, such as nucleophilic substitution, catalytic hydrogenation, Friedel–Crafts reaction, Diels–Alder reaction, and many transition-metal-catalyzed cross-coupling reactions, have witnessed the benefits of ILs.[7]

Organohalides are found not only in synthetic intermediates, but also in many final products, some of which are biologically active compounds.[8] One of the representative synthetic methods that can be used to form primary and secondary alkyl halides is based on the S_N2 reaction of the activated substrates derived from the starting alcohols

with halide nucleophiles.[9] Preparation of alkyl halides through nucleophilic substitution reactions of sulfonate esters, however, often requires large amounts of metal halides and harsh reaction conditions.[10] Several research groups have reported that such nucleophilic halogenation reactions are greatly facilitated when the conventional polar solvents are substituted either entirely or in part by ILs.[11] Chi and co-workers found that the halogenation reaction of the mesylates from primary alcohols was significantly improved due to the increased nucleophilicity of metal halides (MX, X = F, Cl, Br, I) when ILs such as [bmim][BF₄] (1-*n*-butyl-3-methylimidazolium tetrafluoroborate) were used as a mixture with acetonitrile.[12] Direct conversion of hydroxyl groups into halogens in the presence of ILs has also been reported. Raru and co-workers demonstrated that alkyl alcohols were converted into alkyl halides by hydrogen halides generated in situ from *tert*-butyl halides in the presence of [pmim][Br] (1-*n*-pentyl-3-methyl imidazolium bromide) under sonication conditions.[13] Similarly, in the presence of strong protic acids, the halide ions of ILs participated in the conversion of alkyl alcohols into alkyl halides, suggesting sufficient nucleophilicity of the halide counter anions.[14] Such transformations can be further facilitated under microwave irradiation conditions.[15] These previously reported reaction protocols indicate that ILs can be used as both solvents and reagents for the synthesis of organohalides, providing efficient synthetic methods that are complementary to traditional approaches. Despite their novelty and efficiency, the methods mentioned above are, however, not entirely free from drawbacks. First, they have rather limited substrate scope; the reactions are usually optimized for less sterically hindered substrates derived from simple primary alcohols. Preparation of alkyl halides from secondary alcohol derivatives through S_N2 reactions is often complicated by competitive side reactions such as elimination. Second, in the case of direct conversion, strong protic acid typically needs to be added to activate the hydroxyl groups. Strong acidic conditions are often incompatible with vulnerable substrates, and thus hamper the versatility of the reaction protocols. Third, some reactions employ a large excess of ILs and/or additional activating additives along with conventional solvents, and others require special equipment such as microwave reactors or sonicators.

trialkyl sulfonium   tetraalkyl ammonium   tetraalkyl phosphonium

pyrrolidinium   imidazolium   pyridinium

X = Cl⁻, Br⁻, I⁻, PF₄⁻, SbF₆⁻, ZnCl₃⁻, (CF₃SO₃)₂N⁻, (CF₃SO₂)₃C⁻, MeCO₂⁻
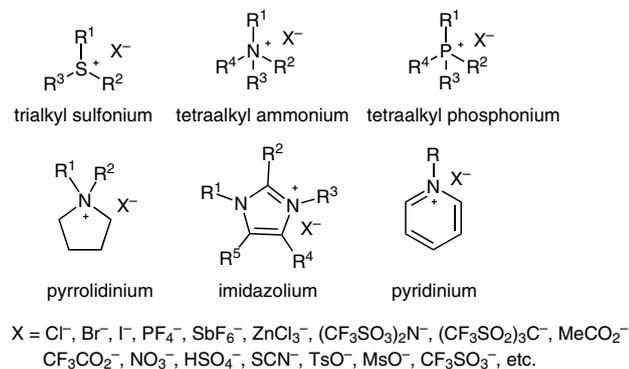CF₃CO₂⁻, NO₃⁻, HSO₄⁻, SCN⁻, TsO⁻, MsO⁻, CF₃SO₃⁻, etc.

Figure 1 Examples of common ionic liquids

The nucleophilicities of the halide counter anions of ILs have been studied and their relative nucleophilicities correspond with those of gas-phase halide ions.[16] Recently, we reported that halide ions of ILs took part in the cleavage of alkyl aryl ethers, most likely in an S_N2 manner.[17] The transformation was accomplished in the absence of any other activating reagents or solvents, under microwave irradiation. This finding led us to explore halogenation reactions of electrophilic substrates derived from alcohols by the nucleophilic halides of ILs.

Herein, we report an efficient and mild preparation of primary and secondary alkyl halides using a minimum amount of ILs, [bmim][X]. In the reactions, [bmim][X] plays a dual role as both solvent and nucleophilic halogenating reagent, making the process environmentally friendly by eliminating the need for additional reagents or solvents. A variety of primary and secondary alkyl halides (RX, X = Cl, Br, I) were obtained in excellent yields under the developed reaction protocol. We further expanded our work to other nucleophilic counter anions of ILs such as [bmim][OAc] and [bmim][SCN], and also demonstrated that ILs, [bmim][X], can be recycled several times without loss of efficiency.

In view of our earlier study, we envisioned that the reaction conditions for the halogenation could be much simplified because we anticipated that the halide-containing ILs could be used alone, unlike previously reported conditions in which metal halides and excess ILs were used in polar solvents.[12e] Initially, we investigated the reactivity of [bmim][Br], which was chosen for the bromination reactions. 3-Phenylpropyl methanesulfonate (**1a**) was treated with [bmim][Br] under several reaction conditions (Table 1). To our delight, complete bromination occurred at room temperature when **1a** was stirred with 3.0 equivalents of [bmim][Br] for three days without adding any other reagents or solvents (entry 2). We found the observed complete conversion to be even more remarkable because the reaction mixture remained heterogeneous all the way to completion, as [bmim][Br] is a crystalline solid at room temperature. Nevertheless, the heterogeneity seemed to be responsible for the need for more than one equivalent of [bmim][Br] and longer reaction times. A slightly elevated reaction temperature (50 °C) allowed the reaction

mixture to become a clear solution and the bromination was complete within one hour, in the presence of only one equivalent of [bmim][Br] (entry 4). The *p*-toluenesulfonate ester leaving group, as in **1b**, was found to be as good as the methanesulfonate ester for the bromination reaction (entry 5).

Table 1 Bromination of 3-Phenylpropyl Sulfonate Esters **1** with [bmim][Br][a]

1a (R = Ms), **1b** (R = Ts)   **2**
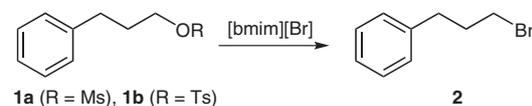
Entry	Sulfonate ester	[bmim][Br] (equiv)	Temp (°C)	Time (h)	Yield (%)[b]
1	**1a**	3.0	25	24	79
2	**1a**	3.0	25	72	100
3	**1a**	1.0	50	0.5	85
4	**1a**	1.0	50	1	100
5	**1b**	1.0	50	1	100

[a] Reaction was carried out on a 1.0 mmol scale.
[b] Yield determined by GC analysis.

Encouraged by these results, we attempted the bromination reaction of secondary alcohol sulfonate esters. As stated earlier, activated secondary alcohols are prone to give alkene by-products due to competing elimination reactions. We chose 1-phenylpropan-2-yl methane sulfonate (**3**) as a model substrate since the reaction with this substrate was expected to be particularly challenging because of its tendency to form the alkene by-product **5**, with the newly formed double bond conjugated to the phenyl group (Table 2). The bromination did not proceed completely at 50 °C even with 2.0 equivalent of [bmim][Br] for a prolonged reaction time (entry 2). However, the reaction went to completion upon increasing the reaction temperature and time (entries 3–6). It was observed that although a higher reaction temperature shortened the reaction time, more elimination product was formed (up to 34% at 90 °C). Gratifyingly, we identified reaction conditions that gave a fairly good selectivity of bromination over elimination (95:5), without significant loss of the benefits of the developed reaction protocols (entry 4).
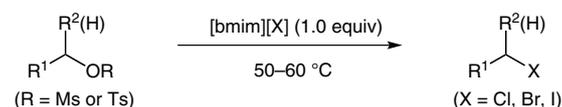
To assess the versatility of the halogenation methods, similar reaction conditions were applied to a range of primary and secondary sulfonate substrates by reaction with [bmim][Cl], [bmim][Br], and [bmim][I] (Table 3). The primary alcohol sulfonate esters were readily converted into the corresponding alkyl halides using 1.0 equivalent of IL at 50 °C (entries 1–7). It turned out that chlorination was as effective as bromination, but iodination required longer reaction time, presumably due to the weaker nucleophilicity and the better leaving-group ability nature of the iodide anion. For acyclic secondary alcohol sulfonate

Table 2 Bromination of 1-Phenylpropan-2-yl Sulfonate Ester (**3**) with [bmim][Br][a]

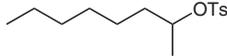| Entry	[bmim][Br] (equiv)	Temp (°C)	Time (h)	Conv. (%)[b]	Yield (%)[b] 4	5
1	1.0	50	1	25	24	1
2	2.0	50	24	90	86	4
3	1.0	60	1	40	38	2
4	1.0	60	8	>99	95	5
5	1.0	70	3	>99	90	10
6	1.0	90	1	>99	62	34

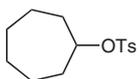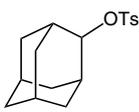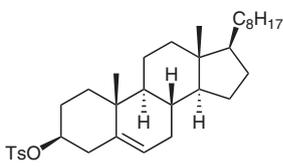[a] Reaction was carried out on a 1.0 mmol scale.
[b] Conversion and yields were determined by GC analysis.

Table 3 Halogenation of Sulfonate Esters with [bmim][X][a]

Entry	Substrate	Yield (reaction time)[b] X= Cl	Br	I
1		95% (1 h)	95% (1 h)	–[e]
2		99% (1 h)	95% (1 h)	94% (8 h)
3		98% (1 h)	97% (1 h)	92% (8 h)
4		92% (1 h)	95% (1 h)	–[e]
5		97% (3 h)	95% (3 h)	–[e]
6		98% (1 h)	99% (1 h)	–[e]
7		98% (2 h)	93% (5 h)	94% (8 h)
8		94% (8 h)	95% (8 h)	–[e]
9		93% (8 h)	92% (8 h)	88% (24 h)

esters, highly selective halogenations over eliminations were achieved; less than 5% of the by-products were observed under the optimized conditions (entries 8–11). Cyclic secondary substrates, the structural conformations of which are less favorable for elimination, also gave halides as predominant products (entries 12 and 13).[18] However, cholesteryl tosylate suffered lowered reaction yields, presumably because it can easily assume an antiperiplanar conformation between OTs and the α-protons, so that competitive elimination becomes more pronounced, and therefore alkene by-products were produced in considerable amounts (entry 14). Highly hydrophobic substrates with high melting points required larger amounts of ILs (up to 5.0 equiv) because they were not fully dissolved in 1.0 equivalent of IL at the reaction temperature (entries 13 and 14). Due to the clean conversion in the reaction and the solubility of the resulting salts such as [bmim][OTs] or [bmim][OMs] in water, in most cases, a typical aqueous work-up provided the desired halide products with high purity, which was confirmed by ^{1}H NMR analysis, and no further purification was necessary.[19]

Table 3 Halogenation of Sulfonate Esters with [bmim][X]^a (continued)

Entry	Substrate	Yield (reaction time)^b		
		X= Cl	Br	I
10		93% (8 h)	95% (8 h)	–^e
11		90% (8 h)	93% (8 h)	99% (24 h)
12		77% (8 h)	78% (8 h)	–^e
13^c		92% (24 h)	92% (24 h)	99% (24 h)
14^d		60% (24 h)	51% (24 h)	–^e
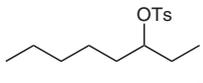
^a All reactions were carried out on a 1.0 mmol scale at 50 °C for substrates in entries 1–7 and at 60 °C for substrates in entries 8–12 and 14.
^b Isolated yield.
^c IL (5.0 equiv) was used at 90 °C.
^d IL (5.0 equiv) and MeCN (2.0 mL) were used.
^e The reaction was not tested.

With successful halogenation reactions developed, we turned our attention to other ILs composed of nucleophilic counter anions such as [bmim][OAc] and [bmim][SCN]. Under similar reaction conditions to those discussed above, these ILs were also effective in the nucleophilic substitution reactions of sulfonate esters (Table 4). Sulfonate esters derived from both primary and secondary alcohols reacted smoothly to give the desired products when the IL was the only reagent added (entries 1–6). Because the anions in [bmim][OAc] or [bmim][SCN] were found to be ineffective in cleaving alkyl aryl ethers in our previous study,[17] this result demonstrated the dependency of the S_N2 reactions on the nature of the leaving group. There seems to be some difference in the nucleophilicities of [bmim][SCN] and [bmim][OAc], because the substitution reactions with the former usually required a longer time to reach completion. Since sulfonate esters are comparable to halides as leaving groups, one could expect similar reactivity from the two substrates. Indeed, it was shown that an alkyl bromide was cleanly transformed into the corresponding alkyl acetate and thiocyanate upon treatment with ILs (entry 7). Similar to the previous halogenation reactions, the work-up process was very simple and products were obtained in more than 98% purity by simple extraction, avoiding further purification steps.

To gain information on the mode of the substitution reaction by ILs, the stereochemistry of the substitution prod-

uct was studied. When enantiomerically pure (*S*)-octan-2-yl 4-methylbenzenesulfonate (**6**) was treated with [bmim][OAc], only (*R*)-octan-2-yl acetate (**7**) was produced (Scheme 1). The stereochemistry was determined by chiral GC analysis, showing that the *S*-configuration of the sulfonate was fully inverted into the *R*-configuration of the acetate. No racemized product was formed during the reaction. This result strongly favors the conclusion that the nucleophilic substitution of ILs proceeds through an S_N2 mechanism.
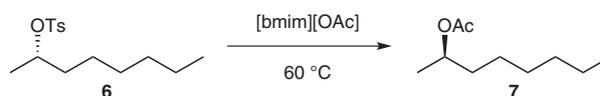
Scheme 1 Stereochemistry of the substitution reaction

Recycling is an important aspect in developing green strategies. As [bmim], the cation of the ionic liquid [bmim][X], remains intact upon completion of the reaction, the regeneration of [bmim][X] can be considered.[15b] As mentioned above, the clean conversion of the reaction and the high water-miscibility of the resulting [bmim][OTs] made it possible to separate the product RX and [bmim][OTs] simply by partitioning them between organic and water layers, respectively. Concentration of the aqueous layer produced the solid [bmim][OTs] with

Table 4 Nucleophilic Substitution of Sulfonate Esters with [bmim][OAc] and [bmim][SCN][a]

Entry	Substrate	Yield (temp, time)[b]	
		X = OAc	SCN
1		99% (50 °C, 1 h)	99% (50 °C, 5 h)
2		96% (50 °C, 1 h)	95% (50 °C, 5 h)
3		99% (50 °C, 1 h)	99% (50 °C, 5 h)
4		98% (60 °C, 8 h)	97% (60 °C, 24 h)
5		99% (60 °C, 8 h)	99% (60 °C, 24 h)
6[c]		98% (90 °C, 24 h)	99% (100 °C, 24 h)
7[d]		96% (80 °C, 12 h)	96% (80 °C, 24 h)

[a] All reactions were carried out on a 1.0 mmol scale.
[b] Isolated yield.
[c] IL (5.0 equiv) was used.
[d] IL (2.0 equiv) was used.

more than 99% purity (confirmed by ^{1}H NMR analysis) and it was further treated with 1.0 equivalent of metal halides or thiocyanate in acetonitrile to regenerate [bmim][X]. Because no side product was observed in the reactions, the regeneration yields were essentially the same as the extent of conversion into the desired [bmim][X]. Therefore, it was important to search for suitable halide salts that can drive the ion exchange reactions to the forward direction. Interestingly, we found that the reaction conversions were greatly affected by the metal cations (Li$^+$, Na$^+$, and K$^+$) of the metal halide salts under the specific reaction conditions.[20] Lithium halides were generally much more effective than sodium or potassium halides in the conversions (Table 5). Unlike halides or thiocyanate, in case of [bmim][OAc], only ca. 30% conversion was achieved from [bmim][OTs] and the recyclability was not tested. Regenerated [bmim][X] was employed for the substitution under the same reaction conditions and almost identical results were obtained. Furthermore, by three reiterations of regeneration followed by reuse of the [bmim][X] in the substitutions, we established a closed-loop process using [bmim][X], thereby providing a more effective route than conventional substitutions using metal halides or thiocyanate (Table 5). It should be noted that our newly developed protocol of-

fers remarkably improved reaction efficiency by employing ILs that may be considered as catalysts because of their recyclability. Furthermore, the organic solvents employed during the process are not mixed, so that, in principle, they can be readily recycled after simple distillation. Because our protocol involves later-stage regeneration of [bmim][X], and the reaction conditions are similar to those used for direct nucleophilic substitutions of sulfonate esters, we tested the direct halogenation of 2-octanyl tosylate (**8**) in a conventional manner. The same reaction conditions [NaBr (1.0 equiv), MeCN, 80 °C, 8 h] that were used to regenerate [bmim][X], were applied to **8**. Only incomplete conversion (ca. 65%) and poor yield (<40%) of the desired product along with side products were observed (determined by GC analysis). This result clearly demonstrates the better utility of our protocol over the conventional approach.

In conclusion, we have developed a very efficient, atom-economic, green reaction protocol for nucleophilic substitution using ILs [bmim][X]. We demonstrated that the counter anions (X$^-$) can be readily applied for nucleophilic substitution reactions. The nucleophiles from ILs in this work are halides, acetates, and thiocyanides. Sulfonate esters are smoothly transformed into the corresponding sub-

Table 5 Recyclability of [bmim][X]

Entry	X	Regeneration of [bmim][X][a]		Recycling use of [bmim][X][c] and yield (%)			
		MX	Conv. (%)[b]	Cycle 1	Cycle 2	Cycle 3	Cycle 4
1	Cl	NaCl/LiCl	0/88	90	92	91	91
2	Br	KBr/NaBr/LiBr	33/90/99	93	92	92	91
3	I	NaI	99	99	95	94	95
4	SCN	NaSCN	99	97	96	95	95

[a] Reaction conditions: [bmim][OTs] (1.0 mmol), MX (1.0 equiv), MeCN (1.0 mL), 80 °C, overnight.
[b] The conversions were determined by ^{1}H NMR spectroscopic analysis.
[c] All reactions were carried out on a 1.0 mmol scale and isolated yields are given.

stitution products by the ILs in excellent yields. In most cases, the reactions do not require co-solvent systems, additional reagents, sophisticated equipment, or special precautions. The effectiveness of the reactions can be explained by the two distinctive characteristics of the ILs: the intrinsic, pronounced nucleophilicity of the anions (X⁻), and their polar aprotic nature as the reaction media. These favorable aspects allow very small amounts of the IL to be used (1.0 equiv of the reactant) and relatively mild reaction conditions to be applied, providing much greener reaction protocols than those in reported corresponding work. Furthermore, under the developed reaction conditions, we found that sulfonate esters derived from secondary alcohols also undergo the substitution smoothly, without much loss of reaction yield or selectivity over the elimination reactions. The reaction protocols usually resulted in very clean conversions and therefore simple work-up procedures involving phase separation and concentration of the organic layers afforded the desired products with high purity, avoiding expensive and time-consuming purification steps. We also demonstrated that the ILs could be regenerated and reused several times without loss of reactivity, therefore, the ILs can be considered as catalysts. These aspects of minimum use of reagent, simple work-up procedures, and recyclability of the reagent render the developed protocol a green chemical process.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(18) Since no elimination by-product was detected, the low yield of entry 12 was attributed to substrate instability.

(19) The products in Table 3, except those in entry 14, did not need further purification. The products from entry 14 were purified by column chromatography (see the Supporting Information).

(20) Sodium halides were previously reported for a similar reaction, but details on the reaction conversions or yields were not provided. See ref. 15b.