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A new convenient synthesis of *N*-acyl-2-(dimethoxyphosphoryl)glycinates

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Abstract—Easily accessible *N*-acyl-2-triphenylphosphonioglycinate tetrafluoroborates react smoothly with trimethylphosphite in the presence of methyltriphenylphosphonium iodide to give *N*-acyl-2-(dimethoxyphosphoryl)glycinates in good or very good yields. The dimethoxyphosphorylglycinates may be isolated by column chromatography, or used directly for the Wadsworth–Emmons synthesis of α,β-dehydro-α-amino acids in a one-pot procedure without purification.

N-Acyl-2-(dialkoxyphosphoryl)glycinates (DAPGs) **1** have been attracting significant attention from organic chemists since 1973, when they were employed by Ratcliffe and Christensen in the synthesis of cephalosporins.[1] Since then, they have been used as key building blocks for the construction of fused β-lactam rings in total syntheses of various important β-lactam antibiotics,[1,2] for example, derivatives of cephalosporic acid,[1,3] 2-carbapenemic acid[4] and 1-carbocephalotin.[5] However, the widest application of DAPGs **1** is their use in the Wadsworth–Emmons synthesis of α,β-dehydro-α-amino acids **8**. The latter compounds are common components of naturally occurring peptides.[6] In addition, their hydrogenation using Wilkinson-type chiral catalysts is considered to be one of the most general methods for the enantioselective synthesis of α-amino acids,[6,7] including non-proteinogenic α-amino acids of high biological activity.[8]

All the important methods for the synthesis of DAPGs **1** have been summarised by Ferris et al.[9] Many are poor in their yield or are not suitable for large scale synthesis, because they include hazardous reagents such as *O*-mesitylenesulfonylhydroxylamine,[3] chloramine,[10] tosyl azide or diazo compounds.[9,10] As a result, the multi-step synthesis described by Schmidt et al. (Scheme 1)[11] is the most frequently used method for the preparation of DAPGs **1**.

Schmidt's method gives directly only *N*-benzyloxycarbonyl-2-(dialkoxyphosphoryl)glycinate; the synthesis of derivatives with other N-protecting groups requires a laborious hydrogenolysis of the benzyloxycarbonyl group and re-acylation of the amino group, this is the main drawback of the method.

A few years ago, we described a simple and effective synthesis of *N*-acyl-2-triphenylphosphonioglycinates (TPPGs) **5** from easily accessible 4-triphenylphosphoranylidene-5(4*H*)-oxazolones **3** (Scheme 2, Procedure A).[12] The compounds obtained were crystalline and quite stable, the procedure being useful for the synthesis of TPPGs **5** even on a kilogram scale. Recently, we described another complementary synthesis of TPPGs **5**, which involves a new kind of Mitsunobu alkylation of triphenylphosphine with 2-hydroxyglycinate **4** (Scheme 2, Procedure B).[13] We also demonstrated that TPPGs **5** react with aldehydes via the Wittig reaction to give the corresponding α,β-dehydro-α-amino acid derivatives **8**; they do not react, however, with ketones.[14]

In the present letter, we report an easy method for the transformation of TPPGs **5** into the much more reactive DAPGs **1**.

Keywords: *N*-Acyl-2-(dimethoxyphosphoryl)glycinates; Wadsworth–Emmons reaction; Mitsunobu reaction; Michaelis–Arbuzov reaction; α,β-Dehydro-α-amino acids.
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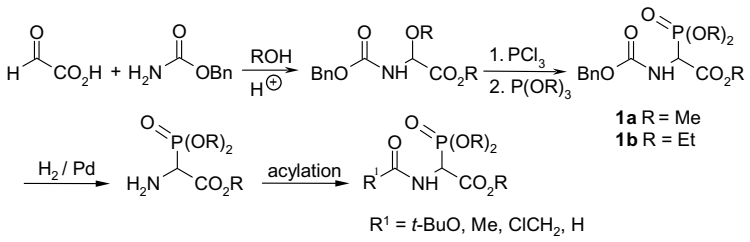
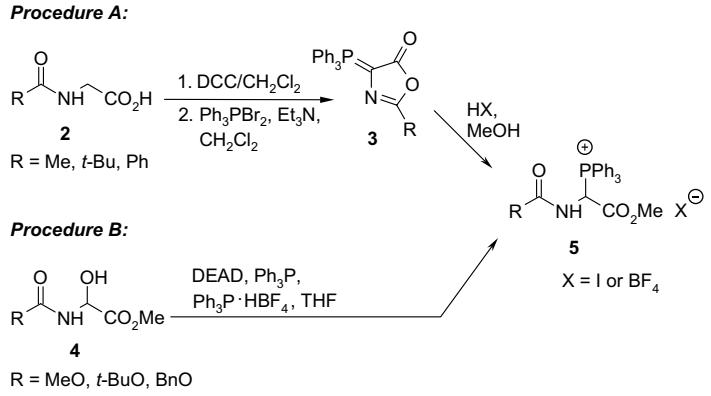


Scheme 1.

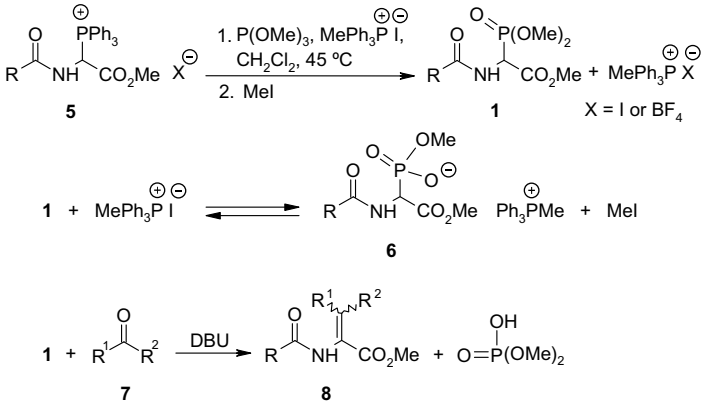


Scheme 2.

Our first attempt to carry out the reaction of *N*-pivaloyl-2-triphenylphosphonioglycinate iodide (**5**, R = *t*-Bu, X = I) with trimethylphosphite in methylene chloride gave only a moderate yield of the expected *N*-pivaloyl-2-(dimethoxyphosphoryl)glycinate (57%) in a mixture with *N*-pivaloyl-2-(hydroxymethoxyphosphoryl)glycinate derivative **6** (43%, Scheme 3). The formation of the latter compound may be rationalised as a result of the reversible demethylation of *N*-pivaloyl-2-(dimethoxyphosphoryl)glycinate with iodide.

In order to restrain the undesired demethylation reaction we used easily accessible *N*-acyl-2-triphenylphosphonioglycinate tetrafluoroborates (**5**, X = BF_4) instead of the iodides in further experiments. However, iodide anions were necessary in this reaction, to transform the primarily formed trimethoxyphosphonium salt into the phosphonate via the Michaelis–Arbuzov rearrangement. As demonstrated, the application of a substoichiometric amount of iodide anions in the form of methyltriphenylphosphonium iodide (0.25 mol per 1 mol of TPPG **5**) allows *N*-pivaloyl-2-triphenylphosphonioglycinate tetrafluoroborate (**5**, R = *t*-Bu, X = BF_4) to be transformed into the corresponding DAPG **1** in 84% yield, whereas the yield of the demethylation product was reduced to about 16%. Further improvement in the yields of DAPG **1** was achieved by adding methyl iodide to the reaction mixture, which also diminished the yield of the demethylation reaction product **6** to no more than a few percent.

The optimised procedure for synthesizing DAPGs **1** is very simple and convenient, and consists of heating the solution of TPPG tetrafluoroborate **5**, tri-



Scheme 3.

Table 1. Synthesis of DAPGs **1** and their reaction with carbonyl compounds

TPPGs **5**			DAPGs **1**			*N*-Acyl-α,β-dehydro-α-amino acid esters **8**					Ref.[e]
No.	R	Procedure	No.	Yield (%)	Mp (°C)	No.	R^1	R^2	Yield (%)	Mp (°C)	
5c	Me	A	**1c**	88[a]	88.0–88.5						16
5d	*t*-Bu	A	**1d**	91[a]	74.0–75.0						—
5e	Ph	A	**1e**	85[a]	111.5–112.5						17
5f	MeO	B	**1f**	51[b]	—						17
5g	*t*-BuO	B	**1g**	51[b]	60.5–61.5						18
5a	BnO	B	**1a**	76[b]	77.5–78.0						16
5c	Me	A	—	—	—	**8c**	H	2-Quinolyl	87[a,c]	106.0–107.0	14
5d	*t*-Bu	A	—	—	—	**8d**	Me	Me	71[a]	91.0–93.0	—
5a	BnO	B	—	—	—	**8a**	H	Et	70[b,d]	Oil	11

[a] Based on phosphonium salt **5**.
[b] Based on 2-hydroxyglycinate **4**.
[c] *Z*-Isomer.
[d] A mixture of *Z*- and *E*-isomers in the ratio of 13:1.
[e] References on the physical and spectroscopic properties of products.

methylphosphite and a substoichiometric amount of methyltriphenylphosphonium iodide in methylene chloride in a sealed ampoule at 45 °C for 8 h, followed by adding methyl iodide and leaving the reaction mixture for 24 h at room temperature.

In the case of simple *N*-acyl-2-triphenylphosphonioglycinates (**5**, R = Me, *t*-Bu, Ph) we used pure, crystalline starting compounds, which were easily accessible from 4-phosphoranylidene-5(4*H*)-oxazolones **3**, and we obtained the expected DAPGs **1** in high yields (85–91%).[†] Unfortunately, *N*-alkoxycarbonyl-2-triphenylphosphonioglycinates could not be obtained in a similar way, because of the instability of the corresponding 2-alkoxy-5(4*H*)-oxazolones.[15] In this case, we prepared the starting *N*-alkoxycarbonyl-2-triphenylphosphonioglycinates (**5**, R = MeO, *t*-BuO, BnO) in situ, applying the Mitsunobu alkylation of triphenylphosphine with *N*-alkoxycarbonyl-2-hydroxyglycinate **4** (Scheme 2)[13] and, eventually, obtained the corresponding DAPGs **1** in good yields (51–76% based on 2-hydroxyglycinates).[‡]

The DAPGs obtained could be isolated from the reaction mixture by column chromatography, or used directly for the Wadsworth–Emmons synthesis of α,β-dehydro-α-amino acids **8** with aldehydes or ketones in the presence of DBU in a one-pot procedure without isolation and purification[§] (Table 1).

The structures of the DAPGs **1** as well as the Wadsworth–Emmons reaction products **8** were confirmed by comparison of their physical and spectroscopic properties (IR, ^{1}H and ^{13}C NMR) with the literature data;[19,20] in the case of new compounds **1d** and **8d**, we also obtained satisfactory elemental analyses results.[21]

Acknowledgements

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[†] Procedure I: To a solution of TPPG tetrafluoroborate **5** (1 mmol) and methyltriphenylphosphonium iodide (0.10 g, 0.25 mmol) in CH_2Cl_2 (1.6 cm^3) a solution of trimethylphosphite (0.15 cm^3, 1.25 mmol) in CH_2Cl_2 (0.2 cm^3) was added. The mixture was heated in a sealed ampoule at 45 °C for 8 h, then left for 16 h at room temperature. Methyl iodide (0.2 cm^3, 3 mmol) was added and the mixture was left for 24 h at room temperature. After evaporation of the solvent the product was isolated from the residue by column chromatography on silica gel eluting with a mixture of CH_2Cl_2 and methanol in the ratio of 50:1 or 20:1.

[‡] Procedure II: DEAD (0.2 cm^3, 1.25 mmol), triphenylphosphine (0.29 g, 1.1 mmol) and triphenylphosphonium tetrafluoroborate (0.38 g, 1.1 mmol) were added to a stirred suspension of methyl *N*-alkoxycarbonyl-2-hydroxyglycinate **4** (1 mmol) in THF (5 cm^3) under Ar at room temperature. The homogeneous mixture was left for 3 days at room temperature without stirring, and after evaporation of THF, the residue containing *N*-alkoxycarbonyl-2-triphenylphosphonioglycinate tetrafluoroborate **5** was transformed into *N*-alkoxycarbonyl-2-(dimethoxyphosphoryl)glycinate as described in Procedure I using, however, 0.24 cm^3 (2 mmol) of trimethylphosphite.

[§] One-pot synthesis of *N*-acyl-α,β-dehydro-α-amino acid esters **8**: Reaction with aldehydes: The reaction mixture containing a solution of DAPG **1** in CH_2Cl_2, obtained according to Procedure I or II described above, was diluted with CH_2Cl_2 (2 cm^3), aldehyde (3 mmol) and DBU (0.19 cm^3, 1.25 mmol) were added at 0 °C and the reaction mixture was left for 20 h at room temperature. After evaporation of the solvent the product was isolated by column chromatography on silica gel eluting with a mixture of toluene and ethyl acetate in the ratio of 2:1 or 5:1.
Reaction with ketones: The residue, containing DAPG **1**, obtained according to Procedure I or II described above, was dissolved in the ketone (4 cm^3), DBU (0.19 cm^3, 1.25 mmol) was added at 0 °C, and the reaction mixture was left for 20 h at room temperature. The mixture was worked-up as described above.

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19. ^{1}H NMR spectral data (300 MHz, $CDCl_3$, δ (ppm)) of **1a**: 7.37–7.32 (m, 5H), 5.61 (br d, $J = 8.7$ Hz, 1H), 5.17 (d, $J = 12.3$ Hz, 1H), 5.12 (d, $J = 12.6$ Hz, 1H), 4.93 (dd, $J = 22.4$ Hz, $J = 9.2$ Hz, 1H), 3.84 (s, 3H), 3.83 (d, $J = 9.0$ Hz, 3H), 3.80 (d, $J = 10.8$ Hz, 3H); compound **1c**: 6.68 (br d, $J = 8.7$ Hz, 1H), 5.26 (dd, $J = 22.2$ Hz, $J = 8.7$ Hz, 1H), 3.84 (s, 3H), 3.84 (d, $J = 10.8$ Hz, 3H), 3.82 (d, $J = 11.1$ Hz, 3H), 2.09 (d, $J = 0.6$ Hz, 3H); compound **1d**: 6.41 (br d, $J = 7.5$ Hz, 1H), 5.25 (dd, $J = 22.2$ Hz, $J = 9.0$ Hz, 1H), 3.84 (d, $J = 0.6$ Hz, 3H), 3.84 (d, $J = 11.1$ Hz, 3H), 3.80 (d, $J = 11.1$ Hz, 3H), 1.25 (s, 9H); compound **1e**: 7.87–7.83 (m, 2H), 7.59–7.44 (m, 3H), 6.98 (br d, $J = 7.5$ Hz, 1H), 5.47 (dd, $J = 22.1$ Hz, $J = 8.9$ Hz, 1H), 3.88 (d, $J = 10.8$ Hz, 3H), 3.87 (s, 3H), 3.83 (d, $J = 10.8$ Hz, 3H); compound **1f**: 5.57 (br d, $J = 8.4$ Hz, 1H), 4.92 (dd, $J = 22.2$ Hz, $J = 9.3$ Hz, 1H), 3.84 (s, 3H), 3.84 (d, $J = 10.8$ Hz, 3H), 3.83 (d, $J = 10.8$ Hz, 3H), 3.73 (s, 3H); compound **1g**: 5.36 (br d, $J = 8.4$ Hz, 1H), 4.89 (dd, $J = 22.8$ Hz, $J = 9.3$ Hz, 1H), 3.84 (s, 3H), 3.84 (d, $J = 10.8$ Hz, 3H), 3.83 (d, $J = 10.8$ Hz, 3H), 1.46 (s, 9H); compound **8a** (*Z*): 7.38–7.31 (m, 5H), 6.62 (t, $J = 7.5$ Hz, 1H), 6.20 (br s, 1H), 5.14 (s, 2H), 3.75 (s, 3H), 2.23 (dq, $J = 7.5$ Hz, $J = 7.5$ Hz, 2H), 1.06 (t, $J = 7.7$ Hz, 3H); compound **8a** (*E*): 7.38–7.33 (m, 6H), 6.79 (br s, 1H), 5.14 (s, 2H), 3.81 (s, 3H), 2.57 (dq, $J = 7.5$ Hz, $J = 7.5$ Hz, 2H), 1.08 (t, $J = 7.7$ Hz, 3H); compound **8c**: 12.58 (br s, 1H), 8.14 (d, $J = 8.4$ Hz, 1H), 7.94 (d, $J = 8.7$ Hz, 1H), 7.80 (d, $J = 8.1$ Hz, 1H), 7.77–7.71 (m, 1H), 7.58–7.52 (m, 1H), 7.31 (d, $J = 8.4$ Hz, 1H), 6.35 (s, 1H), 3.91 (s, 3H), 2.29 (s, 3H); compound **8d**: 6.81 (br s, 1H), 3.74 (s, 3H), 2.16 (d, $J = 0.6$ Hz, 3H), 1.82 (s, 3H), 1.27 (s, 9H).
20. ^{13}C NMR spectral data (75 MHz, $CDCl_3$, δ (ppm)/J_{C-P} (Hz)) of **1a**: 167.2/2.2, 155.6/7.3, 135.8, 128.5, 128.3, 128.1, 67.6, 54.1/6.3, 54.0/7.0, 53.3, 52.0/147.2; compound **1c**: 169.7/6.0, 167.1/2.0, 54.1/6.5, 53.9/6.4, 53.3, 49.9/146.6, 22.7; compound **1d**: 178.0/5.2, 167.3/1.5, 54.2/6.5, 53.8/7.0, 53.3, 50.0/146.2, 38.8, 27.2; compound **1e**: 167.2/2.0, 166.8/5.5, 133.0, 132.2, 128.7, 127.3, 54.3/6.0, 54.0/7.1, 53.4, 50.4/146.7; compound **1f**: 167.2/2.2, 156.2/8.0, 54.1/6.4, 54.0/7.0, 53.3, 52.9, 52.0/147.2; compound **1g**: 167.5/3.0, 154.8/7.5, 54.1/6.0, 54.0/6.0, 53.3, 51.6/147.2, 29.7, 28.2; compound **8a** (*Z*): 165.1, 154.0, 139.7, 136.0, 128.5, 128.2, 128.1, 124.6, 67.3, 52.3, 21.9, 12.7; compound **8a** (*E*): 164.5, 158.0, 136.1, 128.6, 128.3, 128.2, 124.0, 66.9, 52.2, 21.7, 14.2; compound **8c**: 168.5, 165.7, 155.4, 146.6, 136.8, 135.4, 130.2, 128.3, 127.7, 126.8, 126.7, 123.2, 112.3, 52,7, 23.8; compound **8d**: 177.0, 165.3, 145.4, 121.1, 51.7, 38.9, 27.4, 22.4, 21.2.
21. The results of C, H, N and P-microanalyses of **1d**: $C_{10}H_{20}NO_6P$, calcd/found C 42.71/42.53, H 7.17/7.36, N 4.98/5.22, P 11.01/11.07%; compound **8d**: $C_{11}H_{19}NO_3$, calcd/found C 61.95/61.76, H 8.98/8.98, N 6.57/6.55%.