Organic reactions in ionic liquids: *N*-alkylation of cyclic imides with alkyl halides promoted by potassium fluoride

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An ionic liquid based on 1-butyl-3-methylimidazolium hexafluorophosphate is used as an efficient reusable reaction medium in the *N*-alkylation of cyclic imides with alkyl halides promoted by fluoride ion.

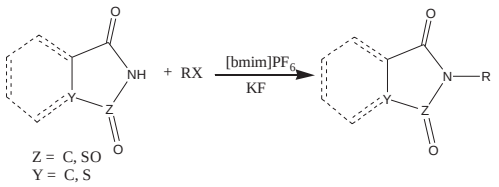
Keyword: ionic liquids, cyclic imides, *N*-alkylation, phthalimide, potassium fluoride

Cyclic imide derivatives constitute an important class of chemically, biologically and pharmaceutically significant compounds.[1] Despite their wide applicability, available routes for their synthesis are somewhat limited. Generally, most methods involve Lewis acid mediated condensation of an amine with the appropriate cyclic acid anhydrides,[1c,2a,2c] and cyclisation of the *N*-substituted amic acid in the presence of acidic reagents.[2b] Direct *N*-alkylation under Mitsunobu conditions is also a method for the synthesis of imide derivatives.[1c,2a] However, most of these routes have their own synthetic problems when applied to a range of derivatives, such as low yield, by-product formation, expensive reagents and harsh reaction conditions.[3]

As for the readily available imides such as phthalimide, saccharin, succinimide and 2,4-thiazolidinedione, direct *N*-alkylation with alkyl halides is also one of the most important methods to prepare imide derivatives. Usually, these reactions require a long reaction time, high temperature, strong base, tedious work-up and result sometimes in poor yields.[4] Recently, phase transfer catalysts (PTCs),[5] MW irradiation,[5b,6] ultrasound[7] and a supported solid catalyst[8] have been applied to facilitate *N*-alkylation reactions. Commonly, there are some apparent drawbacks: polar aprotic solvents such as DMF, HMPA, DMSO, acetonitrile, *etc*. are often used which are toxic, odorous, expensive, volatile, thermal instable and also difficult to remove during isolation of the product. Moreover, the imides are required to be transformed to the corresponding imide salts beforehand or generated in situ using a strong base such as Na, NaH, *t*-BuOK and KOH. Therefore, preparation of imide derivatives using facile and efficient methods with an environmentally benign technology is still a major challenge in organic synthesis.

The importance of the fluoride anion as a catalyst for the promotion of various types of base-catalysed reactions in organic synthesis has been previously recognised. The work of Clark and Miller,[9] in particular, revealed that the fluoride ion has an effect on condensation reactions because of its high capability for hydrogen bond formation. On the other hand, room temperature ionic liquids have recently gained recognition as possible environmental friendly alternative chemical process solvents.[10] Additionally, because ionic liquids are comprised of bulky organic cations, they seem well suited for the type of reactions for which PTC is effective. So we tried to examine the *N*-alkylation of cyclic imides in ionic liquids in the presence of potassium fluoride to develop a facile and efficient method for the synthesis of cyclic imide derivatives.

First, we examined the efficacy of different ionic liquids in the *N*-benzylation of phthalimide with benzyl chloride (Scheme1). We found that the tested ionic liquids, [bmim]BF_4, [bmim]PF_6, [bmim]Cl, [bpy]PF_6 and [bpy]BF_4, ([bmim]$^+$=1-butyl-3-methylimidazolium, [bpy]$^+$=butyl pyridinium) were all efficient for *N*-benzylation of phthalimide and that [bmim]PF_6 gave the best results in terms of yield and reaction time. The results are summarised in Table 1. So we selected the [bmim]PF_6 as reaction medium in the subsequent reactions.



Scheme 1

Table 1 *N*-benzylation of phthalimide with benzyl chloride in different ionic liquids[a]

Entry	Ionic liquids	Time/h	Yield[b]/%
1	[bmim]BF_4	3.0	95
2	[bmim]PF_6	1.5	97
3	[bmim]Cl	6.0	91
4	[bpy]BF_4	5.0	96
5	[bpy]PF_6	2.5	95

[a]Reactions were run with phthalimide 2mmol, benzyl chloride 2.2mmol, KF 4.4mmol in 2ml ionic liquids at 85°C. [b]Isolated yield based on phthalimide.

Subsequently, the scope of the reaction of various alkyl halides with phthalimide catalysed by KF in [bmim]PF_6 was investigated. The reaction was found to be general and applicable to primary alkyl iodides, bromides, chlorides and even to secondary bromides. On the basis of these results, we extended our method to saccharin, 2,4-thiazolidinedion and succinimide (Scheme 1), the results are listed in Table 2. The products were characterised by ^{1}H NMR, IR and m.p. which were consistent with the literature data.

The results presented in Table 2 suggest that a variety of cyclic imides can be efficiently *N*-alkylated using this procedure. The preparation of *N*-alkylphthalimides is of special significance because these compounds are intermediates in the Gabriel synthesis of pure primary amines.[4b] Significantly, the *N*-alkylation of 2,4-thiazolidinedione exhibited high selectivity considering the different nucleophilic substituent centres of N, O, S in the same molecule.[4c,4d] In all cases, the halogen exchange reaction (Cl–F) was limited to <1.5%, as was shown by results from GC analysis, although Song and coworkers reported that the nucleophilicity of KF was enhanced greatly in ionic liquids.[11] In order to test the effect of moisture on the reaction we conducted the *N*-alkylation of phthalimide with benzyl chloride in the presence of 2.0 equivalent molar water (0.072g, 4mmol, Entry 10). TLC analysis showed no detectable amounts of alcohol in the reaction mixture and the product was also obtained in excellent yield (96%). As we expect, in the absence of KF reactions did not proceed. We also tried the

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Table 2 *N*-alkylation of cyclic imides with alkyl halides catalysed by KF in [bmim]PF_6[a]

Entry	Substrate	Alkyl halides	Temp/°C	Time/h	product	Yield[b]/%	M.p[c]./°C	Lit.m.p./°C
1	Phthalimide	MeI	25°C	5	1a	88	132–133	133–134[15]
2		*n*-PrBr	85°C	4	1b	92	63–64	64[13]
3		*i*-PrBr	85°C	8	1c	73	84–85	84–86[13]
4		*n*-BuBr	85°C	5	1d	94	31–32	31–32[5a]
5		*n*-BuCl	85°C	8	1d	88	31–32	
6		Ethyl chloroacetate	85°C	1.5	1e	91	110–111	111–112[5a]
7		Epichlorohydrin	85°C	6	1f	87	95–96	96–98[4b]
8		BzBr	85°C	1	1g	96	114–115	113–114[13]
9		BzCl	85°C	1.5	1g	97	114–115	
10		BzCl[d]	85°C	1.5	1g	96	114–115	
11	Saccharin	MeI	25°C	5	2a	89	130–131	131–132[4a]
12		Ethyl chloroacetate	85°C	1.5	2b	90	106–107	106–108[7]
13		BzBr	85°C	1	2c	97	110–111	109–110[5c]
14		BzCl	85°C	1.5	2c	96	110–111	
15	2,4-Thiazo-lidinedione	*n*-BuBr	85°C	5	3a	92	Oil	Oil[17]
16		Ethyl chloroaectate	85°C	2	3b	90	Oil	Oil[4e]
17		BzBr	85°C	1.5	3c	96	61–62	62-63[4c]
18		BzCl	85°C	1.5	3c	95	61–62	
19	Succinimide	*n*-BuBr	85°C	6	4a	90	Oil	Oil[16]
20		BzBr	85°C	2.5	4b	92	100–101	97–99[14]
21		BzCl	85°C	3.5	4b	93	100–101	

[a]Reaction conditions: cyclic imide 2 mmol, KF4.4 mmol, [bmim]$PF_6$2ml, BzCl and BzBr 2.2 mmol, the other alkyl halide 4 mmol (2.0 eq). [b]Isolated yield based on cyclic imide. [c]Melting points were uncorrected. [d]4 mmol H_2O was added to the reaction mixture.

reactions without the ionic liquids as the reaction medium when the reactions also did not proceed.

Further investigation was into the recyclability of ionic liquids as solvents. Upon completion of the reaction the solid was filtered from the mixture, the product was extracted with diethyl ether and fresh materials were added following prior drying of the ionic liquids for half an hour at room temperature under vacuum. As a result the reused ionic liquids gave similar yield and reaction rate as is shown in Table 3.

In order to compare with the reported methods, some representative literature data are summarised in Table 4. Obviously, our method exhibits pronounced rate accelerations and higher yields are obtained.

In conclusion, this paper describes a convenient and efficient method for the *N*-alkylation of cyclic imides with alkyl halides promoted by KF in [bmim]PF_6. Our method offers many obvious advantages over classical procedures, including simplicity of the methodology, the easy of product isolation, high yields, the potential of recycling ionic liquids, without using PTCs, polar aprotic solvents and strong base at any stage of the reaction. We believe this is a useful means for the alkylation of imides containing alkali-liable groups as KF is a mild base.

Experimental

Melting points were determined on digital melting point apparatus and were uncorrected. Infrared spectra were recorded on a VECTOR22 (Brucker). ^{1}H NMR spectra were recorded on a BRUKER-400MHz spectrometer using $CDCl_3$ as the solvent with TMS as an internal standard. Gas chromatographic analyses were performed on a SHIMADZU GC-14A gas chromatograph. The ionic liquids [bmim]PF_6, [bmim]BF_4, [bmim]Cl, [bpy]PF_6 and [bpy]BF_4 were synthesised according to literature procedures.[12] The other materials are commercially available and were used without further purification.

General procedure for the N-alkylation of cyclic imides

Cyclic imide (2mmol), alkyl halide (2.2 or 4mmol) and potassium fluoride (4.4mmol) were added to [bmim]PF_6 (2ml). The mixture was stirred magnetically at room temperature for 5 min and then the flask was placed in an oil bath which was preheated up to 85°C, Stirring was continued for 1.0–8.0h at which time TLC analysis indicated completion of the reaction and that the *N*-substituted imide was the single product. The product was extracted with diethyl ether (3 × 10ml), the solvent was removed by evaporation and the residue was purified by preparative thin-layer chromatography (silica gel).

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Table 3 Recycling of [bmim]PF_6 in the benzylation of phthalimide and succinimide with BzCl

Cyclic	Time/h	Product	Yield/%[a]	Cyclic	Time/h	Product	Yield/%[b]
1	1.5	**1g**	97	1	1.5	**4b**	93
2	1.5	**1g**	95	2	1.5	**4b**	92
3	1.5	**1g**	96	3	1.5	**4b**	94

[a]Isolated yield based on phthalimide. [b]Isolated yield based on succinimide.

Table 4 Alkylation of cyclic imides under different conditions

Product	Yield /% This work	Yield /% Literature work	
1d	94	66.7[5a]	Butyl bromide, PEG-400 as PTC, K_2CO_3, 70–80°C,12h
1g	96/97	86[8b]	Benzyl bromide, CsF-Celite, acetonitrile, reflux, 48h
		94[5a]	Benzyl chloride, PEG-400 as PTC, K_2CO_3, 80–90°C,4h
2c	97/96	72[6b]	Benzyl chloride, Silicagel GF254, microwave irradition, TEBA as PTC
		10[5c]	Benzyl chloride, TBAB as PTC, toluene, 80°C,6h
		89[7]	Benzyl bromide, KF-Al_2O_3, toluene, 85°C,8h

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