A Facile Method for the Transformation of *N*-(*tert*-Butoxycarbonyl) α-Amino Acids to *N*-Unprotected α-Amino Methyl Esters

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Methyl *N*-unprotected α-amino esters are important intermediates in organic synthesis.[1] They can be conveniently prepared by a Fisher-type esterification of the corresponding free α-amino acids in methanol using gaseous HCl,[1a] $SOCl_2$,[1b] or TMSCl.[1c] In addition, an increasing number of methods have been developed for the preparation of α-amino acids with the α-nitrogen atom already protected by a Boc group.[2−7] For example, oxidations of *N*-Boc *β*-amino alcohols,[2] *N*-Boc benzylamines,[3] *N*-Boc furfurylamines,[4] and *N*-Boc allylamines[5] afford directly *N*-Boc α-amino acids. Reduction of *N*-Boc α-amino-α,*β*-unsaturated carboxylic acids also gives *N*-Boc α-amino acids.[6] It is therefore of importance to develop a method for the direct transformation of *N*-Boc α-amino acids to methyl *N*-unprotected α-amino esters without prior deprotection of the *N*-Boc group and isolation of the free α-amino acid intermediate.

Previously, the transformation of *N*-Boc α-amino acids to methyl *N*-unprotected α-amino esters was carried out in two steps: (i) ester formation of the carboxylic acid using diazomethane[1d,8,9] or iodomethane in the presence of a base[1d−f,10] and (ii) deprotection of the *N*-Boc group of the resulting ester with an acid such as hydrochloric acid,[1e−g,11] trifluoroacetic acid,[1d,12] or boron trifluoride.[13] Although the overall yields are usually satisfactory, this method is limited, especially for large scale preparation, as a result of the safety concern with diazomethane and the competitive *N*-methylation in the case of iodomethane.[14] Treatment of *N*-Boc-*O*-methyl tyrosine with methanolic HCl was reported by Rosenberg and coworkers in a footnote without experimental details or yield to give *O*-methyl tyrosine methyl ester hydrochloride.[15]

MeOH/TMSCl is a facile system for the preparation of methyl esters from carboxylic acids.[16] Compared to the conventional gaseous HCl in methanol used for esterification, use of TMSCl is more advantageous not only because it is more convenient to use and measure but also because it acts as a water scavenger so that the esterification is faster and cleaner. In theory, at least 1 equiv of HCl is generated in the esterification of carboxylic acid with TMSCl/MeOH. We envisioned that this HCl generated in situ may affect the deprotection of the *N*-Boc group if an *N*-Boc α-amino acid is used. Thus, treatment of L-*N*-Boc-phenylalanine in methanol with TMSCl at room temperature for 2 h gave 19% of the desired product, phenylalanine methyl ester (**4**, M + H = 180), in addition to two intermediate peaks and complete disappearance of the starting material by reverse-phase HPLC and LC/MS. The major peak, moving more slowly than **4** or **1**, was *N*-Boc-phenylalanine methyl ester (**2**, 62%, M + H = 280), whereas the fastest eluting peak was the *N*-Boc deprotection intermediate phenylalanine (**3**, 19%). Upon further stirring, both **2** and **3** underwent *N*-Boc deprotection and esterification, respectively, to give **4**, with the former reaction being faster than the latter. After stirring overnight, the desired product, L-phenylalanine methyl ester hydrochloride (**4**), was obtained in 94% yield by removing the solvent and crystallizing the product with ether (Scheme 1 and Table 1, entry 1). Importantly, no racemization took place in

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Scheme 1

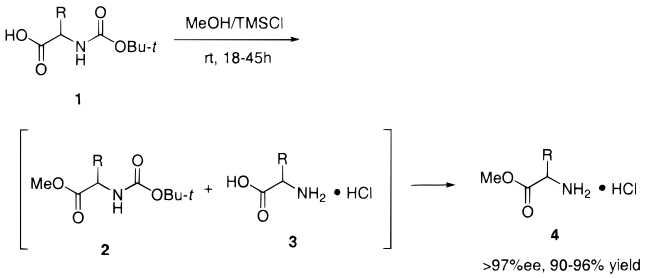


Table 1. Preparation of α-Amino Methyl Esters 4 from *N*-Boc α-Amino Acids 1

entry	substrate	R	time (h)	product	% ee[b]	yield (%)[a]
1	(*S*)-**1a**	$PhCH_2$	19	(*S*)-**4a**	>99.9	94
2	(*R*)-**1a**	$PhCH_2$	19	(*R*)-**4a**	>99.9	96
3	(*S*)-**1b**	$4\text{-MeOC}_6H_4CH_2$	18	(*S*)-**4b**	98.2	95
4	(*R*)-**1b**	$4\text{-MeOC}_6H_4CH_2$	22	(*R*)-**4b**	99.7	90
5	(*S*)-**1c**	$4\text{-HOC}_6H_4CH_2$	21	(*S*)-**4c**	>99.9	93
6	(*R*)-**1d**	$4\text{-FC}_6H_4CH_2$	24	(*R*)-**4d**	>99.9	97
7	(*S*)-**1e**	Me	18	(*S*)-**4e**	>99.9[c]	91
8	(*R*)-**1f**	Ph	45	(*R*)-**4f**	97.4	91

[a] Isolated yield by crystallization. [b] Determined by chiral HPLC. [c] As *N*-Cbz derivative.

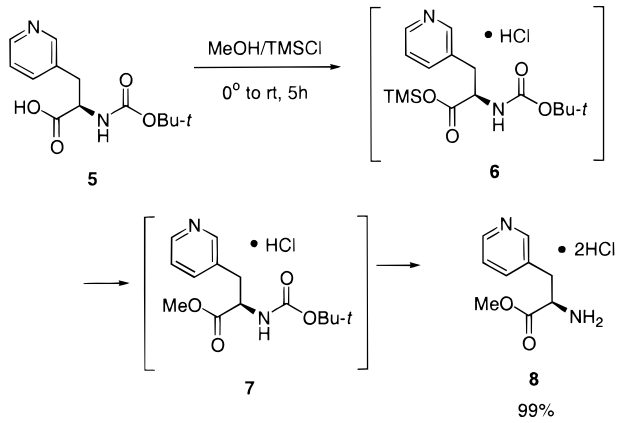
the reaction as evidenced by chiral HPLC analyses of the isolated product and the reaction mixture prior to work-up.

As can be seen from the results summarized in Table 1, this new reaction works well not only for *N*-Boc-phenylalanines (Table 1, entries 1−6) but also for *N*-Boc-alanine itself (Table 1, entry 7). In all cases, the desired α-amino methyl ester hydrochlorides **4** are isolated in >90% yield by simply removing solvent and crystallizing the product with ether. It should be pointed out *N*-Boc-tyrosine (**1c**) gives tyrosine methyl ester hydrochloride (**4c**) in 93% yield and >99.9% ee without any effect on the free 4-hydroxy group. This is advantageous compared to the previous method using iodomethane and base for the ester formation, in which ether formation takes place competitively.[17] More importantly, the racemization-prone phenylglycine methyl ester hydrochloride (**4f**) can be obtained in 97.4% ee and 91% yield (Table 1, entry 8) under the new reaction conditions.[24]

The new reaction also worked well with *N*-Boc amino acids having a basic side chain. For example, reaction of (*R*)-*N*-Boc-3-(3-pyridyl)alanine (**5**) with methanol and TMSCl at room temperature for 5 h afforded (*R*)-3-(3-pyridyl)alanine methyl ester dihydrochloride (**7**) in quantitative yield (Scheme 2). The shorter reaction time needed for this reaction may be a consequence of the faster formation of ester **7** resulting from rapid methanolysis of the initially formed TMS ester intermediate **6** due to the internal pyridine base in the starting material.[18] With neutral *N*-Boc amino acids **1**, the Fischer-type esterification of the intermediate **3** was a much slower process under these reaction conditions.

In summary, a facile method for the transformation of *N*-Boc α-amino acids to *N*-unprotected α-amino methyl esters has been developed. Compared to the previous stepwise procedures for the same transformation, the new one-pot synthesis not only is simpler in manipulations but also gives higher yields. The new method does not require chromatographic separation of products and can be readily scaled up for the preparation of α-amino methyl esters in excellent enantiomeric excesses (>97% ee) and yields (90−97%).

Scheme 2



Experimental Section

Proton and carbon-13 NMR spectra were recorded in DMSO-d_6 using TMS as internal standard. Melting points are uncorrected. Chiral HPLC analyses on compounds **4a**−**d** and **4f** were performed using a DAICEL Crownpak CR(+) chiral column, with 0.01 N HCl_4/H_2O (90:10 v/v) as eluent, 1.0 mL/min flow rate, and 200 nm detection wavelength. The enantiomeric excess of compound **4e**, after being derivatized to *N*-benzyloxycarbonyl alanine methyl ester with CbzCl and diisopropylethylamine in dichloromethane at room temperature, was determined using a Chiralpak-AS column, with a 35 min gradient from 0:100 to 50:50 2-PrOH/hexane, 1.0 mL/min flow rate, and 254 nm detection wavelength.

Preparation of α-Amino Methyl Ester Hydrochloride 4 from *N*-Boc α-Amino Acid 1. In a 100 mL round-bottomed flask equipped with a magnetic stirrer was placed an *N*-Boc α-amino acid (**1**, 10 mmol) and methanol (30 mL). The mixture was stirred at room temperature to give a solution. TMSCl (5 mL, 50 mmol) was added. The reaction mixture was stirred at room temperature for 18−45 h. The solvent was removed under vacuo. Anhydrous ether (60 mL) was added. The slurry was stirred for 15 min and then filtered. The cake was washed with ether (2 × 5 mL) and dried to give α-amino methyl ester hydrochloride **4**.

(*S*)-Phenylalanine methyl ester hydrochloride, *(S)*-4a: 94% yield; >99.9% ee by chiral HPLC; $[\alpha]_D$ +35.7° (*c* 1.06, abs EtOH), lit.[19] $[\alpha]_D$ +35.0° (*c* 1.0, abs EtOH); mp 160−161 °C, lit.[19] mp 153−154 °C. The spectroscopic data were consistent with the structure of the product.

(*R*)-Phenylalanine methyl ester hydrochloride, (*R*)-4a: 96% yield; >99.9% ee by chiral HPLC; $[\alpha]_D$ −35.7° (*c* 1.1, abs EtOH), lit.[19] $[\alpha]_D$ +35.0° (*c* 1.0, abs EtOH) for (*S*)-**4a**; mp 160−162 °C, lit.[19] mp 153−154 °C for (*S*)-**4a**. The spectroscopic data were consistent with the structure of the product.

(*S*)-*O*-Methyltyrosine methyl ester hydrochloride, (*S*)-4b: 95% yield; 98.2% ee by chiral HPLC; $[\alpha]_D$ +68.4° (*c* 1.65, pyridine), lit.[20] $[\alpha]_D$ +68° (*c* 1.04, pyridine); mp 191−193 °C, lit.[20] mp 194−196 °C. The spectroscopic data were consistent with the structure of the product.

(*R*)-*O*-Methyltyrosine methyl ester hydrochloride, (*R*)-4b: 90% yield; 99.7% ee by chiral HPLC; $[\alpha]_D$ −66.6° (*c* 1.55, pyridine), lit.[20] $[\alpha]_D$ −68° (*c* 1.04, pyridine); mp 182−184 °C, lit.[20]

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mp 189−190 °C. The spectroscopic data were consistent with the structure of the product.

(*S*)-Tyrosine methyl ester hydrochloride, (*S*)-4c: 93% yield; >99.9% ee by chiral HPLC; $[\alpha]_D$ +71.4° (*c* 2.92, pyridine), lit.[21] $[\alpha]_D$ +75.4° (*c* 2.3, pyridine); mp 190−191 °C, lit.[21] mp 191−192 °C. The spectroscopic data were consistent with the structure of the product.

(*R*)-4-Fluorophenylalanine methyl ester hydrochloride, (*R*)-4d: 97% yield; >99.9% ee by chiral HPLC; $[\alpha]_D$ −34.3° (*c* 1.025, EtOH), lit.[22] $[\alpha]_D$ +32.2° (*c* 1, EtOH) for (*S*)-**2c** with 99.4% ee; mp 199−200 °C, lit.[22] mp 195−199 °C for (*S*)-**4c**. The spectroscopic data were consistent with the structure of the product.

(*S*)-Alanine methyl ester hydrochloride, (*S*)-4e: 91% yield; >99.9% ee by chiral HPLC determined as *N*-Cbz derivative; $[\alpha]_D$ +7.4° (*c* 1.76, MeOH), lit.[23] $[\alpha]_D$ +6.8° (*c* 2, MeOH); mp 98−99 °C, lit.[23] mp 100 °C. The spectroscopic data were consistent with the structure of the product.

(*R*)-Phenylglycine methyl ester hydrochloride, (*R*)-4f: 91% yield; 97.4% ee by chiral HPLC; $[\alpha]_D$ −142.7° (*c* 1.03, MeOH), lit.[24] $[\alpha]_D$ −131.0° (*c* 1.0, MeOH); mp 203−204 °C, lit.[24] mp 200−203 °C. The spectroscopic data were consistent with the structure of the product.

Preparation of (*R*)-3-(3-Pyridyl)alanine Methyl Ester Dihydrochloride (8). To a 2 L three-necked round-bottomed flask equipped with a mechanical stirrer was added (*R*)-*N*-Boc-3-(3-pyridyl)alanine (**5**, 90.4 g, 0.3394 mol) and methanol (400 mL). The mixture was stirred under nitrogen to give a solution. After the mixture was cooled to 0 °C with an ice−water bath, TMSCl (204 mL, 1.6074 mol) was added over 30 min. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 5 h. Anhydrous ether (600 mL) was added. The slurry was stirred for 30 min and then filtered. The cake was washed with anhydrous ether (2 × 200 mL) and dried under vacuum to give (*R*)-3-(3-pyridyl)alanine methyl ester dihydrochloride, **8** (84.9 g, 98.8%): mp 182−186 °C; $[\alpha]_D$ −19.6° (*c* 1.0, MeOH); IR (KBr) 3119, 2945, 2799, 1744, 1558, 1501, 1218 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.83−9.05 (m, 5H), 8.59−8.63 (m, 1H), 8.07−8.11 (m, 1H), 4.42−4.55 (m, 1H), 3.75 (s, 3H), 3.43−3.55 (m, 3H); ^{13}C NMR (DMSO-d_6) δ 169.0, 147.4, 142.7, 140.6, 135.7, 127.4, 53.4. 52.5, 32.3; MS, M + H, 181. Anal. Calcd for $C_9H_{12}N_2O_2 \cdot 2HCl$: C, 42.71; H, 5.57; N, 11.07; Cl, 28.01. Found: C, 42.51; H 5.59; N, 11.00; Cl, 28.08.

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