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Nitrolysis of Carboxylic *t*-Butyl and 1-Adamantyl Esters

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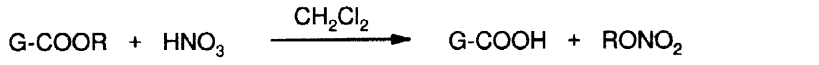
Abstract

A cheap, less problematic, efficient and selective reagent for the removal of the *t*-butyl and 1-adamantyl protecting groups from carboxylic esters was found to be commercial 100% HNO_3 in CH_2Cl_2. Incidentally, 1,1-dimethylethyl nitrate and tricyclo[3.3.1.1^{3,7}]dec-1-yl (1-adamantyl) nitrate are coproducts in a clean reaction. The procedure is in many ways superior to the method employing CF_3COOH.

Keywords: Carboxylic acids and derivatives; Deblocking; Nitric acid and derivatives; Protecting groups

t-Butylation of free carboxylic acids is a widespread procedure for the protection of the carboxyl function, receiving continuous attention in many fields of chemistry.[2] The same kind of protection of the carboxyl function is also achieved by formation of 1-adamantyl esters.[3] Removal of the protecting groups is usually performed in a number of ways,[2a,4] among which the procedure using excess CF_3COOH (TFA), neat or in its concentrated CH_2Cl_2 (or other suitable solvent) solution, is, by and large, the most common.[5] Under these acidic conditions, reactive substrates may be attacked by *t*-butyl cations present in high concentrations:[6] ***inter alia***, thiols, thioethers, anisole and triethylsilane may be added as scavengers to avoid unwanted reactions with the substrate.[7]

Scheme 1



1 R = t-Bu or 1-adamantyl 2 3, R = t-Bu 4, R = 1-adamantyl

We now find that treating a number of *t*-butyl esters **1**, prepared from carboxylic acids with different steric properties and potentially reactive functionality, with only twice the stoichiometric amount of commercial 100% HNO_3 (d = 1.50) in CH_2Cl_2 at 0 °C for 2 h, yields, in a smooth reaction, the complete restoration of the free organic acid, accompanied by the almost quantitative formation of 1,1-dimethylethyl nitrate (**3**) (Scheme 1, Table 1).

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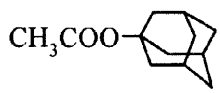
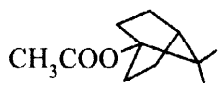
Table 1
Nitrolysis of *t*-butyl and 1-adamantyl esters of various carboxylic acids (Scheme 1) [a,10]

Entry	Substrate **1**	Acid **2** (%) [b]
1	CH_3COOt-Bu (**1a**)	**98** (n. d.) [c]
2	CH_3COCH_2COOt-Bu (**1b**)	**92** (20) [d]
3	$(CH_3)_3CCOOt$-Bu (**1c**)	**99** (91)
4	$CH_3(CH_2)_4COOt$-Bu (**1d**)	**98** (95)
5	(*E*)-C_2H_5CH=$CHCH_2COOt$-Bu (**1e**)	**97** (90)
6	$PhCH_2COOt$-Bu (**1f**)	**99** (96)
7	(*E*)-PhCH=CHCOO*t*-Bu (**1g**)	**98** (96)
8	PhCOO*t*-Bu (**1h**)	**99** (97)
9	 (**1i**)	**97** (n. d.)
10	 (**1m**)	**0** (0)

[a] Unless otherwise specified, the reaction was carried out by treating a chilled solution of the ester **1** (50 mmol) in CH_2Cl_2 (30 mL) at 0 °C for 2 h with a solution of commercial 100% HNO_3 (106 mmol) in CH_2Cl_2 (20 mL), pouring the reaction mixture into 10% aqueous Na_2CO_3 (100 mL), washing with Et_2O (2 x 30 mL), acidifying the separated aqueous phase with concentrated HCl, extracting with Et_2O (2 x 50 mL), drying over Na_2SO_4 and eventually evaporating the solvent. 1,1-Dimethylethyl nitrate (**3**) and tricyclo[3.3.1.1^{3,7}]dec-1-yl (1-adamantyl) nitrate (**4**) were obtained by drying over Na_2SO_4, evaporating the solvent and finally distilling the residue of the combined ethereal phases resulting from the Na_2CO_3 solution washing.
[b] Reported conversions were determined by ^1H NMR on intact reaction mixtures, after dilution with $CDCl_3$: the spectra for all reactions revealed only the resonances of unreacted **1** and the products **2**, **3**, and **4**. Yields of separated acids are in parentheses.
[c] n. d. : not determined.
[d] Isolated as the methyl ester after treating of the final ethereal solution with a suitable amount of ethereal CH_2N_2. The low separated yield of the methyl ester of **2b** is consistent with the work up procedure of isolation of the corresponding acid (**2b**), notoriously a very unstable compound, from the reaction mixture.

2-Methylpropene, a possible reaction product by proton abstraction from the intermediate *t*-butyl cation, was absent (< 1%), as well as 2-methyl-2-propanol. Tricyclo[3.3.1.1^{3,7}]dec-1-yl (1-adamantyl) acetate (**1i**) reacted similarly under the same conditions, yielding tricyclo[3.3.1.1^{3,7}]dec-1-yl (1-adamantyl) nitrate (**4**) as the sole fate of the protecting moiety.

The soft, but efficient nature of HNO_3 in CH_2Cl_2, is clearly apparent from the result of the reaction: oxidations of double bonds or benzylic hydrogens did not take place, nor was there any evidence for additions or aromatic substitutions, in sharp contrast to earlier reports.[8] This latter fact is particularly notable for the reaction with 1,1-dimethylethyl benzeneacetate (**1f**), if one thinks that other esters of this acid underwent smooth 100% nitration with HNO_3 in CH_2Cl_2.[9] The reaction appears particularly selective and efficient because of the prompt formation of the carbenium ion, followed by its fast capture by NO_3^-. The observed higher efficiency of this system, in comparison with the solvolysis with TFA, may be attributed to a

higher concentration of NO_3^-, possibly closely associated with emerging *t*-butyl or 1-adamantyl cation, at hand than that of free CF_3COO^- in the case of CF_3COOH. Incidentally, the S_N1 reaction mechanism may be inferred by the unreactivity of 7,7-dimethylbicyclo[2.2.1]hept-1-yl (1-apocamphanyl) acetate (**1m**), which is unable to form the corresponding carbenium ion.

The superiority of the present procedure, compared to the TFA one, is evidenced, *inter alia*, by some rough rate measurements. Using the same molar ratio acid (Table 1, note a) *vs.* *t*-butyl acetate (**1a**), nitrolysis was found to occur much faster than trifluoroacetolysis (Table 2). A reduced concentration of acidic, hydrogen bonding and solvating material, as used in our experiments, offers the advantage of a medium less prone to catalyze carbenium ion formation and so any subsequent related reaction.

Table 2
Comparison of deprotection rates of *t*-butyl acetate (**1a**) using HNO_3 or CF_3COOH

Reaction conditions [a]	Conversion into **2a** (%) [b]	
	HNO_3	CF_3COOH
0 °C, 1 h	92	15
0 °C, 2 h	97	37
rt, 1 h	-	58
rt, 72 h	-	97

[a] See note a in Table 1.
[b] Determined by ^1H NMR on intact reaction mixtures, after dilution with $CDCl_3$.

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10. All the compounds reported in the present work which were not commercially available were fully characterized by spectroscopic techniques (IR, ^{1}H and ^{13}C NMR, MS).
100% HNO_3 was purchased from Hydro Chemicals France (Nanterre, France) and used as received.
1,1-Dimethylethyl 2,2-dimethylpropanoate (**1c**). Prepared from 1,1-dimethylethanol and 2,2-dimethylpropanoyl chloride in pyridine: 88% yield, bp 47 °C/4000 Pa;[2c] ν_{max} (KBr, film) 2979, 1727, 1481, 1394, 1369, 1292, 1149, 854, 758 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 1.15 (9H, s), 1.43 (9H, s); ^{13}C NMR;[11] MS (EI, 70 eV, *m/z* (%)) 143 (5), 85 (19), 59 (7), 57 (100), 41 (18).
1,1-Dimethylethyl hexanoate (**1d**). Prepared from 1,1-dimethylethanol and hexanoyl chloride in pyridine: 95% yield, bp 66 °C/1066 Pa;[12] ν_{max} (KBr, film) 2961, 2933, 1734, 1457, 1368, 1253, 1156 cm^{-1}; ^{1}H NMR;[12] δ_C (50 MHz, $CDCl_3$, TMS) 173.21, 79.74, 35.48, 31.21, 28.01, 24.72, 22.28, 13.84; MS (EI, 70 eV, *m/z* (%)) 117 (49), 116 (11), 100 (10), 99 (100), 57 (21).
1,1-Dimethylethyl (*E*)-3-hexenoate (**1e**). Prepared according to the procedure reported in ref. 2b: 41% yield, bp 71 °C/1466 Pa; ν_{max} (KBr, film) 2969, 1735, 1369, 1257, 1151, 968, 848 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 0.99 (3H, t, J = 7.4 Hz), 1.45 (9H, s), 2.04 (2H, m), 2.94 (2H, d, J = 5.5 Hz), 5.40-5.66 (2H, m); δ_C (50 MHz, $CDCl_3$, TMS) 171.56, 135.73, 121.12, 80.24, 39.17, 28.00, 25.45, 13.43; MS (EI, 70 eV, *m/z* (%)) 170 (M^+, 1), 114 (100), 97 (89), 69 (91), 57 (84), 41 (58).
1,1-Dimethylethyl benzeneacetate (**1f**).[13]
1,1-Dimethylethyl (*E*)-benzenepropenoate (**1g**). Prepared from 1,1-dimethylethanol and (*E*)-benzenepropenoyl chloride in pyridine: 89% yield, bp 103 °C/133 Pa.[14]
1,1-Dimethylethyl benzoate (**1h**). Prepared from 1,1-dimethylethanol and benzoyl chloride in pyridine: 92% yield, bp 115 °C/2933 Pa;[15] ν_{max} (KBr, film) 2979, 1713, 1451, 1369, 1294, 1256, 1169, 1116, 1027, 849, 711 cm^{-1}; ^{1}H and ^{13}C NMR;[15] MS (EI, 70 eV, *m/z* (%)) 178 (M^+, 1), 124 (18), 123 (100), 122 (19), 105 (76), 77 (14).
Tricyclo[3.3.1.1^{3,7}]dec-1-yl (1-adamantyl) acetate (**1i**) and 7,7-dimethylbicyclo[2.2.1]hept-1-yl (1-apocamphanyl) acetate (**1m**).[16]
3-Oxobutanoic acid (**2b**).[17] δ_H (200 MHz, $CDCl_3$, TMS) 2.32 (3H, s), 3.53 (2H, s), 7.25 (1H, br s); δ_C (50 MHz, $CDCl_3$, TMS) 201.74, 171.04, 49.08, 30.21.
1,1-Dimethylethyl nitrate (**3**).[18] See Table 1, note a: 60% yield, bp 24 °C/2000 Pa;[19] IR;[20] δ_H (200 MHz, $CDCl_3$, TMS) 1.55 (9H, s); δ_C (50 MHz, $CDCl_3$, TMS) 89.93, 26.60; MS (EI, 70 eV, *m/z* (%)) 104 (14), 61 (38), 59 (36), 58 (35), 43 (100).
Tricyclo[3.3.1.1^{3,7}]dec-1-yl (1-adamantyl) nitrate (**4**). See Table 1, note a: 66% yield, mp 104 °C (pentane).[21]
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