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Efficient cleavage of carboxylic *tert*-butyl and 1-adamantyl esters, and *N*-Boc-amines using H_2SO_4 in CH_2Cl_2

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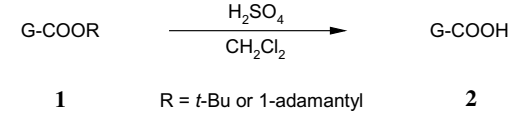
Abstract—A new procedure for the deprotection of carboxylic *tert*-butyl and 1-adamantyl esters, and *N*-Boc-amines using H_2SO_4 in CH_2Cl_2 is described. The proposed method is simple, cheap, eco-friendly and represents a valid alternative to existing ones, with special significance in large scale applications.

tert-Butylation of free carboxylic acids is a widespread procedure for the protection of the carboxyl function, receiving continuous attention in many fields of chemistry.[1] Moreover, this kind of protection found a variety of applications in peptide synthesis, both in the semipermanent masking of the α-carboxyl group of amino acids[2] and for the purpose of protecting some side chain functions.[3] A similar protection of the carboxyl function is also achieved by formation of 1-adamantyl esters.[1b,4] In the same fashion, the *tert*-butoxycarbonyl (Boc) group has been widely employed to mask the amino function,[5] finding widespread use in both organic[6] and peptide[7] synthesis.

Numerous methods are presently available for removing either the above mentioned ester protections[1a,b] or the *N*-Boc group,[5a,b,8] usually based on their easy cleavage by acids, and among them the procedure employing CF_3COOH (TFA), neat or in its concentrated CH_2Cl_2 solution, appears to be of choice.[9] Nevertheless, large scale employment of TFA presents a number of drawbacks[10] and its use in some applications is not acceptable.[11] We have recently published a convenient procedure for selective cleavage of *tert*-butyl and 1-adamantyl esters,[12] as well as for the removal of *N*-Boc protections,[13] employing HNO_3 in CH_2Cl_2. This method proved very efficient, but in some instances, involving oxidation sensitive substrates, the unmasking reaction failed, giving rise to tarry mixtures.[13] Therefore, it appeared of potential interest to perform the reaction in the same solvent, but using H_2SO_4 instead of HNO_3 as the acid, in order to avoid the oxidative action of the latter and evaluate the effectiveness of the method.[10a]

We have found that treating a number of *tert*-butyl esters (**1a**–**e**, Scheme 1, Table 1), prepared from carboxylic acids with different steric properties and potentially reactive functionality, with just the stoichiometric amount of commercial 96% H_2SO_4 in CH_2Cl_2, at rt for 6 h, gave in a smooth reaction the complete deprotection of the corresponding organic acids, which were recovered in very good yields after a simple work up (Table 1). The double bond present in substrate **1d** was remarkably left intact, as well as the amide function of the ester **1e**. Tricyclo[3.3.1.1^{3,7}]dec-1-yl 2,2-dimethylpropanoate (1-adamantyl pivalate, **1f**) reacted similarly under the same conditions, yielding 2,2-dimethylpropanoic acid (**2f**) in almost quantitative yield. In a typical procedure, a solution of the selected ester (**1**, 25.0 mmol) in CH_2Cl_2 (12.5 mL) was added dropwise into a chilled, well stirred mixture consisting of 96% H_2SO_4 (12.5 mmol) and CH_2Cl_2 (12.5 mL), and the resulting mixture was stirred for 6 h at room temperature. After this time, the reaction mixture was extracted with 2 M



Scheme 1.

Keywords: Sulfuric acid; Dichloromethane; Deprotection; *tert*-Butyl ester; *N*-Boc-amine.
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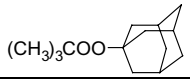
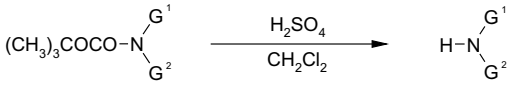
Table 1. Deprotection of *tert*-butyl and 1-adamantyl esters of carboxylic acids according to Scheme 1

Entry	Substrate	Conversion (%)[a]	Product	Yield (%)[b]
1	$(CH_3)_3CCOO$*t*-Bu (**1a**)[12a]	>99	$(CH_3)_3CCOOH$ (**2a**)	89
2	$PhCH_2COO$*t*-Bu (**1b**)[12a]	>99	$PhCH_2COOH$ (**2b**)	98
3	PhCOO*t*-Bu (**1c**)[12a]	>99	PhCOOH (**2c**)	98
4	(*E*)-PhCH=CHCOO*t*-Bu (**1d**)[12a]	98	PhCH=CHCOOH (**2d**)	96
5	$PhCH_2(AcNH)C_{(S)}HCOO$*t*-Bu (**1e**)[14]	>99	$PhCH_2(AcNH)C_{(S)}HCOOH$ (**2e**)	90
6	 (**1f**)[15]	>99	$(CH_3)_3CCOOH$ (**2f**)	96

[a] Reported conversions were determined by ^1H NMR, on intact reaction mixtures, after dilution with CH_2Cl_2, washing with 10% aqueous Na_2SO_4, drying over anhydrous Na_2SO_4, evaporation of the solvent, and redissolution in $CDCl_3$.
[b] Yields refer to isolated products.

NaOH (2 × 25 mL); the combined water phase was made acidic by addition of 37% HCl (10 mL), extracted with Et_2O (2 × 25 mL), and the combined organic phase washed with 10% aqueous Na_2SO_4, dried over anhydrous Na_2SO_4, and concentrated to dryness, affording the expected free acid (**2**) in almost quantitative yield (Table 1). The use of less than the stoichiometric amount of H_2SO_4 resulted in a marked drop of efficiency, most likely due to the consumption of the acid, captured by forming *tert*-butyl cation with production of the corresponding ester, the latter only slowly decomposing to 2-methylpropene.

The above conditions (Scheme 2) were then tested (Table 2) to perform the deblocking of a number of *N*-Boc-protected amines (**3a**–**g**) and derivatives of amino acids (**3h**,**i**). The method proved equally efficient, but a moderate excess of acid (1.5 mol H_2SO_4 per mol of substrate) was required to bring the unmasking reaction to completion, being consumed in neutralizing the formed free amine and compensating some basicity present in the substrates. The reaction was carried out by adding dropwise a solution of the selected *N*-Boc-amine (**3**, 4.0 mmol) in CH_2Cl_2 (15 mL) into a chilled, well stirred mixture consisting of 96% H_2SO_4 (6.0 mmol) and CH_2Cl_2 (5.0 mL), and stirring the resulting mixture for 6 h at room temperature. After this time, the reaction mixture was extracted with H_2O (2 × 10 mL), the aqueous phase made alkaline by addition of 4 M NaOH (4.5 mL, 18.0 mmol), treated with solid Na_2SO_4 (1.0 g), and finally extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phase was washed with 10% aqueous Na_2SO_4 (20 mL), dried over anhydrous Na_2SO_4 and concentrated to dryness, giving the desired free amine (**4**) in very good yield (Table 2). In the case of *N*-Boc-amino acid amides (**3h**,**i**), the final reaction mixture was concentrated to a small volume, the residue washed twice with hexane (2 × 10 mL), treated with NaOH (4.5 mL, 18.0 mmol), extracted with EtOAc (2 × 20 mL) and the expected products (**4h**,**i**) recovered as described above. Also in this case, the proposed method proved very efficient, being suitable even when applied to oxidation sensitive substrates,[13] like **3f** and **3g**, which were smoothly deprotected and the corresponding amines recovered in almost quantitative yields (Table 2).

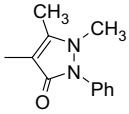


3 **4**

Scheme 2.

In conclusion, the present work has shown the advantages of the procedure employing H_2SO_4 in CH_2Cl_2 for the deprotection of carboxylic *tert*-butyl and 1-adam-

Table 2. Deprotection of *N*-Boc-amines according to Scheme 2

Entry	Substrate	G^1, G^2	Conversion (%)[a]	Product	Yield (%)[b]
1	**3a**[13]	CH_2Ph, H	>99	**4a**	93
2	**3b**[13]	CH_2Ph, CH_3	>99	**4b**	93
3	**3c**[13]	Ph, H	>99	**4c**	97
4	**3d**[13]	Ph, CH_3	>99	**4d**	96
5	**3e**[13]	$(C_6H_4)_m$-CH_3, H	>99	**4e**	98
6	**3f**[16]	$(C_6H_3)_{m,m'}$-$(CH_3)_2$, H	>99	**4f**	96
7	**3g**[13]	 , H	>99	**4g**	98
8	**3h**[17]	$C_{(S)}H(CONHCH_2Ph)CH_2Ph$, H	>99	**4h**[8,9c,18]	98
9	**3i**[19]	$C_{(S)}H(CONHCH_2Ph)CH_2OCH_2Ph$, H	>99	**4i**[20]	94

[a] Reported conversions were determined by ^1H NMR, on intact reaction mixtures, after dilution with CH_2Cl_2, washing with 10% aqueous Na_2CO_3, drying over anhydrous Na_2SO_4, evaporation of the solvent, and redissolution in $CDCl_3$.
[b] Yields refer to isolated products.

antyl esters, as well as *N*-Boc-amines and amino acids derivatives, without affecting additional functions present in the substrates. The proposed method represents a useful simple, cheap, eco-friendly and safe protocol, which is a valid alternative to existing ones, being especially suitable in large scale applications.

Acknowledgements

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16. Prepared according to Ref. 13. (3,5-dimethylphenyl)carbamic acid 1,1-dimethylethyl ester (**3f**). White solid (92% yield): mp (from pentane) 93 °C. IR (pellet) ν_{max}: 3360s, br; 2969m, br; 1696s; 1612m; 1523s; 1434m; 1365w; 1279m; 1236m; 1162s; 1078w; 1011w; 1021w; 979w; 847m; 761w; 688w; 618w cm^{-1}. ^1H NMR δ (ppm): 6.99 (app br s, 2 H, Ar–*H*); 6.71–6.64 (m, 1 H, Ar–*H*); 6.44 (br s, 1 H, BocN*H*); 2.28–2.25 (m, 6 H, ArCH_3); 1.51 [s, 9 H, OC(CH_3)$_3$]. ^{13}C NMR δ (ppm): 152.78; 138.58; 138.13; 124.70; 116.20; 80.24; 28.30; 21.31. MS (T = 20 °C) *m/z*: 121 (100); 165 (93); 57 (22); 41 (21); 120 (16); 221 (M^+, <1). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.41; H, 8.69; N, 6.31.
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19. Prepared essentially as **3h**. [(1*S*)-2-oxo-1-[(phenylmethoxy)methyl]-2-[(phenylmethyl)amino]ethylcarbamic acid 1,1-dimethylethyl ester (**3i**). White solid (54% yield): mp (from hexane) 79 °C; $[\alpha]_D^{20}$ +50.0 (*c* 1.0; $CHCl_3$). IR (pellet) ν_{max}: 3334s, br; 2930m, br; 1686s; 1659s; 1529s; 1456w; 1368w; 1304m; 1241m; 1170m; 1109w; 1021w; 873w; 739w; 697m cm^{-1}. ^1H NMR δ (ppm): 7.36–7.17 (m, 10H, Ar–*H*); 6.87 (t, J = 5.5 Hz, 1H, BnN*H*); 5.48 (d, J_{MX} = 6.3 Hz, 1H, BocN*H*); 4.53 (d, J_{AB} = 11.7 Hz, 1H, PhCH_2O); 4.47 (d, J_{AB} = 11.7 Hz, 1H, PhCH_2O); 4.44 (d,

J = 5.8 Hz, 2H, PhCH_2NH); 4.33 (br m, 1H, CH); 3.92 (dd, J_{AB} = 9.2, J_{BX} = 4.0 Hz, 1H, CHCH_2); 3.60 (dd, J_{AB} = 9.2, J_{AX} = 6.2 Hz, 1H, CHCH_2); 1.42 [s, 9H, OC(CH_3)$_3$]. ^{13}C NMR δ (ppm): 170.11; 155.32; 137.85; 137.30; 128.48; 128.33; 127.73; 127.61; 127.38; 127.24; 80.08; 73.31; 69.92; 54.05; 43.31; 28.13. MS (T = 50 °C) m/z: 91 (100); 57 (33); 150 (25); 106 (17); 41 (11); 384 (M^+, <1). Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.54; H, 7.35; N, 7.27.

20. (*S*)-2-amino-3-(phenylmethoxy)-*N*-(phenylmethyl)propanamide (**4i**). Yellow paste (94% yield): mp, n.d.; $[\alpha]_D^{20}$ +5.0 (c 1.0; $CHCl_3$). IR (pellet) ν_{max}: 3323s, br; 2928m, br; 1664s; 1624s; 1455m; 1429w; 1362w; 1248m; 1095s; 1030w; 868w; 739m; 701m; 604w; 466w cm^{-1}. ^{1}H NMR δ (ppm): 7.79 (br s, 1 H, BnNH); 7.39–7.21 (m, 10 H, Ar–H); 4.53 (s, 2 H, PhCH_2O); 4.45 (dd, J = 6.0 Hz, J_{all} = 1.3 Hz, 2H, PhCH_2NH); 3.75 (part A of an ABC spin system, J_{AB} = 9.1, J_{AC} = 6.7 Hz, 1H, CHCH_2); 3.73 (part B of an ABC spin system, J_{AB} = 9.1, J_{BC} = 3.8 Hz, 1H, CHCH_2); 3.62 (part C of an ABC spin system, J_{AC} = 6.7, J_{BC} = 3.8Hz, 1H, CH); 1.81 (br s, 2 H, NH_2). ^{13}C NMR δ (ppm): 172.59; 138.25; 137.73; 128.56; 128.38; 127.73; 127.70; 127.54; 127.27; 73.23; 72.29; 54.96; 43.05. MS (T = 50 °C) m/z: 150 (100); 91 (90); 43 (16); 151 (13); 92 (8); 284 (M^+, <1). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.75; H, 7.11; N, 9.83.