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Convenient primary amidation of N-protected phenylglycine and dipeptides without racemization or epimerization

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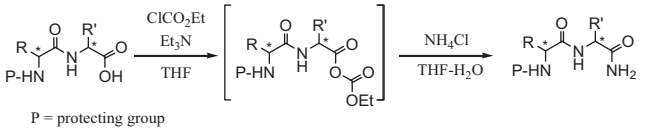
ABSTRACT

Primary amidation of N-protected phenylglycine and dipeptide proceeded easily to afford the corresponding amides in 57–95% yields with 99% ee and 81–99% de, respectively. The procedure is very easy to avoid racemization and epimerization of the products in the reactions by keeping exactly the reaction temperature at −15 °C when the activation of carboxylic acids, followed by the reaction of the mixed carbonic carboxylic anhydride with NH_4Cl.

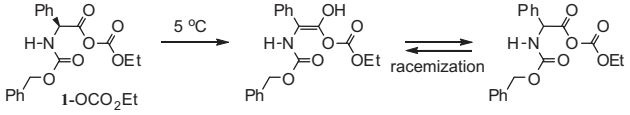
Recently, we have developed that the amidation of N-protected α-amino acids with unprotected α-amino acids, NH_4Cl, and aniline derivatives via the mixed carbonic carboxylic anhydrides provided the corresponding dipeptides, primary amides, and anilides in good to excellent yields.[1] Unfortunately, it was found that the produced primary amides of phenylglycine and dipeptides were racemized or epimerized[2] under the reaction conditions in our developed method.

Herein, we describe preparation of primary amides from the corresponding phenylglycine (Phg-OH) and dipeptides with NH_4Cl via activation by $ClCO_2Et$ and Et_3N without racemization or epimerization (Scheme 1).

In a preliminary investigation, the reaction of Cbz-L-Phg-OH (**1**) with 1.5 equiv of NH_4Cl in the presence of 1.4 equiv of $ClCO_2Et$ and 3.0 equiv of Et_3N in aqueous tetrahydrofuran (THF) at ice-cooled temperature (5 °C) afforded Cbz-L-Phg-NH_2 (**1**) in 43% yield with 46% ee as indicated in entry 1 of Table 1. When the reaction was carried out for 0.5 h at 0 °C on the step (2), the ee was improved to 67% (entry 3). When the reaction temperature was decreased to −5 °C on both steps (1) and (2), the corresponding primary amide **2** was obtained with 83% ee as shown in entry 6. Effect of decreasing the reaction temperature until −15 °C was amazingly well and an excellent enantioselectivity (93% ee) was observed. The reaction conditions were further optimized by using precooled reagents on both steps (1) and (2) and the best results (83% yield, 99% ee) were obtained when the reaction was carried out for



Scheme 1.



Scheme 2. Possible pathway for racemization of **1**-OCO_2Et.

10 min at −15 °C on the step (1) and for 24 h at −15 °C on the step (2) as described in entry 11. In order to make sure that the optimized reaction conditions are best, the reaction time was checked on 15, 60, and 120 min for the step (1) and on 0.5, 3, and 48 h for the step (2) as indicated in entries 12–17. Longer reaction times of the step (1) decreased the enantiomer excesses (97–26% ee, entries 12, 13, and 14). Then, shorter reaction times of the step (2) decreased the reaction yields (77–73% yields, entries 16 and 15) and longer reaction time of the step (2) did not give any change in both the yield and the enantiomer excess (entry 17). It is well known that Cbz-L-Phg-OH (**1**) is easily racemized under various kinds of reaction conditions because of the reactivity of the benzyl position on it as shown in Scheme 2.

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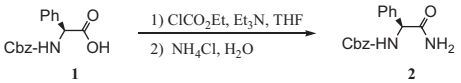
Table 1
Primary amidation of Cbz-L-Phg-OH (**1**)[a]

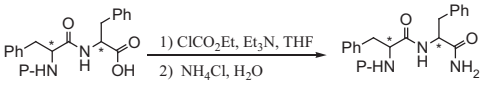


1 2

Entry	Step (1)		Step (2)		Yield[d] (%)	% ee[e]
	Temp (°C)	Time (min)	Temp (°C)	Time (h)		
1	5	30	5	0.5	43	46
2[b]	5	30	5	0.5	44	47
3	5	30	0	0.5	47	67
4	5	30	0	24	58	51
5	0	30	0	24	59	59
6	−5	30	−5	24	63	83
7	−10	30	−10	24	63	86
8	−15	30	−15	24	68	93
9[c]	−15	30	−15	24	79	92
10[c]	−15	5	−15	24	73	99
11[c]	−15	10	−15	24	83	99
12[c]	−15	15	−15	24	89	97
13[c]	−15	60	−15	24	58	75
14[c]	−15	120	−15	24	32	26
15[c]	−15	10	−15	0.5	73	99
16[c]	−15	10	−15	3	77	99
17[c]	−15	10	−15	48	82	98

[a] All reactions were carried out with 0.5 mmol of **1**, 0.7 mmol of $ClCO_2Et$, and 1.5 mmol of Et_3N in 10 mL of THF. After stirring for 30 min, 0.75 mmol of 1.0 M aqueous solution of NH_4Cl was added to the reaction mixture.
[b] The D-form was used instead of Cbz-L-Phg-OH.
[c] $ClCO_2Et$ and 1.0 M aqueous solution of NH_4Cl precooled at −15 °C were added at −15 °C to the prepared solutions on the steps (1) and (2), respectively.
[d] Isolated yield.
[e] Determined by HPLC analysis with 4:1 mixture of hexane and 2-propanol as an eluent using Chiralcel AD.

Table 2
Optimization of the reaction conditions on the primary amidation of Cbz-Phe-Phe-OH (**3aa**)[a]



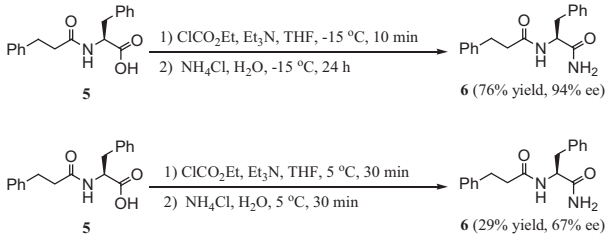
3aa 4aa

Entry	**3aa**	Yield[d] (%)	% de[e]	% de[f]	Ratio of products[g] (%)			
					LL	DL	DD	LD
1	Cbz-L-Phe-L-Phe-OH	63	52	48	73.8	0	0	26.2
2	Cbz-L-Phe-D-Phe-OH	66	88	83	8.6	0	0	91.4
3[b]	Cbz-L-Phe-L-Phe-OH	94	13	15	57.7	0	0	42.3
4[b]	Cbz-L-Phe-D-Phe-OH	86	67	68	16.1	0	0	83.9
5[b]	Cbz-D-Phe-L-Phe-OH	90	59	58	0	79.0	21.0	0
6[b]	Cbz-D-Phe-D-Phe-OH	86	23	25	0	37.7	62.3	0
7[c]	Cbz-L-Phe-L-Phe-OH	72	>99	>99	>99	0	0	0
8[c]	Cbz-L-Phe-D-Phe-OH	84	>99	>99	0	0	0	>99
9[c]	Cbz-D-Phe-L-Phe-OH	81	>99	>99	0	>99	0	0
10[c]	Cbz-D-Phe-D-Phe-OH	74	>99	>99	0	0	>99	0

[a] All reactions were carried out with 0.30 mmol of **3aa**, 0.42 mmol of $ClCO_2Et$, and 0.90 mmol of Et_3N in 6 mL of THF. After stirring for 30 min at 5 °C, 0.45 mmol of 1.0 M aqueous solution of NH_4Cl was added at 5 °C to the reaction mixture.
[b] The reaction time on the step (2) was 24 h.
[c] $ClCO_2Et$ and 1.0 M aqueous solution of NH_4Cl precooled at −15 °C were added at −15 °C to the prepared solutions on the steps (1) and (2), respectively. Then, the reaction times on the steps (1) and (2) were 10 min and 24 h, respectively.
[d] Isolated yield.
[e] Determined by ^1H NMR analysis.
[f] Determined by HPLC analysis with a 95:5:0.05 mixture of hexane, ethanol, and diethylamine as an eluent using Chiralcel OD (1.0 mL/min).
[g] Retention times of LL-, DL-, DD-, and LD-forms on HPLC analysis were 34.5, 41.2, 49.5, and 53.6 min, respectively.

Next, the results of the primary amidation of Cbz-Phe-Phe-OH (**3aa**) using NH_4Cl via the corresponding mixed carbonic carboxylic anhydride are collected in Table 2. The reactions of Cbz-L-Phe-L-Phe-OH (**3aLaL**) and Cbz-L-Phe-D-Phe-OH (**3aLaD**) in our original conditions (for 30 min at 5 °C on the step (1) then for 30 min at 5 °C on the step (2)) afforded the corresponding primary amides (**4aLaL** and **4aLaD**) in 63% and 66% yields, respectively (entries 1 and 2). Unfortunately, these diastereomer excesses were not good (52% de and 88% de, respectively), by epimerization. The reactions of **3aLaL** and **3aDaD** for 24 h at 5 °C on the step (2) proceeded further epimerization to afford worse diastereomer excesses (13% de and 23% de, respectively), as shown in entries 3 and 6. The reaction conditions were optimized well by using precooled reagents at −15 °C on both steps (1) and (2) and the results (72–84% yields, >99% de) were drastically improved as described in entries 7–10.

Furthermore, the primary amidations of N-protected dipeptides **3** with NH_4Cl were carried out using the precooled dropping method and the results are collected in Table 3. The reaction of Cbz-L-Phe-L-Phe-OH (**3aLaL**) with NH_4Cl using $ClCO_2Et$ and Et_3N afforded Cbz-L-Phe-L-Phe-NH_2 (**4aLaL**) in 72% yield with >99% de by ^1H NMR analysis.[3] Cbz-L-Phe-D-Phe-OH (**3aLaD**) reacted with NH_4Cl in the similar conditions (entry 1) to afford Cbz-L-Phe-D-Phe-NH_2 (**4aLaD**) in 84% with >99% de as the diastereoiomer (entry 2). The reactions of the dipeptides **3′aLaL**, **3′aLaD** and **3″aLaL**, **3″aLaD** protected other conventional groups such as *tert*-butoxycarbonyl (Boc) and 9-fluorenylmethoxycarbonyl (Fmoc) with NH_4Cl afforded the corresponding primary amides **4′aLaL**, **4′aLaD** and **4″aLaL**, **4″aLaD**, respectively, in 85–95% yields with 81–99% de by HPLC analysis using Chiralcel OD (entries 3–6), and slight epimerization was observed in the cases of entries 3 and 5. Finally, the reactions of several kinds of dipeptides **3aLbL**–**3aLeL** and **3aLbD**–**3aLeD** with NH_4Cl gave the corresponding primary amides **4aLbL**–**4aLeL** and **4aLbD**–**4aLeD**, respectively, in 75–93% yields with >99% de (entries 7–14). The reactions of Cbz-L-Phe-D-Ser-OH (**3aLfD**) with NH_4Cl using $ClCO_2Et$ and Et_3N afforded Cbz-L-Phe-D-Ser-NH_2 (**4aLfD**) in 57% yield with 92% de by ^1H NMR analysis (entry 15). Unfortunately, the reaction of Cbz-L-Phe-D-Cys-OH (**3aLgD**) with NH_4Cl using $ClCO_2Et$ and Et_3N gave a complex mixture (entry 16).

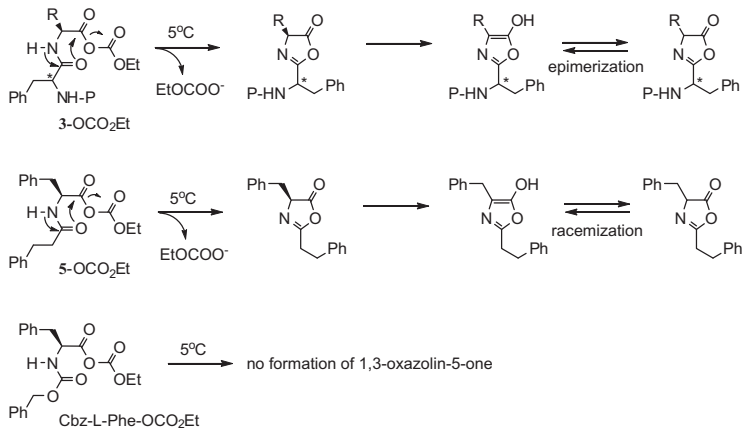


5 5

Scheme 3. The amidation of **5** with NH_4Cl at 5 °C or −15 °C.

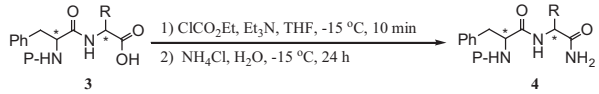
As shown in Scheme 3, the reaction of N-phenethyl-L-Phe-OH (**5**) with NH_4Cl in the presence of $ClCO_2Et$ at 5 °C proceeded with racemization via the easier formation of the corresponding 1,3-oxazol-5-one and 2,4-disubstituted 1,3-oxazolin-5-ol.[4] In addition, the unprotected side of dipeptides **3** is epimerized on the basis of the similar reason as indicated in Scheme 4. On the other hand, Cbz-L-Phe-OCO_2Et was not converted to the corresponding 1,3-oxazol-5-one and was not racemized by the stronger electron-donating effect of the benzyloxy group compared with the phenethyl group of **5**-OCO_2Et.

In conclusion, we have found that primary amides **2** and **4** were easily prepared in 83% yield with 99% ee and 57–95% yields with 81–99% de from the corresponding phenylglycine **1** and dipeptides **3** using NH_4Cl under extremely mild conditions by the precooled dropping method. Particularly, it is amazing that racemization or epimerization does not proceed in the reactions of Cbz-protected



Scheme 4. Possible pathway for epimerization of **3**-OCO_2Et and for racemization of **5**-OCO_2Et.

Table 3
Preparation of primary amides derived from various dipeptides (**3**)[a]



Entry	Dipeptide	**3**	Yield[b] (%)	% de[c]
1	Cbz-L-Phe-L-Phe-OH	**3aLaL**	72 (63)	>99 (52)
2	Cbz-L-Phe-D-Phe-OH	**3aLaD**	84	>99
3	Boc-L-Phe-L-Phe-OH	**3′aLaL**	85	81[d]
4	Boc-L-Phe-D-Phe-OH	**3′aLaD**	94	>99[d]
5	Fmoc-L-Phe-L-Phe-OH	**3″aLaL**	90	90[d]
6	Fmoc-L-Phe-D-Phe-OH	**3″aLaD**	95	98[d]
7	Cbz-L-Phe-L-Ala-OH	**3aLbL**	89 (83)	>99 (43)[e]
8	Cbz-L-Phe-D-Ala-OH	**3aLbD**	76	>99[e]
9	Cbz-L-Phe-L-Val-OH	**3aLcL**	93 (69)	>99 (88)
10	Cbz-L-Phe-D-Val-OH	**3aLcD**	90	>99
11	Cbz-L-Phe-L-Met-OH	**3aLdL**	78 (70)	>99 (56)
12	Cbz-L-Phe-D-Met-OH	**3aLdD**	85	>99
13	Cbz-L-Phe-L-Phg-OH	**3aLeL**	79 (0)	>99 (-)
14	Cbz-L-Phe-D-Phg-OH	**3aLeD**	75	>99
15	Cbz-L-Phe-D-Ser-OH	**3aLfL**	57	92
16	Cbz-L-Phe-D-Cys-OH	**3aLfD**	0	—

[a] All reactions were carried out with 0.30 mmol of **3**, 0.42 mmol of $ClCO_2Et$, and 0.90 mmol of Et_3N in 6 mL of THF. After stirring for 10 min at −15 °C, 0.45 mmol of 1.0 M aqueous solution of NH_4Cl was added at −15 °C to the reaction mixture. $ClCO_2Et$ and 1.0 M solution of NH_4Cl precooled at −15 °C were added at −15 °C to the prepared solutions on the steps (1) and (2), respectively.

[b] Isolated yield. The yields of the products obtained in the reactions at 5 °C are described in parentheses.

[c] Determined by ^1H NMR analysis. The diastereomer excesses of the products obtained in the reactions at 5 °C are described in parentheses.

[d] Determined by HPLC analysis with a 4:1 mixture of hexane and 2-propanol as an eluent using Chiralcel OD (1.0 mL/min).

[e] Determined by HPLC analysis with a 9:1 mixture of hexane and 2-propanol as an eluent using Chiralcel OD (1.0 mL/min).

dipeptides **3aLaL**–**3aLeL** and **3aLaD**–**3aLfD** using our developed method. Further investigations about this type of reaction are under way in our group.

References and notes

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3. A typical procedure of the primary amidation of **3aLaL** using $ClCO_2Et$ is as follows. To a solution of 134 mg (0.30 mmol) of Cbz-L-Phe-L-Phe-OH (**3aLaL**) and 40 μL (0.42 mmol, 1.4 equiv) of $ClCO_2Et$ in 6 mL of THF, 125 μL (0.90 mmol, 3.0 equiv) of Et_3N precooled at −15 °C was added at −15 °C. After stirring for 30 min at −15 °C, 0.45 mL of 1.0 M aqueous solution of NH_4Cl (0.45 mmol, 1.5 equiv) precooled at −15 °C was added at −15 °C to the colorless suspension. The mixture was stirred for 24 h at −15 °C, and 15 mL of water was added at −15 °C to the mixture. 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 chromatographed on silica gel with a 1:1 mixture of hexane and EtOAc to afford 97.2 mg (72% yield) of **4aLaL** (Cbz-L-Phe-L-Phe-NH_2). Compound **4aLaL**: colorless powder; ^1H NMR (DMSO-d_6): δ 2.67 (1H, dd, J = 10.7, 13.7 Hz, $CHCH_APh$), 2.84 (1H, dd, J = 8.7, 13.5 Hz, $CHCH_{A'}Ph$), 2.92 (1H, dd, J = 3.7, 13.7 Hz, $CHCH_BPh$), 3.02 (1H, dd, J = 5.0, 13.5 Hz, $CHCH_{B'}Ph$), 4.20–4.25 (1H, m, NHCH), 4.44–4.49 (1H, m, NHCH), 4.94 (2H, s, OCH_2Ph), 7.05–7.39 (17H, m, $C_6H_5\times3$, NH_2), 7.48 (1H, d, J = 8.6 Hz, NH), 8.02 (1H, d, J = 8.3 Hz, NH).
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