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Ionic liquids as reaction media for esterification of carboxylate sodium salts with alkyl halides

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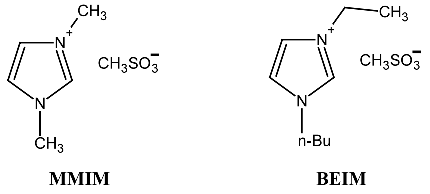
Abstract—Ionic liquids based on 1,3-dialkylimidazolinium methanesulfonate have been used as effective reusable reaction media in the esterification of several carboxylate sodium salts with different alkyl halides. Products are easily isolated by extraction with ether, and the protocol is mild and green, compared to the existing methods based on toxic solvents. Proper 'design' of the ionic liquid allows us to obtain esters always in quantitative yields. © 2003 Elsevier Science Ltd. All rights reserved.

Ionic liquids (ILs) are low melting point (<100°C) salts which represent a new class of non-molecular, ionic solvents. Interesting features of these liquids are their ability to solvate a broad spectrum of both organic and inorganic compounds, low vapour pressure, recyclability, high thermal stability and ease of handling.[1] But, their intriguing aspect is the possibility to alter their physical and chemical properties by varying their structure, with respect to the choice of organic cations and anions, and side-chain attached to the organic cation: thus, IL have been described as 'designer solvents'.[1a] All these properties make these systems very good candidates for application in developing environmentally benign chemical processes, and, actually, nowadays, ILs are widely diffused as greener alternatives to classical volatile organic solvents in chemical transformation[1].

Particularly ILs based on 1,3-dialkylimidazolinium cations such as 1-*n*-butyl-3-methylimidazolinium tetrafluoroborate and 1-*n*-butyl-3-methylimidazolinium haxafluorophosphate have been widely used for organic synthesis.[1b]

Within a wide research program aimed to investigate structure-properties relationship for novel IL, here we set up a simple, speed, one-pot and quantitative synthesis to prepare new systems, with modifications in the side-chain of the organic cation, and with an unusual, inert counterion: 1,3-dimethylimidazolinium (MMIMs) and 1-butyl-3-ethylimidazolinium (BEIMs) methanesulfonates (Scheme 1).[†] We are showing that these new ionic liquids can be used as an efficient and clean technology for the esterifications of carboxylates with alkyl halides, in mild conditions, with facile isolation of products and reuse of the reaction media (Scheme 2).



Scheme 1. 1,3-Dimethylimidazolinium methanesulfonate (MMIM) and 1-butyl-3-ethylimidazolinium methanesulfonate (BEIM).

Keywords: ionic liquids; esterification; carboxylate; alkyl halides.

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[†] MIMM (m.p. 82–83°C) was prepared from methyl methanesulfonate and 1-methylimidazole, with 1,1,1-trichloroethane as solvent. The mixture is exothermic and reaches reflux: it was allowed to stay for 2 hours, and a white solid formed, that was washed twice with 1,1,1-trichloroethane and dried under vacuum. Yield: 97%. ^{1}H NMR (200 MHz, CD_3OD) δ 2.64 (s, 3 H), 3.86 (s, 6 H), 7.50 (s, 2 H), 8.78 (s, 1 H). BEIM (m.p. below room temperature) was prepared from ethyl methanesulfonate and 1-butylimidazole in 1,1,1-trichloroethane, refluxing for 6 hours. The liquid IL layer was separated by the solvent in a separatory funnel, washed with fresh solvent and dried under vacuum (50 mtorr) at 70°C. Yield: 95%. ^{1}H NMR (200 MHz, CD_3OD) δ 0.93 (m, 3 H), 1.47 (m, 3 H), 1.20–1.40 (m, 2 H), 1.73–1.90 (m, 2 H), 2.64 (s, 3 H), 4.11–4.28 (m, 4 H), 7.51 (m, 1 H), 7.58 (m, 1 H), 8.89 (s, 1 H).

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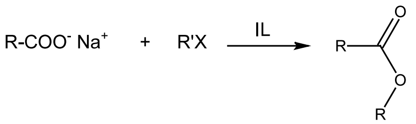
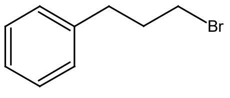
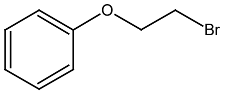
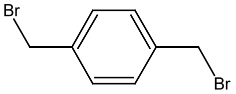
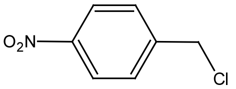
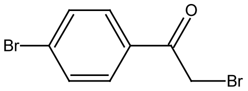
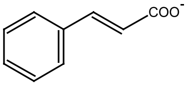
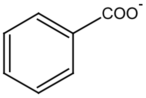


Scheme 2. Esterification.

Organic esters are valuable intermediates in chemical and pharmaceutical industry. Recently, efforts have been made to replace the traditional synthesis of esters by Fischer method catalyzed by a concentrated inorganic acid, and to develop clean catalytic methods such as supported sulfuric acid or a solid superacid[2] and by carrying out the reaction in ionic liquids[3,4]. Another frequent preparation of esters is based on the alkylation of carboxylate salts, and the development of procedures alternative to polar aprotic solvents such as DMF, HMPA, DMSO or to the PTC is of key importance. These media are usually used because they accelerate the reaction,[5,6] although they have several drawbacks: polar aprotic solvents are toxic, noxious, expensive, and also difficult to remove during isolation of the carboxylate ester[7], whereas PTC generally makes use of toxic halogenated or aromatic solvents. Moreover in both cases elimination can become a serious side-reaction with secondary and tertiary alkylating agents[7].

Table 1. Esterifications of carboxylates in ionic liquid[a]

Entry	Carboxylate	RX	IL	Time, h	Carboxylate/ substrate	Yield %
1	CH_3COO^-	$CH_3(CH_2)_7Br$	MMIM	2	5	>95
2	"	$CH_3(CH_2)_{11}Br$	"	24	10	>95
3	"	$CH_3CH_2CH(Br)CH_2CH_3$	"	2	5	92
4	"	$BrCH_2CH_2CH_2Br$	"	"	"	94
5	"	$BrCH_2CH_2\ CH_2CH_2CH_2Br$	"	"	"	93
6	"	$CH_3(CH_2)_2O(CH_2)_2Br$	"	4	"	90
7	"		"	1	1.2	>95
8	"		"	0.5	"	>95
9	"		"	"	2.2	>95
10	"	$PhCH_2Cl$	"	"	1.2	>95
11	"		"	"	"	>95
12	"		"	1	"	>95
13	$CH_3(CH_2)_2COO^-$	$PhCH_2Cl$	"	0.5	"	>95
14		"	"[b]	"	"	>95
15	"	"	"	"	"	>95[c]
16		"	"[b]	"	"	>95
17	"	"	"	"	"	>95[d]
18	$CH_3(CH_2)_{10}COO^-$	"	"[b]	"	"	60
19	"	"	BEIM[b]	"	"	93
20	"	"	"	"	"	>95[e]

[a] at 90°C, $IL/RCOO^-=1.5$; [b] ratio $IL/RCOO^- = 3$; [c] yield by weight is 89%; [d] yield by weight is 95%; [e] yield by weigth is 95%.

The esterification we carried out in a new ionic liquid is operationally simple and safe, fast, and allows reuse of the reaction media (Scheme 2).[‡] Table 1 summarizes optimized conditions with a variety of alkyl halides and carboxylate sodium salts, and shows that the desired esters were generally obtained in excellent yields, generally better than 95%. These results are comparable, and sometimes even better, than those for similar reactions carried out in solvents such as DMF, HMPA and DMSO[7] with the main difference that the Ionic liquids are not toxic. In the absence of the ionic liquid as reaction media, reactions do not proceed: we tried the reaction of acetate and liquid benzyl chloride, and also the reaction of benzoate with benzyl chloride, but no reaction occurs in the experimental conditions that give quantitative yields in the presence of the ionic liquid. When the esters produced were not volatile, yields by weight were evaluated, and they were comparable to yields determined by g.c. with the internal standard (entries 15, 17, 20). The amount of ionic liquid used as reaction media was generally small, the ratio of IL/carboxylate being 1.5. Furthermore after reaction, it was possible to reuse the IL in a further run: after extraction with diethyl ether, the ionic liquid is dried under vacuum to eliminate traces of the solvent and simply reused.

The time and the ratio carboxylate/alkyl halide required for complete esterification varied depending on the carboxylate and alkyl halide used. Not only primary alkyl halide (entry 1) react fast with acetate, but also secondary halides (entry 3) and dibromides (entries 4, 5). Both liquid and solid halides (entries 9, 11, 12) do react similarly. The more hydrophobic lauryl bromide (entry 2) requires a longer time, and a higher excess of carboxylate (entry 2), When an aromatic moiety is present in the alkyl halides (entries 7, 8) the reactions proceed easier, as is the case for benzyl and phenacyl halides (entries 9, 10, 11, 12, 13).

The procedure has proven to have validity also with several carboxylates, including butyrate (entry 13), cinnamate (entries 14, 15) and benzoate (entries 16, 17). As we have already pointed out, the ratio of IL/carboxylate was generally 1.5, but with benzoate and cinnamate this low ratio gives rise to very heterogeneous and quite viscous systems. Therefore, we initially used a higher ratio, up to 3, thinking that it was necessary to work with more fluid systems (entries 14, 16). Nevertheless, both quite heterogeneous, viscous and fluid systems give the same excellent results.

For the more hydrophobic laurate the ionic liquid MMIM, also used at the ratio IL/carboxylate of 3, gives poor results (entry 18). In this case only a modification in the structure of the ionic liquid, and the use of the more hydrophobic BEIM (entry 19) really leads to a quantitative yield. Also in this case the system is fluid with a ratio of BEIM/laurate of 3, and is very heterogenous and viscous with a ratio of 1.5, but results are excellent in both cases (entries 19 and 20). This change in the ionic liquid structure, with a small increase in the hydrophobicity, allows the reaction of laurate with benzyl chloride to proceed quantitatively: in this case, therefore, the concept of 'designer solvent' is at work. We are currently proceeding more deeply to search for possible structure-function relationships, in order to finally be able to predict and modulate the properties of the solvent.

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[‡] General procedure for esterification in ionic liquid. In a 4-ml vial a mixture of ionic liquid and the sodium carboxylate was heated to 90°C with stirring for ca. 15 minutes. The alkyl halide was then added, under nitrogen, and the mixture was stirred for the necessary time. At the end of reaction, after cooling to room temperature, ^{t}Bu-benzene was added, as internal standard; water was added, and the mixture was extracted with diethyl ether (3×10 ml); the combined organic extracts were washed with sodium bicarbonate, dried over Na_2SO_4, and analyzed by GC. When yields by weight were determined, no internal standard was added at the end of reaction, and the organic solvent was eliminated from the combined extracts by rotatory evaporation.