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PREPARATION OF PROTECTED α-ALKOXYGLYCINES

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Abstract: *N*-Carbobenzoxy-α-alkoxyglycine esters were synthesized by H_2SO_4-catalyzed *O*-alkylation of *N*-carbobenzoxy-α-hydroxyglycine and also by base treatment of *N*-carbobenzoxy-*N*-chloroglycine methyl ester in the corresponding alcohol. Saponification of the protected α-alkoxyglycines gave free acids which can be used for the synthesis of α-alkoxyglycine residue-containing peptides.

Introduction

α-Alkoxyglycines, Gly(OR), are unique unnatural amino acids possessing an electronegative oxygen atom directly attached to the α-carbon atom which makes these amino acid residues unstable especially in their *N*-unprotected form. *N*-Carbobenzoxy-α-methoxyglycine methyl ester, Cbz-Gly(OMe)-OMe, was prepared by H_2SO_4-catalyzed *O*-methylation of α-hydroxyglycine derivative Cbz-Gly-OH,[1] or base-catalyzed dehydrochlorination followed by MeOH addition of the *N*-chloro derivative of protected glycine Cbz-Gly-OMe.[2] Although the *N*-deprotected Gly(OMe) residue is too labile to be used as an amino component for

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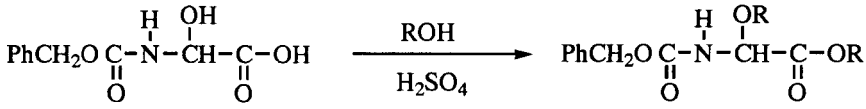
peptide bond formation under standard conditions, we have developed a method for synthesizing Gly(OMe)-containing peptides, which involves hydrogenolytic deprotection of the Cbz-Gly(OMe) group in the presence of a mixed anhydride prepared from a carboxyl component and isobutyl chloroformate.[2] Optical resolution of (±)-Cbz-Gly(OMe)-OH and determination of their absolute configuration were also accomplished.[3] The analogs of dermorphin *N*-terminal tetrapeptide[4] possessing D/L-Gly(OMe) residue were actually synthesized.[2,3] These results indicated the possibility of synthesizing new type of peptide analogs containing Gly(OR) residue. No other Gly(OR) derivatives than Gly(OMe) were known, however, and we have attempted to synthesize protected Gly(OR) with various R groups for the purpose of enabling the synthesis of peptide analogs possessing these β-oxa analogs of α-amino acids.

Results and Discussion

Synthesis from α-hydroxyglycine derivative

The method for the synthesis of Cbz-Gly(OMe)-OMe reported by Zoller and Ben-Ishai[1] has been applied to other alkoxyglycine derivatives. Cbz-Gly(OH)-OH prepared from benzyl carbamate and glyoxylic acid was dissolved in ROH with various alkyl group, to which H_2SO_4 was added and the reaction mixture was stirred at room temperature. As summarized in Table 1, primary alcohols generally afforded the corresponding Cbz-Gly(OR)-OR in good yield although benzyl alcohol gave lower yield of the product. The propoxy and butoxy compounds prepared in 92% and 86% yields, respectively, were low-melting solid, which were distilled under reduced pressure without decomposition revealing their considerable stability. Secondary alkoxyglycine derivatives were also prepared in good yield. In the case of cyclohexanol which is solid at room temperature,



Cbz-Gly(OH)-OH Cbz-Gly(OR)-OR

Table 1. Synthesis of Cbz-Gly(OR)-OR from Cbz-Gly(OH)-OH using ROH and H_2SO_4.

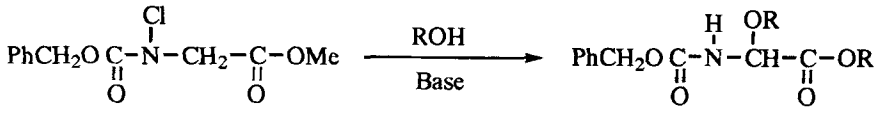
R	time/day	yield/%	mp/°C	R	time/day	yield/%	mp/°C
Me[a)]	3	84	77.5–78.5	*i*-Pr	6	88	57.5–58.5
Et	3	82	70.5–72	*c*-C_6H_{11}	6	72	oil
n-Pr	5	92	19–19.5	*t*-Bu	7	<7	–
n-Bu	6	86	9–11	Ph	7	0	
$PhCH_2$	5	27	83–85.5				

a) Ref. 1: yield 92%, mp 76–78°C.

tetrahydrofuran (THF) was added to dissolve the reactants. *tert*-Butoxyglycine derivative Cbz-Gly(O-*t*-Bu)-O-*t*-Bu, however, was obtained only in very low yield (<7%), and phenol failed to give the corresponding phenoxy compound. Thus, the method for the preparation of Cbz-Gly(OR)-OR using Cbz-Gly(OH)-OH and ROH has been shown applicable to primary and secondary alkoxyglycine derivatives.

Synthesis from *N*-Chloroglycine derivative

Base-catalyzed dehydrochlorination-ROH addition of the *N*-chloro derivative of Cbz-Gly-OMe[2] was also examined for the preparation of various α-alkoxyglycine derivatives. The protected *N*-chloroglycine prepared from Cbz-Gly-OMe and *tert*-butyl hypochlorite was dissolved in ROH or ROH-THF mixture and was cooled to –78°C, to which the solution of RONa in ROH was added and the mixture was stirred at this temperature. As summarized in Table 2, primary alkoxyglycine derivatives Cbz-Gly(OR)-OR were obtained in satisfactory yields and no Cbz-Gly(OR)-OMe were produced, *i.e.*, complete transesterification proceeded during



Cbz-Gly(OR)-OR

Table 2. Synthesis of Cbz-Gly(OR)-OR' from $CbzNClCH_2CO_2Me$ using ROH and base.

R-	Base	Yield/%
Me	MeONa	96 (R' = Me)
Et	EtONa	72 (R' = Et)
n-Pr	*n*-PrONa	49 (R' = *n*-Pr)
i-Bu	*i*-BuONa	64 (R' = *i*-Bu)
i-Pr	*i*-PrONa	0 (Cbz-Gly-O-*i*-Pr 30, CBz-Gly-OMe 66)
	i-PrOK	25 (R' = *i*-Pr), 9 (R' = Me)
	Et_3N	0 (Cbz-Gly-OMe 95)
Ph	PhONa	54 (R' = Me)
	Et_3N	20 (R' = Me)

the reaction. Sodium isopropoxide in isopropyl alcohol under the same conditions, however, did not afford Gly(O-*i*-Pr) derivative but the mixture of Cbz-Gly-O-*i*-Pr and Cbz-Gly-OMe was obtained in 96% yield, suggesting that homolytic N–Cl bond cleavage followed by hydrogen abstraction from the solvent took place instead of base-catalyzed dehydrochlorination. When potassium isopropoxide was used as a base, the α-isopropoxyglycine derivatives Cbz-Gly(O-*i*-Pr)-O-*i*-Pr and Cbz-Gly(O-*i*-Pr)-OMe were produced in low yield. Use of triethylamine resulted in the formation of dechlorinated product Cbz-Gly-OMe (95%). Synthesis of α-*tert*-butoxyglycine derivative was also unsuccessful, indicating that the present method is inappropriate for the synthesis of Gly(OR) derivatives with secondary and tertiary alkoxyl groups. On the other hand α-phenoxyglycine derivative Cbz-Gly(OPh)-OMe was obtained in moderate yield when phenol and sodium phenoxide were used in THF.

Saponification to Free Acids

In order to resolve these Gly(OR) derivatives to enantiomers and/or to incorporate the Gly(OR) residues into peptide chains, it is necessary to convert the ester function of the protected Gly(OR) derivatives to free carboxyl group.

Alkaline hydrolysis of the primary and secondary alkyl esters proceeded almost quantitatively, and the corresponding carboxylic acids Cbz-Gly(OR)-OH were isolated in 84–90% yield. The free acids were stable enough to be subjected to optical resolution *via* diastereomeric salts with chiral amines and/or to coupling reaction with amino components. Storing the acids in the refrigerator over weeks, however, resulted in significant deterioration, although their salts were stable over months. Therefore, it is advisable to store optically resolved Gly(OR) derivatives in diastereomeric salt form.

Saponification of Cbz-Gly(OPh)-OMe with NaOH in aqueous MeOH was found to yield Cbz-Gly(OMe)-OH instead of the expected Cbz-Gly(OPh)-OH, indicating the formation of an imino species Cbz-N=CH-CO_2R (R = H or Me) followed by the addition of a MeOH molecule. Alkaline hydrolysis of Cbz-Gly(OPh)-OMe in aqueous EtOH afforded Cbz-Gly(OEt)-OH in 86% yield, while only the decomposition product Cbz-NH_2 was isolated when the reaction was attempted in aqueous isopropyl alcohol. Since the imino species Cbz-N=CH-CO_2Me was also considered as an intermediate from CbzNClCH$_2$$CO_2$Me to protected Gly(OR) derivative, alkaline hydrolysis of the *N*-chloroglycine derivative in aqueous ROH could be expected to yield directly the free acid Cbz-Gly(OR)-OH. Treatment of the protected *N*-chloroglycine with NaOH in aqueous ROH (R = Me or Et), however, afforded a mixture of the expected Cbz-Gly(OR)-OH (50–60%) and the side product Cbz-Gly-OH (15–20%) indicating no advantage of this direct preparation of the free acid.

Experimental

Melting points were determined on a hot plate apparatus and are uncorrected. Distillation was undertaken using a glass-tube oven apparatus. ^{1}H NMR spectra (200 or 90 MHz) were measured in $CDCl_3$ solutions unless otherwise stated.

Synthesis of Cbz-Gly(OR)-OR from CBz-Gly(OH)-OH

N-Carbobenzoxy-α-ethoxyglycine ethyl ester [Cbz-Gly(OEt)-OEt]. Cbz-Gly(OH)-OH (225 mg, 1 mmol), prepared from Cbz-NH_2 and $HCOCO_2H$,[1] was dissolved in 2.5 ml of EtOH, to which conc H_2SO_4 (0.045 ml) was added at 0°C. After stirring for 3 days at room temperature, the reaction mixture was cooled to

0°C, to which 0.5 M $NaHCO_3$ aqueous solution (20 ml) was added. The mixture was extracted with AcOEt and the organic layer was washed with 0.5 M $NaHCO_3$, 0.5 M HCl, and saturated NaCl solutions and was dried over Na_2SO_4. Evaporation of the solvent yielded a colorless oil which was crystallized on addition of hexane to give Cbz-Gly(OEt)-OEt (230 mg, 82%); mp 70.5–72°C. ^1H NMR δ 1.21 (3H, *t*, *J* = 7 Hz, α-OCH_2CH_3), 1.28 (3H, *t*, *J* = 7 Hz, $CO_2CH_2CH_3$), 3.70 (2H, *q*, *J* = 7 Hz, α-OCH_2CH_3), 4.26 (2H, *q*, *J* = 7 Hz, $CO_2CH_2CH_3$), 5.14 (2H, *s*, CH_2 in Cbz), 5.37 (1H, *d*, *J* = 10 Hz, α-CH), 5.85 (1H, *br d*, *J* = 10 Hz, NH), 7.36 (5H, *s*, C_6H_5). Anal. Calc for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.56; H, 6.84; N, 5.02.

The following Cbz-Gly(OR)-OR were prepared in essentially the same manner as the preparation of Cbz-Gly(OEt)-OEt described above. Yields and melting points are given in Table 1.

N-Carbobenzoxy-α-propoxyglycine propyl ester [Cbz-Gly(O-n-Pr)-O-n-Pr]. Bp 115–125°C/2.5 Torr. ^1H NMR δ 0.90 (3H, *t*, *J* = 6.5 Hz, CH_3 in α-O-*n*-Pr), 0.95 (3H, *t*, *J* = 7 Hz, CH_3 in CO_2-*n*-Pr), 1.6–1.7 (4H, *m*, CH_2 in α-O-*n*-Pr and CO_2-*n*-Pr), 3.59 (2H, *t*, *J* = 6.5 Hz, α-OCH_2), 4.15 (2H, *t*, *J* = 7 Hz, CO_2CH_2), 5.15 (2H, *s*, CH_2 in Cbz), 5.37 (1H, *d*, *J* = 9 Hz, α-CH), 5.8 (1H, *br d*, *J* = 9 Hz, NH), 7.35 (5H, *s*, C_6H_5). Anal. Calc for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 61.92; H, 7.61; N, 4.47.

N-Carbobenzoxy-α-butoxyglycine butyl ester [Cbz-Gly(O-n-Bu)-O-n-Bu]. Bp. 185–190°C/2.5 Torr. ^1H NMR δ 0.90 (3H, *t*, *J* = 6.5 Hz, CH_3 in α-O-*n*-Bu), 0.94 (3H, *t*, *J* = 6.5 Hz, CH_3 in CO_2-*n*-Bu), 1.4–1.6 (8H, *m*, CH_2CH_2 in α-O-*n*-Bu and CO_2-*n*-Bu), 3.63 (2H, *t*, *J* = 6 Hz, α-OCH_2), 4.19 (2H, *t*, *J* = 6.5 Hz, CO_2CH_2), 5.15 (2H, *s*, CH_2 in Cbz), 5.35 (1H, *d*, *J* = 9 Hz, α-CH), 5.85 (1H, *br d*, *J* = 9 Hz, NH), 7.35 (5H, *s*, C_6H_5). Anal. Calc for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 64.10; H, 8.28; N, 4.19.

N-Carbobenzoxy-α-benzyloxyglycine benzyl ester [Cbz-Gly(OCH$_2$Ph)-OCH$_2$Ph]. ^1H NMR δ 4.69 (2H, *s*, α-OCH_2Ph), 5.14 (2H, *s*, CH_2 in Cbz), 5.19 (2H, *s*, CO_2CH_2Ph), 5.54 (1H, *d*, *J* = 9 Hz, α-CH), 5.9 (1H, *br d*, *J* = 9 Hz, NH), 7.29 (5H, *s*, α-$OCH_2C_6H_5$), 7.29 (5H, *s*, $CO_2CH_2C_6H_5$), 7.33 (5H, *s*, C_6H_5 in Cbz). Anal. Calc for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45. Found: C, 70.75; H, 5.84; N, 3.43.

N-Carbobenzoxy-α-isopropoxyglycine isopropyl ester [Cbz-Gly(O-i-Pr)-O-i-Pr]. ^{1}H NMR δ 1.20 (6H, *d*, *J* = 6 Hz, α-OCH(C*H*$_3$)$_2$), 1.28 (6H, *d*, *J* = 6 Hz, $CO_2CH(CH_3)_2$), 3.98 (1H, *sep*, *J* = 6 Hz, α-OCH), 5.06 (1H, *sep*, *J* = 6 Hz, CO_2CH), 5.14 (2H, *s*, CH_2), 5.35 (1H, *d*, *J* = 9 Hz, α-CH), 5.8 (1H, *br d*, *J* = 9 Hz, NH), 7.35 (5H, *s*, C_6H_5). Anal. Calc for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 61.98; H, 7.60; N, 4.59.

N-Carbobenzoxy-α-cyclohexyloxyglycine cyclohexyl ester [Cbz-Gly(O-c-C$_6$H$_{11}$)-O-c-C$_6$H$_{11}$]. ^{1}H NMR δ 1.2–1.9 (20H, *m*, 2(CH_2)$_5$), 3.65 (1H, *m*, α-OCH), 4.85 (1H, *m*, CO2CH), 5.15 (2H, *s*, CH_2 in Cbz), 5.41 (1H, *d*, *J* = 10 Hz, α-CH), 5.9 (1H, *br d*, *J* = 10 Hz, NH), 7.35 (5H, *s*, C_6H_5).

N-Carbobenzoxy-α-tert-butoxyglycine tert-butyl ester [Cbz-Gly(O-t-Bu)-O-t-Bu]. This compound was not isolated in pure form. ^{1}H NMR δ 1.27 (9H, *s*, α-O-*t*-Bu), 1.48 (9H, *s*, CO_2-*t*-Bu), 5.16 (2H, *s*, CH_2 in Cbz), 5.33 (1H, *d*, *J* = 10 Hz, α-CH), 5.8 (1H, *br*, NH), 7.34 (5H, *s*, C_6H_5).

Synthesis of Cbz-Gly(OR)-OR' from CbzNClCH$_2$CO$_2$Me.

N-Carbobenzoxy-N-chloroglycine methyl ester. To the ice-cooled solution of Cbz-Gly-OMe (2.23 g, 10 mmol) in MeOH (3 ml) was added *t*-BuOCl (1.80 ml, 15 mmol) and the reaction mixture was stirred at 0°C for 17 h. After evaporation of the volatile compounds, AcOEt (20 ml) was added to the residue, washed successively with aqueous solutions of 0.5M HCl, 0.5M $NaHCO_3$, and saturated NaCl, and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded $CbzNClCH_2CO_2Me$ as a colorless oil (2.6 g, *ca.* 100%). ^{1}H NMR δ 3.74 (3H, *s*, OCH_3), 4.32 (2H, *s*, α-CH_2), 5.22 (2H, *s*, CH_2 in Cbz), 7.36 (5H, *s*, C_6H_5).

N-Carbobenzoxy-α-ethoxyglycine ethyl ester [Cbz-Gly(OEt)-OEt]. A solution of $CbzNClCH_2CO_2Me$ (1.29 g, 5 mmol) in EtOH (10 ml) was cooled to –78°C, to which a solution of NaOEt (10 mmol) prepared from Na (230 mg) and EtOH (10 ml) was added and the mixture was stirred for 6 h at –78°C. After neutralization by the addition of AcOH, the reaction mixture was evaporated and the residue was extracted with AcOEt, which was washed successively with aqueous solutions of 10% citric acid, 0.5M $NaHCO_3$, and saturated NaCl and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded a colorless oil which was crystallized on addition of hexane and recrystallized from EtOH to give

Cbz-Gly(OEt)-OEt as colorless needles (1.01 g, 72%); mp 71–72°C. This compound was indistinguishable from the authentic sample synthesized from Cbz-Gly(OH)-OH as described above.

Cbz-Gly(OMe)-OMe and *Cbz-Gly(O-n-Pr)-O-n-Pr* were synthesized in essentially the same manner as the synthesis of Cbz-Gly(OEt)-OEt as described above and the yields are shown in Table 2. *N-Carbobenzoxy-α-isobutoxyglycine isobutyl ester [Cbz-Gly(O-i-Bu)-O-i-Bu]* was also similarly synthesized as an oil; ^{1}H NMR δ 0.89 (6H, *d*, *J* = 6 Hz, $2CH_3$ in α-O-*i*-Bu), 0.94 (6H, *d*, *J* = 6.5 Hz, $2CH_3$ in CO_2-*i*-Bu), 1.8–2.0 (2H, *m*, CH in α-*i*-Bu and CO_2-*i*-Bu), 3.40 (2H, *d*, J = 6.5 Hz, α-OCH_2), 3.97 (2H, *d*, *J* = 6.5 Hz, CO_2CH_2), 5.15 (2H, *s*, CH_2 in Cbz), 5.36 (1H, *d*, *J* = 9 Hz, α-CH), 5.8 (1H, *br d*, *J* = 9 Hz, NH), 7.35 (5H, *s*, C_6H_5).

N-Carbobenzoxy-α-phenoxyglycine methyl ester [Cbz-Gly(OPh)-OMe]. A solution of $CbzNClCH_2CO_2Me$ (310 mg, 1.2 mmol) in THF (2 ml) was cooled to –78°C, to which a THF solution of PhONa (1.8 mmol) prepared from Na (42 mg, 1.8 mmol), PhOH (660 mg, 7.0 mmol), and THF (3 ml) was added and the mixture was stirred for 6 h at -78°C. The reaction mixture was worked up as described above to yield Cbz-Gly(OPh)-OMe as a colorless oil (205 mg, 54%). ^{1}H NMR (CD_3OD) δ 3.83 (3H, *s*, CH_3), 5.15 (2H, *s*, CH_2), 6.13 (1H, *s*, α-CH), 7.1–7.3 (5H, *m*, OC_6H_5), 7.36 (5H, *s*, C_6H_5 in Cbz). Anal. Calc for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.37; H, 5.52; N, 4.86.

Preparation of Cbz-Gly(OR)-OH by alkaline hydrolysis of Cbz-Gly(OR)-OR.

N-Carbobenzoxy-α-methoxyglycine [Cbz-Gly(OMe)-OH]. To a solution of Cbz-Gly(OMe)-OMe (5.06 g, 20 mmol) in MeOH (20 ml) was added 1M NaOH (21 ml, 21 mmol) and the mixture was stirred for 1 h at room temperature. CO_2 was introduced to the solution and MeOH was evaporated. Under ice-cooling the concentrated mixture was acidified (pH *ca.* 2) by the addition of 1M HCl and was extracted with AcOEt, which was washed with saturated aqueous NaCl solution and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded a colorless oil, which crystallized on addition of hexane, mp 90–90.5°C (2.27 g, 95%). ^{1}H

NMR δ 3.47 (3H, *s*, OCH_3), 5.16 (2H, *s*, CH_2), 5.34 (1H, *d*, *J* = 9 Hz, α-CH), 5.9 (1H, *br d*, *J* = 9 Hz, NH), 7.34 (5H, *s*, C_6H_5), 8.3 (1H, *br s*, CO_2H).

The following Cbz-Gly(OR)-OH was prepared from the corresponding Cbz-Gly(OR)-OR in essentially the same manner as described above for the preparation of Cbz-Gly(OMe)-OH.

N-Carbobenzoxy-α-ethoxyglycine [Cbz-Gly(OEt)-OH]. Mp 98.5–99.5°C (yield 94%). ^{1}H NMR δ 1.23 (3H, *t*, *J* = 7 Hz, CH_3), 3.71 (2H, *q*, *J* = 7 Hz, α-OCH_2), 5.15 (2H, *s*, CH_2 in Cbz), 5.41 (1H, *d*, *J* = 9 Hz, α-CH), 5.9 (1H, *br*, NH), 7.34 (5H, *s*, C_6H_5), 8.7 (1H, *br s*, CO_2H).

N-Carbobenzoxy-α-propoxyglycine [Cbz-Gly(O-n-Pr)-OH]. Mp 62–63.5°C (yield 86%). ^{1}H NMR δ 0.90 (3H, *t*, *J* = 7 Hz, CH_3), 1.63 (2H, *m*, CH_2), 3.62 (2H, *t*, *J* = 6 Hz, α-OCH_2), 5.14 (2H, *s*, CH_2 in Cbz), 5.41 (1H, *d*, *J* = 9 Hz, α-CH), 5.8 (1H, *br*, NH), 6.35 (1H, *br s*, CO_2H), 7.33 (5H, *s*, C_6H_5).

N-Carbobenzoxy-α-butoxyglycine [Cbz-Gly(O-n-Bu)-OH]. Mp 56–58.5°C (yield 83%). ^{1}H NMR δ 0.89 (3H, *t*, *J* = 6 Hz, CH_3), 1.3–1.6 (4H, *m*, CH_2CH_2), 3.64 (2H, *t*, *J* = 6 Hz, α-OCH_2), 5.15 (2H, *s*, CH_2 in Cbz), 5.40 (1H, *d*, *J* = 9 Hz, α-CH), 5.85 (1H, *br*, NH), 7.14 (1H, *br s*, CO_2H), 7.34 (5H, s, C_6H_5).

N-Carbobenzoxy-α-isobutoxyglycine [Cbz-Gly(O-i-Bu)-OH]. Mp 63–64.5°C (yield 89%). ^{1}H NMR δ 0.88 (6H, *d*, *J* = 6 Hz, $2CH_3$), 1.87 (1H, *m*, CH in *i*-Bu), 3.41 (2H, *d*, *J* = 6.5 Hz, OCH_2), 5.15 (2H, *s*, CH_2 in Cbz), 5.38 (1H, *d*, *J* = 9 Hz, α-CH), 5.9 (1H, *br*, NH), 7.34 (5H, *s*, C_6H_5), 7.9 (1H, *br s*, CO_2H).

N-Carbobenzoxy-α-isopropoxyglycine [Cbz-Gly(O-i-Pr)-OH]. Mp 82–83°C (yield 94%). ^{1}H NMR δ 1.20 (3H, *d*, *J* = 6 Hz, CH_3), 1.23 (3H, *d*, *J* = 6 Hz), 4.00 (1H, *sep*, *J* = 6 Hz, α-OCH), 5.15 (2H, *s*, CH_2 in Cbz), 5.48 (1H, *d*, *J* = 9 Hz, α-CH), 5.85 (1H, *br d*, *J* = 9 Hz, NH), 7.34 (5H, *s*, C_6H_5), 8.68 (1H, *br s*, CO_2H).

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