Activation of Imidazolides Using Methyl Trifluoromethanesulfonate: A Convenient Method for the Preparation of Hindered Esters and Amides

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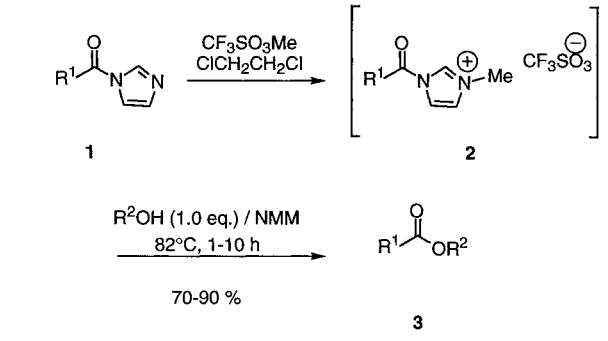
Treatment of imidazolides with methyl trifluoromethanesulfonate followed by reaction with alcohols or amines provides a convenient one-pot procedure for the preparation of esters and amides. The method is applicable to imidazolides of low reactivity as well as to hindered nucleophiles.

The conversion of carboxylic acids to esters or amides is of singular importance in synthetic organic chemistry and considerable effort has therefore been devoted to carbonyl activation.[2-7] Among the conventional coupling methods, 1,1′-carbonyldiimidazole (CDI) is one of the most widely used reagents, largely due to the mild reaction conditions employed and to the ease of workup. The utility of 1,1′-carbonyldiimidazole is, however, limited by the low reactivity of the intermediate imidazolide towards amines of low nucleophilicity and towards alcohols.[8]

In order to circumvent this problem a number of solutions have been proposed such as replacement of 1,1′-carbonyldiimidazole by the 1,1′-carbonylbis(3-methylimidazolium) analogue.[9] This method gives high yields of products even in difficult peptide coupling reactions, but suffers from the disadvantage that for best results the formation of the bis(imidazolium) reagent and its condensation with nucleophiles must be carried out in different solvents.[10] The use of 1-acyl-3-methylimidazolium chlorides prepared from 1-methylimidazole and an acid chloride has been reported[11] to give amides (but not esters) in good yield.

In an alternative approach 1-acylimidazoles, prepared under the usual mild conditions, have been activated towards nucleophilic attack by using a variety of alkylating agents.[12] In each case complicated manipulations are encountered, for example, the use of a benzyl halide gives good yields of esters and amides using a variety of alco-



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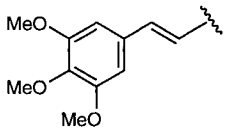
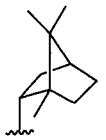
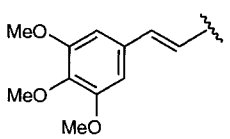
a		
b		$C_6H_5CH_2$
c	4-ClC_6H_4	
d	4-ClC_6H_4	4-CNC_6H_4

Scheme 1

Table 1. Esters **3** Prepared

Product[a]	Reaction Conditions		Yield[b] (%)	mp (°C)	IR (KBr/film) $\nu_{C=O}$ (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
	Time (h)	Temp. (°C)				
3a	10	82	90	oil	1704	7.58 (d, 1H, J = 16), 7.09 (s, 2H), 6.68 (d, 1H, J = 16), 4.96 (br s, 1H), 3.83 (s, 6H), 3.69 (s, 3H), 2.34 (ddd, 1H, J = 11, 10, 4), 2.03 (ddd, 1H, J = 11, 11, 4), 1.80–1.68 (m, 2H), 1.40–1.20 (m, 2H), 1.00 (dd, 1H, J = 14, 3), 0.91 (s, 3H), 0.88 (s, 3H), 0.84 (s, 3H)
3b	4	82	85	87–89	1703	7.64 (d, 1H, J = 16), 7.45–7.30 (m, 5H), 6.75 (s, 2H), 6.40 (d, 1H, J = 16), 5.25 (s, 2H), 3.88 (s, 9H)
3c	2	20	72	29–30	1720	7.99 (d, 2H, J = 8), 7.42 (d, 2H, J = 8), 5.10 (ddd, 1H, J = 9, 5, 3), 2.47 (ddd, 1H, J = 12, 12, 4), 2.09 (ddd, 1H, J = 12, 9, 4), 1.81 (m, 1H), 1.74 (t, 1H, J = 4), 1.40 (m, 1H), 1.30 (ddd, 1H, J = 12, 9, 4), 1.11 (dd, 1H, J = 12, 4), 0.96 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H)
3d	1	20	70	111–112[c]	1735	8.13 (d, 2H, J = 9), 7.76 (d, 2H, J = 8), 7.51 (d, 2H, J = 9), 7.36 (d, 2H, J = 8)

[a] Satisfactory microanalyses obtained: C ± 0.33, H ± 0.07, N ± 0.03.
[b] Overall yield of pure isolated product.
[c] Lit.[13] mp 107–113°C.

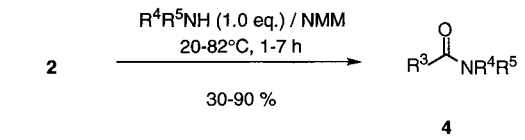
hols and amines, including those of low nucleophilicity, but represents a two-step procedure entailing *N*-benzylation of the acylimidazole in acetonitrile, isolation of the product, followed by reaction with the nucleophile in chloroform. Nevertheless, in the light of the apparent generality of this method it seemed worthwhile to develop an operationally simpler procedure for the acylation of nucleophiles based on this approach. We now report that imidazolides can be activated using methyl trifluoromethanesulfonate (MeOTf), and converted to esters (Scheme 1) or amides (Scheme 2) in a one-pot procedure.

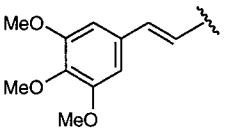
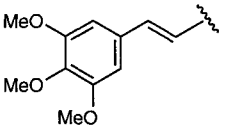
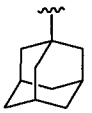
In a typical procedure methyl trifluoromethanesulfonate was added to a stirred 1,2-dichloroethane solution of the imidazolide (prepared according to classical methods or in situ as described in the experimental section). After five minutes at room temperature *N*-methylmorpholine (NMM) and the alcohol were added and the reaction mixture stirred at room temperature or heated at reflux. Aqueous workup followed by chromatography afforded esters **3**, as shown in Table 1.

The reaction of **2** with alcohols proved to work efficiently. The sensitive derivative **2** of 3,4,5-trimethoxycinnamic acid reacted with bornyl and benzyl alcohol to give esters **3a** and **3b**, respectively, in excellent overall yields. The benzoates **3c** and **3d** were similarly obtained in good yield even at room temperature.

The reaction of compounds **2** with amines gave amides **4** in an analogous fashion as shown in Scheme 2.

Imidazolides and amines of low reactivity were chosen in order to test the limits of the method. As shown in Table 2, the results obtained for compounds **4a, 4d**, and **4e** are noteworthy and even use of the highly hindered diisopropylamine afforded amides (**4b, 4f**), albeit in moderate overall yields.



4	R^3	R^4	R^5
a		Pr	Pr
b		*i*-Pr	*i*-Pr
c		Pr	Pr
d	4-ClC_6H_4	4-ClC_6H_4	H
e	4-ClC_6H_4	Pr	Pr
f	4-ClC_6H_4	*i*-Pr	*i*-Pr
g	Ph_2CH	Pr	Pr

Scheme 2

Melting points were measured using a Buchi (capillary) apparatus and are uncorrected. Elemental analyses were carried out using a Fisons EA-1108 apparatus. IR spectra (ir) were obtained on a Bruker FTIR-IFS 28 spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$, with TMS as internal standard, using one of the following spectrometers: Bruker WH-100 (100 MHz), or Bruker ARX-400 (400 MHz). $ClCH_2CH_2Cl$ and CH_2Cl_2 were dried over 4 Å molecular sieves. MeOTf, CDI and NMM were used as received from Aldrich Chemical Co.

(*E*)-3-(3,4,5-Trimethoxyphenyl)prop-2-enoic Acid Bornyl Ester (3a); Typical Procedure:

(*E*)-3-(3,4,5-trimethoxyphenyl)prop-2-enoic acid (510 mg, 2.11 mmol) was dissolved in anhyd CH_2Cl_2 (10 mL) under an atmo-

Table 2. Amides **4** Prepared

Product[a]	Reaction Conditions		Yield[b] (%)	mp (°C)	IR (KBr/film) $\nu_{C=O}$ (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)
	Time (h)	Temp. (°C)				
4a	1.5	82	90	71–73[c]	1645	7.41 (d, 1H, $J = 15$), 7.04 (d, 1H, $J = 15$), 7.00 (s, 2H), 3.82 (s, 6H), 3.68 (s, 3H), 3.46 (t, 2H, $J = 7$), 3.30 (t, 2H, $J = 7$), 1.60–1.45 (m, 4H), 0.88 (t, 3H, $J = 7$), 0.85 (t, 3H, $J = 7$)
4b	3	82	40	91–92	1647	7.30 (d, 1H, $J = 15$), 7.02 (d, 1H, $J = 15$), 6.97 (s, 2H), 3.82 (s, 6H), 3.68 (s, 3H), 3.30 (s, 2H), 1.32 (brs, 6H), 1.23 (brs, 6H)
4c	2	20	30	oil	1622	3.30 (brs, 4H), 2.03 (brs, 3H), 1.99 (s, 6H), 1.73 (s, 6H), 1.56 (q, 4H, $J = 7$), 0.88 (t, 6H, $J = 7$)
4d	4	20	61	210–211[d]	1645	10.44 (s, 1H), 7.98 (d, 2H, $J = 8$), 7.81 (d, 2H, $J = 9$), 7.62 (d, 2H, $J = 8$), 7.42 (d, 2H, $J = 9$)
4e	1.5	82	81	oil	1633	7.49 (d, 2H, $J = 8$), 7.35 (d, 2H, $J = 8$), 3.35 (brs, 2H), 3.09 (brs, 2H), 1.58 (brs, 2H), 1.47 (brs, 2H), 0.90 (brs, 3H), 0.66 (brs, 3H)
4f	7	20	32	85–87	1683	7.36 (d, 2H, $J = 8$), 7.25 (d, 2H, $J = 8$), 3.66 (brs, 2H), 1.45 (brs, 6H), 1.21 (brs, 6H)
4g	2	20	36	49–50	1634	7.35–7.20 (m, 10H), 5.38 (s, 1H), 3.23 (dd, 2H, $J = 9, 8$), 3.20 (dd, 2H, $J = 9, 8$), 1.50–1.35 (m, 4H), 0.81 (s, 3H), 0.78 (s, 3H)

[a] Satisfactory microanalyses obtained: C ± 0.37, H ± 0.11, N ± 0.10.
[b] Overall yield of pure isolated product.
[c] Lit.[14] mp 72–73 °C.
[d] Lit.[15] mp 207–208 °C.

sphere of argon. CDI (350 mg, 2.13 mmol) was slowly added at r. t., and the mixture was stirred until no further gas (CO_2) evolution was observed. Complete evaporation of the solvent under reduced pressure (vacuum pump) gave an oily residue which was redissolved in anhyd $ClCH_2CH_2Cl$ (10 mL) under Ar. MeOTf (290 mL, 2.54 mmol) was added at r. t. and stirred for 5 min and a solution of borneol (390 mg, 2.54 mmol) and NMM (0.28 mL, 2.54 mmol) in anhyd $ClCH_2CH_2Cl$ (5 mL) was added. The mixture was refluxed for 10 h, and allowed to cool to r. t. The organic layer was washed with water (2 × 10 mL) and brine (1 x 10 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Flash chromatography on silica gel using EtOAc (0–20 %) in heptane as eluent gave **3a** as a colorless oil; yield: 602 mg (90 %) (Table 1).

4-Chloro-*N*,*N*-dipropylbenzamide (4e); Typical Procedure:
4-Chlorobenzoic acid (760 mg, 4.85 mmol) was dissolved in anhyd CH_2Cl_2 (10 mL) under an atmosphere of argon. CDI (795 mg, 4.90 mmol) was slowly added at r. t., and the mixture was stirred until no further gas (CO_2) evolution was observed. Complete evaporation of the solvent under reduced pressure (vacuum pump) gave an oily residue which was redissolved in $ClCH_2CH_2Cl$ (10 mL) under Ar. MeOTf (0.66 mL, 5.83 mmol) was added at r. t., and stirred for 5 min before the addition of a solution of freshly distilled *N*,*N*-dipropylamine (0.80 mL, 5.83 mmol) and NMM (0.65 mL, 5.83 mmol) in anhyd $ClCH_2CH_2Cl$ (5 mL). The mixture was refluxed for 1.5 h, and allowed to cool to r. t. The organic layer was washed with water (2 × 10 mL) and brine (1 × 10 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Flash chromatography on silica gel using EtOAc (0–20 %) in heptane as eluent gave **4e** as a colorless oil; yield: 940 mg (81 %) (Table 2).

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