Chemoselective *N*-deprotection of *tert*-butyl 2-(trifluoroacetylamino) esters under PTC conditions: synthesis of *tert*-butyl 2-aminocarboxylates

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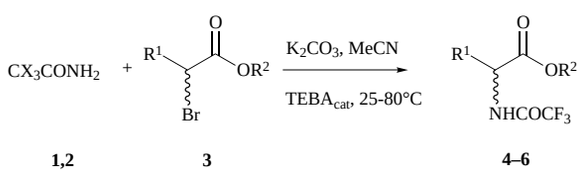
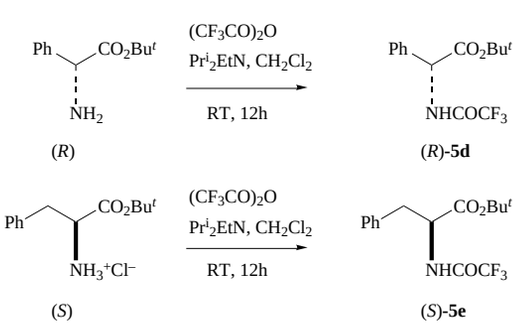
Trifluoroacetamide 1 is alkylated in good yields (77–83%) by *tert*-butyl 2-bromocarboxylates 3 under solid-liquid phase transfer catalysis (PTC) conditions [anhydrous K_2CO_3, triethyl(benzyl)ammonium chloride (TEBA; 10%), MeCN, 80 °C]. The resulting *tert*-butyl 2-(trifluoroacetylamino) carboxylates 5 are chemoselectively hydrolysed in 75–95% yields to the corresponding *tert*-butyl 2-amino carboxylates, isolated as hydrochlorides 8, under liquid-liquid PTC conditions [CH_2Cl_2 or Et_2O, aqueous 20% KOH, TEBA (10%), 25–40 °C].

Earlier we reported[1] a new method leading to α-amino acids **7** through *N*-alkylation of trihalogenoacetamides **1**, **2** (Scheme 1) with methyl or ethyl 2-bromo carboxylates **3** (R^2 = Me, Et) under solid-liquid phase transfer catalysis (SL-PTC) conditions and hydrolysis of the intermediate 2-(trihalogenoacetylamino) esters **4**, **6** with aqueous methanolic KOH. Under the above conditions both the amino acid protective groups, trihalogenoamide and ester, are simultaneously and quantitatively removed (Scheme 1), even using *tert*-butyl esters **5**, that in



1,4,5 X = F; **2,6** X = Cl; **3-5,7** R^1 = H, Alkyl, Aryl; **6** R^1= H, Alkyl; **3** R^2 = Me, Et, Bu^t; **4,6** R^2 = Me, Et; **5** R^2 = Bu^t

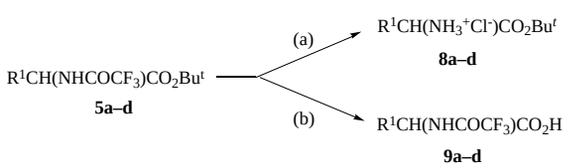


Scheme 1

the literature are described to be more resistant to basic hydrolysis conditions.

Several literature procedures[2] for the selective removal of the trifluoroacetyl group used in peptide chemistry were applied by us to the *N*-deprotection of the phenylglycine derivative **5d**: by $NaBH_4$–EtOH hydrogenolysis, 61% of the amino ester **8d** was isolated; hydrolysis with K_2CO_3–MeOH–H_2O at 25 °C after 6 h produced only 59% of **8d** together with 33% of phenylglycine **7d**; reaction of **5d** with an excess of Et_3N in MeOH at reflux gave **8d** in 26% yield and partial transesterification to the corresponding methyl amido ester.

Here we report that *tert*-butyl 2-(trifluoroacetylamino) carboxylates **5** can be converted, selectively and in good yields, into the corresponding *tert*-butyl 2-amino carboxylates **8** under liquid-liquid (LL) PTC conditions (Scheme 2, path a). Substrates **5** have, in turn, been transformed into the 2-(trifluoroacetylamino) carboxylic acids **9** in quantitative yields with trifluoroacetic acid (Scheme 2, path b), according to a known procedure.[2]



(a) (i) KOH, $TEBA_{cat}$, H_2O–organic solvent, 25–35 °C; (ii) HCl, Et_2O;
(b) CF_3CO_2H, $CHCl_3$, 70 °C

R^1 **a** = Me, **b** = Bu, **c** = $C_{10}H_{21}$, **d**: Ph

Scheme 2

Results and discussion

The starting *tert*-butyl 2-(trifluoroacetylamino) carboxylates **5a–d** were prepared in 77–83% yield (Table 1) by *N*-alkylation of trifluoroacetamide **1** under SL-PTC conditions (Scheme 1), as previously reported,[1] using the corresponding *tert*-butyl 2-bromo carboxylates **3a–d** (R^2 = Bu^t) as alkylating agents. The enantiomerically pure (*R*)-phenylglycine and (*S*)-phenylalanine derivatives, (*R*)-**5d** and (*S*)-**5e** respectively, were prepared starting from the corresponding 2-amino acid *tert*-butyl esters through amidation with trifluoroacetic anhydride (*vide infra*).

Hydrolysis of the amido function of the products **5a–e** (Scheme 2) was realised under LL-PTC conditions: a heterogeneous mixture containing an organic solution of **5** (1 mol), a PTC catalyst (0.1 mol) and 20% aqueous KOH (2.5–10 mol) was stirred at 25–40 °C. The reactions were stopped when the

highest yield of the 2-amino ester **8** product had been achieved. After work-up (see Experimental section) the products **8a–e** were isolated as hydrochlorides in 75–95% yield (Table 2). Minor amounts (4–9%) of the corresponding α-amino acids **7a–e** were obtained from the crude reaction mixture (Table 2), whereas they were the sole products isolated from the hydrolysis, under LL-PTC conditions, of methyl and ethyl amido esters **4**.

The presence of a PTC agent, like triethyl(benzyl)ammonium chloride (TEBA) or tetrabutylammonium bromide (TBAB), is essential for hydrolysis selectivity. In fact, in the absence of such catalysts, the starting esters **5** gave either low yields of the amino esters **8** or failed to react altogether. For the less lipophilic esters **5a**,**d** the solvent of choice is CH_2Cl_2, whereas the use of this solvent in the hydrolysis of the lipophilic **5b**,**c** resulted in poor yields of the corresponding amino esters **8b**,**c**. By contrast, good results, both in terms of chemoselectivity and in isolated product yields (88 and 95% of **8b** and **8c**, respectively), were obtained by conducting these reactions in Et_2O. The concentration and the molar excess of KOH used in each reaction was optimised.

The optically pure (*R*)-phenylglycine amido ester (*R*)-**5d** when hydrolysed gave *tert*-butyl 2-amino-2-phenylacetate **8d** with complete racemization of the stereogenic centre. In contrast, *tert*-butyl (*S*)-2-(trifluoroacetylamino)-3-phenylpropanoate (*S*)-**5e** gave 75% of the corresponding *N*-deprotected product (*S*)-**8e** with 77% ee (Table 2). This difference in behaviour probably arises as a result of the two α-protons having different acidity and because of the longer reaction time necessary for the reaction of the phenylglycine derivative (*R*)-**5d**. This is supported by the complete racemization observed when (*S*)-**8e** was left in contact with the hydrolysis reaction mixture for 1 month.

The hydrolysis under LL-PTC conditions probably proceeds through selective attack by the hydroxide ion on the amide carbonyl group. In fact, the presence of $CF_3CO_2^-K^+$ was detected by ^{19}F NMR analysis of the aqueous phase at the end of the reaction [$\delta(CF_3) - 56.19$ measured in water, using PhF as external standard]. Moreover no *N*-methylation of **5a** occurred when MeI was added to the LL-PTC reaction mixture (20% KOH, CH_2Cl_2, TEBA), **8a** being isolated as the sole reaction product (Scheme 3). In contrast, the aza anion of **5a**, formed with KH in MeCN under anhydrous conditions, was readily *N*-methylated in 75% yield. These last experiments confirmed that the hydrolysis of substrates **5** proceeds, as expected, without deprotonation of the trifluoroacetamide group.

The *tert*-butyl esters **5** were selectively *O*-deprotected to the corresponding 2-(trifluoroacetylamino) acids **9**, by heating a chloroform solution of **5** and an excess of anhydrous CF_3CO_2H at 70 °C.[2] After 2 h, no starting material remained, and the products **9** were isolated in quantitative yields and with high purity (> 99%).

Table 1 *tert*-Butyl 2-(trifluoroacetylamino) carboxylic esters **5a–d** prepared by alkylation of CF_3CONH_2[a]

2-Bromo ester	R^1	R^2	*t*/h	Product[b]	Yield (%)[c]	n_D^{20} or mp (*T*/°C)
3a	Me	Bu^t	24	**5a**	83	1.4024
3b	Bu	Bu^t	48	**5b**	77	1.4081
3c	$C_{10}H_{21}$	Bu^t	48	**5c**	80	41
3d	Ph	Bu^t	24	**5d**	82	85

[a] For reaction conditions see ref. 1. [b] $\delta(CDCl_3)$ **5a**, 1.45 (d, 3 H, *J* 6.0), 1.47 (s, 9 H), 4.26–4.62 (m, 1 H) and 6.92 (br s, 1 H); **5b**, 0.90 (t, 3 H, *J* 8.0), 1.12–1.95 (m, 6 H), 1.50 (s, 9 H), 4.33–4.56 (m, 1 H) and 6.81 (br s, 1 H); **5c**, 0.86 (t, 3 H, *J* 6.4), 1.08–1.97 (m, 18 H), 1.44 (s, 9 H), 4.31–4.53 (m, 1 H) and 6.81 (br s, 1 H); **5d**, 1.43 (s, 9 H), 5.41 (d, 1 H, *J* 7.3), 7.24 (br s, 1 H) and 7.38 (m, 5 H); $\delta_F(CDCl_3)$ −76.22 (s). [c] Isolated yields.

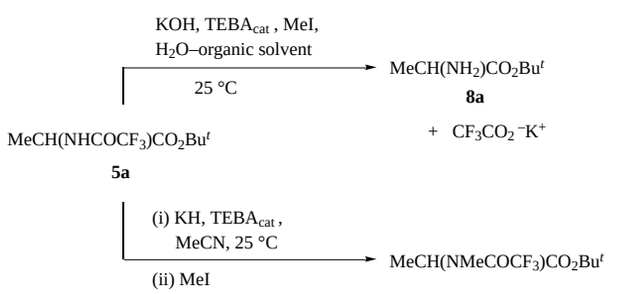
Experimental

Materials and solvents

Starting *tert*-butyl 2-bromo carboxylates **3a**,[3] **3b**,[4] **3c**[5] and **3d**[6] were prepared by standard procedures and are known compounds. (*S*)-Phenylalanine *tert*-butyl ester hydrochloride is commercially available (Sigma). (*R*)-Phenylglycine *tert*-butyl ester ($[\alpha]_D^{20}$ −107,† *c* 1.66, $CHCl_3$) was prepared by acid-catalysed esterification of (*R*)-phenylglycine with isobutylene at −78 °C, as previously reported.[7] A sample of this compound was transformed in quantitative yield into its hydrochloride with hydrogen chloride in anhydrous Et_2O; (*R*)-phenylglycine *tert*-butyl ester hydrochloride: mp 237 °C; $[\alpha]_D^{20}$ −87 (*c* 0.98, MeOH). Commercial trifluoroacetamide **1** was recrystallised from $CHCl_3$, mp 71–72 °C. *N*,*N*-Diisopropylethylamine was distilled from K_2CO_3 before use. AnalaR grade Me_3CN was dried over 0.3 nm molecular sieves and used as such. K_2CO_3 was carefully dried by heating at 140 °C *in vacuo* (0.05 mmHg) for 6 h. Amberlite IRA–93 was used to prepare the free amino acids **7a–e** from the corresponding hydrochlorides.

General methods

^{1}H NMR Spectra were recorded at 80, 200 and 300 MHz using $SiMe_4$ as external standard, ^{19}F NMR spectra were recorded at 282 MHz using fluorobenzene as external standard. Enantiomeric excesses of products (*R*)-**5d** and (*S*)-**5e** were determined by ^{19}F and ^{1}H NMR spectroscopy using $Eu(hfc)_3$ as shift reagent. Melting points are corrected. GLC analyses were obtained with an Alltech RSL-150 column (10 m × 0.35 mm, polydimethylsiloxane, 0.25 μm thickness) or a Superox II column (10 m × 0.35 mm, polyethyleneglycol, 0.25 μm thickness).



Scheme 3

† $[\alpha]_D$ Values are recorded in units of 10^{-1} deg cm^2 g^{-1}.

Table 2 *tert*-Butyl 2-amino carboxylate hydrochlorides **8a–e** prepared under PTC-LL conditions[a]

						Product		α-Amino acid	
	Substrate	R^1	Solvent	KOH (mol equiv.)	*T*/°C	Time	Yield (%)[b]		Yield (%)[c]	
	5a	Me	CH_2Cl_2	2.5	25	18 h	**8a**	89	**7a**	8
	5b	Bu	Et_2O	10.0	25	4 d	**8b**	88	**7b**	7
	5c	$C_{10}H_{21}$	Et_2O	10.0	35	7 d	**8c**	95	**7c**	4
	5d	Ph	CH_2Cl_2	2.5	25	7 d	**8d**	88	**7d**	7
	(*S*)-**5e**	Bn	CH_2Cl_2	2.5	40	24 h	(*S*)-**8e**	75[d]	(*S*)-**7e**	9

[a] For reaction conditions see Experimental section. [b] Isolated yields. [c] Isolated as hydrochlorides. [d] 77% ee.

Preparation of *tert*-butyl 2-(trifluoroacetylamino) esters (*R*)-5d and (*S*)-5e

(*R*)-*tert*-Butyl 2-(trifluoroacetylamino)phenylacetate (*R*)-5d. To a solution of (*R*)-phenylglycine *tert*-butyl ester (245 mg, 1.18 mmol) and *N*,*N*-diisopropylethylamine (234 μl, 1.20 mmol) in CH_2Cl_2 (2 ml), under argon, was added trifluoroacetic anhydride (180 μl, 1.30 mmol) by syringe. The mixture was stirred at room temperature overnight after which it was diluted with hexane (5 ml), washed with brine (3 × 5 ml), dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the residue by flash chromatography on silica gel (230–400 mesh) using Et_2O–light petroleum (1:5) as eluent afforded the enantiomerically pure (*R*)-**5d** (262 mg, 73%): mp 85 °C; $[\alpha]_D^{20}$ −148 (*c* 0.48, CH_2Cl_2). For ^{1}H NMR data see Table 1.

(*S*)-*tert*-Butyl 2-(trifluoroacetylamino)-3-phenylpropanoate (*S*)-5e. A similar procedure to that described above with (*S*)-phenylalanine *tert*-butyl ester hydrochloride (1.29 g, 5.0 mmol) and *N*,*N*-diisopropylethylamine (1.8 ml, 10 mmol) in CH_2Cl_2 (20 ml) and trifluoroacetic anhydride (0.76 ml, 5.5 mmol) gave, after work-up and flash chromatography (Et_2O–light petroleum, 1:6) enantiomerically pure (*S*)-**5e** (1.47 g, 93%); mp 40 °C; $[\alpha]_D^{20}$ +71 (*c* 1.07, CH_2Cl_2); ν_{max}(neat)/cm^{-1} 3315, 1740 and 1715; δ_H($CDCl_3$) 1.42 (s, 9 H), 3.15 (d, 2 H, *J* 5.8), 4.71 (dt, 1 H, *J* 6.0, 7.5), 6.81 (br s, 1 H), 7.13–7.19 (m, 2 H) and 7.25–7.32 (m, 3 H); δ_F($CDCl_3$) −76.37 (s) (Found: C, 56.93; H, 5.67; N, 4.32. Calc. for $C_{15}H_{18}F_3NO_3$: C, 56.77; H, 5.73; N, 4.41%).

Synthesis under PTC of *t*-butyl 2-amino carboxylates 8a–e

An organic solution (CH_2Cl_2 or Et_2O; 5 ml) of **5a–e** (1 mmol) and TEBA (23 mg, 0.1 mmol) was stirred with aqueous 20% KOH (2.5 or 10 mmol) until the highest yield of the product **8** had been reached (GLC analysis). The two layers were separated and the aqueous phase extracted twice with Et_2O. The organic phases were collected, dried ($MgSO_4$) and evaporated. The residue was dissolved in anhydrous Et_2O and anhydrous HCl was bubbled through the solution at 0 °C for a few minutes. The *tert*-butyl 2-amino carboxylate hydrochlorides crystallised from the cold solution and were filtered off. The α-amino acids **7a–d** were isolated as hydrochlorides by acidifying the aqueous phase at pH 2 with 37% HCl. On cooling, the hydrochlorides crystallised and were filtered off, washed twice with water and dried in an oven at 80 °C overnight. Starting materials, solvents, molar equivalents of 20% KOH, reaction temperature and time, yield and physical and spectroscopic data of the reaction products are as follows.

***tert*-Butyl 2-aminopropanoate hydrochloride 8a.** From **5a**; CH_2Cl_2; 20% KOH, (2.5 mol equiv.); 25 °C; 18 h; **8a**, 89%; mp 147–149 °C, (decomp.) [lit.,[3] mp 144 °C, (decomp.)]; δ_H($CDCl_3$) 1.38 (d, 3 H, *J* 7.2), 1.44 (s, 9 H), 3.89 (q, 1 H, *J* 7.2) and 8.48 (br s, 3 H). Alanine hydrochloride was obtained in 8% yield; free alanine **7a** was obtained by exchange with a basic polymeric resin and had mp 290 °C (lit.,[8] mp 298 °C).

***tert*-Butyl 2-aminohexanoate hydrochloride 8b.** From **5b**; Et_2O; 20% KOH (10 mol equiv); 25 °C; 4 d; **8b**, 88%; mp 129–131 °C (decomp.) (lit.,[9] mp not reported); δ_H($CDCl_3$) 0.79–0.97 (m, 3 H), 1.16–1.49 (m, 4 H), 1.48 (s, 9 H), 1.73–2.20 (m, 2 H), 3.90 (t, 1 H, *J* 5.9) and 8.78 (br s, 3 H) (Found: C, 53.80; H, 9.86; N, 6.35. Calc. for $C_{10}H_{22}ClNO_2$: C, 53.67; H, 9.93; N, 6.26%). 2-Aminohexanoic acid hydrochloride was obtained in 7% yield; free amino acid **7b** had mp 295–297 °C (decomp.) (lit.,[8] mp 297–300 °C).

***tert*-Butyl 2-aminododecanoate hydrochloride 8c.** From **5c**; Et_2O; 20% KOH (10 mol equiv.); 35 °C; 7 d; **8c**, 95%; mp 103–104 °C; δ_H($CDCl_3$) 0.85 (t, 3 H, *J* 7.1), 0.94–1.71 (m, 16 H), 1.48 (s, 9 H), 1.73–1.88 (m, 2 H), 3.80–3.84 (m, 1 H) and 7.68 (br s, 3 H) (Found: C, 62.23; H, 11.27; N, 4.40. Calc. for $C_{16}H_{34}ClNO_2$: C, 62.40; H, 11.15; N, 4.55%). 2-Aminododecanoic acid hydrochloride was obtained in 4% yield; free amino acid **7c** had mp 260 °C, (decomp.) [lit.,[8] mp 263 °C (decomp.)].

***tert*-Butyl phenylglycinate hydrochloride 8d.** From **5d**; CH_2Cl_2; 20% KOH (2.5 mol equiv.); 25 °C; 7 d; **8d**, 88%; mp 226–228 °C, (decomp.); δ_H($CDCl_3$) 1.38 (s, 9 H), 5.03 (s, 1 H), 7.47 (m, 5 H) and 9.03 (br s, 3 H) (Found: C, 59.01; H, 7.57; N, 5.68. Calc. for $C_{12}H_{18}ClNO_2$: C, 59.12; H, 7.46; N, 5.75%). Phenylglycine hydrochloride was obtained in 7% yield; free amino acid **7d** had mp 263–265 °C (decomp.) [lit.,[8] mp 256 °C. (subl.)].

(*S*)-*tert*-Butyl 3-phenylalaninate hydrochloride (*S*)-8e. From **(*S*)-5e**; 20% KOH (2.5 mol equiv.); 40 °C; 24 h; (*S*)-**8e**, 75% $[\alpha]_D^{20}$ +20 (*c* 0.75, MeOH), 77% ee [a commercial sample of (*S*)-**8e** had $[\alpha]_D^{20}$ +26; *c* 0.75, MeOH]. (*S*)-Phenylalanine hydrochloride was obtained in 9% yield; free amino acid (*S*)-**7e** had mp 280–281 °C (decomp.) [lit.,[8] 283–284 °C (decomp.)].

Synthesis of 2-(trifluoroacetyl-2-amino)carboxylic acids 9a–e

A solution of **5a–d** (1 mmol) and CF_3CO_2H (20 mmol) in $CHCl_3$ (1 ml) was heated at 70 °C for 2 h and then evaporated. The crude reaction mixture was recrystallised (Pr^i_2O–hexane) and the products **9a–d** were isolated in quantitative yield by filtration. Physical and spectroscopic data are as follows: **9a**, mp 119–120 °C (lit.,[10] 120–121 °C); **9b**, mp 78–80 °C (lit.,[11] 79–82.5 °C); **9c**, mp 101 °C; δ_H($CDCl_3$) 0.88 (t, 3 H, *J* 8.0), 1.06–1.59 (m, 16 H), 1.65–2.18 (m, 2 H), 4.53–4.87 (m, 1 H), 5.74 (br s, 1 H) and 6.78 (d, 1 H, *J* 8.4); **9d**, mp 153–154 °C (lit.,[12] 153–155 °C); (*S*)-**9e**, mp 121 °C (lit.,[10] 121–122 °C).

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