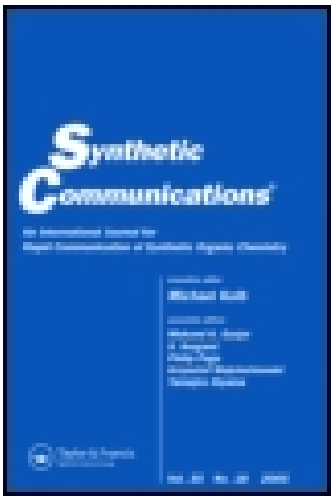

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A Facile Approach to γ,δ-Unsaturated Amides

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A FACILE APPROACH TO γ,δ-UNSATURATED AMIDES

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Abstract: A convenient synthesis of γ-substituted γ,δ-unsaturated amides by modified Horner-Wadsworth-Emmons reaction of γ-diethoxyphosphorylbutyric acid (**1**) with aldehydes is described.

Recently we have developed a new synthesis of β,γ-unsaturated amides starting from β-diethoxyphosphorylpropionic acid.[1] Now we would like to report that γ-diethoxyphosphorylbutyric acid (**1**) is a convenient reagent for the preparation of γ,δ-unsaturated amides **6**.

γ,δ-Unsaturated amides have been utilized in a number of transformations eg. in the synthesis of γ-lactones and γ-lactames[2-4] or in remote lithation of carboxamides.[5] These compounds also display an important biological activity as herbicides,[6,7] active component of many capsicums (eg. hot peppers),[8] or inactivatores of cytochrome P450.[9,10] γ,δ-Unsaturated amides are commonly obtained from the corresponding acids[11] but some other methods are described as well. The most general of these methods involve the Claisen rearrangement of O-allyl-O,N-

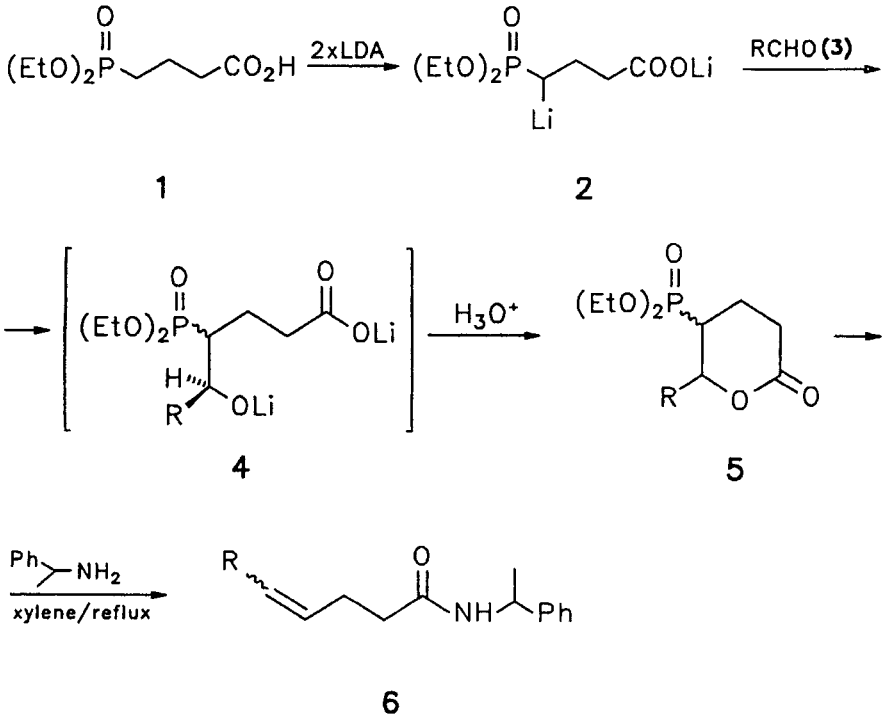
acetals,[12-14] 1,4-addition of Grignard reagents to N,N-diethylsorbamide,[15] and the reaction of HMPA with lactones.[16]

Our procedure starts with the reaction of **1** with two equivalents of LDA resulting in the dilithium salt **2**. This salt reacts with aldehydes **3**, as d^4 synthon to yield intermediate adducts **4**. As phosphonates **4** have no activation group in the α position, their cyclization rather then the Horner-Wadsworth-Emmons olefination takes place[17] to afford lactones **5** after the acidic work up. However, when the crude **5** are refluxed with 1-phenylethylamine in xylene thermal elimination of diethylphosphoric acid occurs and γ,δ-unsaturated amides **6** are formed as mixtures of E and Z isomers (Table). Crude **6** are purified by column chromatography and separated into individual isomers in selected cases. The proportions of isomers and their configuration were easily determined from the ^{1}H NMR spectra.

In summary we have presented an easy, simple, and general method for the preparation of γ-substituted γ,δ-unsaturated amides **6** from the readily accessible γ-diethoxyphosphorylbutyric acid (**1**).

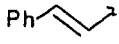
Experimental Section

Melting points were determined on a Büchi SMP-20 instrument and are uncorrected. ^{1}H NMR spectra were recorded on Bruker MSL-300 MHz using TMS as an internal standard. γ-Diethoxyphosphorylbutyric acid (**1**) was prepared by selective hydrolysis of ethyl γ-diethoxyphosphorylbutyrate according to the literature procedure.[18] Ethyl γ-diethoxyphosphorylbutyrate was obtained from triethylphosphite and ethyl γ-bromobutyrate as described in the literature.[19]



1 2 4 5 6

Table. γ,δ-Unsaturated amides **6** prepared.

Amide	R	E/Z[a]	Yield (%)[b]
6a	CH_3	70/30	31
6b	i-Pr	60/40	45
6c	Ph	40/60	59
6d	$pBrC_6H_4$	30/70	48
6e		80/20	33
6f		45/55	25

a) Estimated from the integrated intensities of the ^1H NMR peaks of the crude product.
b) Yield of isolated product based on **1**.

γ,δ-Unsaturated Amides 6. General Procedure: A 2M solution of LDA (12 mL, 24 mmol) in heptane/tetrahydrofuran/ benzene (Aldrich) is added at -70°C to a solution of γ-diethoxyphosphorylbutyric acid (**1**) (2.24 g, 10 mmol) in THF (20 mL). The reaction mixture is maintained at -20°C for 1 h, and then the aldehyde (15 mmol) in THF (15 mL) is added at -70°C. After stirring for 1 h at room temperature water (30 mL) is added. The aqueous layer is washed with ether (2 x 20 mL), acidified to pH 1 with 10% HCl solution and extracted with $CHCl_3$ (3 x 30 mL). The combined organic layers are dried and the solvent is evaporated. The residue is heated under reflux with 1-phenylethylamine (2.91 g, 24 mmol) in xylene (30 mL) for 14 h. The resultant mixture is cooled to room temperature, washed with 5% HCl solution (15 mL) and the aqueous layer is extracted with $CHCl_3$ (2 x 10 mL). The combined organic layers are dried and solvent is evaporated to give the crude amides **6** which are purified and separated into individual isomers (for **6c** and **6d**) by column chromatography (silica gel, EtOAc/hexane, 9 : 1, as eluent).

N-(1-Phenylethyl)-4-hexenamide (6a): oil; ^1H NMR[20] ($CDCl_3$) (E)-**6a**: δ 1.38 (d, J=7.0 Hz, 3H), 1.54 (d, J=5.5 Hz, 3H), 2.13 (t, J=6.5 Hz, 2H), 2.17 - 2.34 (m, 2H), 5.04 (quint, J=7.0 Hz, 1H), 5.32 (dt, J=14.6, 5.0 Hz, 1H), 5.37 (dq, J=14.6, 5.5 Hz, 1H), 6.03 (bd, J=7.0 Hz, 1H), 7.13 - 7.29 (m, 5H); (Z)-**6a**: δ 1.38 (d, J=7.0 Hz, 3H), 1.51 (dd, J=6.5, 2.0 Hz, 3H), 2.13 (t, J=6.5 Hz, 2H), 2.17 - 2.34 (m, 2H), 5.04 (quint, J=7.0 Hz, 1H), 5.28 (dtq, J=10.5, 7.0, 2.0 Hz, 1H), 5.40 (dqt, J=10.5, 6.5, 1.5 Hz, 1H), 6.03 (bd, J=7.0 Hz, 1H), 7.13 - 7.29 (m, 5H). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.21; H, 8.74; N, 6.58.

6-Methyl-N-(1-phenylethyl)-4-heptenamide (6b): oil; ^{1}H NMR[20] ($CDCl_3$) (E)-**6b**: δ 0.89 (d, J=6.5 Hz, 6H), 1.43 (d, J=7.0 Hz, 3H), 2.09 - 2.38 (m, 5H), 5.08 (quint, J=7.0 Hz, 1H), 5.29 (dt, J=15.0, 6.5 Hz, 1H), 5.39 (dd, J=15.0, 6.5 Hz, 1H), 5.95 (bs, 1H), 7.25 - 7.42 (m, 5H); (Z)-**6b**: δ 0.89 (d, J=6.5 Hz, 6H), 1.44 (d, J=7.0 Hz, 3H), 2.09 - 2.38 (m, 4H), 2.56 (d heptet, J=8.0, 6.5 Hz, 1H), 5.07 (quint, J=7.0 Hz, 1H), 5.14 (dt, J=10.5, 6.5 Hz, 1H), 5.19 (dd, J=10.5, 8.0 Hz, 1H), 5.95 (bs, 1H), 7.25 - 7.42 (m, 5H). Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.15; H, 9.43; N, 5.59.

(E)-5-Phenyl-N-(1-phenylethyl)-4-pentenamide (E)-(6c): oil; ^{1}H NMR ($CDCl_3$) δ 1.34 (d, J=6.5 Hz, 3H), 2.20 (t, J=7.5 Hz, 1H), 2.21 (t, J=7.5 Hz, 1H), 2.56 (dq, J=7.5, 1.5 Hz, 2H), 5.02 (quint, J=6.5 Hz, 1H), 5.79 (bd, J=7.5 Hz, 1H), 6.06 (dt, J=16.0, 7.5 Hz, 1H), 6.29 (dt, J=16.0, 1.5 Hz, 1H), 7.02 - 7.32 (m, 10H). Anal Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.83; H, 7.32; N, 5.28.

(Z)-5-Phenyl-N-(1-Phenylethyl)-4-pentenamide (Z)-(6c): oil; ^{1}H NMR ($CDCl_3$) δ 1.32 (d, J=6.5 Hz, 3H), 2.18 (t, J=7.5 Hz, 2H), 2.47 (dq, J=7.5, 1.5 Hz, 2H), 5.00 (quint, J=6.5 Hz, 1H), 5.50 (dt, J=12.0, 7.5 Hz, 1H), 5.97 (bd, J=7.5 Hz, 1H), 6.35 (dt, J=12.0, 1.5 Hz, 1H), 7.04 - 7.35 (m, 10H). Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.75; H, 7.37; N, 5.23.

(E)-5-(4-Bromophenyl)-N-(1-phenylethyl)-4-pentenamide (E)-(6d): m.p. 85-86°C; ^{1}H NMR ($CDCl_3$) δ 1.48 (d, J=7.0 Hz, 3H), 2.29 - 2.39 (m, 2H), 2.50 - 2.59 (m, 2H), 5.15 (quint, J=7.0 Hz, 1H), 5.73 (bd, J=7.0 Hz, 1H), 6.18 (dt, J=15.8, 6.7 Hz, 1H), 6.35 (d, J=15.8 Hz, 1H), 7.16 (d, J=8.5 Hz, 2H), 7.24 -

7.31 (m, 5H), 7.40 (d, J=8.5 Hz, 2H). Anal. Calcd for $C_{19}H_{20}BrNO$: C, 63.69; H, 5.63; N, 3.91. Found: C, 63.52; H, 5.78; N, 3.80.

(Z)-5-(4-Bromophenyl)-N-(1-phenylethyl)-4-pentenamide (Z)-(6d): m.p. 44-46°C; ^1H NMR ($CDCl_3$) δ 1.45 (d, J=7.0 Hz, 3H), 2.28 (t, J=7.0 Hz, 2H), 2.62 (q, J=7.0 Hz, 2H), 5.11 (quint, J=7.0 Hz, 1H), 5.64 (dt, J=11.6, 7.0 Hz, 1H), 5.84 (bd, J=7.0 Hz, 1H), 6.37 (d, J=11.6 Hz, 1H), 7.12 (d, J=8.5 Hz, 2H), 7.23 - 7.35 (m, 5H), 7.43 (d, J=8.5 Hz, 2H). Anal. Calcd for $C_{19}H_{20}BrNO$: C, 63.69; H, 5.63; N, 3.91. Found: C, 63.45; H, 5.50; N, 4.11.

7-Phenyl-N-(1-phenylethyl)-4,6-heptadienamide (6e): oil; ^1H NMR[20] ($CDCl_3$) (E,E)-**6e**: δ 1.52 (d, J=7.0, 3H), 2.34 (t, J=7.0 Hz, 2H), 2.53 (q, J=7.0 Hz, 2H), 5.19 (quint, J=7.0 Hz, 1H), 5.82 (dt, J=15.0, 7.0 Hz, 1H), 5.91 (bd, J=7.0 Hz, 1H), 6.27 (dd, J=15.0, 10.0 Hz, 1H), 6.49 (d, J=15.5 Hz, 1H), 6.75 (dd, J=15.5, 10.0 Hz, 1H), 7.22 - 7.48 (m, 5H); (Z,E)-**6e**: δ 1.51 (d, J=7.0 Hz, 3H), 2.31 (t, J=7.0 Hz, 2H), 2.68 (q, J=7.0 Hz, 2H), 5.17 (quint, J=7.0 Hz, 1H), 5.52 (dt, J=10.5, 7.0 Hz, 1H), 5.91 (bd, J=7.0 Hz, 1H), 6.24 (t, J=10.5 Hz, 1H), 6.58 (d, J=15.5 Hz, 1H), 7.11 (dd, J=15.5, 10.5 Hz, 1H), 7.22 - 7.48 (m, 5H). Anal. Calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.31; H, 7.72; N, 4.39.

5-(2-Furyl)-N-(1-phenylethyl)-4-pentenamide (6f): oil; ^1H NMR[20] ($CDCl_3$) (E)-**5f**: δ 1.50 (d, J=7.0 Hz, 3H), 2.29 - 2.43 (m, 2H), 2.85 (dq, J=1.5, 7.0 Hz, 2H), 5.06 - 5.23 (m, 1H), 6.15 (dt, J=15.5, 7.0 Hz, 1H), 6.21 - 6.43 (m, 3H), 7.24 - 7.41 (m, 6H); (Z)-**6f**: δ 1.47 (d, J=7.0 Hz, 3H), 2.29 - 2.43 (m, 2H), 2.55 (q, J=7.0 Hz, 2H), 5.06 - 5.23 (m, 1H), 5.53 (dt, J=11.8, 7.0 Hz, 1H), 6.21 - 6.43

(m, 3H), 7.24 - 7.41 (m, 6H). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.69; H, 7.22; N, 5.41.

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