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Convenient Preparation of Primary Amides via Activation of Carboxylic Acids with Ethyl Chloroformate and Triethylamine under Mild Conditions

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Primary amides were easily prepared in 22–99% yields from the corresponding carboxylic acids **1** or **5** with NH_4Cl via activation with $ClCO_2Et$ and Et_3N. The enantiomers of the corresponding primary amides of Cbz-, Boc-, or Fmoc-α-amino acids can be separated by using a chiral column.

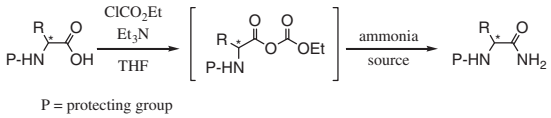
The classical methods for amide synthesis are the reactions of amines with activated carboxylic acids such as acyl halides, acyl azides, acyl imidazoles, esters, anhydrides, or carbonic carboxylic anhydrides.[1] However, the syntheses of primary amides from these intermediates with ammonia have been limited because the nucleophilicity of ammonia is lower than those of primary and secondary amines. The reaction must be carried out at a high pressure and/or low temperature because ammonia boils at −33 °C under a pressure of 1 atm. In these cases, the solubility of the starting materials in water is also important. Recently, the preparation of primary amides using NH_4OH via the activation of carboxylic acids with 1-(methanesulfonyl)benzotriazole and Et_3N[2] or with 1-hydroxybenzotriazole (HOBt) and *N*,*N*′-dicyclohexylcarbodiimide (DCC)[3] has been reported. Kunishima has reported a simple and practical method for the preparation of primary amides, in which NH_4Cl, Et_3N, and a typical coupling reagent for peptide synthesis, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM), were used.[4] We have just shown that the amidation of N-protected α-amino acids with unprotected α-amino acids via the mixed carbonic carboxylic anhydrides provides the corresponding dipeptides without *C*-protection in good to excellent yields.[5]

Herein, we describe the preparation of primary amides from the corresponding carboxylic acids with an ammonia source via activation with $ClCO_2Et$ and Et_3N (Scheme 1). It was found that the enantiomers of the corresponding primary amides of Cbz-, Boc-, and Fmoc-phenylalanines or Cbz-α-amino acids are separable by high-pressure liquid chromatography (HPLC) using Chiralcel AD, OD, or OJ.

In a preliminary investigation, the reaction of 3-phenylpropanoic acid (**1a**) with 1.5 equivalents of an ammonia source (NH_3, NH_4OH, NH_4Cl, or $MeCO_2NH_4$) in the presence of 1.4 equivalents of $ClCO_2Et$ and 3.0 equivalents of Et_3N in tetrahydrofuran (THF) afforded 3-phenylpropanamide (**2a**) in excellent yields, as indicated in Table 1. The best yield (99%, Entry 3) was obtained using NH_4Cl, which is very easy to handle.

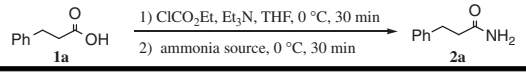
The results of the primary amidation of several kinds of carboxylic acids **1a**–**1i** using NH_4Cl via the corresponding mixed carbonic carboxylic anhydride are collected in Table 2. The reactions of cinnamic acid (**1b**) and the derivative **1c** as a conjugated carboxylic acid afforded the corresponding primary amides **2b** and **2c** in 77% and 70% yields, respectively (Entries 2 and 3). Even with the sterically hindered pivalic acid (**1d**), the reaction proceeded easily to afford the corresponding primary amide **2d** in excellent yield (Entry 4), which was similar to the case of **2a**. 4-Methoxybenzoic acid (**1i**) containing an electron-donating group reacted to afford 4-methoxybenzamide (**2i**) in 22% yield (Entry 9), although benzoic acid (**1e**), 4-nitrobenzoic acid (**1f**), and acetylsalicylic acid (**1g**) containing electron-withdrawing groups were converted to benzamide (**2e**), 4-nitrobenzamide (**2f**), and acetylsalicylamide (**2g**) in 67%, 85%, and 65% yields, respectively (Entries 5–7). Salicylic acid (**1h**) reacted with NH_4Cl using 2.8 equivalents of $ClCO_2Et$ to afford 2-ethoxycarbonyloxybenzamide in 52% yield (Entry 8). Unfortunately, the reaction of 4-methoxybenzoic acid (**1i**) gave a low yield because the presence of a strong electron-donating group on the aromatic ring deactivates the carbonyl carbon (**A**) through the resonance effect (Entry 9). Then, the amidation of **1i** with NH_4Cl via activation with $ClCO_2i$-Bu was carried out to afford the corresponding amide **2i** in 19% yield (Entry 10). For example, the reaction of the mixed carbonic carboxylic anhydride of **1i** with benzylamine afforded the corresponding *N*-benzyl-4-methoxybenzamide (**3i**) in 31% yield with 50% yield (based on benzylamine) of the by-product **4i** and 40% yield of **1i**, as shown in Scheme 2.

Furthermore, the primary amidation of Cbz-L-Phe-OH **5a** with NH_3/MeOH, NH_4OH/H_2O, $MeCO_2NH_4/H_2O$, or NH_4Cl/H_2O as the ammonia source using $ClCO_2Et$ and Et_3N afforded Cbz-L-Phe-NH_2 **6a** in 83%, 90%, 88%, and 92% yields,



Scheme 1.

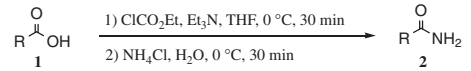
Table 1. Primary amidation of 3-phenylpropanoic acid (**1a**)[a]



Entry	Ammonia source	Yield[e]/%
1	NH_3/MeOH[b]	97
2	NH_4OH/H_2O[c]	97
3	NH_4Cl/H_2O[d]	99
4	$MeCO_2NH_4/H_2O$[d]	93

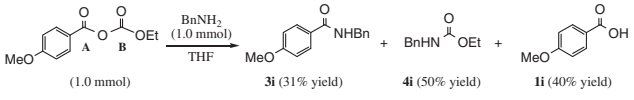
[a]All reactions were carried out with 1.0 mmol of **1a**, 1.4 mmol of $ClCO_2Et$, and 3.0 mmol of Et_3N in 20 mL of THF. After stirring for 30 min at 0 °C, 1.5 mmol of ammonia source was added at 0 °C to the reaction mixture. [b]2.0 mol L^{-1} methanol solution was used. [c]28% aqueous solution was used. [d]1.0 mol L^{-1} aqueous solution was used. [e]Isolated yield.

Table 2. Primary amidation of carboxylic acids **1** with ammonium chloride[a]



Entry	R	2	Yield[b]/%
1	$C_6H_5CH_2CH_2$	**2a**	99
2	$C_6H_5CH{=}CH$	**2b**	77
3[c]	4-$MeOC_6H_5CH{=}CH$	**2c**	70
4	*t*-Bu	**2d**	94
5	C_6H_5	**2e**	67
6	4-$NO_2C_6H_4$	**2f**	85
7	2-$AcOC_6H_4$	**2g**	65
8[d]	2-HOC_6H_4	**2h**	0[e]
9	4-$MeOC_6H_4$	**2i**	22
10[f]	4-$MeOC_6H_4$	**2i**	19

[a]All reactions were carried out with 1.0 mmol of **1**, 1.4 mmol of $ClCO_2Et$, and 3.0 mmol of Et_3N in 20 mL of THF. After stirring for 30 min at 0 °C, 1.5 mmol of a 1.0 mol L^{-1} aqueous solution of NH_4Cl was added at 0 °C to the reaction mixture. [b]Isolated yield. [c]This reaction was carried out with 0.5 mmol of **1c**, 0.7 mmol of $ClCO_2Et$, and 1.5 mmol of Et_3N in 10 mL of THF. After stirring for 30 min at 0 °C, 0.75 mmol of a 1.0 mol L^{-1} aqueous solution of NH_4Cl was added at 0 °C to the reaction mixture. [d]This reaction was carried out with 1.0 mmol of **1h**, 2.8 mmol of $ClCO_2Et$, and 3.0 mmol of Et_3N in 20 mL of THF. After stirring for 30 min at 0 °C, 1.5 mmol of a 1.0 mol L^{-1} aqueous solution of NH_4Cl was added at 0 °C to the reaction mixture. [e]This reaction afforded 2-ethoxycarbonyloxybenzamide in 52% yield. [f]$ClCO_2$*i*-Bu was used instead of $ClCO_2Et$.

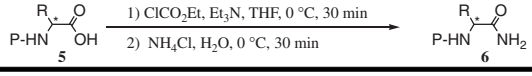


Scheme 2. Reaction of the mixed carbonic carboxylic anhydride of **1i** with benzylamine.

respectively, as a single enantiomer through HPLC analysis using Chiralcel AD in these cases.[6] The best result (92% yield) was obtained using NH_4Cl, as indicated in Entry 1 of Table 3. The reactions of N-protected α-amino acids **5a**–**5g** with NH_4Cl as an ammonia source were carried out, and the results are collected in Table 3. Cbz-D-Phe-OH **5a′** reacted with NH_4Cl under similar conditions to Entry 1 to afford Cbz-D-Phe-NH_2 **6a′** in 92% yield as the D-form enantiomer (Entry 2). The reactions of L- and D-phenylalanine derivatives **5b**, **5c** and **5b′**, **5c′** protected with other conventional groups such as 9-fluorenylmethoxycarbonyl (Fmoc) and *tert*-butoxycarbonyl (Boc) afforded the corresponding primary amides **6b**, **6c** and **6b′**, **6c′** through HPLC analysis using Chiralcel OJ in 87–96% yields, and no racemization was observed (Entries 3–6). Finally, the reactions of several kinds of Cbz-L- and D-α-amino acids **5d**–**5g** and **5d′**–**5g′** with NH_4Cl under mild conditions gave the corresponding primary amides **6d**–**6g** and **6d′**–**6g′** through HPLC analysis using Chiralcel AD or OD in 69–96% yields with >99% *ee* (Entries 7–14).

In conclusion, we have found that primary amides **6** are prepared in 69–96% yields from the corresponding N-protected

Table 3. Preparation of primary amides derived from N-protected α-amino acids **5**[a]



Entry	Product **6**	Yield[c] /%	%ee[d]	Chiralcel	Eluent /%	Retention time /min
1	Cbz-L-Phe-NH_2 **6a**	92	>99	AD	10	23.6
2	Cbz-D-Phe-NH_2 **6a′**	92	>99	AD	10	19.2
3[b]	Fmoc-L-Phe-NH_2 **6b**	87	>99	OJ	10	20.9
4[b]	Fmoc-D-Phe-NH_2 **6b′**	90	>99	OJ	10	40.0
5	Boc-L-Phe-NH_2 **6c**	90	>99	OJ	2	45.6
6[b]	Boc-D-Phe-NH_2 **6c′**	96	>99	OJ	2	29.0
7	Cbz-L-Ala-NH_2 **6d**	91	>99	OD	8	31.5
8	Cbz-D-Ala-NH_2 **6d′**	91	>99	OD	8	38.5
9	Cbz-L-Val-NH_2 **6e**	96	>99	OD	5	31.8
10	Cbz-D-Val-NH_2 **6e′**	91	>99	OD	5	37.6
11	Cbz-L-Met-NH_2 **6f**	90	>99	AD	10	21.7
12	Cbz-D-Met-NH_2 **6f′**	94	>99	AD	10	26.8
13	Cbz-L-Gln-NH_2 **6g**	69	>99[e]	AD	10	50.2
14	Cbz-D-Gln-NH_2 **6g′**	74	>99[e]	AD	10	43.0

[a]All reactions were carried out with 0.5 mmol of **5**, 0.7 mmol of $ClCO_2Et$, and 1.5 mmol of Et_3N in 10 mL of THF. After stirring for 30 min at 0 °C, 0.75 mmol of a 1.0 mol L^{-1} aqueous solution of NH_4Cl was added at 0 °C to the reaction mixture. [b]These reactions were carried out with 0.2 mmol of **5**, 0.28 mmol of $ClCO_2Et$, and 0.6 mmol of Et_3N in 4 mL of THF. After stirring for 30 min at 0 °C, 0.3 mmol of a 1.0 mol L^{-1} aqueous solution of NH_4Cl was added at 0 °C to the reaction mixture. [c]Isolated yield. [d]Determined by HPLC analysis with a mixture of hexane–isopropanol as an eluent using Chiralcel AD, OD, or OJ (1.0 mL min^{-1}). [e]Determined by HPLC analysis with a 90:10:0.1 mixture of hexane–isopropanol–Et_2NH as an eluent using Chiralcel AD (1.0 mL min^{-1}).

α-amino acids **5** by using NH_4Cl under mild conditions, and that racemization does not occur in our developed method. Further investigations on this type of reaction are underway in our group.

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6 A typical procedure of the primary amidation of **5a** using $ClCO_2Et$ is as follows. To a solution of 150 mg (0.5 mmol) of Cbz-L-Phe-OH **5a** in 10 mL of THF, 67 µL (0.7 mmol, 1.4 equiv) of $ClCO_2Et$ and 208 µL (1.5 mmol, 3.0 equiv) of Et_3N were added at 0 °C. After stirring for 30 min at 0 °C, 0.75 mL of a 1.0 M aqueous solution of NH_4Cl (0.75 mmol, 1.5 equiv) was added at 0 °C to the colorless suspension. The mixture was stirred for 30 min at 0 °C, and 10 mL of water was added at 0 °C to the mixure. The resulted colorless clear solution was extracted with 100 mL of EtOAc, washed with 10 mL of brine, and dried over anhydrous $MgSO_4$. The crude product was recrystallized from 60 mL of a 1:9 mixture of chloroform and hexane to afford 137 mg (92% yield) of **6a** (Cbz-L-Phe-NH_2). **6a**: colorless powder; ^{1}H NMR ($CDCl_3$): δ 3.02–3.15 (2H, m, CH_2), 4.42–4.45 (1H, m, CH), 5.08 (2H, s, CH_2), 5.34 (1H, d, $J = 7.5$ Hz, NH), 5.49 (1H, brs, NH), 5.74 (1H, brs, NH), 7.20–7.38 (10H, m, $C_6H_5 \times 2$).

