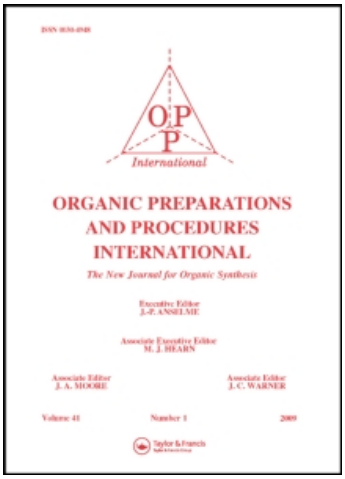

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N-ALKYLATION OF *N*-MONOSUBSTITUTED SULFONAMIDES IN IONIC LIQUIDS†

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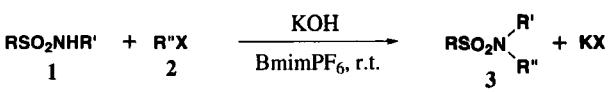
The *N*-alkylation of *N*-monosubstituted sulfonamides is a key step in the Gabriel-type synthesis of secondary amines by subsequent cleavage of the sulfonamides *via* known reduction procedures of the S-N bond.[1] In addition, sulfonamides themselves constitute a class of pharmaceutically important compounds.[2] However, available routes for this transformation are somewhat limited. This reaction usually requires strong bases such as Na,[3] $NaNH_2$,[4] NaOR,[5] KOH[6] etc. and the use of organic solvents such as methanol,[5a] ethanol,[3] *N*,*N*-dimethylformamide,[2,7,9c] and xylene.[4] This method involves harsh reaction conditions, long reaction times and low yields in organic solvents. This reaction also can be accomplished *via* phase-transfer catalysts process,[8] but involves the use of organic solvents. Recently, the *N*-alkylation of *N*-monosubstituted sulfonamides *via* the Mitsunobu reaction has been reported.[9] However, these conditions require the use of expensive reagents, inert gas, organic solvents, long reaction times and sometimes give low yields. Therefore, the *N*-alkylation of *N*-monosubstituted sulfonamides using facile and efficient methods is still a challenge in organic synthesis.



In recent years, room temperature ionic liquids (**RTILs**) have attracted increasing interest as green and reusable reaction media.[10] The many reports of great improvements in the yields and rates[11] prompted us to investigate the *N*-alkylation of *N*-monosubstituted sulfonamides in ionic liquids. For this study, 1-*n*-butyl-3-methylimidazolium hexafluorophosphorate (**BmimPF$_6$**), 1-*n*-butyl-3-methylimidazoliumtetrafluoroborate (**BmimBF$_4$**), and *n*-butylpyri-

dinium tetrafluoroborate (**$BpyBF_4$**) were synthesized according to the procedures reported in the literature.[12] We examined the efficacy of different ionic liquids in the *N*-benzylation of *N*-phenyl *p*-toluenesulfonamide with benzyl chloride. **$BpyBF_4$** and **$BmimPF_6$** are comparable with classical solvents such as DMF (*Table 1*), with the advantage of rate acceleration and increase of yield. **$BmimPF_6$** gave the best results in terms of yield and reaction times, while **$BmimBF_4$** was no more effective than DMF for this reaction, which suggests both the cations and the anions of ionic liquids play an important role in this reaction.

Table 1. *N*-Benzylation of *N*-Phenyl *p*-toluenesulfonamide with $PhCH_2Cl$ in Different Solvents[a]

Solvent	DMF	$BpyBF_4$	$BmimPF_6$	$BmimBF_4$
Time (hrs)	8	2	1	8
Yield[b] (%)	83	92	97	85

a) All reactions were run with benzyl chloride (2mmol), *N*-phenyl *p*-toluenesulfonamide (1mmol) and KOH (2mmol) in 2ml solvent at room temperature. b) Yields based on *N*-phenyl *p*-toluenesulfonamide

Subsequently, the scope of the *N*-alkylation of various *N*-monosubstituted sulfonamides with various alkyl halides in **$BmimPF_6$** was investigated. In fact, simple stirring of a mixture of *N*-monosubstituted sulfonamide **1**, alkyl halide **2** and KOH in **$BmimPF_6$** at room temperature for about 1-5 hrs gave, after extraction with diethyl ether, the desired *N,N*-disubstituted sulfonamide **3** in high yields. The results are summarized in *Table 2*. The products were characterized by IR, ^1H NMR, and melting points which were consistent with the literature data. As can be seen from *Table 2*, the reaction is general and applicable to primary alkyl chloride, bromide, iodide, activated chloride and even to secondary alkyl halide (*Entry 7*). Our method exhibits pronounced rate accelerations and gave high yields. For example, the literature[5b] reported that **3b** was obtained in 51% yield after 9-10 hrs using NaOEt as the base in refluxing ethanol while, in our experiment, **3b** was produced in 95% yield using KOH as the base after 1.5 hrs at room temperature. We attempted to removal of the sulfonyl group to release the secondary amines in the ionic liquid system; unfortunately, the results were not comparable to the conventional methods carried out in organic solvents.[1]

The recyclability of ionic liquids as solvents was investigated. Upon completion of the reaction, the product was extracted with diethyl ether first and the ionic liquid was dried for 1 hr at room temperature under vacuum followed by filtration of the suspension by suction to remove residual potassium hydroxide and potassium halide. The recovered ionic liquid could be reused for three additional cycles with no appreciable decrease in yields and in reaction rates in the benzylation of *N*-phenyl *p*-toluenesulfonamide with benzyl chloride.

Table 2. *N*-Alkylation of *N*-Monosubstituted Sulfonamides with Alkyl Halides in $BmimPF_6$[a]

Entry	Cmpd	R	R'	R"X	Time (hrs)	Yield[b] (%)	mp[c] (°C)	*lit.* mp
1	**3a**	*p*-MeC_6H_4	C_6H_5	MeI	1	94	90-91	90-92[13]
2	**3b**	*p*-MeC_6H_4	C_6H_5	EtO_2CCH_2Cl	1.5	95	108-109	107-108[5b]
3	**3c**	*p*-MeC_6H_4	C_6H_5	$PhCH_2Cl$	1	97	140-141	139.5-140[9b]
4	**3d**	*p*-MeC_6H_4	C_6H_5	*n*-BuCl	5	92	53-54	53-54[14]
5	**3d**	*p*-MeC_6H_4	C_6H_5	*n*-BuBr	3	94	53-54	53-54[14]
6	**3e**	*p*-MeC_6H_4	C_6H_5	*n*-PrBr	3	93	55-56	56[6a]
7	**3f**	*p*-MeC_6H_4	C_6H_5	*i*-PrBr	5	85	98-99	99.5-100[6a]
8	**3g**	*p*-MeC_6H_4	C_6H_5	*i*-BuBr	4	87	124-125	124-126[15]
9	**3h**	*p*-MeC_6H_4	*p*-MeC_6H_4	MeI	2	93	59-60	65-67[16]
10	**3i**	*p*-MeC_6H_4	*p*-MeC_6H_4	$PhCH_2Cl$	2	95	121-122	$(C_{21}H_{21}NO_2S)$[d]
11	**3j**	*p*-MeC_6H_4	*p*-MeC_6H_4	EtO_2CCH_2Cl	3	94	74-75	$(C_{18}H_{21}NO_4S)$[d]
12	**3k**	*p*-MeC_6H_4	*p*-MeC_6H_4	*n*-BuBr	4.5	92	53-55	15.5[17]
13	**3l**	*p*-MeC_6H_4	*p*-$NO_2C_6H_4$	MeI	1	91	178-179	182[18]
14	**3m**	*p*-MeC_6H_4	*p*-$NO_2C_6H_4$	$PhCH_2Cl$	1	94	121-122	128[6b]
15	**3n**	*p*-MeC_6H_4	CH_3CH_2	MeI	3	92	27-28	28[14]
16	**3o**	*p*-MeC_6H_4	CH_3CH_2	$PhCH_2Cl$	3	95	47-48	48-49[19]
17	**3p**	*o*-MeC_6H_4	C_6H_5	MeI	3	91	Oil	Oil[20]
18	**3q**	*o*-MeC_6H_4	C_6H_5	$PhCH_2Cl$	3	93	88-89	$(C_{20}H_{19}NO_2S)$[d]
19	**3r**	CH_3	C_6H_5	MeI	2	89	76-77	76.5[21]
20	**3s**	CH_3	C_6H_5	$PhCH_2Cl$	2	93	122-123	122[21]

a) All reactions were performed with *N*-monosubstituted sulfonamide (1 mmol), alkyl halides (2 mmol) and KOH (2 mmol) in 2 mL $BmimPF_6$ at r.t. b) Yields based on *N*-monosubstituted sulfonamide. c) Melting points are uncorrected. d) Satisfactory elemental analysis are reported in the Experimental Section.

In conclusion, we have shown that the alkylation of *N*-monosubstituted sulfonamides could be efficiently performed with alkyl halides at room temperature in **$BmimPF_6$**. Aside from being environmentally benign, the present methodology has many advantages such as generality and simplicity, ease of product isolation, higher yields, shorter reaction times and the potential for recycling of ionic liquids.

EXPERIMENTAL SECTION

Melting points were determined on digital melting point apparatus and are not corrected. Infrared spectra were obtained as KBr pellets on a VECTOR-22 Infrared Spectrophotometer. ^1H NMR spectra were recorded on a BRUKER-400MHz spectrometer using $CDCl_3$ as the solvent with TMS as an internal standard. Elemental analyses were performed on a Carlo Erba EA 1106 instrutment. All materials are commercially available and were used without further purification.

General Procedure for the N-Alkylation of N-Monosubstitut Sulfonamides with Alkyl Halides.- *N*-Monosubstituted sulfonamide **1** (1 mmol), alkyl halide **2** (2 mmol) and KOH (2 mmol) were added in ionic liquid $BmimPF_6$ (2 mL). The reaction mixture was stirred for 1.0-5.0 hrs at room temperature. After TLC indicated that the starting material of sulfonamide had disappeared, the resulting mixture was extracted with Et_2O (3 x 10 mL). The combined ethereal extract was evaporated under reduced pressure to give the crude product **3** which was purified by recrystallization or preparative thin-layer chromatography (silica gel). After isolation of the product, the remainder of the ionic liquids can be typically recovered by drying at vacuum first and filtering the suspension by suction to remove the residual potassium hydroxide and potassium halide.

Table 3. Spectroscopic Data and Elemental Analysis of Compounds **3i**, **3j** and **3q**

Cmpd	IR (cm^{-1})	^1H NMR (δ)	EA (%)
3i	3029, 2951, 1599, 1509, 1455, 1370, 1345, 1159, 1088, 859, 681	7.57 (dd, 2H, J = 8.4, 1.6 Hz), 7.31-7.22 (m, 7H), 7.01 (d, 2H, J = 6.8 Hz), 6.87 (dd, 2H, J = 8.4, 1.6 Hz), 4.71 (s, 2H), 2.47 (s, 3H), 2.28 (s, 3H)	*Anal.* Calcd For $C_{21}H_{21}NO_2S$: C, 71.76; H, 6.02; N, 3.99; S, 9.12. Found: C, 71.62; H, 6.08; N, 3.89; S, 9.18
3j	3029, 2977, 2927, 1750, 1600, 1509, 1458, 1379, 1340, 1206, 1165, 1091, 860, 694	7.57 (dd, 2H, J = 8.4, 1.6 Hz), 7.27 (d, 2H, J = 8.0 Hz), 7.14-7.04 (m, 4H), 4.38 (s, 2H), 4.15 (q, 2H, J = 7.2 Hz), 2.43 (s, 3H), 2.33 (s, 3H), 1.23 (t, 3H, J = 7.2 Hz)	*Anal.* Calcd. For $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N ,4.03; S, 9.23. Found: C, 62.42; H, 6.12; N, 3.99; S, 9.18
3q	3027, 2972, 2922, 1598, 1506, 1454, 1342, 1161, 1132, 1094, 869, 695	7.44 (t, 1H, J = 8.0 Hz), 7.29-7.02 (m, 13 H), 4.80 (s, 2H), 2.39 (s, 3H)	*Anal.* Calcd. For $C_{20}H_{19}NO_2S$: C, 71.19; H, 5.68; N, 4.03; S, 9.50. Found: C, 71.32; H, 5.75; N, 3.98; S, 9.38

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