Efficient condensation of carboxylic acids with alcohols catalyzed by fluorous ammonium triflates

László Mercs,[†] Gianluca Pozzi[*] and Silvio Quici

CNR-Istituto di Scienze e Tecnologie Molecolari (ISTM), via Golgi 19, I-20133 Milano, Italy

Abstract—The use of fluorous ammonium salts as metal-free catalysts for the direct condensation of equimolar amounts of carboxylic acids and aliphatic alcohols has been investigated. Esterification reactions were thus conveniently carried out under mild fluorous biphasic conditions, in the presence of 1 mol % of fluorous ammonium triflate and without recourse to any additional water removal technique. Good to excellent ester yields were obtained in the case of primary and secondary aliphatic alcohols. The fluorous salt was easily recovered by simple phase separation and reused at least three times without considerable loss of activity.
© 2007 Elsevier Ltd. All rights reserved.

Esterification of carboxylic acids with alcohols has a great importance in organic synthesis both at a laboratory and industrial scale.[1] Esterification methods relying on the use of stoichiometric amounts of coupling reagents that activate carboxylic acids in the presence of either a base or a Lewis acid are well-documented in the literature.[2] This approach is particularly apt for the protection of hydroxyl and carboxyl groups,[3] and it is also widely applied in the synthesis of elaborate natural and unnatural molecules containing carboxylic esters functionalities.[4] Nevertheless, the direct condensation of a carboxylic acid with an alcohol remains the most ideal esterification process, which ensures higher atom economy[5] and, in theory, higher reaction mass efficiency[6] and lower mass ratio of waste to desired product than any other alternative method.[1,7] In practice this equilibrium process needs to be shifted to the product side and this is typically achieved by using one reactant in excess over the other and/or by continuously removing the water formed. The addition of not negligible amounts of a catalyst is also required in order to achieve reasonable reaction rates. To this purpose, strong bases or protic acids, which must be neutralized and removed from the final product, are still widely used. These cir-

cumstances have a negative impact on the economic and environmental viability of conventional direct condensation reactions. There is thus a considerable interest in developing new, more efficient catalytic techniques in order to take full advantage of the considerable potential of this process. Impressive examples include the dehydrative esterification of equimolar mixtures of carboxylic acids and alcohols in the presence of small amounts (0.1–3 mol %) of Hf(IV) or Zr(IV) salts,[8] or of other water-tolerant Lewis acids such as $Zn(ClO_4)_2 \cdot 6H_2O$ (5 mol %),[9] $TiO(acac)_2$ (5 mol %),[10] or Zr(IV)–Fe(III) combined salts (0.2–2 mol %).[11] In all these instances, removal of water by either azeotropic distillation or by addition of a drying agent is required to form the desired esters in good to excellent yields. Such a drawback can be circumvented if diarylammonium salts of Brønsted acids are used as catalysts, as first reported by Tanabe and co-workers in the case of readily available diphenylammonium triflate (DPAT).[12] More recently, Ishihara and co-workers have shown that sterically hindered diarylammonium pentafluorobenzene-sulfonates and tosylates serve as extremely active esterification catalysts and that the hydrophobic effect due to the presence of bulky *N*-aryl and *S*-aryl groups surrounding the acidic NH_2^+ site has a key role in promoting the dehydrative reaction.[13] Quite interestingly, also the hydrophobic/organophobic reaction environment generated by the addition of an immiscible perfluorocarbon solvent has a somewhat beneficial effect on the catalytic activity of DPAT in the case of the esterification of certain sterically hindered carboxylic acids

[*] Corresponding author. Tel.: +39 02 503 14163; fax: +39 02 503 14159; e-mail: gianluca.pozzi@istm.cnr.it

[†] Present address: Department of Chemistry, University of Fribourg, Chemin du Musée 9, CH 1700 Fribourg, Switzerland.

and alcohols.[14] Here we report that the direct condensation of equimolar amounts of carboxylic acids and aliphatic alcohols can be conveniently run under mild conditions in the presence of ammonium triflates endowed with fluorophilic character.

Ammonium triflate **1** (Fig. 1), a fluorous analogue of DPAT, was prepared by addition of one equivalent of CF_3SO_3H to 4,4′-bis(perfluorooctyl)diphenylamine[19] in accordance with the method previously applied to diphenylamine.[12] Fluorous ammonium triflates **2** and **3** were obtained in the same way from bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluoroundecyl)amine[15] and 3,5-bis(perfluorooctyl)aniline,[16] respectively. Although solubilities of **1**–**3** in apolar organic solvents slightly increased with temperature, solvents commonly used in direct esterification reactions, such as hydrocarbons, did not dissolve substantial amounts of these salts even under refluxing conditions. On the other hand, clear solutions of **1**–**3** in warm perfluoro-1,3-dimethylcyclohexane (PDMC) were easily obtained, from which partial precipitation of the solute was observed upon standing at room temperature.

These salts were first investigated as catalysts for the esterification of 3-phenylpropionic acid with an equimolar amount of 1-octanol following the experimental procedure set up for DPAT (Table 1).[12] Reactions were thus carried out in toluene at 80 °C in the presence of 1 mol % of catalyst and the water formed was not removed. Despite its limited solubility in hot toluene, diarylammonium triflate **1** proved to be fairly more active than its non-fluorous analogue DPAT (entry 2 vs 1) affording 97% conversion of 1-octanol to 1-octyl 3-phenylpropanoate with 100% selectivity in 7 h. Aliphatic ammonium triflates are poor esterification catalysts in comparison with DPAT,[12] and this was confirmed in the fluorous series: triflate **2** gave inferior results with respect to **1** and DPAT (entry 3 vs 2 and 1) and a larger amount of catalyst (5 mol %) had to be used in order to quickly drive reaction to completion (entry 4). However, in agreement with our expectations, the introduction of perfluoroalkyl substituents on the amine moiety can also deeply alter the catalytic activity of the corresponding triflate, as exemplified by the behavior of anilinium triflate (AT, entry 5) and of its fluorous analogue **3** (entry 6). The latter showed the
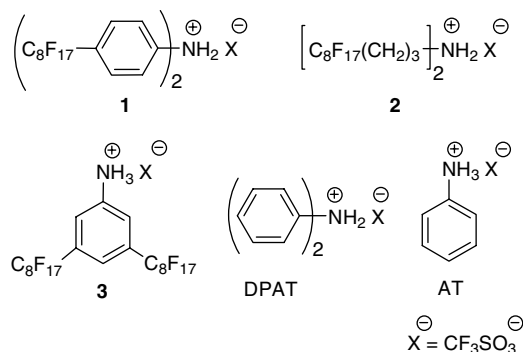
Table 1. Direct esterification of 3-phenylpropionic acid with 1-octanol[a]

Entry	Catalyst	Time (h)	Alcohol conversion[b] (%)	Ester yield[c] (%)
1	DPAT	7	90	89
2	**1**	7	97	97
3	**2**	24	89	87
4[d]	**2**	7	98	98
5	AT	5	27	27
6	**3**	5	97	97
7[e]	**3**	3	99	99
8[f]		2	94	94
9		2	94	94
10		2	92	92
11		2	89	88
12		2	76	73

[a] Reaction conditions: acid = 1 mmol, alcohol = 1 mmol, catalyst = 0.01 mmol, toluene = 1 mL, $T = 80$ °C.
[b] Determined by GC (external standard: *n*-decane).
[c] Ester yield determined by GC (external standard: *n*-decane).
[d] Catalyst = 0.05 mmol; toluene = 5 mL.
[e] Fluorous biphasic conditions: toluene = 1 mL, perfluoro-1,3-dimethylcyclohexane (PDMC) = 1 mL.
[f] Entries 8–12: catalyst recycling. Each reaction was carried out with the fluorous layer recovered from the preceding run.

highest activity among the triflates tested, in spite of the scanty results obtained with AT.

We were also pleased to find that the remarkable catalytic activity of **3** could be further enhanced if fluorous biphasic (FB) conditions were employed (entry 7).[17] In that case the catalyst dissolved in perfluoro-1,3-dimethylcyclohexane (PDMC) was vigorously stirred with a solution of the reagents in toluene and at the end of the reaction the fluorous layer containing the catalyst was easily removed by simple phase separation after cooling to room temperature. Recycling of the fluorous layer (entries 8–12) was studied while maintaining reaction time = 2 h (conversion of 1-octanol with fresh **3** = 94%) in order to better evaluate any loss of activity. Constant conversions and yields were achieved in three subsequent runs, with a minor loss of activity in the fourth and fifth run (entries 10 and 11) and a more severe drop of activity in the sixth run (entry 12). This can be mainly ascribed to small losses of fluorous layer occurring during the recovery operations. Indeed, evaporation of PDMC after six subsequent runs afforded a brown solid (7.3 mg over 10.8 mg of **3** added in the first run) showing NMR spectra identical to those of the fresh catalyst.

The esterification of representative carboxylic acids R^1COOH with an equimolar amount of 1-octanol was then studied under FB conditions, in the presence of 1 mol % of **3** with no water removing system whatsoever (Table 2, entries 1–6).[18] 2-Alkoxycarboxylic acids (entries 1, 2) and phenylpropiolic acid (entry 4) gave excellent results, analogously to what was found in the case of bulky diarylammonium pentafluorobenzenesulfonates and tosylates.[13] Sterically demanding cyclohexanecarboxylic acid was also smoothly condensed with 1-octanol to produce the corresponding ester in

Figure 1. Ammonium triflates tested as direct esterification catalysts.

Table 2. Direct FB esterification of R^1COOH with R^2OH catalyzed by **3**[a]

Entry	R^1COOR^2	Time (h)	Yield[b] (%)
1	MeO~CO$_2$(CH$_2$)$_7$CH$_3$	1	94
2	MeO—C(Ph)H—CO$_2$(CH$_2$)$_7$CH$_3$	2.5	93
3	Cyclohexyl—CO$_2$(CH$_2$)$_7$CH$_3$	3	96
4	Ph—≡—CO$_2$(CH$_2$)$_7$CH$_3$	5	92
5	Ph~CO$_2$(CH$_2$)$_7$CH$_3$	22	91
6	PhCO$_2$(CH$_2$)$_7$CH$_3$	24	90
7	Ph~CO$_2$(CH$_2$)$_9$CH=CH$_2$	3	95
8	Ph~CO$_2$(CH$_2$)$_5$CH$_2$Cl	3	97
9	Ph~CO$_2$(CH$_2$)$_2$Ph	3	97
10	Ph~CO$_2$CH$_2$Ph	2	96
11	Ph~CO$_2$CH$_2$C≡CH	5	82
12	Ph~CO$_2$-cyclooctyl	7	84
13	Ph~CO$_2$CH((CH$_2$)$_5$CH$_3$)(CH$_3$)	12	76
14	Ph~CO$_2$CH((CH$_2$)$_2$CH$_3$)(CH$_2$CH$_3$)	48	70
15	Ph~CO$_2$C(CH$_3$)$_3$	24	/

[a] Reaction conditions: $R^1COOH = 1$ mmol, $R^2OH = 1$ mmol, **3** = 0.01 mmol, toluene = 1 mL, PDMC = 1 mL, $T = 80\,°C$.

[b] Isolated yield. Physical data were in agreement with those reported in the literature.

almost quantitative yield (entry 3). Very good results were obtained with low reactive substrates such as benzoic and cinnamic acids, albeit relatively long reaction times were required (entries 5 and 6). It should be noted that the esterification of benzoic acid with 1-octanol required 48 h and 5 mol % of catalyst in the case of the homogeneous system based on DPAT.[12] Moreover, similar esterifications of both simple aromatic carboxylic acids and α,β-unsaturated acids catalyzed by 5 mol % of a fluorous distannoxane proceeded sluggishly under FB conditions even at 150 °C.[17a] The metal-free FB catalytic system was next applied to the condensation of 3-phenylpropionic acid with various types of alcohols (Table 2, entries 7–15). The esterification process worked well with functionalized primary alcohols (entries 7–9) and with benzyl alcohol (entry 10). In the case of propargyl alcohol (entry 11) the ester

yield was comparable to that obtained using dimesitylammonium pentafluorobenzenesulfonate under homogeneous conditions,[13] but a shorter reaction time was required. On the other hand, esterification of sterically hindered secondary alcohols (entries 12–14) afforded the desired esters in moderate to good yields, together with not negligible amounts of alkenes: such a drawback was not observed with bulky diarylammonium catalysts.

As observed by Gacem and Jenner for DPAT-catalyzed reactions,[14] the use of neat perfluorocarbons as reaction medium might have a beneficial effect on the reactivity of sterically hindered, liquid substrates. As an example, esterification of cyclohexanecarboxylic acid with 2-butanol carried out in neat PDMC afforded 60% ester yield after 8 h, whereas a similar yield was obtained after 16 h when the reaction was run under FB conditions PDMC/toluene. Finally, tertiary alcohols failed to give the desired esters (entry 15), which appears to be a general limitation of the mild catalytic esterification procedures reported so far in the literature.

In conclusion, simple fluorous ammonium triflates efficiently promote the esterification of carboxylic acids with equimolar amounts of primary and secondary alcohols. Reactions can be run under either solid/liquid or FB conditions at a moderate temperature and do not necessitate the use of dehydrating agents and/or azeotropic removal of water. Work in our laboratory is now focussed on bulkier fluorous ammonium salts in the hope to further enhance the selectivity and recyclability of the catalytic system.

Acknowledgments

References and notes

1. Otera, J. *Esterification: Methods, Reactions and Applications*; Wiley-VCH: Weinheim, 2003.
2. See for instance: (a) Wakasugi, K.; Iida, A.; Misaki, T.; Nishii, Y.; Tanabe, Y. *Adv. Synth. Catal.* **2003**, *345*, 1209–1214; (b) Mukaiyama, T.; Oohashi, Y.; Fukumoto, K. *Chem. Lett.* **2004**, *33*, 552–553; (c) Oohashi, Y.; Fukumoto, K.; Mukaiyama, T. *Bull. Soc. Chim. Jpn.* **2005**, *78*, 1508–1519; (d) Saito, Y.; Watanabe, T.; Takahata, H. *Tetrahedron Lett.* **2006**, *47*, 3099–3102, and references cited therein.
3. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.
4. Recent examples: (a) Kobayashi, S.; Hori, M.; Wang, G. X.; Hirama, M. *J. Org. Chem.* **2006**, *71*, 636–644; (b) Cohen, F.; Overman, L. E. *J. Am. Chem. Soc.* **2006**, *128*, 2594–2603; (c) Bruyère, H.; Dos Reis, C.; Samaritani, S.; Ballereau, S.; Royer, J. *Synthesis* **2006**, 1673–1681.
5. Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259–281.

6. Curzons, A. D.; Constable, D. J. C.; Mortimer, D. N.; Cunningham, V. L. *Green Chem.* **2001**, *3*, 1–6.

7. Otera, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2044–2045.

8. (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *Science* **2000**, *290*, 1140–1142; (b) Nakayama, M.; Sato, A.; Ishihara, K.; Yamamoto, H. *Adv. Synth. Catal.* **2004**, *346*, 1275–1279; (c) Mantri, K.; Komura, K.; Sugi, Y. *Synthesis* **2005**, 1939–1944.

9. Bartoli, G.; Boeglin, J.; Bosco, M.; Locatelli, M.; Massaccesi, M.; Melchiorre, P.; Sambri, L. *Adv. Synth. Catal.* **2005**, *347*, 33–38.

10. Chen, C.-T.; Munot, Y. S. *J. Org. Chem.* **2005**, *70*, 8625–8627.

11. (a) Sato, A.; Nakamura, Y.; Maki, T.; Ishihara, K.; Yamamoto, H. *Adv. Synth. Catal.* **2005**, *347*, 1337–1340; (b) Nakamura, Y.; Maki, T.; Wang, X.; Ishihara, K.; Yamamoto, H. *Adv. Synth. Catal.* **2006**, *348*, 1505–1510, 1340.

12. Wakasugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahedron Lett.* **2000**, *41*, 5249–5252.

13. (a) Ishihara, K.; Nakagawa, S.; Sakakura, A. *J. Am. Chem. Soc.* **2005**, *127*, 4168–4169; (b) Sakakura, A.; Nakagawa, S.; Ishihara, K. *Tetrahedron* **2006**, *62*, 422–433.

14. Gacem, B.; Jenner, G. *Tetrahedron Lett.* **2003**, *44*, 1391–1393.

15. Holczknecht, O.; Cavazzini, M.; Quici, S.; Shepperson, I.; Pozzi, G. *Adv. Synth. Catal.* **2005**, *347*, 677–688.

16. ten Brink, G.-J.; Vis, J. M.; Arends, I. W. C. E.; Sheldon, R. A. *Tetrahedron* **2002**, *58*, 3977–3983.

17. Only a few examples of FB direct esterification reactions are known. Catalyst = fluorous distannoxane (3–5 mol %): (a) Xiang, J.; Orita, A.; Otera, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4117–4119; Catalyst = Sn(IV) and Hf(IV) bis(perfluorooctanesulfonyl)amide complexes (5 mol %): (b) Hao, X.; Yoshida, A.; Nishikido, J. *Tetrahedron Lett.* **2004**, *45*, 781–785; (c) Hao, X.; Yoshida, A.; Nishikido, J. *Green Chem.* **2004**, *6*, 566–569; (d) Hao, X.; Yoshida, A.; Nishikido, J. *J. Fluorine Chem.* **2006**, *127*, 193–199.

18. Typical procedure: a vial fitted with a stirring bar was charged with a solution of carboxylic acid (1 mmol) and alcohol (1 mmol) in toluene (1 mL). Triflate **3** (10.8 mg, 0.01 mmol) and PDMC (1 mL) were then added. The vial was sealed with a screw cap and the biphasic reaction mixture was vigorously stirred at 80 °C for the time indicated in Table 2. After this time the mixture was cooled to rt. The upper organic layer was separated and the fluorous layer was washed with cold toluene (3 × 0.5 mL). The combined organic extracts were evaporated under reduced pressure to give the ester that was purified by column chromatography (light petroleum ether/diethyl ether) on a short silica pad if required.

19. 4,4′-Bis(perfluorooctyl)diphenylamine was obtained in 52% yield from 4,4′-bis(bromo)diphenylamine by copper catalyzed cross coupling with $C_8F_{17}I$: ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, $J = 8.6$ Hz, 4H), 7.19 (d, $J = 8.6$ Hz, 4H), 6.14 (s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 144.9, 128.4, 121.7 (t, $J = 24$ Hz), 117.4, 118–105 (m, C_nF_{2n+1}); ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.2 (t, $J = 10$ Hz, 6F), −110.3 (t, $J = 13$ Hz, 4F), −121.6 (br s, 4F), −122.2 (br s, 12F), −123.1 (br s, 4F), −126.5 (br s, 4F). Triflate **1**: ^1H NMR (300 MHz, CD_3OD) δ 7.51 (d, $J = 8.7$ Hz, 4H), 7.31 (d, $J = 8.7$ Hz, 4H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 146.2, 127.9, 119.7 (t, $J = 25$ Hz), 116.6, 118–105 (m, C_nF_{2n+1}); ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.8 (s, 3F, CF_3SO_3), −81.1 (t, $J = 10$ Hz, 6F), −109.4 (t, $J = 13$ Hz, 4F), −120.9 (br s, 4F), −121.6 (br s, 12F), −122.4 (br s, 4F), −125.9 (br s, 4F). Triflate **2**: ^1H NMR (300 MHz, CD_3OD) δ 1.96–2.06 (m, 4H), 2.28–2.46 (m, 4H), 3.16 (t, $J = 7.8$ Hz, 4H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 118–105 (m, C_nF_{2n+1}), 46.5, 27.4 (t, $J = 23$ Hz), 17.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.8 (s, 3F, CF_3SO_3), −81.1 (t, $J = 10$ Hz, 6F), −114.0 (t, $J = 16$ Hz, 4F), −121.5 (m, 12 F), −122.4 (br s, 4F), −123.1 (br s, 4F), −125.9 (br s, 4F). Triflate **3**: ^1H NMR (300 MHz, CD_3OD) δ 7.62 (br s, 2H), 7.51 (br s, 1H); ^{13}C NMR (75.4 MHz, CD_3OD) δ 141.4, 130.9 (t, $J = 24$ Hz), 120.8, 118.8, 118–105 (m, C_nF_{2n+1}); ^{19}F NMR (282 MHz, CD_3OD) δ −78.8 (s, 3F, CF_3SO_3), −81.1 (t, $J = 10$ Hz, 6F), −110.8 (t, $J = 13$ Hz, 4F), −120.8 (br s, 4F), −121.6 (br s, 8F), −122.2 (br s, 4F), −122.4 (br s, 4F), −126.0 (br s, 4F).