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Three New *in situ* Syntheses of *N*-Acyl-α-triphenylphosphonioglycinates

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Summary. *N*-Acyl-α-hydroxyglycinates were transformed into *N*-acyl-α-triphenylphosphonioglycinates by (*i*) phosphorylation with Ph_3PBr_2 in the presence of Et_3N or (*ii*) in reaction with *DCC* and $Ph_3P \cdot HBF_4$ in the presence of catalytic amounts of Ph_3P as well as (*iii*) by a new kind of *Mitsunobu* reaction with $Ph_3P \cdot HBF_4$ as a nucleophile conjugated acid. The *N*-acyl-α-triphenylphosphonioglycinates can be effectively used without isolation for a nucleophilic displacement of the triphenylphosphonium group to obtain corresponding α-substituted α-amino acid derivatives.

Keywords. *N*-Acyl-α-triphenylphosphonioglycinates; Cationic glycine equivalent; Glycine α-functionalization; Nucleophilic substitution; α-Heterosubstituted glycine derivatives.

Introduction

Since the pioneering works of *Ben-Ishai et al.* [1] on the first synthetic equivalents of glycine α-cation, the important problem of synthesizing α-amino acids by reactions of glycine α-cation equivalents with nucleophiles has drawn the attention of many authors [1–4]. Many electrophilic glycine equivalents have been introduced for the synthesis of α-amino acids in the course of the last 25 years [1–20]. With the advent of peptide-derived chemotherapeutics, the synthesis of both, natural non-proteinogenic and unnatural α-amino acids by the functionalization of the glycine α-position with nucleophiles has attracted significant attention of organic chemists [2].

In our previous paper [21] we described a convenient and effective synthesis of crystalline stable *N*-acyl-α-triphenylphosphonioglycinates **2** from 4-triphenylphosphoranylidene-5(4*H*)-oxazolones **1** and a simple method of displacing their triphenylphosphonium group by a variety of oxygen, sulfur, nitrogen, and carbon nucleophiles, demonstrating in this way that *N*-acyl-α-triphenylphosphonioglycinates may be considered as new interesting cationic glycine equivalents [21, 22] (Scheme 1).

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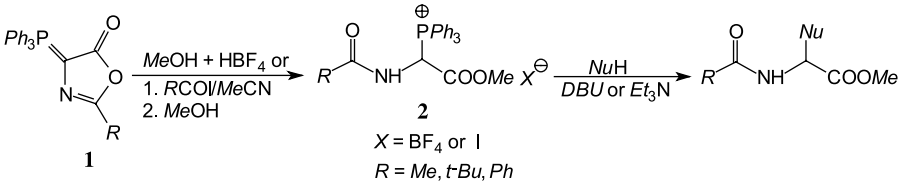


Scheme 1

Phosphoranylidene-5(4*H*)-oxazolones **1** were obtained by the phosphorylation of 5(4*H*)-oxazolones with dibromotriphenylphosphorane (Ph_3PBr_2) in the presence of triethylamine; 5(4*H*)-oxazolones being obtained *in situ* from the corresponding *N*-acylglycine and *DCC* [23]. The described transformations enable an easy and effective functionalization of the glycine α-position with heteroatom or carbon nucleophiles. Our attempts to synthesize in this way the especially interesting *N*-alkoxycarbonyl-α-triphenylphosphonioglycinates have failed, because of the instability of the corresponding 2-alkoxy-5(4*H*)-oxazolones [24].

N-Acyl-α-triphenylphosphonioglycinates were obtained for the first time by *Kober* and *Steglich* in 1983 by the photochemical bromination of *N*-benzoylglycinates with bromine or *NBS* to α-bromoglycinates, followed by the displacement of the bromide anion by triphenylphosphine [7]. The authors did not examine the reaction of the obtained compounds with nucleophiles.

In the present paper we report three new convenient *in situ* syntheses of *N*-acyl-α-triphenylphosphonioglycinates from easily accessible *N*-acyl-α-hydroxyglycinates, which allow to synthesize also *N*-alkoxycarbonyl-α-triphenylphosphonioglycinates.

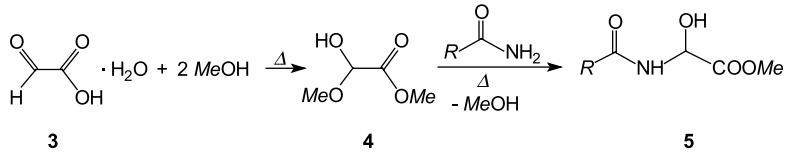
Results and Discussion

Syntheses of *N*-acyl-α-hydroxyglycinates **5** were carried out from the glyoxalic acid methyl ester hemiacetale **4** according to the procedure described by *Bernstein* [25] and *Abood* and *Losse* [26]. The latter compound was also obtained according to *Bernstein*'s procedure from glyoxalic acid hydrate [25] (Scheme 2).

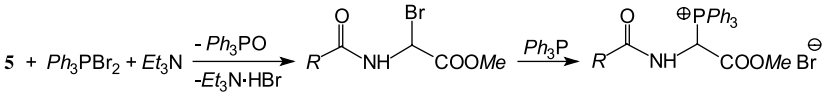
The following three methods for the transformation of *N*-acyl-α-hydroxyglycinates into *N*-acyl-α-triphenylphosphonioglycinates were developed.

The first one consists in the bromination of *N*-acyl-α-hydroxyglycinates with dibromotriphenylphosphorane followed by the displacement of the bromide anion by triphenylphosphine (Scheme 3). The second step of this method is analogous to the method mentioned above described by *Kober* and *Steglich* [7].

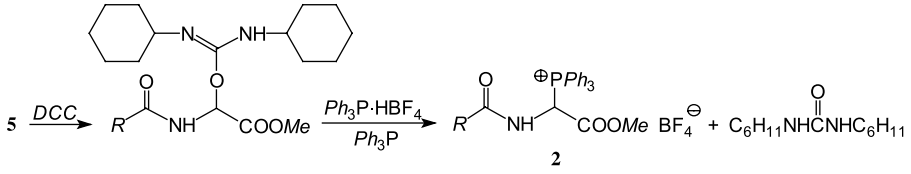
Referring to the second method, we believe that the hydroxy group of *N*-acyl-α-hydroxyglycinate is first activated by *DCC* and then replaced by triphenyl-



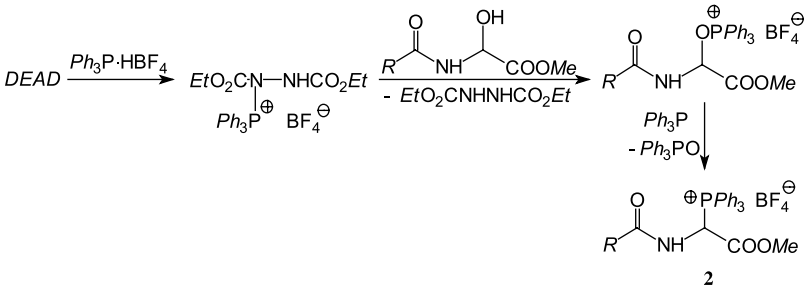
Scheme 2



Scheme 3



Scheme 4



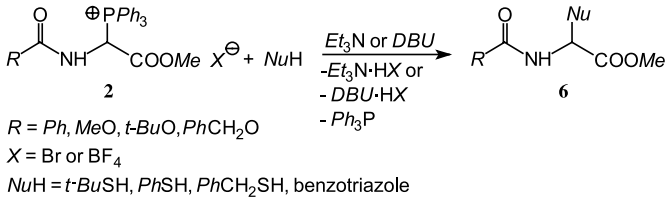
Scheme 5

phosphine to give the corresponding *N*-acyl-α-triphenylphosphonioglycinate (Scheme 4). A small amount of free triphenylphosphine is necessary in this reaction as an active nucleophile to facilitate the displacement of the activated hydroxyl group.

The third reaction can be considered as a kind of the *Mitsunobu* reaction with triphenylphosphine tetrafluoroborate as a nucleophile conjugated acid. According to our best knowledge, the *Mitsunobu* reaction has not been used up to now for the condensation of alcohols with phosphorus nucleophiles [27] (Scheme 5).

Previously, we have described a method for the isolation and purification of crude *N*-acyl-α-triphenylphosphonioglycinates which consists in dissolving the crude product in dichloromethane and precipitation of the pure phosphonium salt with diethyl ether [21]. Our attempts to apply this method to isolate *N*-acyl-α-triphenylphosphonioglycinates in all the described syntheses failed. Nevertheless, the presence of the expected products in reaction mixtures was confirmed by IR, ^{1}H and ^{13}C NMR spectroscopies. The spectral data of the synthesized compounds are closely similar to those described earlier [21]. In all the three cases the yields of the expected products **2** in the reaction mixtures were estimated based on the ratio of the ^{1}H NMR signals of the methine groups (in some cases also the methoxy group) to the signals of all aromatic protons. The estimated yields were, in most cases, fairly good.

We have also demonstrated further, that *N*-acyl-α-triphenylphosphonioglycinates synthesized *in situ* by any one of the three methods described above can be



Scheme 6

used without purification for the nucleophilic displacement of the triphenylphosphonium group by a variety of nucleophiles in order to get the corresponding α-substituted-α-aminoacid derivatives **6** in good yields. The structure of the obtained nucleophilic substitution products was confirmed by spectral data (IR, ^{1}H and ^{13}C NMR) and satisfactory elemental analyses or, in some cases, by the results of high-resolution mass spectrometry.

Experimental

Mps were determined in capillary tubes. IR spectra were recorded on a Zeiss Specord M 80 spectrophotometer; the measurements were carried out in $CHCl_3$ (0.2 *M*) using cells of 0.075 mm. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian UNITY INOVA-300 spectrometer at operating frequencies of 300 and 75.5 MHz using *TMS* as an internal standard. High-resolution mass spectra were recorded on an AMD 604 Spectrometer with ESI ionisation (*Me*OH, CH_2Cl_2, NaO*Ac*). The yields of isolated products **6** given were based on the *N*-acyl-α-hydroxyglycinates and were not optimized.

Starting Materials

Commercial grade acetonitrile, methylene chloride, *THF*, and triethylamine were distilled and dried over molecular sieves 4 Å. Kieselgel 60 Merck (0.063–0.200 mm) was used for column chromatography. The glyoxalic acid methyl ester hemiacetale was obtained according to *Bernstein*'s procedure from glyoxalic acid hydrate [25]. Synthesis of *N*-acyl-α-hydroxyglycinate was carried out according to the procedure described by *Bernstein* [25] and *Abood* and *Losse* [26]. The other reagents were of commercial quality.

Synthesis of N-Acyl-α-triphenylphosphonioglycinates ***2***

Procedure A

A solution of 0.18 g of Br_2 (1.1 mmol) in 0.5 cm^3 of CH_2Cl_2 was added at 0–2°C under Ar to a stirred solution of 0.29 g of triphenylphosphine (1.1 mmol) in 5 cm^3 of CH_2Cl_2. The pale-yellow crystals of Ph_3PBr_2 precipitated almost immediately. The suspension was stirred at room temperature for 30 min, the mixture was cooled to 0–5°C and then 0.15 cm^3 of triethylamine (0.11 g, 1.1 mmol), 0.26 g of triphenylphosphine (1.0 mmol) and 1 mmol of *N*-acyl-α-hydroxyglycinate **5** were added with stirring. The mixture was stirred for the time given below. The yield of **2** in the reaction mixture was estimated by ^{1}H NMR spectroscopy. The reaction mixture was evaporated to dryness *in vacuo* and the residue was used for farther syntheses without purification.

Procedure B

To a stirred suspension of 1 mmol of *N*-acyl-α-hydroxyglycinate **5** in 3 cm^3 of CH_2Cl_2, 0.21 g of *DCC* (1 mmol), a catalytic amount of triphenylphosphine (0.026 g, 0.1 mmol) and 0.70 g of triphenyl-

phosphine tetrafluoroborate (2 mmol) were added at room temperature. The mixture was stirred for the time given below. The yield of the product in the reaction mixture was estimated by ^{1}H NMR spectroscopy. The reaction mixture was evaporated to dryness *in vacuo* and the residue was used for farther syntheses without purification.

Procedure C

To a stirred suspension of 1 mmol of *N*-acyl-α-hydroxyglycinate **5** in 5 cm^3 of *THF*, 0.20 cm^3 of *DEAD* (0.22 g, 1.25 mmol), 0.29 g of triphenylphosphine (1.1 mmol), and 0.38 g of triphenylphosphine tetrafluoroborate (1.1 mmol) were added at room temperature. The mixture was stirred for the time given below. The yield of the product in the reaction mixture was estimated by ^{1}H NMR spectroscopy. The reaction mixture was evaporated to dryness *in vacuo* and the residue was used for farther syntheses without purification.

Methyl N-benzoyl-α-triphenylphosphonioglycinate bromide (**2a**, $C_{28}H_{25}BrNO_3P$)

Procedure A, 48 hrs; yield 62%; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 10.50$ (s, br, NH), 8.00–7.20 (m, $Ph_3P^{\oplus}$, Ph), 6.74 (dd, $J_{P-H} = 16.5$ Hz, $J_{H-H} = 7.4$ Hz, CH), 3.59 (s, MeO) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 166.7$ (d, $J = 0.5$ Hz, CONH), 54.6 (d, $J = 58.9$ Hz, CHP^+), 164.8 (d, $J = 8.7$ Hz, $\underline{C}OOMe$), 53.2 (OMe), 118.3 (d, $J = 85.1$ Hz, Ph_3P, C_1), 134.4 (d, $J = 10.1$ Hz, Ph_3P, C_2), 129.3 (d, $J = 12.8$ Hz, Ph_3P, C_3), 134.2 (d, $J = 0.5$ Hz, Ph_3P, C_4), 132.6, 130.8, 127.9, 127.2 (Ph) ppm; IR (CH_2Cl_2): $\bar{\nu} = 3040$, 1770, 1730, 1662 cm^{-1}.

Methyl N-benzoyl-α-triphenylphosphonioglycinate tetrafluoroborate (**2b**, $C_{28}H_{25}BF_4NO_3P$) [21]

Procedure B, 96 hrs; yield 71%; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 9.00$ (dd, $J_{P-H} = 4.3$ Hz, $J_{H-H} = 7.6$ Hz, NH), 8.00–7.20 (m, $Ph_3P^{\oplus}$, Ph), 6.59 (dd, $J_{P-H} = 15.6$ Hz, $J_{H-H} = 7.6$ Hz, CH), 3.60 (s, MeO) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 167.6$ (d, $J = 0.5$ Hz, CONH), 54.8 (d, $J = 59.8$ Hz, CHP^+), 164.9 (d, $J = 7.6$ Hz, $\underline{C}OOMe$), 53.7 (OMe), 118.0 (d, $J = 85.1$ Hz, Ph_3P, C_1), 134.5 (d, $J = 10.1$ Hz, Ph_3P, C_2), 129.8 (d, $J = 13.1$ Hz, Ph_3P, C_3), 134.9 (d, $J = 0.5$ Hz, Ph_3P, C_4), 132.2, 130.8, 128.4, 127.2 (Ph) ppm; IR (CH_2Cl_2): $\bar{\nu} = 3310$, 1770, 1730, 1670 cm^{-1}.

Methyl N-benzyloxycarbonyl-α-triphenylphosphonioglycinate tetrafluoroborate (**2c**, $C_{29}H_{27}BF_4NO_4P$)

Procedure B, 120 hrs; yield 62%; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.18$ (dd, $J_{P-H} = 13.8$ Hz, $J_{H-H} = 6.7$ Hz, NH), 7.90–7.28 (m, $Ph_3P^{\oplus}$, Ph), 6.37 (dd, $J_{P-H} = 16.3$ Hz, $J_{H-H} = 8.2$ Hz, CH), 4.88 (d, $J = 12.2$ Hz, 1H, PhC$\underline{H}_2$), 4.81 (d, $J = 12.4$ Hz, 1H, PhC$\underline{H}_2$), 3.59 (s, MeO) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 155.8$ (d, $J = 0.5$ Hz, CONH), 55.2 (d, $J = 59.4$ Hz, CHP^+), 165.1 (d, $J = 9.6$ Hz, $\underline{C}OOMe$), 53.9 (OMe), 117.3 (d, $J = 84.6$ Hz, Ph_3P, C_1), 134.4 (d, $J = 10.1$ Hz, Ph_3P, C_2), 129.9 (d, $J = 13.1$ Hz, Ph_3P, C_3), 135.1 (d, $J = 0.5$ Hz, Ph_3P, C_4), 132.5, 130.5, 128.3, 127.8 ($\underline{Ph}CH_2$), 67.5 (Ph$\underline{C}H_2$) ppm; IR (CH_2Cl_2): $\bar{\nu} = 3310$, 1772, 1725–1680 cm^{-1}.

Procedure C, 170 hrs; yield 78%; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.90$–7.28 (m, $Ph_3P^{\oplus}$, Ph), 7.10 (m, NH), 6.40 (dd, $J_{P-H} = 16.5$ Hz, $J_{H-H} = 7.8$ Hz, CH), 4.85 (d, $J = 12.3$ Hz, 1H, PhC$\underline{H}_2$), 4.81 (d, $J = 12.6$ Hz, 1H, PhC$\underline{H}_2$), 3.60 (s, MeO) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 155.6$ (d, $J = 0.5$ Hz, CONH), 55.0 (d, $J = 58.4$ Hz, CHP^+), 164.7 (d, $J = 9.6$ Hz, $\underline{C}OOMe$), 53.5 (OMe), 116.8 (d, $J = 84.6$ Hz, Ph_3P, C_1), 134.1 (d, $J = 10.1$ Hz, Ph_3P, C_2), 129.7 (d, $J = 12.6$ Hz, Ph_3P, C_3), 134.0 (d, $J = 0.5$ Hz, Ph_3P, C_4), 132.2, 129.4, 128.0, 127.5 ($\underline{Ph}CH_2$), 67.4 (Ph$\underline{C}H_2$) ppm; IR (CH_2Cl_2): $\bar{\nu} = 3320$, 1780, 1750, 1738 cm^{-1}.

Methyl N-t-butoxycarbonyl-α-triphenylphosphonioglycinate tetrafluoroborate (**2d**, $C_{26}H_{29}BF_4NO_4P$)

Procedure B, 24 hrs; yield 79%; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.14$ (dd, $J_{P-H} = 14.2$ Hz, $J_{H-H} = 7.6$ Hz, NH), 7.99–7.35 (m, $Ph_3P^{\oplus}$), 6.31 (dd, $J_{P-H} = 16.2$ Hz, $J_{H-H} = 8.1$ Hz, CH), 3.56 (s, MeO), 1.17 (s, *t*-Bu) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 154.6$ (d, $J = 0.5$ Hz, CONH), 55.3 (d, $J = 59.5$ Hz, CHP^+), 165.2 (d, $J = 9.5$ Hz, $\underline{C}OOMe$), 53.4 (OMe), 117.8 (d, $J = 84.5$ Hz, Ph_3P, C_1), 134.5 (d, $J = 9.8$ Hz, Ph_3P, C_2), 129.9 (d, $J = 12.8$ Hz, Ph_3P, C_3), 135.0 (d, $J = 0.5$ Hz, Ph_3P, C_4), 81.6 ($Me_3\underline{C}O$), 27.6 ($\underline{Me}_3CO$) ppm; IR (CH_2Cl_2): $\bar{\nu} = 3320$, 1774, 1730–1686 cm^{-1}.

Methyl N-methoxycarbonyl-α-triphenylphosphonioglycinate tetrafluoroborate (**2e**, $C_{23}H_{23}BF_4NO_4P$)

Procedure B, 96 hrs; yield 87%; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.10$ (dd, $J_{P-H} = 13.2$ Hz, $J_{H-H} = 7.1$ Hz, NH), 7.88–7.38 (m, $Ph_3P^{\oplus}$), 6.33 (dd, $J_{P-H} = 16.5$ Hz, $J_{H-H} = 8.4$ Hz, CH), 3.60 (s, MeO), 3.41 (s, MeO) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 154.4$ (d, $J = 0.5$ Hz, CONH), 55.6 (d, $J = 58.9$ Hz, CHP^+), 165.1 (d, $J = 9.9$ Hz, $\underline{C}OOMe$), 53.9 (OMe), 117.4 (d, $J = 85.1$ Hz, Ph_3P, C_1), 134.6 (d, $J = 10.0$ Hz, Ph_3P, C_2), 130.0 (d, $J = 13.1$ Hz, Ph_3P, C_3), 135.2 (d, $J = 0.5$ Hz, Ph_3P, C_4), 53.1 (MeO) ppm; IR (CH_2Cl_2): $\bar{\nu} = 3060$, 1770, 1729, 1700 cm^{-1}.

Procedure C, 120 hrs; yield 94%; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.85$–7.41 (m, $Ph_3P^{\oplus}$ and NH), 6.37 (dd, $J_{P-H} = 16.6$ Hz, $J_{H-H} = 8.6$ Hz, CH), 3.61 (s, MeO), 3.40 (s, MeO) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 156.7$ (d, $J = 0.5$ Hz, CONH), 55.4 (d, $J = 58.9$ Hz, CHP^+), 165.0 (d, $J = 9.6$ Hz, $\underline{C}OOMe$), 53.7 (OMe), 117.3 (d, $J = 84.6$ Hz, Ph_3P, C_1), 134.4 (d, $J = 10.1$ Hz, Ph_3P, C_2), 129.9 (d, $J = 13.1$ Hz, Ph_3P, C_3), 135.0 (d, $J = 0.5$ Hz, Ph_3P, C_4), 52.9 (MeO) ppm; IR (CH_2Cl_2): $\bar{\nu} = 3060$, 1750, 1730, 1686 cm^{-1}.

General Procedure for Reactions of N-Acyl-α-triphenylphosphonioglycinates ***2*** *with Heteroatom Nucleophiles*

A nucleophile (2 mmol) and 0.37 cm^3 of *DBU* (0.38 g, 2.5 mmol) or 0.35 cm^3 of triethylamine (0.25 g, 2.5 mmol) were added to a stirred solution of the crude *N*-acyl-α-triphenylphosphonioglycinates **2** in 4 cm^3 of acetonitrile. The mixture was stirred at room temperature for the time given below. The solvent was removed under reduced pressure. The pure product **6** was isolated by column chromatography on silica gel (Kieselgel 60 Merck, 0.063–0.200 mm, 45 cm^3) eluting with a mixture of ethyl acetate and benzene in a volume ratio of 1:10. The product was recrystallized from benzene or from a mixture of benzene and *n*-hexane.

Methyl N-benzoyl-α-t-butylthioglycinate (**6a**, $C_{14}H_{19}NO_3S$)

Starting from **2a** (procedure A) and carrying out the reaction in the presence of Et_3N for 120 h 64% yield of **6a** was obtained; mp 71.0–71.5°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.82$–7.39 (m, 5H-Ph), 6.88 (d, $J = 8.4$ Hz, NH), 5.80 (d, $J = 8.7$ Hz, CH), 3.80 (s, MeO), 1.45 (s, Me_3CS) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 170.4$ (CONH), 53.0, 52.6 ($\underline{C}$HNu and MeO), 166.0 ($\underline{C}$OOMe), 133.4, 132.0, 128.6, 127.1 (Ph), 46.0 ($Me_3\underline{C}S$), 31.1 ($\underline{Me}_3CS$) ppm; IR (CH_2Cl_2): $\bar{\nu} = 3440$, 1740, 1660 cm^{-1}.

Methyl N-benzyloxycarbonyl-α-(benzotriazol-1-yl)glycinate (**6b**, $C_{17}H_{16}N_4O_4$)

Starting from **2c** (procedure B) and carrying out the reaction in the presence of *DBU* for 24 h 60% yield of **6b** was obtained; mp 116.5–117.5°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.14$–7.28 (m, 9H, $C_6H_4N_3$ and Ph), 7.01 (d, $J = 8.4$ Hz, CH), 6.66 (d, $J = 7.8$ Hz, NH), 5.17 (d, $J = 12.1$ Hz, $PhC\underline{H}_2O$), 5.04 (d, $J = 12.1$ Hz, $PhC\underline{H}_2O$), 3.82 (s, MeO) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 155.1$ (CONH), 63.8

(CHNu), 165.5 (COOMe), 53.9 (MeO), 131.9, 128.4, 128.3, 128.2 ($\underline{Ph}CH_2$), 67.8 ($Ph\underline{C}H_2$), 145.7, 132.1, 128.5, 124.4, 120.0, 109.9 ($C_6H_4N_3$: C_{3a}, C_{7a}, C_6, C_5, C_4, C_7) ppm; IR (CH_2Cl_2): $\bar{\nu} = 3310$, 1698, 1652 cm^{-1}.

Methyl N-benzyloxycarbonyl-α-benzylthioglycinate (**6c**, $C_{18}H_{19}NO_4S$)

Starting from **2c** (procedure B) and carrying out the reaction in the presence of Et_3N for 24 h 76% yield of **6c** was obtained; mp 54.0–54.5°C; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.40$–7.19 (m, 10H, $\underline{Ph}CH_2S$ and $\underline{Ph}CH_2O$), 5.79 (d, br, $J = 8.4$ Hz, NH), 5.35 (d, $J = 8.8$ Hz, CH), 5.09 (s, 2H, $PhC\underline{H}_2O$), 3.90 (d, 1H, $J = 13.4$ Hz, $PhC\underline{H}_2S$), 3.84 (d, 1H, $J = 13.3$ Hz, $PhC\underline{H}_2S$), 3.65 (s, MeO) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 154.5$ (CONH), 55.5 (CHNu), 169.0 (COOMe), 52.8 (MeO), 135.8, 128.4, 128.1, 128.0 ($\underline{Ph}CH_2O$), 67.2 ($Ph\underline{C}H_2$), 136.8, 128.8, 128.4, 127.2 ($\underline{Ph}CH_2S$), 35.0 ($Ph\underline{C}H_2S$) ppm; IR (CH_2Cl_2): $\bar{\nu} = 3430$, 1742, 1728 cm^{-1}.

Starting from **2c** (procedure C) and carrying out the reaction in the presence of Et_3N for 96 h 42% yield of **6c** was obtained.

Methyl N-t-butoxycarbonyl-α-(benzotriazol-1-yl)glycinate (**6d**, $C_{14}H_{18}N_4O_4$)

Starting from **2d** (procedure B) and carrying out the reaction in the presence of *DBU* for 190 h 46% yield of **6d** was obtained; mp 117.5–118.0°C; ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 8.10$–7.36 (m, 4H, $C_6H_4N_3$), 6.98 (d, $J = 8.6$ Hz, CH), 6.37 (d, $J = 7.0$ Hz, NH), 3.82 (s, MeO), 1.41 (s, Me_3CO) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 154.1$ (CONH), 63.6 (CHNu), 165.9 (COOMe), 53.9 (MeO), 81.7 ($Me_3\underline{C}O$), 28.1 ($\underline{Me}_3CO$), 145.7, 132.0, 128.2, 124.4, 120.0, 110.0 ($C_6H_4N_3$: C_{3a}, C_{7a}, C_6, C_5, C_4, C_7) ppm; IR (CH_2Cl_2): $\bar{\nu} = 3430$, 1762, 1722 cm^{-1}; MS (ESI): calcd. for $C_{14}H_{18}N_4O_4Na$ 329.1220, found 329.1236.

Methyl N-t-butoxycarbonyl-α-benzylthioglycinate (**6e**, $C_{15}H_{21}NO_4S$)

Starting from **2d** (procedure B) and carrying out the reaction in the presence of Et_3N for 190 h 45% yield of **6e** was obtained (resin); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.40$–7.20 (m, 5H-Ph), 5.34 (d, br, $J = 0.5$ Hz, NH), 5.25 (d, $J = 8.7$ Hz, CH), 3.85 (d, $J = 13.2$ Hz, 1H, $PhC\underline{H}_2S$), 3.78 (d, $J = 13.5$ Hz, 1H, $PhC\underline{H}_2S$), 3.62 (s, MeO), 1.36 (s, Me_3CO) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 153.9$ (CONH), 55.4 (CHNu), 169.3 (COOMe), 52.8 (MeO), 80.6 ($Me_3\underline{C}O$), 28.2 ($\underline{Me}_3CO$), 137.1, 128.9, 128.5, 127.2 ($\underline{Ph}CH_2S$), 35.0 ($Ph\underline{C}H_2S$) ppm; IR (CH_2Cl_2): $\bar{\nu} = 3435$, 1718, 1745 cm^{-1}; MS (ESI): calcd. for $C_{15}H_{21}NO_4NaS$ 334.1084, found 334.1102.

Methyl N-methoxycarbonyl-α-phenylthioglycinate (**6f**, $C_{11}H_{13}NO_4S$)

Starting from **2e** (procedure B) and carrying out the reaction in *Me*CN in the presence of Et_3N for 24 h 84% yield of **6f** was obtained (resin); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.55$–7.28 (m, Ph), 6.64 (d, $J = 8.5$ Hz, NH), 5.54 (d, $J = 9.2$ Hz, CH), 3.74 (s, MeO), 3.71 (s, MeO) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 154.9$ (CONH), 58.8 (CHNu), 168.6 (COOMe), 52.8, 52.6 (COOMe and MeO(CO)NH), 135.5, 129.8, 129.5, 129.1 (PhS) ppm; IR (CH_2Cl_2): $\bar{\nu} = 3422$, 1685br cm^{-1}; MS (ESI): calcd. for $C_{11}H_{13}NO_4NaS$ 278.0458, found 278.0473.

Starting from **2e** (procedure C) and carrying out the reaction in *Me*CN in the presence of Et_3N for 96 h 45% yield of **6f** was obtained.

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