Horner Synthesis of Didehydroamino Acid Derivatives in a Liquid-Liquid Two-Phase System

Pier Giuseppe Ciattini, Enrico Morera, Giorgio Ortar*

Centro di Studio per la Chimica del Farmaco del C.N.R., Istituto di Chimica Farmaceutica dell' Università 'La Sapienza', I-00185 Rome, Italy

Horner olefination of aldehydes **1** with *N*-acyl-2-(diethoxyphosphoryl)glycin ethyl esters **2** to give didehydroamino acid derivatives **3** can be performed advantageously in a 20% aqueous sodium hydroxide/dichloromethane two-phase system in the absence of any typical phase-transfer catalyst.

Didehydroamino acids are of major concern in the field of bioactive dehydropeptides and of asymmetric homogeneous reductions.[1] A straightforward synthesis of dehydroamino acid derivatives such as **3** by condensation of aldehydes with *N*-acyl-2-(dialkoxyphosphoryl)glycin esters in aprotic solvents and in the presence of strong bases such as sodium hydride, lithium diisopropylamide, and potassium *tert*-butoxide has been recently reported.[2-5]

1 **2** **3**

Table. Ethyl 2-Alkoxycarbonylamino-2-alkenoates **3** Prepared by Horner Reaction in a Liquid-Liquid Two-Phase System

Product[a]	R^1	R^2	*Z*/*E*-Ratio[b]	Yield[c] (%)	mp[d] (°C)	Molecular Formula[e] or Lit. mp (°C)	IR ($CHCl_3$)[f] ν (cm^{-1})	MS (70 eV)[g] *m/z* (%)	^{1}H-NMR ($CDCl_3$/TMS)[h] δ, *J* (Hz)
3a	C_6H_5	Z	4.8	80	(*E*): oil	oil[2]	(*E*): 3405, 1708, 1637, 1516	(*E*): 325 (M^+, 3); 234 (9)	(*E*): 0.95 (t, 3H, *J* = 7); 4.07 (q, 2H, *J* = 7); 5.17 (s, 2H); 7.12 (br s, 1H); 7.25 (s, 5H); 7.38 (s, 5H); 7.72 (s, 1H)
					(*Z*): oil	oil[2], 58[3]	(*Z*): 3415, 1711, 1643, 1495	(*Z*): 325 (M^+, 3); 234 (9)	(*Z*): 1.23 (t, 3H, *J* = 7); 4.22 (q, 2H, *J* = 7); 5.07 (s, 2H); 6.67 (br s, 1H); 7.1–7.6 (m, 11H)
3b	$3\text{-}NO_2C_6H_4$	Z	9.7	97	(*E*): 62–63	$C_{19}H_{18}N_2O_6$ (370.3)	(*E*): 3400, 1730, 1704, 1641, 1528, 1518	(*E*): 370 (M^+, 1); 297 (7); 279 (6)	(*E*): 0.97 (t, 3H. *J* = 7); 4.10 (q, 2H, *J* = 7); 5.20 (s, 2H); 7.3–7.6 (m, 8H); 7.87 (s, 1H); 8.1–8.2 (m, 2H)
					(*Z*): 135–136		(*Z*): 3395, 1711, 1648, 1530, 1493	(*Z*): 297 (1); 279 (1); 91 (100)	(*Z*): 1.30 (t, 3H, *J* = 7); 4.30 (q, 2H, *J* = 7); 5.05 (s, 2H); 7.00 (br s, 1H); 7.2–8.5 (m, 10H)
3c	$4\text{-}NO_2C_6H_4$	Z	42.8	87	(*E*): 76–77	$C_{19}H_{18}N_2O_6$ (370.3)	(*E*): 3401, 1710, 1636, 1518	(*E*): 162 (3); 91 (100)	(*E*): 1.00 (t, 3H, *J* = 7); 4.10 (q, 2H, *J* = 7); 5.20 (s, 2H); 7.2–7.7 (m, 8H); 7.93 (s, 1H); 8.22 (d, 2H, *J* = 9)
					(*Z*): 121–122		(*Z*): 3394, 1711, 1646, 1517, 1493	(*Z*): 262 (8); 162 (15); 91 (100)	(*Z*): 1.32 (t, 3H, *J* = 7); 4.32 (q, 2H, *J* = 7); 5.05 (s, 2H); 6.93 (br s, 1H); 7.2–7.5 (m. 6H); 7.57 (d, 2H, *J* = 10); 8.12 (d. 2H, *J* = 10)
3d	$2\text{-}CH_3OC_6H_4$	Z	1.4	45	(*E*): oil	oil[2,4]	(*E*): 3407, 1727, 1703, 1639, 1515	(*E*): 355 (M^+, 12)	(*E*): 0.95 (t, 3H, *J* = 7); 3.77 (s, 3H); 4.05 (q, 2H, *J* = 7); 5.17 (s, 2H); 6.7–7.6 (m, 10H); 7.67 (s, 1H)
			1.3[i]	69[i]	(*Z*): 77–78	81,[2] 77–78[4]	(*Z*): 3415, 1712, 1642, 1488	(*Z*): 355 (M^+, 17); 264 (4)	(*Z*): 1.27 (t, 3H, *J* = 7); 3.80 (s, 3H); 4.27 (q, 2H, *J* = 7); 5.07 (s, 2H); 6.67 (br s, 1H); 6.8–7.6 (m, 10H)
3e	$2\text{-}ClC_6H_4$	Z	3.6	78	(*E*): oil	$C_{19}H_{18}ClNO_4$ (359.8)	(*E*): 3404, 1730, 1704, 1641, 1519	(*E*): 359 (M^+, 4); 268 (23)	(*E*): 0.87 (t, 3H, *J* = 7); 4.00 (q, 2H, *J* = 7); 5.18 (s, 2H); 7.2–7.5 (m, 10H); 7.83 (s, 1H)
					(*Z*): oil		(*Z*): 3415, 1712, 1645, 1591	(*Z*): 359 (M^+, 3); 268 (25)	(*Z*): 1.27 (t, 3H, *J* = 7); 4.27 (q, 2H, *J* = 7); 5.00 (s, 2H); 6.67 (br s, 1H); 7.1 7.6 (m, 9II); 7.47 (s, 1H)

Table. (continued)

Product[a]	R^1	R^2	*Z*/*E*-Ratio[b]	Yield[c] (%)	mp[d] (°C)	Molecular Formula[e] or Lit. mp (°C)	IR ($CHCl_3$)[f] ν (cm^{-1})	MS (70 eV)[g] *m/z* (%)	^{1}H-NMR ($CDCl_3$/TMS)[h] δ, *J*(Hz)
3f	2-furyl	Z	5.5	66	(*E*): oil	$C_{17}H_{17}NO_5$ (315.3)	(*E*): 3435, 1729, 1698, 1650, 1517	(*E*): 315 (M^+, 32)	(*E*): 1.28 (t, 3H, *J* = 7); 4.32 (q, 2H, *J* = 7); 5.17 (s, 2H); 6.43 (dd, 1H, *J* = 2, 3.5); 7.00 (br s and d superimposed, 2H, *J* = 3.5); 7.4–7.5 (m, 6H); 7.27 (s, 1H)
					(*Z*): oil		(*Z*): 3428, 1712, 1644, 1499	(*Z*): 315 (M^+, 21)	(*Z*): 1.23 (t, 3H, *J* = 7); 4.22 (q, 2H, *J* = 7); 5.13 (s, 2H); 6.43 (dd, 1H, *J* = 2, 3.5); 6.60 (d, 1H, *J* = 3.5); 6.97 (br s, 1H); 7.03 (s, 1H); 7.33 (s, 5H); 7.45 (d, 1H, *J* = 2)
3g	(*E*)-C_6H_5CH=CH	Z	10.4	81	(*E*): 69–70	$C_{21}H_{21}NO_4$ (351.4)	(*E*): 3398, 1725, 1692, 1614, 1510	(*E*): 351 (M^+, 1); 131 (41)	(*E*): 1.40 (t, 3H, *J* = 7); 4.37 (q, 2H, *J* = 7); 5.17 (s, 2H); 6.83 (d, 1H, *J* = 15); 7.1–7.6 (m, 11H); 7.70 (d, 1H, *J* = 12); 7.98 (dd, 1H, *J* = 15, 12)
					(*Z*): 100–102		(*Z*): 3413, 1704, 1629, 1501	(*Z*): 351 (M^+, 15)	(*Z*): 1.27 (t, 3H, *J* = 7); 4.22 (q, 2H, *J* = 7); 5.17 (s, 2H); 6.72 (br s, 1H); 6.8–7.6 (m, 13H)
3h	*n*-C_3H_7	Z	6.1	59	(*E*): oil	oil[2,4]	(*E*): 3407, 1728, 1697, 1642, 1517	(*E*): 200 (14); 145 (10); 91 (100)	(*E*): 0.93 (t, 3H, *J* = 7); 1.28 (t, 3H, *J* = 7); 1.2–1.7 (m, 2H); 2.4–2.7 (m, 2H); 4.27 (q, 2H, *J* = 7); 5.13 (s, 2H); 6.80 (t, 1H, *J* = 7); 6.83 (br s, 1H); 7.37 (s, 5H)
					(*Z*): oil	oil[2,4]	(*Z*): 3422, 1711, 1658, 1500	(*Z*): 200 (26); 156 (9); 91 (100)	(*Z*): 0.88 (t, 3H, *J* = 7); 1.18 (t, 3H, *J* = 7); 1.2–1.6 (m, 2H); 2.0–2.3 (m, 2H); 4.17 (q, 2H, *J* = 7); 5.12 (s, 2H); 6.62 (br s and t superimposed, 2H, *J* = 7); 7.32 (s, 5H)
3i	*n*-C_7H_{15}	Z	6.3	72	(*E*): oil	$C_{20}H_{29}NO_4$ (347.4)	(*E*): 3407, 1727, 1697, 1641, 1517	(*E*): 145 (34); 91 (100)	(*E*): 0.7–1.7 (m, 16H); 2.4–2.7 (m, 2H); 4.28 (q, 2H, *J* = 7); 5.13 (s, 2H); 6.80 (br s and t superimposed, 2H, *J* = 7); 7.37 (s, 5H)
					(*Z*): oil		(*Z*): 3421, 1710, 1658, 1501	(*Z*): 256 (20); 212 (21)	(*Z*): 0.7–1.7 (m, 16H); 2.0–2.3 (m, 2H); 4.20 (q, 2H, *J* = 7); 5.13 (s, 2H); 6.33 (br s, 1H); 6.63 (t, 1H, *J* = 7); 7.33 (m, 5H)
3j	*c*-C_6H_{11}	Z	1.4	47[i]	(*E*): oil	$C_{19}H_{25}NO_4$ (331.4)	(*E*): 3407, 1729, 1694, 1639, 1513	(*E*): 240 (26); 196 (26)	(*E*): 0.8–3.3 (m, 11H); 1.30 (t, 3H, *J* = 7); 4.27 (q, 2H, *J* = 7); 5.13 (s, 2H); 6.65 (d, 1H, *J* = 10.5); 6.80 (br s, 1H); 7.37 (s, 5H)
					(*Z*): 76–77		(*Z*): 3425, 1710, 1658, 1500	(*Z*): 240 (18); 196 (30)	(*Z*): 0.8–2.7 (m, 11H); 1.25 (t, 3H, *J* = 7); 4.20 (q, 2H, *J* = 7); 5.17 (s, 2H); 6.07 (br s, 1H); 6.50 (d, 1H, *J* = 10.5); 7.38 (s, 5H)
3k	C_6H_5	Boc	5.5	69[j]	(*E*): oil	oil[2]	(*E*): 3415, 1720, 1697, 1635, 1511	(*E*): 291 (M^+, 2); 191 (100)	(*E*): 0.97 (t, 3H, *J* = 7); 1.47 (s, 9H); 4.08 (q, 2H, *J* = 7); 6.83 (br s, 1H); 7.33 (s, 5H); 7.60 (s, 1H)
					(*Z*): oil	oil[2]	(*Z*): 3421, 1710, 1643, 1480	(*Z*): 191 (100)	(*Z*): 1.32 (t, 3H, *J* = 7); 1.35 (s, 9H); 4.30 (q, 2H, *J* = 7); 6.30 (br s, 1H); 7.2–7.6 (m, 6H)
3l	*n*-C_3H_7	Boc	4.1	52[j]	(*E*): oil	oil[2]	(*E*): 3415, 1720, 1694, 1641, 1509	(*E*): 201 (4); 155 (9)	(*E*): 0.8–1.0 (m, 3H); 1.1–1.7 (m, 2H); 1.32 (t, 3H, *J* = 7); 1.43 (s, 9H); 2.4–2.6 (m, 2H); 4.28 (q, 2H, *J* = 7); 6.60 (br s, 1H); 6.70 (t, 1H, *J* = 7)
					(*Z*): oil	oil[2]	(*Z*): 3424, 1711, 1658, 1490	(*Z*): 201 (12); 155 (33)	(*Z*): 0.8–1.0 (m, 3H); 1.1–1.7 (m, 2H); 1.28 (t, 3H, *J* = 7); 1.43 (s, 9H); 2.0–2.3 (m, 2H); 4.23 (q, 2H, *J* = 7); 6.17 (br s, 1H); 6.57 (t, 1H, *J* = 7)

[a] Z = Benzyloxycarbonyl; Boc = *tert*-Butoxycarbonyl.
[b] Determined by column chromatography on silica gel using the following eluents: C_6H_6/EtOAc (97 : 3) for **3b**, **c**, **d**, **e**, **f**; C_6H_6/EtOAc (98 : 2) for **3a**, **h**, **j**, **k**, **l**; C_6H_6/EtOAc (99 : 1) for **3g**, **i**.
[c] Isolated yield based on **1**.
[d] Uncorrected.
[e] Satisfactory microanalyses obtained: C ±0.29, H ±0.21, Cl ±0.09, N ±0.32; exception: (E)-**3f**, C −0.49.
[f] Recorded on a Perkin-Elmer 983 spectrophotometer.
[g] Recorded on a Hewlett-Packard 5930-A instrument.
[h] Recorded on a Varian EM-390 spectrometer.
[i] 2 equiv of phosphonate used.
[j] Reaction time 2 h.

An analogous phase-transfer catalyzed reaction has, however, not yet been described despite the fact that well established advantages of phase-transfer catalysis[6] would increase the convenience of this elegant route to didehydroamino acids.

We have now found that the Horner reaction of **2** [R^2 = benzyloxycarbonyl (Z), *tert*-butyloxycarbonyl(Boc)] with both aromatic and aliphatic aldehydes **1** may be easily carried out under typical two-phase conditions (dichloromethane/20% aqueous sodium hydroxide) in the absence of any phase-transfer catalyst (Table). This result is precedented[7] and has been considered as an indication that phosphonates are themselves able to catalyze two-phase reactions.

The condensations proceed rapidly at room temperature and afford dehydroamino acid derivatives **3** as *E*/*Z*-mixtures in satisfactory to good yields. The stereoselectivity of the two-phase reactions is definitely higher than that in homogeneous media, at least where direct comparison exists (products **3a, h, k, l**),[2] and *Z*-isomers are formed predominantly in all cases with the exception of **3d** and **3j**, where the *Z*/*E*-ratio does not exceed 1.4.

The Wittig or Horner reactions in liquid-liquid two-phase systems using aliphatic aldehydes as substrates and sodium hydroxide as the base are known to yield generally only very low amounts of the corresponding alkenes, because of prevailing aldol condensation.[8] The extension of the effectiveness of the present methodology to aliphatic aldehydes is thus noteworthy and renders the recourse to lithium diisopropylamide at low temperature (−60 °C)[2,4] no longer compulsory.

Contrary to what has been reported in the literature for a number of different phosphonates,[9] the use of a solid-liquid two-phase system does not afford better yields nor affects markedly the *Z*/*E*-ratios, in comparison with the present liquid-liquid procedure. Thus for instance, treatment of benzaldehyde and of 2-methoxybenzaldehyde with ethyl 2-benzyloxycarbonylamino-2-(diethoxyphosphoryl)acetate (1.1 equivalents) under solid-liquid conditions results in 74 and 50% yields of **3a** and **3d**, respectively (*Z*/*E*-ratios: 4.0 and 2.0, respectively).[9]

In conclusion, the present method provides an experimentally simple and economically advantageous alternative to the original procedures developed by Schmidt and coworkers.[2,4] Unfortunately, unprotected indole-3-carboxaldehyde, 4-dimethylaminobenzaldehyde, piperonal, and ketones fail to undergo condensation with **2** under our conditions.

***N*-Protected Didehydroamino Acid Ethyl Esters 3; General Procedure:**
A 20% aq. NaOH solution (30 mL) is added dropwise during 2–3 min to a vigorously stirred solution of aldehyde **1** (10 mmol) and phosphonate **2**[2,4] (11 mmol) in CH_2Cl_2 (30 mL). Stirring is continued for 30 min (2 h for compounds **3k, l**) at room temperature. The reaction mixture is diluted with water (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phase is washed with brine (100 mL), and dried (Na_2SO_4). The solvent is evaporated to give product **3** as an *E*/*Z*-mixture, which is separated by column chromatography on silica gel (60 g for 1 g of residue) using the eluents given in the Table.

Received: 24 July 1987

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