Monatshefte für Chemie 135, 807–815 (2004)
DOI 10.1007/s00706-003-0167-1

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

N-Acyl-α-triphenylphosphonioglycinates in the Synthesis of α,β-Dehydro-α-amino Acid Derivatives

Roman Mazurkiewicz[1,*], **Anna Kuźnik**[1], **Mirosława Grymel**[1], and **Nikodem Kuźnik**[2]

[1] Department of Organic and Bioorganic Chemistry and Biotechnology, Silesian University of Technology, PL-44100 Gliwice, Poland
[2] Department of Analytical and General Chemistry, Silesian University of Technology, PL-44100 Gliwice, Poland

Received November 24, 2003; accepted (revised) December 5, 2003
Published online April 22, 2004

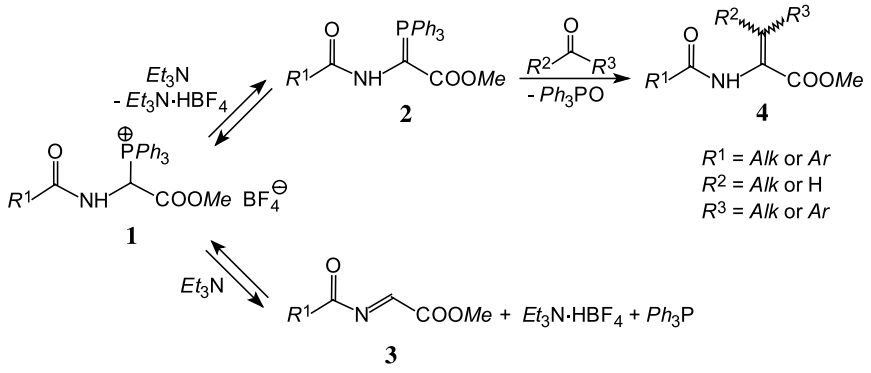
Summary. *N*-Acyl-α-triphenylphosphonioglycinates when treated with triethylamine are transformed to an equilibrium mixture of the corresponding *N*-acyliminoacetates and *N*-acyl-α-triphenylphosphoranylideneglycinates. *Wittig* reaction of the latter ylides with aromatic and aliphatic aldehydes or ketones enables a new easy entry to *N*-acyl-α,β-dehydro-α-amino acid esters.

Keywords. *N*-Acyl-α-triphenylphosphonioglycinates; *N*-Acyl-α-triphenylphosphoranylideneglycinates; Ylides derived from glycine; α,β-Dehydro-α-amino acids; *Wittig* reaction.

Introduction

α,β-Dehydro-α-amino acids are one of the most interesting groups of nonproteinogenic α-amino acids. They are common components of naturally occurring peptides of high biological activity, including enzymes, antibiotics, hormones, and phytotoxins [1, 2]. The synthesis of α,β-dehydro-α-amino acids has become an area of great importance with the advent of peptide-derived chemotherapeutics [2, 3]. The substitution of proteinogenic α-amino acids by α,β-dehydro-α-amino acid residues usually affects markedly the physiological activity of peptides, changing their secondary structure and increasing their resistance to protease catalyzed hydrolysis [4–6]. Apart from that, the hydrogenation of α,β-dehydro-α-amino acids using *Wilkinson*-type chiral catalysts is considered to be one of the most general and useful methods for the enantioselective synthesis of α-amino acids [1, 2, 7–10].

* Corresponding author. E-mail: romanm@zeus.polsl.gliwice.pl



Scheme 1

Recently, we have developed a new convenient and effective synthesis of *N*-acyl-α-triphenylphosphonioglycinates **1**, starting from 4-phosphoranylidene-5(4*H*)-oxazolones [11]. *N*-Acyl-α-triphenylphosphonioglycinates are a stable, crystalline, hardly known class of phosphonium salts derived from glycine [11]. They 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 [12]. We have also proved that *N*-acyl-α-triphenylphosphonioglycinates, when treated with an organic base, are transformed to an equilibrium mixture of the corresponding *N*-acyliminoacetates **3** and phosphonium ylides derived from glycine **2** (Scheme 1) [13].

In this contribution, we report a novel synthesis of α,β-dehydro-α-amino acid derivatives **4** in the *Wittig* reaction, starting from easily accessible *N*-acyl-α-triphenylphosphonioglycinates **1** as precursors of ylides **2** (Scheme 1).

Results and Discussion

N-Acyl-α-triphenylphosphoranylideneglycinates **2**, generated *in situ* from the phosphonium salts **1** under the influence of triethylamine in acetonitrile, react easily with aromatic and aliphatic aldehydes in a *Wittig* reaction to give, as a rule, a mixture of (*Z*) and (*E*) isomers of *N*-acyl-α,β-dehydro-α-amino acid esters **4**, usually in good or even excellent yields. In a few cases only the (*Z*) isomer was isolated from a reaction mixture (Scheme 1, Table 1).

Our attempts to use simple ketones in this reaction failed. However, we were able to obtain the expected products using a ketone with electron-withdrawing groups R^2 and R^3 (methyl trifluoropyruvate). The reactions were carried out in the presence of some amount of triphenylphosphine, to shift the equilibrium between the iminoacetic acid derivative **3** and ylide **2** towards the ylide.

In the case of the reaction with phenylacetaldehyde, we have also isolated from the reaction mixture methyl (*E*)-2-(*N*-pivaloylamino)-4-phenyl-3-butenoate (**5**) as a product of partial tautomerisation of the primary *Wittig* reaction product **4g**.

The structure of the obtained α,β-dehydro-α-amino acid derivatives was determined based on their spectral data (IR, ^{1}H and ^{13}C NMR, and HETCOR

Table 1. Synthesis of *N*-acyl-α,β-dehydro-α-amino acid esters **4**

Product				Reaction conditions			*(Z)*/*(E)* Ratio
	R^1	R^2	R^3	Procedure	Time/h	Salt **1**:Carbonyl compound ratio	
4a	*t-Bu*	H	*Ph*	A	24	1:3	2.7:1
4b	*t-Bu*	H	4-Pyridyl	A	6	1:3	11.4:1
4c	*t-Bu*	H	2-Furyl	A	6	1:3	5.8:1
4d	*t-Bu*	H	2-Pyrroyl	A	48	1:3	2.9:1
4e	*t-Bu*	H	*Et*	A	6	1:3	4.9:1
4f	*t-Bu*	H	*Me*	B	6	1:5	25:1
4g	*t-Bu*	H	*Ph*CH_2	A	24	1:3	–[a]
4h	*t-Bu*	CF_3	COO*Me*	A	6	1:1.5	–[a, b]
4i	*Ph*	CF_3	COO*Me*	A	6	1:1.5	–[a, b]
4j	*Ph*	H	*Ph*	A	48	1:3	1.6:1
4k	*Ph*	H	2-Furyl	A	6	1:3	–[a]
4l	*Ph*	H	*Me*	B	24	1:5	4:1
4m	*Me*	H	2-Quinolyl	A	6	1:3	–[a]
4n	*Me*	H	2-Thienyl	A	48	1:3	2.6:1
4o	*Me*	H	*Ph*	A	24	1:3	2.3:1

[a] Only one isomer has been detected in the reaction mixture; [b] the configuration of the isomer was not established

experiments) and satisfactory elemental analyses. In two cases, results of high-resolution mass spectrometry also confirmed the structures.

In all cases of reactions with aldehydes we discovered the predominance of the (*Z*) stereoisomer of *N*-acyl-α,β-dehydro-α-amino acid esters. The configuration of stereoisomers was established taking into account the following four criteria: (i) the proton at the β position at the double bond of a (*Z*) isomer is shielded by about 0.2–1 ppm if compared with the respective (*E*) isomer [14], (ii) the proton at the nitrogen atom is also shielded in a (*Z*) isomer in comparison with the (*E*) isomer [15], (iii) the changing of the solvent from $CDCl_3$ to the deuterated trifluoroacetic acid (*TFA*) causes an upfield shift of the olefinic proton of an (*E*) isomer and a downfield shift of the respective proton in the case of the (*Z*) isomer [14, 16], and (iv) in the case of *N*-benzoyl derivatives the protons of the methoxy group are shielded in an (*E*) isomer if compared with the (*Z*) isomer [16]. The configurations of the (*Z*) isomer of compound **4m** and the (*E*) isomers of **4a** and **4o** were also confirmed by single crystal X-ray analyses.

The reported method for the synthesis of α,β-dehydro-α-amino acid derivatives might be compared with a similar method described by *Schmidt et al.* [17–20], which consists in the condensation of aldehydes with *N*-acyl-α-(dialkyloxyphosphinyl)glycinates by way of a *Wadsworth-Emmons* reaction. The reported method seems to have two important advantages if compared with *Schmidt's* method: the starting *N*-acyl-α-triphenylphosphonioglycinates seem to be much easier accessible than *N*-acyl-α-(dialkyloxyphosphinyl)glycinates, and the reported reaction is carried out in the presence of triethylamine instead of strong bases like sodium hydride, lithium diisopropylamide, or potassium *t*-butoxide.

In summary, the *Wittig* reaction starting from *N*-acyl-α-triphenylphosphonioglycinates as the corresponding ylide precursors enables a new easy entry to *N*-acyl-α,β-dehydro-α-amino acid esters.

Experimental

Melting points 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. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or *TFA* on a Varian Unity Inova-300 spectrometer at 300 and 75.5 MHz, respectively, using *TMS* as an internal standard. High-resolution mass spectra were recorded on an AMD 604 Spectrometer with EI ionisation. Kieselgel 60 (Merck, 0.063–0.200 mm) was used for column chromatography. Elemental analyses (C, H, N) proved to be in satisfactory agreement with the calculated values.

Methyl *N*-acyl-α-triphenylphosphonioglycinate tetrafluoroborates **1** ($R^1 = t$-Bu, Ph, and Me) were synthesized as previously described [11]. Commercial grade acetonitrile, CH_2Cl_2, benzene, ethyl acetate, and *n*-hexane were distilled and dried over molecular sieves 4 Å. Triethylamine was purified according to *Sauer* [21].

X-Ray Analyses

The measurements of diffraction intensities were performed on a KUMA KM4 four-circle diffractometer, MoK_α radiation, $\omega/2\Theta$ scan mode, Θ range 2.5–25.0°; temperature of the measured crystalls: 293 K. Crystallographic data for the structures **4a**, **4m**, and **4o** were deposited with the Cambridge Crystallographic Data Centre as supplementary publications number CCDC 221902, CCDC 221901, and CCDC 221900. A complete listing of the atomic coordinates x, y, and z can be obtained free of charge, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (+int) 44-1223 336 033; e-mail: deposit@ccdc.cam.ac.uk], on quoting the depository numbers, the names of the authors, and the journal citation.

Syntheses of N-Acyl-α,β-dehydro-α-amino Acid Methyl Esters ***4***

Procedure A

To a stirred suspension of 1 mmol of methyl *N*-acyl-α-triphenylphosphonioglycinate tetrafluoroborate in 4 cm^3 of CH_3CN, 0.393 g of triphenylphosphine (1.5 mmol), 1.5–3 mmol of the carbonyl compound, and 0.17 cm^3 of triethylamine (1.25 mmol) were added at room temperature. After the reaction was completed the solvent was evaporated and the reaction product was isolated by column chromatography (ethyl acetate:benzene = 1:10 to 1:1). The crude product was recrystallized from a mixture of benzene and *n*-hexane.

Procedure B

A mixture of 1 mmol of methyl *N*-acyl-α-triphenylphosphonioglycinate tetrafluoroborate, 4 cm^3 of CH_3CN, 0.393 g of triphenylphosphine (1.5 mmol), 5 mmol of the carbonyl compound, and 0.17 cm^3 of triethylamine (1.25 mmol) was sealed in a glass tube and shaken at room temperature to make the phosphonium salt dissolved. The reaction mixture was worked up as described above for procedure A.

Methyl (Z)-2-(N-pivaloylamino)-3-phenylpropenoate (*Z*-**4a**, $C_{15}H_{19}NO_3$)

Yield 169.7 mg (65%); mp 105–106°C (Ref. [22] 101–102°C); ^1H NMR ($CDCl_3$, 300 MHz): $\delta = 7.44$–7.26 (m, Ph and –CH=), 7.24 (s, br, NH), 3.84 (s, OMe), 1.29 (s, *t*-Bu) ppm; ^1H NMR (*TFA*, 300 MHz):

$\delta = 7.84$ (s, –CH=) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 176.5$ (CONH), 165.8 (COOMe), 134.0, 124.6 (C_α and C-1), 131.3, 129.2 (C_β and C-4), 52.6 (OMe), 39.2 (CMe_3), 27.2 (CMe_3), 129.5, 128.4 (C-2 and C-3) ppm; IR ($CHCl_3$): $\bar{\nu} = 3430$ m, 1720 s, 1685 vs, 1640 m, 1260 vs cm^{-1}.

Methyl (E)-2-(N-pivaloylamino)-3-phenylpropenoate (*E*-**4a**, $C_{15}H_{19}NO_3$)

Yield 62.9 mg (24%); mp 122–123°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.96$ (s, –CH=), 7.81 (s, br, NH), 7.36–7.20 (m, Ph), 3.64 (s, OMe), 1.30 (s, *t*-Bu) ppm; ^{1}H NMR (*TFA*, 300 MHz): $\delta = 7.25$ (s, –CH=) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 177.1$ (CONH), 165.5 (COOMe), 135.5 (C_α), 125.79 (C_β), 52.2 (OMe), 39.7 (CMe_3), 27.4 (CMe_3), 128.6, 127.8 (C-2 and C-3), 127.2, 125.83 (C-4, C-1) ppm; IR ($CHCl_3$): $\bar{\nu} = 3420$ m, 1700 s, 1680 s, 1650 m, 1220 s cm^{-1}.

Methyl (Z)-2-(N-pivaloylamino)-3-(4-pyridyl)propenoate (*Z*-**4b**, $C_{14}H_{18}N_2O_3$)

Yield 212.2 mg (81%); mp 116–117°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.58$ (d, $J_{3-2} = 6.3$ Hz, H-2), 7.61 (s, br, NH), 7.23 (s, –CH=), 7.21 (d, $J_{2-3} = 6.0$ Hz, H-3), 3.88 (s, OMe), 1.27 (s, *t*-Bu) ppm; ^{1}H NMR (*TFA*, 300 MHz): $\delta = 7.69$ (s, –CH=) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 175.8$ (CONH), 165.3 (COOMe), 127.2 (C_α), 127.0 (C_β), 53.0 (OMe), 39.4 (CMe_3), 27.1 (CMe_3), 149.8, 142.1, 123.0 (C-2, C-4, C-3) ppm; IR ($CHCl_3$): $\bar{\nu} = 3410$ m, 1690 br, 1640 w, 1280 s cm^{-1}.

Methyl (Z)-2-(N-pivaloylamino)-3-(2-furyl)propenoate (*Z*-**4c**, $C_{13}H_{17}NO_4$)

Yield 192.9 mg (77%); mp 98–100°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.82$ (s, br, NH), 7.50 (d, $J_{5-4} = 1.8$ Hz, H-5), 6.92 (s, –CH=), 6.54 (d, $J_{3-4} = 3.6$ Hz, H-3), 6.49 (dd, $J_{4-3} = 3.5$ Hz, $J_{4-5} = 1.6$ Hz, H-4), 3.82 (s, OMe), 1.33 (s, *t*-Bu) ppm; ^{1}H NMR (*TFA*, 300 MHz): $\delta = 7.54$ (s, –CH=) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 176.8$ (CONH), 165.3 (COOMe), 123.6 (C_α), 115.3 (C_β), 52.5 (OMe), 39.1 (CMe_3), 27.3 (CMe_3), 150.1, 144.0, 114.8, 112.2 (C-2, C-5, C-3, C-4) ppm; IR ($CHCl_3$): $\bar{\nu} = 3445$ m, 1725 s, 1685 vs, 1645 m, 1280 s cm^{-1}.

Methyl (E)-2-(N-pivaloylamino)-3-(2-furyl)propenoate (*E*-**4c**, $C_{13}H_{17}NO_4$)

Yield 33.3 mg (13%); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.98$ (s, –CH=), 7.80 (s, br, NH), 7.44 (d, $J_{5-4} = 1.5$ Hz, H-5), 6.96 (d, $J_{3-4} = 3.3$ Hz, H-3), 6.45 (dd, $J_{4-3} = 3.5$ Hz, $J_{4-5} = 1.6$ Hz, H-4), 3.90 (s, OMe), 1.28 (s, *t*-Bu) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 176.9$ (CONH), 164.4 (COOMe), 122.0 (C_α), 114.8, 114.2 (C_β and C-3), 52.4 (OMe), 39.8 (CMe_3), 27.4 (CMe_3), 149.5, 143.3, 112.1 (C-2, C-5, C-4) ppm; IR ($CHCl_3$): $\bar{\nu} = 3410$ m, 1690 s, 1675 vs, 1645 w, 1255 m cm^{-1}.

Methyl (Z)-2-(N-pivaloylamino)-3-(2-pyrroyl)propenoate (*Z*-**4d**, $C_{13}H_{18}N_2O_3$)

Yield 139.6 mg (56%); mp 152–154°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 9.31$ (s, br, NH_{pyr}), 7.48 (s, –CH=), 7.19 (s, br, NH), 6.94–6.92 (m, H-5), 6.54–6.52 (m, H-3), 6.29–6.26 (m, H-4), 3.80 (s, OMe), 1.36 (s, *t*-Bu) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): 179.4 (CONH), 166.3 (COOMe), 116.8 (C_α), 125.1 (C_β), 52.4 (OMe), 39.6 (CMe_3), 27.5 (CMe_3), 126.7, 123.3, 116.7, 110.7 (C-2, C-5, C-3, C-4) ppm; IR ($CHCl_3$): $\bar{\nu} = 3470$ m, 1690 br, 1635 s, 1260 vs cm^{-1}.

Methyl (E)-2-(N-pivaloylamino)-3-(2-pyrroyl)propenoate (*E*-**4d**, $C_{13}H_{18}N_2O_3$)

Yield 48.1 mg (19%); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 11.68$ (s, br, NH_{pyr}), 7.71 (s, –CH=), 7.35 (s, br, NH), 7.00–6.98 (m, H-5), 6.55–6.53 (m, H-3), 6.29–6.26 (m, H-4), 3.86 (s, OMe), 1.29 (s, *t*-Bu)

ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 177.1$ (CONH), 165.3 (COOMe), 114.9 (C_α), 127.6, 126.3 (C_β and C-2), 52.5 (OMe), 39.5 (CMe_3), 27.4 (CMe_3), 122.9, 119.6, 110.4 (C-5, C-3, C-4) ppm; IR ($CHCl_3$): $\bar{\nu} = 3455$ m, 1700 m, 1650 br, 1220 vs cm^{-1}.

Methyl (Z)-2-(N-pivaloylamino)-2-pentenoate (*Z*-**4e**, $C_{11}H_{19}NO_3$)

Yield 166.5 mg (78%); mp 66–67.5°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.01$ (s, br, NH), 6.65 (t, $J = 7.2$ Hz, –CH=), 3.77 (s, OMe), 2.14 (dq, $J = 7.4$, 7.4 Hz, CH_2), 1.28 (s, *t*-Bu), 1.07 (t, $J = 7.5$ Hz, Me) ppm; ^{1}H NMR (*TFA*, 300 MHz): $\delta = 7.18$ (s, –CH=) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 176.7$ (CONH), 165.4 (COOMe), 124.2 (C_α), 139.7 (C_β), 52.3 (OMe), 39.3 (CMe_3), 27.5 (CMe_3), 22.3 (CH_2), 12.7 (Me) ppm; IR ($CHCl_3$): $\bar{\nu} = 3430$ m, 1715 vs, 1685 vs, 1645 m, 1280 s cm^{-1}.

Methyl (E)-2-(N-pivaloylamino)-2-pentenoate (*E*-**4e**, $C_{11}H_{19}NO_3$)

Yield 34 mg (16%); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.69$ (s, br, NH), 7.15 (t, $J = 7.6$ Hz, –CH=), 3.84 (s, OMe), 2.57 (dq, $J = 7.5$, 7.5 Hz, CH_2), 1.25 (s, *t*-Bu), 1.08 (t, $J = 7.5$ Hz, Me) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): 177.1 (CONH), 165.3 (COOMe), 124.3 (C_α), 134.6 (C_β), 52.3 (OMe), 39.6 (CMe_3), 27.4 (CMe_3), 21.9 (CH_2), 14.2 (Me) ppm; IR (CH_2Cl_2): $\bar{\nu} = 3420$ m, 1735 s, 1675 s, 1250 s cm^{-1}.

Methyl (Z)-2-(N-pivaloylamino)-2-butenoate (*Z*-**4f**, $C_{10}H_{17}NO_3$)

Yield 185.8 mg (93%); oil; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.04$ (s, br, NH), 6.79 (q, $J = 7.2$ Hz, –CH=), 3.76 (s, OMe), 1.75 (d, $J = 7.2$ Hz, Me), 1.29 (s, *t*-Bu) ppm; ^{1}H NMR (*TFA*, 300 MHz): $\delta = 7.29$ (s, –CH=) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 176.6$ (CONH), 165.2 (COOMe), 126.0 (C_α), 133.4 (C_β), 52.2 (OMe), 39.3 (CMe_3), 27.5 (CMe_3), 14.6 (Me) ppm; IR ($CHCl_3$): $\bar{\nu} = 3430$ m, 1710 vs, 1680 vs, 1650 m, 1290 vs cm^{-1}.

Methyl (E)-2-(N-pivaloylamino)-2-butenoate (*E*-**4f**, $C_{10}H_{17}NO_3$)

Yield 7.4 mg (4%); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.70$ (s, br, NH), 7.26 (q, $J = 7.7$ Hz, –CH=), 3.85 (s, OMe), 2.08 (d, $J = 7.8$ Hz, Me), 1.25 (s, *t*-Bu) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 177.1$ (CONH), 165.4 (COOMe), 125.6 (C_α), 127.6 (C_β), 52.3 (OMe), 39.7 (CMe_3), 27.4 (CMe_3), 14.4 (Me) ppm; IR ($CHCl_3$): $\bar{\nu} = 3430$ m, 1700 s, 1665 s, 1640 m, 1250 vs cm^{-1}.

Methyl (Z)-2-(N-pivaloylamino)-4-phenyl-2-butenoate (*Z*-**4g**, $C_{16}H_{21}NO_3$)

Yield 115.7 mg (42%); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.40$–7.19 (m, Ph), 7.14 (s, br, NH), 6.82 (t, $J = 7.0$ Hz, –CH=), 3.76 (s, OMe), 3.48 (d, $J = 6.9$ Hz, CH_2), 1.30 (s, *t*-Bu) ppm; ^{1}H NMR (*TFA*, 300 MHz): $\delta = 7.42$–7.18 (m, Ph and –CH=) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 176.9$ (CONH), 165.2 (COOMe), 125.1 (C_α), 135.8 (C_β), 52.4 (OMe), 39.4 (CMe_3), 27.5 (CMe_3), 138.8, 128.6, 126.4 (C-1, C-2 + C-3, C-4), 35.2 (CH_2) ppm; IR ($CHCl_3$): $\bar{\nu} = 3440$ m, 1715 s, 1675 vs, 1650 s, 1260 s cm^{-1}.

Methyl (E)-2-(N-pivaloylamino)-4-phenyl-3-butenoate (*E*-**5**, $C_{16}H_{21}NO_3$)

Yield 96.4 mg (35%); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.40$–7.19 (m, Ph), 6.62 (dd, $J_{H\gamma-H\beta} = 15.6$ Hz, $J_{H\gamma-H\alpha} = 1.2$ Hz, H_γ), 6.36 (d, $J = 6.9$ Hz, NH), 6.19 (dd, $J_{H\beta-H\gamma} = 15.9$ Hz, $J_{H\beta-H\alpha} = 6.6$ Hz, H_β), 5.26 (ddd, $J_{H\alpha-H\beta} = 6.9$ Hz, $J_{H\alpha-NH} = 6.9$ Hz, $J_{H\alpha-H\gamma} = 1.5$ Hz, H_α), 3.79 (s,

OMe), 1.26 (s, *t*-Bu) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 177.9$ (CONH), 171.4 (COOMe), 54.1 (C_α), 123.4 (C_β), 133.2 (C_γ), 52.7 (OMe), 38.7 (CMe_3), 27.4 (CMe_3), 135.8, 128.2 (C-1, C-4), 128.6, 126.6 (C-2 and C-3) ppm.

2-Pivaloylamino-3-trifluoromethylbutendioic Acid Dimethyl Ester (**4h**, $C_{12}H_{16}F_3NO_5$)

Yield 295.7 mg (95%); mp 79–81°C [13].

2-Benzoylamino-3-trifluoromethylbutendioic Acid Dimethyl Ester (**4i**, $C_{14}H_{12}F_3NO_5$)

Yield 152.4 mg (46%); mp 101.5–103.5°C [13].

Methyl (Z)-2-(N-benzoylamino)-3-phenylpropenoate (*Z*-**4j**, $C_{17}H_{15}NO_3$)

Yield 65.8 mg (23%); mp 140.5–141.5°C (Ref. [14] 131°C, Ref. [23] 142–143°C); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.88$–7.82, 7.56–7.41 and 7.34–7.28 (m, 10H_{ar}, NH, and –CH=), 3.83 (s, OMe) ppm; ^{1}H NMR (*TFA*, 300 MHz): $\delta = 7.98$–7.38 (m, 10H_{ar}, and –CH=) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 165.8$, 165.6 (CONH and COOMe), 133.8, 133.5 (C_α and PhCO: C-1), 129.4 (C_β), 52.7 (OMe), 132.1, 131.8 (PhCO: C-4 and PhCH=: C-4), 128.7, 128.6 (PhCO: C-2 and PhCH=: C-3), 127.4 (PhCO: C-3), 129.6, 124.2 (PhCH=: C-2, C-1) ppm; IR ($CHCl_3$): $\bar{\nu} = 3425$ m, 1715 s, 1680 vs, 1645 m, 1275 vs cm^{-1}.

Methyl (E)-2-(N-benzoylamino)-3-phenylpropenoate (*E*-**4j**, $C_{17}H_{15}NO_3$)

Yield 41.1 mg (15%); mp 132.5–133°C (Ref. [14] 125°C, Ref. [23] 134–135°C); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.39$ (s, br, NH), 8.05 (s, –CH=), 7.87–7.82 (m, 2H_{ar}), 7.57–7.42 (m, 3H_{ar}), 7.33–7.24 (m, 5H_{ar}), 3.67 (s, OMe) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 165.8$, 165.4 (CONH and COOMe), 135.2 (C_α), 126.3 (C_β), 52.4 (OMe), 134.1, 132.0, 127.8, 127.0 (PhCO: C-1, C-4, C-2, C-3), 128.75, 128.72 (PhCH=: C-2 and C-3), 127.6, 126.0 (PhCH=: C-4, C-1) ppm; IR ($CHCl_3$): $\bar{\nu} = 3405$ m, 1700 s, 1670 vs, 1630 m, 1250 s cm^{-1}.

Methyl (Z)-2-(N-benzoylamino)-3-(2-furyl)propenoate (*Z*-**4k**, $C_{15}H_{13}NO_4$)

Yield 135.6 mg (50%); mp 136–137°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.28$ (s, br, NH), 7.95–7.85 (m, 2H_{ar}), 7.60–7.46 (m, 3H_{ar} and H-5$_{Fur}$), 7.08 (s, –CH=), 6.58 (d, $J_{3-4} = 3.6$ Hz, H-3$_{Fur}$), 6.47 (dd, $J_{4-3} = 3.4$ Hz, $J_{4-5} = 1.6$ Hz, H-4$_{Fur}$), 3.84 (s, OMe) ppm; ^{1}H NMR (*TFA*, 300 MHz): $\delta = 7.68$ (s, –CH=) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 165.6$, 165.4 (CONH and COOMe), 123.0 (C_α), 116.2, 115.4 (C_β and Furyl: C-3), 52.6 (OMe), 133.5, 132.2 (PhCO: C-1, C-4), 128.7, 127.5 (PhCO: C-2 and C-3), 149.9, 144.4, 112.3 (Furyl: C-2, C-5, C-4) ppm; IR ($CHCl_3$): $\bar{\nu} = 3425$ m, 1720 s, 1675 vs, 1645 m, 1285 vs cm^{-1}.

Methyl (Z)-2-(N-benzoylamino)-2-butenoate (*Z*-**4l**, $C_{12}H_{13}NO_3$)

Yield 115.8 mg (53%); mp 79–80.5°C (Ref. [14] 78.5°C); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.90$–7.86 (m, 2H_{ar}), 7.61 (s, br, NH), 7.58–7.44 (m, 3H_{ar}), 6.90 (q, $J = 7.2$ Hz, –CH=), 3.79 (s, OMe), 1.85 (d, $J = 7.2$ Hz, Me) ppm; ^{1}H NMR (*TFA*, 300 MHz): $\delta = 7.40$ (s, –CH=) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 165.4$, 165.1 (CONH and COOMe), 126.0 (C_α), 133.7 (C_β), 52.4 (OMe), 133.9, 132.0, 128.6, 127.4 (C-1, C-4, C-2, C-3), 15.0 (Me) ppm; IR ($CHCl_3$): $\bar{\nu} = 3420$ m, 1715s , 1675 vs, 1650 m, 1290 vs cm^{-1}.

Methyl (E)-2-(N-benzoylamino)-2-butenoate (*E*-**4l**, $C_{12}H_{13}NO_3$)

Yield 28.9 mg (13%); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.19$ (s, br, NH), 7.85–7.80 (m, $2H_{ar}$), 7.55–7.41 (m, $3H_{ar}$ and –CH=), 3.89 (s, OMe), 2.16 (d, $J = 7.5$ Hz, Me) ppm; ^{1}H NMR (*TFA*, 300 MHz): $\delta = 6.95$ (s, –CH=) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 165.8$, 165.2 (CONH and COOMe), 125.7 (C_α), 128.2 (C_β), 52.4 (OMe), 134.8, 131.7, 128.7, 126.9 (C-1, C-4, C-2, C-3), 14.5 (Me) ppm; IR ($CHCl_3$): $\bar{\nu} = 3410$ m, 1700 m, 1670 s, 1645 m, 1270 s cm^{-1}; MS (EI): calcd. 219.0895, found 219.0890.

Methyl (Z)-2-(N-acetylamino)-3-(2-quinolyl)propenoate (*Z*-**4m**, $C_{15}H_{14}N_2O_3$)

Yield 267.6 mg (99%); mp 106–107°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 12.60$ (s, br, NH), 8.14 (d, $J_{4-3} = 8.4$ Hz, H-4), 7.94 (d, $J_{5-6} = 8.1$ Hz, H-5), 7.80 (d, $J_{8-7} = 8.4$ Hz, H-8), 7.78–7.72 (m, H-7), 7.58–7.52 (m, H-6), 7.32 (d, $J_{3-4} = 8.7$ Hz, H-3), 6.35 (s, –CH=), 3.91 (s, OMe), 2.30 (s, Me) ppm; ^{1}H NMR (*TFA*, 300 MHz): $\delta = 7.82$ (s, –CH=) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 168.6$ (CONH), 165.7 (COOMe), 126.7 (C_α), 112.3 (C_β), 52.7 (OMe), 23.7 (Me), 155.3, 146.6, 136.9, 135.4, 130.2, 128.3, 127.7, 126.8, 123.2 (Quinolyl) ppm; IR ($CHCl_3$): $\bar{\nu} = 3400$ m, 1730 vs, 1690 vs, 1640 s, 1285 vs cm^{-1}.

Methyl (Z)-2-(N-acetylamino)-3-(2-thienyl)propenoate (*Z*-**4n**, $C_{10}H_{11}NO_3S$)

Yield 136.6 mg (61%); mp 119–120°C (Ref. [15] 118–119°C); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.80$ (s, –CH=), 7.50 (d, $J_{5-4} = 4.8$ Hz, H-5), 7.32 (d, $J_{3-4} = 3.6$ Hz, H-3), 7.08 (dd, $J_{4-3} = 3.9$ Hz, $J_{4-5} = 4.8$ Hz, H-4), 6.83 (s, br, NH), 3.82 (s, OMe), 2.23 (s, Me) ppm; ^{1}H NMR (*TFA*, 300 MHz): $\delta = 8.21$ (s, –CH=) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 169.8$ (CONH), 165.3 (COOMe), 121.3 (C_α), 129.8 (C_β), 52.5 (OMe), 23.5 (Me), 136.2, 133.4, 130.8, 127.1 (C-2, C-3, C-5, C-4) ppm; IR ($CHCl_3$): $\bar{\nu} = 3415$ m, 1715 s, 1700 s, 1630 m, 1265 vs cm^{-1}.

Methyl (E)-2-(N-acetylamino)-3-(2-thienyl)propenoate (*E*-**4n**, $C_{10}H_{11}NO_3S$)

Yield 52.6 mg (23%); mp 117–118°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 8.34$ (s, –CH=), 7.52 (s, br, NH), 7.43 (d, $J_{5-4} = 4.8$ Hz, H-5), 7.29 (d, $J_{3-4} = 3.6$ Hz, H-3), 7.03 (dd, $J_{4-3} = 3.8$ Hz, $J_{4-5} = 5.2$ Hz, H-4), 3.92 (s, OMe), 2.15 (s, Me) ppm; ^{1}H NMR (*TFA*, 300 MHz): $\delta = 8.31$ (s, –CH=) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 168.6$ (CONH), 164.1 (COOMe), 120.8 (C_α), 122.5 (C_β), 52.3 (OMe), 24.8 (Me), 136.7, 134.5, 130.1, 126.6 (C-2, C-3, C-5, C-4) ppm; IR ($CHCl_3$): $\bar{\nu} = 3405$ m, 1700 vs, 1675 s, 1630 m, 1270 vs cm^{-1}.

Methyl (Z)-2-(N-acetylamino)-3-phenylpropenoate (*Z*-**4o**, $C_{12}H_{13}NO_3$)

Yield 132.9 mg (61%); mp 121–122°C (Ref. [14] 115°C, Ref. [24] 121–122°C, Ref. [25] 124°C); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.63$–7.21 (m, Ph and –CH=), 7.12 (s, br, NH), 3.84 (s, OMe), 2.11 (s, Me) ppm; ^{1}H NMR (*TFA*, 300 MHz): $\delta = 7.88$ (s, –CH=) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 168.8$ (CONH), 165.7 (COOMe), 133.7 (C_α), 129.4 (C_β), 52.7 (OMe), 23.3 (Me), 132.3, 124.2 (C-4, C-1), 129.6, 128.6 (C-2 and C-3) ppm; IR ($CHCl_3$): $\bar{\nu} = 3420$ m, 1700 br, 1635 m, 1265 vs cm^{-1}.

Methyl (E)-2-(N-acetylamino)-3-phenylpropenoate (*E*-**4o**, $C_{12}H_{13}NO_3$)

Yield 57.8 mg (26%); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.87$ (s, –CH=), 7.58 (s, br, NH), 7.50–7.19 (m, Ph), 3.63 (s, OMe), 2.14 (s, Me) ppm; ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 173.9$ (CONH), 164.1 (COOMe), 133.7 (C_α), 126.0, 125.7 (C_β and C-1), 52.3 (OMe), 24.5 (Me), 128.7, 127.8 (C-2 + C-3,

C-4) ppm; IR ($CHCl_3$): $\bar{\nu} = 3410$ m, 1710 vs, 1685 vs, 1635 m, 1270 s cm^{-1}; MS (EI): calcd. 219.0895, found 219.0903.

Acknowledgements

The financial help of the Polish State Committee for Scientific Research (Grant No 4 T09A 026 24) is gratefully acknowledged.

References

[1] Aguado GP, Moglioni AG, Ortuño RM (2003) Tetrahedron Asymm **14**: 217
[2] Williams RM (1989) Synthesis of Optically Active α-Amino Acids. Pergamon Press, Oxford, p 1; Williams RM (1992) Aldrichimica Acta **25**: 11
[3] Williams RM (1995) Adv Asymmetric Synth **1**: 45; O'Donnell MJ, Bennett WD (1988) Tetrahedron **44**: 5389; Ikegami S, Uchiyama H, Hayama T, Katsuki T, Yamaguchi M (1988) Tetrahedron **44**: 5333
[4] Coghlan PA, Easton ChJ (1999) Tetrahedron Lett **40**: 4745
[5] Thormann M, Hofmann H-J (1998) J Mol Structure **431**: 79
[6] Palmer DE, Pattaroni Ch, Nunami K, Chadha RK, Goodman M, Wakamiya T, Fukase K, Horimoto S, Kitazawa M, Fujita H, Kubo A, Shiba T (1992) J Am Chem Soc **114**: 5634
[7] Tungler A, Fogassy G (2001) J Mol Catalysis **173**: 233
[8] Adamczyk M, Akireddy SR, Reddy RE (2002) Tetrahedron **58**: 6951, 6954
[9] Aguado GP, Alvarez-Larena A, Illa O, Moglioni AG, Ortuño RM (2001) Tetrahedron Asymm **12**: 25
[10] Wang W, Xiong Ch, Zhang J, Hruby VJ (2002) Tetrahedron **58**: 3101
[11] Mazurkiewicz R, Grymel M (1999) Monatsh Chem **130**: 597
[12] Kober R, Steglich W (1983) Liebigs Ann Chem 599
[13] Mazurkiewicz R, Grymel M (2002) Monatsh Chem **133**: 1201
[14] Schöllkopf U, Meyer R (1981) Liebigs Ann Chem 1469
[15] Cativiela C, Diaz de Villegas MD, Mayoral JA, Melendez E (1983) Synthesis **11**: 899
[16] Glaser R, Geresh S, Schöllkopf U, Meyer R (1979) J Chem Soc Perkin Trans 1 1746
[17] Schmidt U, Lieberknecht A, Schanbacher U, Beuttler T, Wild J (1982) Angew Chem Int Ed Engl **21**: 776
[18] Schmidt U, Lieberknecht A, Wild J (1984) Synthesis **53**: 53
[19] Schmidt U, Weller D, Holder A, Lieberknecht A (1988) Tetrahedron Lett **29**: 3227
[20] Schmidt U, Lieberknecht A, Wild J (1988) Synthesis **159**: 159
[21] Sauer JC (1963) Org Synth **4**: 561
[22] Glaser R, Geresh S (1979) Tetrahedron **35**: 2381
[23] Gelbard G, Kagan HB (1976) Tetrahedron **32**: 233
[24] Arcadi A, Cacchi S, Marinelli F, Morera E, Ortar G (1990) Tetrahedron **46**: 7151
[25] Gladiali S, Pinna L (1991) Tetrahedron Asymm **2**: 623