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A mild esterification process in phosphonium salt ionic liquid

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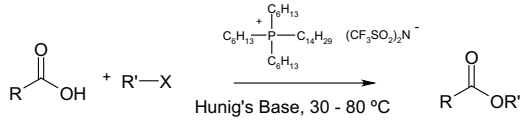
Abstract—A general, high yielding procedure is described for the esterification of carboxylic acids through carboxylate alkylation in phosphonium salt ionic liquid.

Esterification[1] is one of the most fundamental reactions in synthetic chemistry extensively employed for the protection and further manipulation of the carboxylic acid functional group. Esterification processes are widespread in the industrial synthesis of a variety of end-products such as fragrances, monomers, plasticizers etc., many of which are classed as high production volume (HPV) chemicals. In addition, applications to lower volume, high-value pharmaceutical and fine chemicals targets are prominent, and often require more stringent coupling protocols to achieve the desired chemo- and stereoselectivity. In the latter case, situations that proceed with a high degree of inversion of configuration such as in the Mitsunobu reaction are especially sought. In view of their importance, esterification protocols should occupy a prominent place in the desire to advance benign and sustainable chemical technologies into industrial process development.[2] The use of room temperature ionic liquids (ILs) as solvent for chemical reactions offers several advantages from this environmental perspective.[3,4] These solvents are non-flammable, thermally stable, exhibit negligible vapor pressure (non-volatile), and offer the potential for recyclability.[5] For these reasons, the replacement of current esterification protocols with a more environmentally benign process involving the use of ionic liquids appeared to be an area worthy of investigation.

Several general conventional methods are available for the esterification reaction of a carboxylic acid and alcohol often involving the use of stoichiometric activators and condensation or coupling reagents.[1] The use of both imidazolium and pyridinium-based ILs in conjunction with the use of orthoacetate[6a] and sulfuric acid catalyzed esterification[6b] have been recently reported. Consideration of the methods available and the nature of phosphonium salt IL's led us to believe that the alkylation of carboxylic acid salts with alkyl electrophiles would be feasible in such media. Savelli and co-workers have recently reported on the use of imidazolium ILs in the coupling of active alkylating agents with carboxylates.[6c,d] The carboxylate alkylation reaction performed in conventional solvents, outlined in Scheme 1, was first generalized by Mehta[7a] based on the previous findings of Alvarez and Watt,[8] and Raphael et al.[9] In general, this reaction takes place through the addition of an alkylating agent to the carboxylic acid in a dipolar aprotic solvent in the presence of a base.

The reaction is most general for the preparation of methyl esters where iodomethane or dimethylsulfate is employed as alkyating agent.[7b] Several variants of the process have been shown to proceed with inversion of configuration where chiral secondary electrophiles are



Scheme 1. Esterification in ionic liquids.

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employed indicating the involvement of a general S_N2 process.[10] As such, the reaction is sensitive to steric effects although cases involving, separately, hindered acids,[7b] and tertiary alkyl halides[11] have been reported.

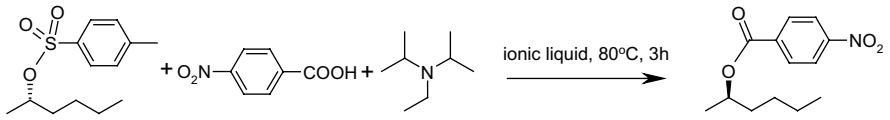
In the present work, we began with an investigation of the reaction of propanoic acid with 1-bromooctane in the phosphonium salt ionic liquid (trihexyl)tetradecyl-phosphonium bis-trilflamide,[12] containing diisopropylethyl amine (Hunig's base). From preliminary experiments a general process quickly evolved. The carboxylic acid (1.0 mmol) was dissolved in the ionic liquid at a concentration of 0.5 M. To this was added the alkylbromide (2.0 mmol) and Hunig's base (2.0 mmol) and the mixture warmed to between 30 °C and 80 °C. The overall results from our study are reported in Table 1. Simple aliphatic and aromatic acids react with primary bromides to give the corresponding esters in high isolated yield. Entries 2 and 4 indicate that no competitive E2-type elimination occurs with the alkyl halide under these conditions. Electronic effects were investigated with a series of 4-substituted benzoic acids reacting with alkyl bromides (entries 5–13) and determined to be minor. Both primary and secondary bromides react without difficulty and even problematic[13] cyclohexyl halides such as bromocyclohexane provided a respectable yield of the cyclohexyl ester (entry 7). Steric effects were shown to be only slightly detrimental to the efficiency of the process (entries 14–17). Even the hindered 2,4,6-trimethylbenzoic acid reacted with the secondary halide 2-bromopropane to provide the ester in 85% isolated yield.[14] β-Aryl acids, for which we have observed decarboxylation under Fischer esterification conditions, also reacted readily with primary and secondary bromides to give high yields of the ester (entries 18 and 19). In addition to bromides, we were delighted to find that tosylates readily entered into the reaction under similar conditions including the cyclic, secondary cyclohexyl-*p*-toluenesulfonate (entries 20 and 21). The use of potassium carbonate as base was shown to be an effective substitute for Hunig's base (entry 22). The di-carboxylic acid phthalic acid also reacted with 4 equiv of bromobutane to give the dibutyl ester in 86% isolated yield (entry 23). Dialkyl phthalates are HPV chemicals utilized both as insect repellents and plasticizers. The reaction was also successful using *tert*-butyl bromide as electrophile (entry 24). The conventional esterification reaction generally fails[12,14] with tertiary halides when conducted in standard solvents. In one report, it was successful using a large excess (48 equiv) of *tert*-butyl bromide.[11] Using the standard IL protocol outlined here and employing only two equivalents of *tert*-butyl bromide, an unoptimized 70% yield of the *tert*-butyl-4-nitrobenzoate ester was realized. The success of this result with only two equivalents of *tert*-butyl bromide indicates that little E1-type elimination takes place in the IL under these conditions. As expected, the reaction is slower when chloroalkanes are employed and particularly sluggish with secondary chloroalkanes. For example, 2-bromohexane reacted with 4-nitrobenzoic acid (50 °C, 3 h) in the presence of Hunig's base to give the ester (81% yield) while under the same conditions 2-chlorohexane gave 12% conversion.

We next investigated the stereochemical outcome of the alkylative esterification using the tosylate derived from (2*S*)-hexanol in reaction with 4-nitrobenzoic acid, Scheme 2. The reaction proceeded in the bis-triflamide IL in the presence of Hunig's base at 80 °C for 3 h to give the ester in 82% isolated yield with a high degree of inversion of stereochemistry (e.r. 4:96, reten-

Table 1. Esterification in ionic liquids[17a]

	R	R′-X	Temp (°C)	Isolated yield of ester (%)
1	C_2H_5–	1-Bromooctane	75	98
2	C_2H_5–	2-Phenyl-1-bromoethane	75	98
3	C_6H_5–	1-Bromooctane	75	98
4	C_6H_5–	2-Phenyl-1-bromoethane	75	98
5	4-Nitrophenyl	Bromoethane	30	95
6	4-Nitrophenyl	2-Bromopropane	40	94
7	4-Nitrophenyl	Bromocyclohexane	70	80
8	4-Chlorophenyl	Bromoethane	30	94
9	4-Chlorophenyl	2-Bromopropane	40	93
10	4-Methoxyphenyl	Bromoethane	30	94
11	4-Methoxyphenyl	2-Bromopropane	40	92
12	4-Methylphenyl	Bromoethane	30	91
13	4-Methylphenyl	2-Bromopropane	40	92
14	2-Methylphenyl	Bromoethane	30	89
15	2-Methylphenyl	2-Bromopropane	40	88
16	2,4,6-Trimethyl phenyl	Bromoethane	30	86
17	2,4,6-Trimethyl phenyl	2-Bromopropane	40	85
18	3,4-Methylenedioxy phenyl acetic	Bromoethane	30	95
19	3,4-Methylenedioxy phenyl acetic	2-Bromopropane	40	93
20	4-Nitrophenyl	Cyclohexyl-*p*-tosylate	80	77
21	4-Nitrophenyl	1-Butyl-*p*-tosylate	80	95
22	4-Nitrophenyl	Bromododecane	80	98[a]
23	Phthalic acid	1-Bromobutane	80	86
24	4-Nitrophenyl	*tert*-Butyl bromide	50	70

[a] K_2CO_3 was used as base.



Scheme 2. Alkylative esterification with (2*S*)-2-hexyl tosylate.

tion:inversion). The reaction was slower at 50 °C but gave complete (>99%) inversion of configuration. These results are consistent with the involvement of essentially an S_N2-type process with some ionization (and racemization) occurring at higher temperatures. This result is in agreement with earlier work carried out in conventional solvents.[10]

Finally, while the use of ionic liquid solvents offers many advantages over conventional solvents, one drawback is that often a volatile organic solvent is employed in the work-up or product isolation,[15] partially defeating the original purpose.[16] Having demonstrated the wide scope of the alkylative esterification method, we next investigated the possibility of a solvent-free product isolation and IL recycling protocol based on the low volatility of phosphonium salt ILs. To this end, the synthesis of the widely used commodity ester butyl acetate was investigated. The reaction of acetic acid (1.10 equiv) and potassium carbonate (1.10 equiv) with butyl bromide (1.0 equiv) was conducted in the phosphonium salt IL under slightly modified conditions.[17b] Thin-layer chromatography indicated clean conversion to the ester which was isolated in 74% yield by direct distillation from the reaction mixture. The ionic liquid phase was washed with water, dried and a second esterification cycle conducted. Butyl acetate was isolated in 85% yield after the second cycle.

The high stereochemical inversion and generality demonstrated by this carboxylate alkylation process in the phosphonium salt IL using primary, secondary and tertiary bromides or primary and secondary tosylates with a large variety of hindered, electron rich or electron deficient acids makes this process attractive from the structural viewpoint. No elimination from the electrophile or α-alkylation of any acid/ester has been observed in any of the cases described. The product ester can be readily isolated from these phosphonium salt ILs using either a standard extraction protocol,[15] or by direct, solvent-free distillation allowing IL re-use. Finally, the reaction takes place at a relatively low temperature in comparison to other processes reported in IL's.[6] Given these desirable features, we believe that this esterification protocol is a prime candidate for the development of economically viable, benign industrial processes for both HPV ester synthesis as well as lower volume, high-value targets. Applications toward the synthesis of biologically important targets is under active investigation in our laboratories.

Acknowledgements

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17. (a) Sample procedure: (a) Table 1 entry 5: 4-nitrobenzoic acid (40 mg, 0.24 mmol), Hunig's base (0.48 mmol) and ionic liquid (0.50 g) were stirred at 30 °C under Ar for 10 min whereupon bromoethane (0.48 mmol) was added. After TLC indicated the reaction to be complete (in all cases within 12 h), the reaction mixture was poured into a methanol/water (3:2) solution (5 mL) and extracted with *n*-hexane (3 × 5 mL). The hexane fractions were dried over anhydrous sodium sulfate, diluted with 5% v/v ethyl acetate and the solution filtered through a plug of silica gel. Concentration of the filtrate gave the ester product in 95% yield. All compounds reported were characterized by

^{1}H, and ^{13}C as well as MS and HRMS data; (b) Recycling protocol: preparation of *n*-butyl acetate. Glacial acetic acid (1.10 g, 18.3 mol) and K_2CO_3 (2.53 g, 18.3 mmol) were dissolved in ionic liquid (10.0 mL) and the solution stirred at 70 °C for 30 min under Ar when bromobutane (1.79 mL, 16.6 mmol) was added. After 6 h the reaction was complete and the temperature was then raised to 130 °C and the *n*-butyl acetate distilled (127–128 °C) directly from the reaction mixture yielding 1.42 g, 74%. The IL was subsequently cooled to rt, partitioned with water (3×20 mL) and dried under vacuum. A second identical reaction was then carried out in the recycled IL yielding butyl acetate in 85% yield after distillation.