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Reaction of *N*-Acyl-α-triphenylphosphonio-α-amino Acid Esters with Organic Bases: Mechanism of the Base-Catalyzed Nucleophilic Substitution of the Triphenylphosphonium Group

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Summary. Reactions of *N*-acyl-α-triphenylphosphonio-α-amino acid methyl esters with organic bases (triethylamine or *DBU*) were investigated as the crucial step of the base-catalyzed displacement of the triphenylphosphonium group by nucleophiles. It was proved that *N*-acyl-α-triphenylphosphonioglycinates are transformed to an equilibrium mixture of the corresponding *N*-acyliminoacetates and *N*-acyl-α-triphenylphosphoranylidene glycinates by bases. In the case of *N*-acyl-α-triphenylphosphonio-α-amino acid esters with quaternary α-carbon, the α-substituted homologues of the *N*-acyliminoacetates were detected to be the only primary reaction product which, however, can undergo further tautomerization to the corresponding α,β-dehydro-α-amino acid derivatives. In both these cases the reaction of *N*-acyl-α-triphenylphosphonio-α-amino acid esters with nucleophiles proceeds *via* the addition of a nucleophile to the activated C=N double bond of the *N*-acylimino intermediate.

Keywords. *N*-α-Triphenylphosphonioglycinates; Nucleophilic substitution; Synthetic equivalents of α-amino acid α-cations; Glycine functionalization.

Introduction

Since the pioneering investigations of *Ben-Ishai et al.* [1] on the first synthetic equivalents of glycine α-cations, the important problem of synthesizing α-amino acids by a new bond formation between the α-position of an α-amino acid electrophilic equivalent and a nucleophile has attracted the attention of organic chemists. In the course of the last twenty five years many synthetic equivalents of α-amino acid α-cations have been introduced [2, 3].

Recently, we have developed and reported convenient and effective syntheses of *N*-acyl-α-triphenylphosphonio glycinates (**2**; [2]) and their α-alkyl substituted analogues (**4**; [4]) from 4-triphenylphosphoranylidene-5(4*H*)-oxazolones **1** or 4-alkyl-4-triphenylphosphonio-5(4*H*)-oxazolone iodides **3**. We have also described

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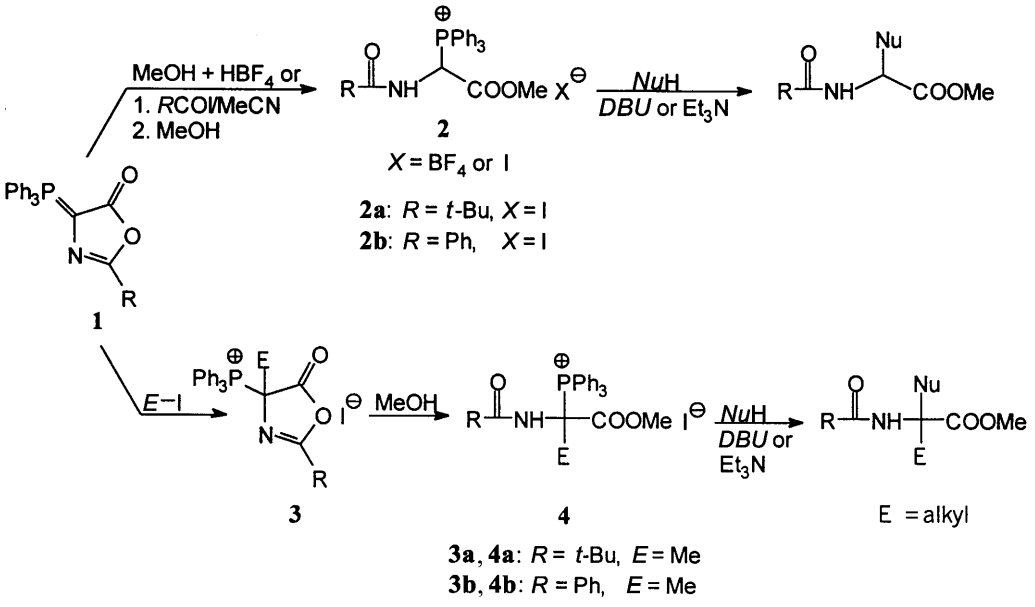


Scheme 1

a simple method for the displacement of the triphenylphosphonium group in these compounds by a variety of oxygen, sulfur, nitrogen, and carbon nucleophiles [2–4] in the presence of triethylamine or *DBU*, demonstrating that the α-triphenylphosphonio-α-amino acid derivatives **2** and **4** may be considered to be new interesting synthetic equivalents of α-amino acid α-cations. The described transformations enable an easy functionalization of the glycine α-position with nucleophiles or even its double functionalization with electrophiles (alkyl halides) and nucleophiles (Scheme 1). In the present paper we report our investigations on the mechanism of the base-catalyzed displacement of the triphenylphosphonium group in phosphonium salts **2** and **4** by nucleophiles.

Results and Discussion

Trying to explain the mechanism of the base-catalyzed displacement of the triphenylphosphonium group of *N*-acyl-α-triphenylphosphonio-α-amino acid esters by nucleophiles, we examined in detail their reaction with triethylamine or *DBU* in CD_3CN at 25°C. We monitored changes of the composition of the reaction mixtures as a function of the reaction time using IR and NMR spectroscopy.

N-Acyl-α-triphenylphosphonioglycinates **2** have been obtained for the first time from α-bromoglycinates and triphenylphosphine by *Kober* and *Steglich* in 1983 [5]. They found that ethyl *N*-benzoyl-α-triphenylphosphonioglycinate bromide is converted into diethyl 2,3-bis-(benzoylamino)-fumarate in the presence of triethylamine. The authors did not examine the reaction of *N*-benzoyl-α-triphenylphosphonioglycinate with nucleophiles. In order to explain the formation of 2,3-bis-(bezoylamino)-fumarate they assumed that *N*-benzoyl-α-triphenylphosphonioglycinate is converted to a mixture of the corresponding ylide (ethyl *N*-benzoyl-α-triphenylphosphoranylidene glycinate) and ethyl *N*-benzoyliminoacetate upon

action of triethylamine at the first step of the reaction. The condensation of the ylide with the *N*-benzoyliminoacetate results in 2,3-bis-(benzoylamino)-fumarate.

As we observed in our first experiment, the treatment of methyl *N*-pivaloyl-α-triphenylphosphonioglycinate tetrafluoroborate with triethylamine resulted in an immediate disappearance of the starting ester. A detailed analysis of spectroscopic data led to the conclusion that the reaction mixtures contained two new compounds which were assigned tentatively as the corresponding ylide and *N*-acyliminoacetate analogous to those proposed by *Kober* and *Steglich* [5]. In addition, the reaction mixtures also contained triphenylphosphine, triethylamine tetrafluoroborate, and the previously isolated and identified dimethyl 2,3-bis-(pivaloylamino)-fumarate. We were able to assign the most characteristic ^{1}H and ^{13}C NMR signals of the ylide **6a** and *N*-pivaloyliminoacetate **5a** (Table 1). Integration of the methoxy resonances in the ^{1}H NMR spectra allowed to estimate the concentration of the components of the reaction mixture (Fig. 1). Evidently, **6** is formed as a result of the deprotonation at the α-carbon, whereas deprotonation at the nitrogen and cleavage of triphenylphosphine results in the formation of *N*-pivaloyliminoacetate **5**.

Attempts to isolate the ylide **6a** and *N*-acyliminoacetate **5a** from the reaction mixture by column chromatography failed, probably because of the instability of these compounds. Nevertheless, we were able to prove the formation of the ylides **6a**, **b** by trapping them in a *Wittig* reaction with methyl trifluoropyruvate. The yield of the *Wittig* reaction product **10a** was much higher than expected from the highest detected concentration of **6a** in the reaction mixture. On the other hand, extraordinary

Table 1. ^{1}H and ^{13}C NMR data of **5a**, **6a**, **7a**, **8a**, and **9a** (CD_3CN)

				^{1}H NMR (δ/ppm)	^{13}C NMR (δ/ppm, J/Hz)											
	R	*E*	CR^1R^2		CONH	COOMe	C=P	N=C	OMe	$(C_6H_5)_3P$=				*R*		Other
										C_1	C_2	C_3	C_4	CMe_3	CMe_3	
5a	*t*-Bu	–	–	3.03 (s, 3H, OCH_3), 0.80 (s, 9H, *t*-Bu)[a]	166.1[b]	163.2[b]	–	183.6	49.4	–	–	–	–	38.88	27.77	–
6a	*t*-Bu	–	–	6.65 (s, 1H, NH), 3.44 (s, 3H, OCH_3), 0.79 (s, 9H, *t*-Bu)[c]	180.7	171.3 34.9	48.2 156.2	–	50.4	127.3 90.9	134.9 9.8	129.5 12.2	133.1 0.5	38.80	27.66	–
7a[d]	*t*-Bu	–	–	3.71 (s, 6H, OCH_3), 1.20 (s, 18H, *t*-Bu)[a]	178.2	164.8	–	–	53.1	–	–	–	–	39.84	27.36	125.4 (>C=)
8a	*t*-Bu	Me	–	3.79 (s, 3H, OCH_3), 2.18 (s, 3H, CH_3), 1.17 (s, 9H, *t*-Bu)	157.3[b]	163.0[b]	–	193.3	53.7	–	–	–	–	41.3	27.1	21.3 (Me)
9a[d]	*t*-Bu	–	CH_2	8.07 (s, 1H, NH), 6.40 (s, 1H, $=CH_2$), 5.75 (s, 1H, $=CH_2$), 3.80 (s, 3H, OCH_3), 1.21 (s, 9H, *t*-Bu)	177.8	165.4	–	–	53.5	–	–	–	–	40.3	27.5	132.9 (C=CH_2) 108.1 (C=CH_2)

[a] The signal of the NH group is hidden under the signals of triphenylphosphine; [b] assignments may be interchanged; [c] signals of the ylide Ph_3P group are hidden under the signals of triphenylphosphine; [d] signals identified and assigned by comparison with the spectrum of the isolated compound

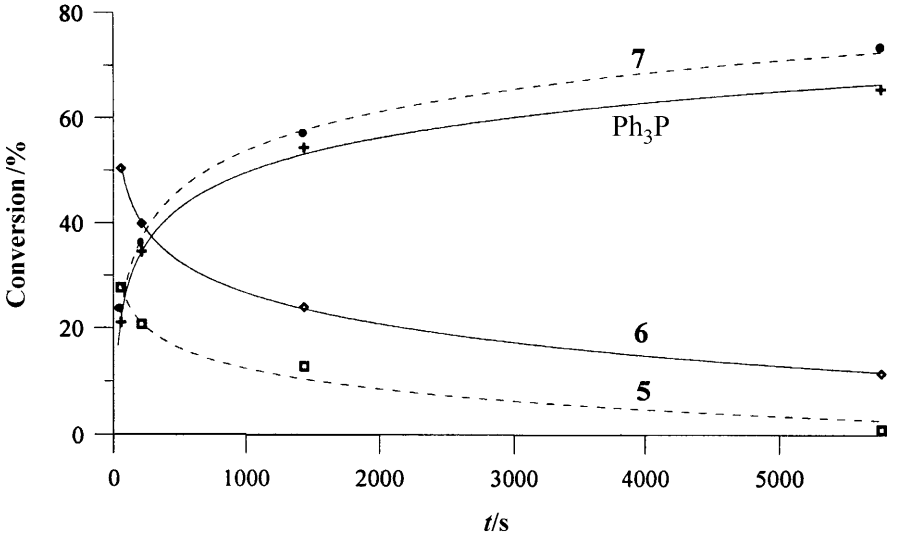
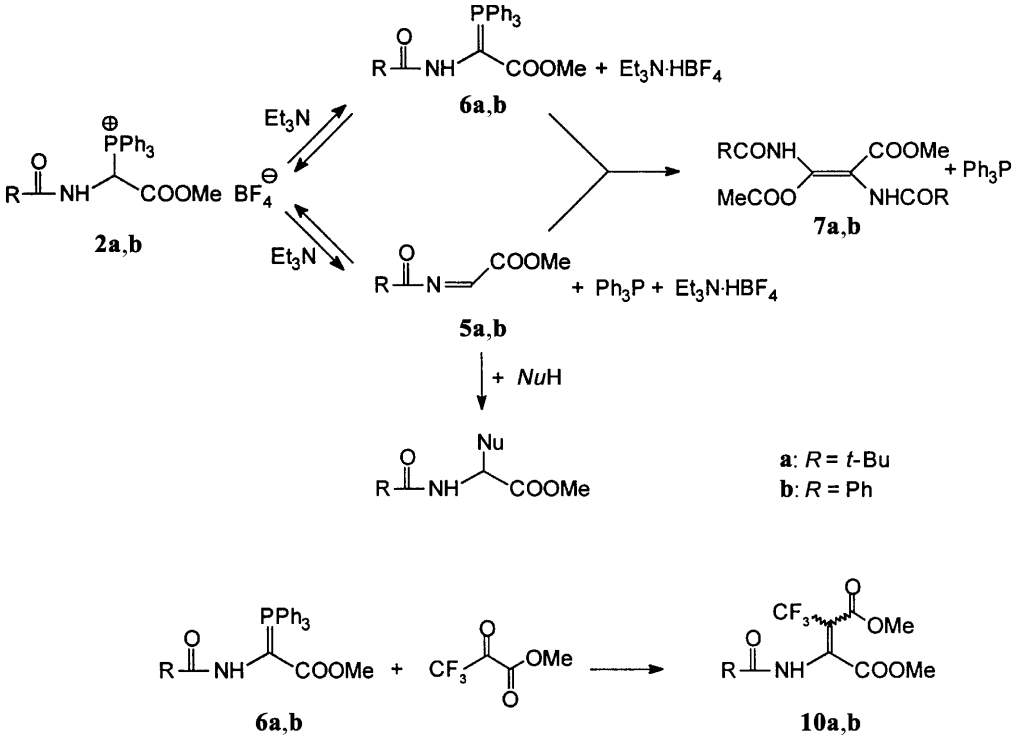


Fig. 1. Conversion of *N*-pivaloyl-α-triphenylphosphonioglycinate **2a** to the corresponding α-triphenylphosphoranylidene glycinate **6a**, iminoacetate **5a**, and their condensation product **7a** under the influence of Et_3N (*cf.* Scheme 2; $R = t$-Bu)

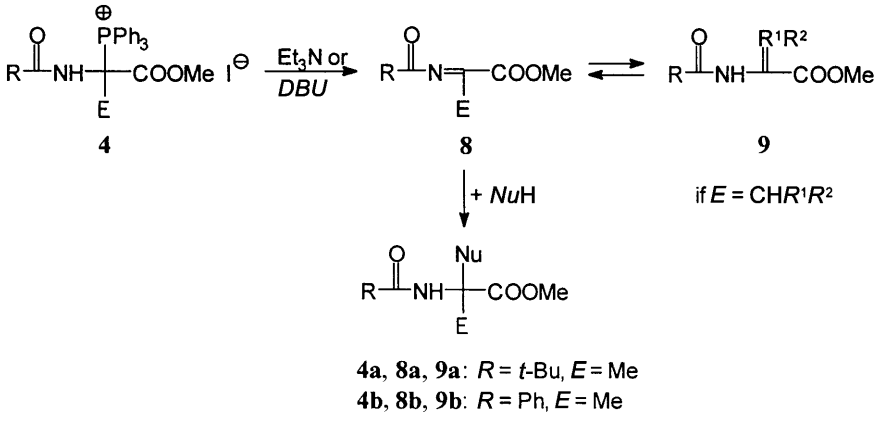
high yields of products of the triphenylphosphonium group displacement were obtained, multiples of the amount that would follow from the highest estimated concentration of *N*-pivaloyliminoacetate **5a** in the reaction mixture [2–4]. These two results clearly indicated an equilibrium between *N*-acyliminoacetate and ylide. The results of an analogous reaction with *DBU* were very similar, although both ^{1}H and ^{13}C NMR spectra of the reaction mixture were difficult to interpret because of the overlapping signals of the protonated *DBU*.

To the best of our knowledge, *N*-acyl-α-triphenylphosphonio-α-amino acid esters with quaternary α-carbon are hitherto unknown compounds. Using the methodology described above, we investigated the reaction of *N*-pivaloyl-α-triphenylphosphonioalanine methyl ester with triethylamine. Again triethylamine causes the disappearance of the ester in less than two minutes. However, as expected, α-(*N*-pivaloylimino)-propionate **8a** was detected to be the only primary reaction product. If esters **8** possess a hydrogen at the β-position, they can undergo a slow tautomerization to the corresponding α,β-dehydro-α-amino acid derivative **9** which can be isolated in good yields (57–65%). The tautomerization can be monitored conveniently by IR as well as ^{1}H and ^{13}C NMR spectroscopy.

Possible mechanisms of the nucleophilic displacement of the triphenylphosphonium group in *N*-acyl-α-triphenylphosphonio-α-amino acid esters with tertiary or quaternary α-carbons are presented in Schemes 2 and 3. We assume that in both these cases the crucial step of the reaction consists in the addition of a nucleophile to the activated C=N double bond of the *N*-acylimino intermediate **5** or **8**. Therefore, the investigated mechanism can be described as an elimination-nucleophilic addition process. *N*-Acyliminoacetates **5** have been considered to be unstable reactive intermediates in reactions of *N*-acyl-α-chloroglycinates or *N*-acyl-α-bromoglycinates with nucleophiles initiated by triethylamine [6] or diazomethane [7] so far in the literature.



Scheme 2



Scheme 3

N-Acyl-α-triphenylphosphonio-α-amino acid esters with tertiary and quaternary α-carbons behave in a different way if no nucleophilic agent is present in the reaction mixture or if it is of low reactivity. In the first case, the ylide acts as a nucleophile; its slow condensation with *N*-acyliminoacetate yields the dimer **7** (Scheme 2). In the second case, as already mentioned, the corresponding *N*-acylimino intermediate can undergo a slow tautomerization to the α,β-dehydro-α-amino acid derivative **9**, provided that it bears a hydrogen atom at the β-position (Scheme 3).

Experimental

Melting points, determined in capillary tubes, are uncorrected. IR spectra were recorded on a Zeiss Specord M 80 spectrophotometer; the measurements were carried out using 0.075 mm cells. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ or CD_3CN on a Varian Unity Inova-300 spectrometer operating at 300, 75.5, and 121.4 MHz; chemical shifts are quoted relative to internal *TMS* (^{1}H, ^{13}C) or external H_3PO_4 (^{31}P). Kieselgel 60 (Merck, 0.063–0.200 mm) was used for column chromatography. Elemental analyses (C, H, N, P) proved to be in satisfactory agreement ($\pm$ 0.4%) with the calculated values.

Methyl *N*-pivaloyl-α-triphenylphosphonioglycinate iodide and methyl *N*-benzoyl-α-triphenylphosphonioglycinate iodide (**2a** and **2b**) as well as 2-*t*-butyl-4-methyl-4-triphenylphosphonio-5(4*H*)-oxazolone iodide and 2-benzoyl-4-methyl-4-triphenylphosphonio-5(4*H*)-oxazolone iodide (**3a** and **3b**) were synthesized as previously described [2, 4].

N-Pivaloyl-α-triphenylphosphonioalanine methyl ester iodide (**4a**; $C_{27}H_{31}INO_3P$)

A solution of 5.4 g **3a** (10 mmol) in 20 cm^3 MeOH was stirred at 20°C for 2.5 h. The excess of MeOH was evaporated, and the crude product was dissolved in 15 cm^3 CH_3CN and precipitated with 30 cm^3 diethyl ether to give 4.8 g (84%) of crystalline product.

M.p.: 132.5–134°C; ^{1}H NMR: $\delta = 8.72$ (d, 1H, $J = 4.9$ Hz, NH), 7.85–7.52 (m, 15H, Ph_3P^+), 3.83 (s, 3H, OMe), 2.27 (d, 3H, $J = 19.0$ Hz, CH_3–C–P^+Ph_3), 0.94 (s, 9H, *t*-Bu) ppm; ^{13}C NMR: $\delta = 170.1$ (d, $J = 0.5$ Hz, CONH), 66.1 (d, $J = 60.2$ Hz, C_α–P^+), 180.3 (d, $J = 12.2$ Hz, COOMe), 54.1 (OMe), 120.1 (d, $J = 80.5$ Hz, Ph_3P, C_1), 135.5 (d, $J = 9.1$ Hz, Ph_3P, C_2), 129.5 (d, $J = 12.4$ Hz, Ph_3P, C_3), 134.2 (d, $J = 0.5$ Hz, Ph_3P, C_4), 38.4 (CMe_3), 27.1 (CMe_3), 28.3 (Me) ppm; ^{31}P NMR: $\delta = 51.0$ ppm; IR: $\nu = 3230$ m, 1764 s, 1732 s, 1660 s, 1512 s cm^{-1}.

N-Benzoyl-α-triphenylphosphonioalanine methyl ester iodide (**4b**; $C_{29}H_{27}INO_3P$)

A solution of 5.6 g **3b** (10 mmol) in 20 cm^3 MeOH was stirred at 20°C for 1 h. The excess of MeOH was evaporated, and the crude product was dissolved in 13 cm^3 CH_3CN and precipitated with 26 cm^3 diethyl ether to give 3.9 g (66%) of the crystalline product.

M.p.: 144–145°C; ^{1}H NMR: $\delta = 9.53$ (d, 1H, $J = 3.1$ Hz, NH), 7.92–7.29 (m, 20H, Ph, Ph_3P^+), 3.85 (s, 3H, OMe), 2.36 (d, 3H, $J = 19.0$ Hz, CH_3–C–P^+Ph_3) ppm; ^{13}C NMR: $\delta = 168.5$ (d, $J = 0.5$ Hz, CONH), 66.7 (d, $J = 58.1$ Hz, C_α–P^+), 169.9 (d, $J = 12.2$ Hz, COOMe), 54.2 (OMe), 119.8 (d, $J = 81.2$ Hz, Ph_3P, C_1), 135.5 (d, $J = 8.8$ Hz, Ph_3P, C_2), 129.6 (d, $J = 12.4$ Hz, Ph_3P, C_3), 134.4 (d, $J = 0.5$ Hz, Ph_3P, C_4), 132.7, 129.9, 128.7, 128.1 (Ph), 28.2 (Me) ppm; ^{31}P NMR: $\delta =$ 51.8 ppm; IR: $\nu = 3168$ m, 1773 s, 1729 s, 1662 s, 1520 s cm^{-1}.

Reactions of N-acyl-α-triphenylphosphonio-α-amino acid esters with triethylamine or DBU

To a stirred suspension of 1 mmol *N*-acyl-α-triphenylphosphonio-α-amino acid ester **2** or **4** in 4 cm^3 CD_3CN, 0.17 cm^3 triethylamine (1.25 mmol) or 0.19 cm^3 *DBU* (1.25 mmol) were added at 25°C. The composition of the reaction mixtures as a function of time was monitored by IR and NMR spectroscopy.

Dimethyl 2,3-bis-(acylamino)-fumarates **7***; general procedure*

To a stirred suspension of 1 mmol methyl *N*-acyl-α-triphenylohosphonioglycinate iodide in 4 cm^3 CH_2Cl_2, 0.17 cm^3 triethylamine (1.25 mmol) were added at room temperature. After 3 h the solvent was evaporated, and the residue was purified by column chromatography (ethyl acetate:benzene = 1:5). The crude product was recrystallized from benzene:hexane = 3:1.

Dimethyl 2,3-bis-(pivaloylamino)-fumarate (**7a**; $C_{16}H_{26}N_2O_6$)

Yield: 89%; m.p.: 164–166°C; ^{1}H NMR: $\delta = 8.72$ (s, 2H, NH), 3.84 (s, 6H, OMe), 1.26 (s, 18H, *t*-Bu) ppm; ^{13}C NMR: $\delta = 176.5$ (CONH), 163.3 (COOMe), 121.5 (=C–), 52.0 (OMe), 38.6 (CMe_3), 26.2 (CMe_3) ppm; IR: $\nu = 3540$ m, 1742 vs, 1684 vs, 1630 s cm^{-1}.

Dimethyl 2,3-bis-(benzoylamino)-fumarate (**7b**; $C_{20}H_{18}N_2O_6$)

Yield: 85%; m.p.: 185–187°C; ^{1}H NMR: $\delta = 9.60$ (s, 2H, NH), 7.96–7.48 (m, 10H, Ph), 3.90 (s, 6H, OMe) ppm; ^{13}C NMR: $\delta = 165.5$ (CONH), 164.2 (COOMe), 122.6 (=C–), 53.2 (OMe), 132.8, 132.4, 128.8, 127.6 (Ph) ppm; IR: $\nu = 3540$ m, 1741 vs, 1676 vs, 1632 s cm^{-1}.

Wittig reaction of methyl N-acyl-α-triphenylphosphonioglycinate iodides with methyltrifluoropyruvate in the presence of triethylamine

To a stirred suspension of 1 mmol methyl *N*-pivaloyl-α-triphenylphosphonioglycinate tetrafluoroborate or *N*-benzoyl-α-triphenylphosphonioglycinate iodide in 2.5 cm^3 CH_3CN, a solution of 0.17 cm^3 methyl trifluoropyruvate (1.5 mmol) in 1.5 cm^3 CH_3CN and 0.17 cm^3 triethylamine (1.25 mmol) was added at room temperature. After 6 h the solvent was evaporated, and the residue was purified by column chromatography (ethyl acetate:benzene = 1:5). The crude product was recrystallized from a mixture of benzene and hexane.

2-Pivaloylamino-3-trifluormethylbutendioic acid dimethyl ester (**10a**; $C_{12}H_{16}F_3NO_5$)

Yield: 95%; m.p.: 79–81°C; ^{1}H NMR: $\delta = 11.90$ (s, 1H, NH), 3.93 (s, 3H, OMe), 3.89 (s, 3H, OMe), 1.29 (s, 9H, *t*-Bu) ppm; ^{13}C NMR: $\delta = 176.6$ (CONH), 167.0 (COOMe), 162.4 (=C(*C*O)OMe), 147.5 (q, $J_{C-F} = 3.4$ Hz, NH*C*=C), 122.5 (q, $J_{C-F} = 269.8$ Hz, CF_3), 99.0 (q, $J_{C-F} = 33.2$ Hz, CF_3C=), 53.4 (OMe), 53.0 (OMe), 40.0 (CMe_3), 27.0 (CMe_3) ppm; IR: $\nu = 3230$ m, 1755 vs, 1721 s, 1682 s, 1605 vs cm^{-1}.

2-Benzoylamino-3-trifluormethylbutendioic acid dimethyl ester (**10b**; $C_{14}H_{12}F_3NO_5$)

Yield: 46%; m.p.: 101.5–103.5°C; ^{1}H NMR: $\delta = 12.60$ (s, 1H, NH), 8.00–7.42 (m, 5H, Ph), 4.00 (s, 3H, OMe), 3.93 (s, 3H, OMe) ppm; ^{13}C NMR: $\delta = 164.1$ (CONH), 167.3 (COOMe), 133.8, 131.3, 129.2, 128.1 (Ph), 162.2 (=C(*C*O)OMe), 147.6 (q, $J_{C-F} = 3.4$ Hz, NH*C*=C), 122.5 (q, $J_{C-F} = 270.0$ Hz, CF_3), 99.6 (q, $J_{C-F} = 33.4$ Hz, CF_3C=), 53.6 (OMe), 53.1 (OMe) ppm; IR: $\nu = 3600$ br, 1758 vs, 1711 s, 1682 s, 1609 vs cm^{-1}.

Methyl α-(N-acylamino)-acrylates **9***; general procedure*

To a stirred suspension of 1 mmol methyl *N*-acylamino-α-triphenylphosphoniopropionate iodide in 4 cm^3 CH_3CN, 5 mg hydroquinone and 0.17 cm^3 triethylamine (1.25 mmol) were added at room temperature. After 2 h the solvent was evaporated, and the residue was purified by column chromatography (ethyl acetate:benzene = 1:5).

Methyl α-(N-pivaloylamino)-acrylate (**9a**; $C_9H_{15}NO_3$)

Yield: 57%; resin; ^{1}H NMR: $\delta = 8.07$ (s, 1H, NH), 6.62 (s, 1H, =CH_2), 5.87 (s, 1H, =CH_2), 3.86 (s, 3H, OCH_3), 1.27 (s, 9H, *t*-Bu) ppm; ^{13}C NMR: $\delta = 177.3$ (CONH), 165.0 (COOMe), 131.0 (>*C*=CH_2), 108.3 (>C=*C*H_2), 53.0 (OMe), 39.9 (CMe_3), 27.4 (CMe_3) ppm; IR: $\nu = 3420$ m, 1724 s, 1682 vs, 1640 m cm^{-1}.

Methyl α-(N-benzoylamino)-acrylate (**9b**; $C_{11}H_{11}NO_3$)

Yield: 65%; resin; ^{1}H NMR: $\delta = 8.56$ (s, br, 1H, NH), 7.85–7.45 (m, 5H, Ph), 6.80 (d, 1H, $J = 1.5$ Hz, $=CH_2$), 6.00 (d, 1H, $J = 1.5$ Hz, $=CH_2$), 3.89 (s, 3H, OCH_3) ppm; ^{13}C NMR: $\delta = 165.8$, 164.8 (CONH and COOMe), 134.3 132.1, 128.8, 127.0 (Ph), 132.1 ($>C=CH_2$), 109.0 ($>C=CH_2$), 53.1 (OMe) ppm; IR: $\nu = 3410$ m, 1720 s, 1680 vs cm^{-1}.

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