Aziridines; 65.[1] Acyclic and Cyclic γ-Amidopropanephosphonic Esters by Amidoethylation of Horner Reagents with Activated Aziridines

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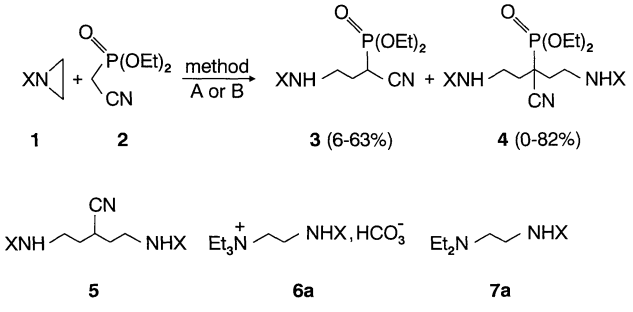
The carbanions of Horner reagents (α-cyanated and α-acylated phosphonic esters **2**, **8** and **11**) are amidoethylated with activated aziridines **1a–e**. Twofold amidoethylation is observed with the phosphononitrile **2** only. The primary products **9** formed from the phosphono acetate **8** tend to cyclize yielding phosphonopyrrolidinones **10**.

α-Acyl (or α-cyano) γ-amidopropylphosphonic esters seem to be unknown at present. We describe herein a simple one-step synthesis of such compounds that may be useful, e. g. as novel Horner reagents carrying a further functionality.

The synthesis is an amidoethylation of the (carbanionic) methylene carbon of simple Horner reagents (**2, 8,** or **11**) by means of activated aziridines **1a–e**. The starting Horner compounds may be regarded as phosphono analogues of β-dicarbonyl compounds (in the wider sense) whose amidoethylations[2–5] serve as a model for the development of methods A and B. In method A, compounds **2, 8,** or **11** were deprotonated[2,4,5] with sodium hydride in the respective solvent and then aziridine **1** was added. In method B triethylamine,[3] aziridine **1** and the Horner reagent **2, 8,** or **11** were mixed, usually without solvent (Scheme 1). Tetrahydrofuran was added in method B when necessary either to dissolve **1d** or to moderate an exothermic reaction (polymerization of **1b** in the reaction with **2**). Side reaction of **1a** with the catalyzing triethylamine formed the quaternary ammonium salt **6a** in an unexpected but twice observed reaction. Ring opening by triethylamine is assumed to form a zwitterion (ammonium amidate) that probably absorbs water and carbon dioxide during workup to form **6a**. The respective reaction was not found with the other aziridines.



1,3,4,6,7 9,10,12	X
a	CO(1-adamantyl)
b	COPh
c	CO_2Et
d	$CONPh_2$
e	Tosyl

Scheme 1

Reactions of phosphononitrile **2** are compiled in Table 1. A twofold amidoethylation plays a role only with this nitrile but not with **8** or **11** in analogy[4] with the behaviour of nitrilic dicarbonyl compounds. Simple dialkylation of **2** has been reported[6] under ion-pair extraction conditions. When the respective product **4d** arises from equimolar amounts of **1d, 2** and sodium hydride in an alcoholic solution (Method A), part of **4d** undergoes elimination of the phosphono group forming nitrile **5d**. The major part of **4d** escapes this elimination by spontaneous crystallization from the reaction mixture. Generally, an excess of Horner reagent (**2, 8** or **11**) is helpful for the suppression of secondary reactions by protonating anionic primary products.

Table 1. Compounds **3**, **4** and **5** Prepared from Aziridines **1** and Phosphonate **2** by Method A or B

Product[a,b]	Method[c]	Solvent	Reaction Time (d)	Yield (%)	mp (°C)
3a	A	THF	5	58	55–58
4a				0.7	218–220
3a	B	NEt_3	10	29[d]	
3b	A	THF	3	62	oil
3b	B	NEt_3/THF	3	63	
3c	B[e]	NEt_3	5	51	oil
3d	A	*t*-BuOH	3	6	oil
4d				82	195
3d	A[e]	*t*-BuOH	4	5	
4d				28	
5d				20	176
3d	B[e]	NEt_3/THF	9	37	
4d				8	
3e	A	*t*-BuOH	2	47	104

[a] Satisfactory microanalyses obtained: C, H, N ± 0.30.

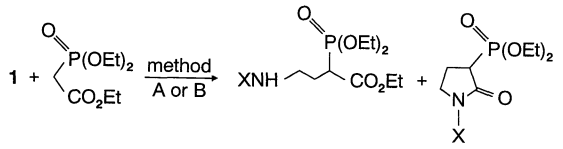
[b] IR spectra showed the expected bands: 3200–3380 (NH), 2235–2250 (C≡N), 1628–1674 (amide I), 1510–1551 (amide II), 1250–1303 (P=O), 1013–1051 (P–O–C), 1331, 1160 (SO_2) cm^{-1}.

[c] Method A: Carbanion of **2** was generated with NaH in the respective solvent under stirring and then **1** was added; mole ratio **2** : NaH : **1** = 3 : 1 : 1. Method B: **1** and **2** (2 equiv) dissolved in NEt_3 under stirring.

[d] 6% of **6a** (see Table 2, footnote d) was also isolated.

[e] **1** : **2** = 1 : 1.

In reactions of phosphonocarboxylate **8** (Table 2), the primary products **9** or rather their *N*-anions can cyclize to form the phosphonopyrrolidinones **10** (Scheme 2). This cyclization seems to be influenced by steric hindrance and by the actual lifetime of the respective *N*-anion (cf. References 2–5).



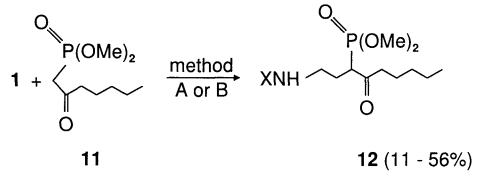
Scheme 2

Table 2. Compounds **9**, and **10** Prepared from Aziridines **1** and Phosphonate **8** by Method A or B

Product[a,b]	Method[c]	Solvent	Reaction Time (d)	Yield (%)	mp (°C)
9a	A	THF	5	85	oil
9a	B	NEt_3	10	32[d]	
9b	A	THF	2	62	oil
9b	B	NEt_3	3	59	
10c	A	THF	2	28	oil
9d	A	THF	14	22[e]	86
10d				41[e]	102
10e	A	THF	1	53	oil

[a] IR spectra showed the expected bands: 3300–3330 (NH), 1786 (**10b**, C=O), 1725–1750 (pyrrolidone C=O), 1730–1735 (ester C=O), 1642–1676 (amide I), 1520–1550 (amide II), 1240–1300 (P=O), 1012–1050 (P–O–C), 1360, 1172 (SO_2) cm^{-1}.
[b] Satisfactory microanalyses obtained: C, H, N ± 0.30.
[c] For definitions of Methods A and B, see Table 1.
[d] 20% of **6a** (mp 115°C, immediate recrystallization; final mp 140°C) was also isolated and identified by thermal conversion (180°C, HMPT) to **7a** (mp 75–76°C); satisfactory microanalyses obtained for both compounds.
[e] 9% of **1d** recovered.

No secondary reactions were observed in reations of the phosphono ketone **11** (Scheme 3, Table 3). A problem was the low solubility of its sodium salt with method A. The best solvent proved to be dimethylformamide. Reaction with the sulfonylaziridine **1e** did not yield **12e**. Most likely (broad ^1H NMR signals, no detectable amount of **11** incorporated) polymeric or oligomeric material was obtained, indicating a sluggish reaction of **11** (sodium salt) that could not compete with the amidoethylation of generated tosylamide anions. A similar phenomenon has previously[7] been found in a reaction of **1e** with an ester of phosphoric acid.



Scheme 3

The adamantoyl products **3a** and **9a** do not have antivirus activity[7] in contrast to their "lower homologue" diethyl 2-(1-adamantylcarbonylamino)ethylphosphonate.[8]

Table 3. Compounds **12** Prepared from Aziridines **1** and Phosphonate **11** by Methods A and B

Product[a,b]	Method[c]	Solvent	Reaction Time (d)	Yield (%)	mp (°C)
12a	A	DMF	21	56	oil
12b	A	DMF	7	54	oil
12b	B[d]	NEt_3	3	25	
12d	A	*t*-BuOH	7	11[e]	94–97

[a] Satisfactory microanalyses obtained: C, H, N ± 0.30.
[b] IR spectra showed the expected bands: 3330–3350 (NH), 1710–1714 (C=O), 1642–1669 (amide I), 1525–1550 (amide II), 1245–1310, 1019–1052 (P–O–C) cm^{-1}
[c] For definitions of Methods A and B, see Table 1.
[d] **1:2** = 1:1.
[e] Isolated yield, more **12d** was difficult to separate from excess **11**.

NMR spectra ($CDCl_3$, TMS) were recorded using a Bruker HX-90 E (^1H NMR) or with a Bruker AC 200 (^{13}C NMR) spectrometer. IR spectra were obtained on a Perkin-Elmer 283 instrument. Melting points (uncorrected) were determined with a Kofler type microscope (Reichelt). Microanalyses for C, H and N were obtained using a Heräus apparatus or from microanalytical laboratories Beetz. Column chromatography was performed with silica gel (0.067–0.2 mm, Merck).

Diethyl 2-[(*N*-Diphenylcarbamoylamino)ethyl]cyanomethylphosphonate (3d); Diethyl 2,2′-Bis[(*N*,*N*′-diphenylcarbamoylamino)-ethyl]cyanomethylphosphonate (4d); 2,2′-Bis[(*N*,*N*-diphenylcarbamoylamino)ethyl]acetonitrile (5d); Typical Procedure:

Method A: To a solution of **2** (1.77 g, 10 mmol) in *tert*-butyl alcohol (40 mL) were added under stirring NaH dispersion (80% in liquid paraffin, 300 mg, 10 mmol) and **1d** (2.38 g, 10 mmol). After 4 d, the precipitated crystals of **4d** were filtered and washed with EtOH; yield: 915 mg (28%). The filtrate was diluted with CH_2Cl_2, washed to neutral with H_2O and evaporated. Chromatography of the residue provided diphenylamine (170 mg, 10%), **5d** (520 mg, 20%) and **3d** (21 mg, 5%).

Diethyl 2-[(*N*-Ethoxycarbonylamino)ethyl]cyanomethylphosphonate (3c); Typical Procedure:

Method B: A mixture of **2** (1.77 g, 10 mmol), **1c** (1.15 g, 10 mmol) and NEt_3 (2 g) was set aside for 5 d. The amine was removed by evaporation. Chromatography of the residue on silica gel using EtOAc as solvent eluted the unreacted **2** first followed by **3c**; yield: 1.49 g (51%).

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Table 4. ^{1}H NMR Data (90 MHz, $CDCl_3$/TMS) of Compounds **3–7**, **9–10** and **12**, δ, J (Hz)

3a	1.40 (t, 6H, J = 7.4), 1.73 (m_c, 6H), 1.90 (m_c, 9H), 1.99–2.50 (m, 2H), 3.12 (ddd, 1H, J = 22.6, J = 9.3, J = 4.8), 3.50 (m_c, 2H), 4.25 (m_c, 4H), 6.62 (t br, 1H, J = 6.3)
3b	1.33 (t, 6H, J = 7.0), 1.95–2.41 (m, 2bH), 3.23 (ddd, 1H, J = 22.8, J = 8.9, J = 4.6), 3.68 (m_c, 2H), 4.21 (m_c, 4H), 6.31 (t br, 1H, J = 7), 7.43 (m_c, 3H), 7.80 (m_c, 2H)
3c	1.23 (t, 3H, J = 7.1), 1.37 (t, 6H, J = 7.2), 2.10 (m_c, 2H), 3.22 (ddd, 1H, J = 22.3, J = 9.0, J = 5.4), 3.43 (m_c, 2H), 4.15 (q, 2H, J = 7.2), 4.32 (m_c, 4H), 5.98 (t br, 1H, J = 6)
3d	1.35 (t, 6H, J = 7.0), 1.94–2.40 (m, 2H), 3.08 (ddd, 1H, J = 23.2, J = 9.0, J = 4.6), 3.38 (m_c, 2H), 4.22 (m_c, 4H), 5.00 (t br, 1H, J = 6), 7.28 (s, 10H)
3e	1.37 (t, 6H, J = 7.0), 1.85–2.4 (m, 2H), 2.43 (s, 3H), 3.13 (m_c, 2H), 3.30 (ddd, 1H, J = 23.0, J = 9.0, J = 6.2), 4.23 (m_c, 4H), 6.16 (t br, 1H, J = 6), 7.20–7.32 (m, 2H), 7.70–7.87 (m, 2H)
4a	1.40 (t, 6H, J = 7.4), 1.73 (m_c, 12H), 1.92 (m_c, 12H), 1.99–2.37 (m, 10H), 3.53 (m_c, 4H), 4.30 (m_c, 4H), 6.40 (t br, 2H, J = 6)
4d	1.32 (t, 6H, J = 7.1), 2.10 (m_c, 4H), 3.47 (m_c, 4H), 4.18 (m_c, 4H), 4.92 (t br, 2H, J = 6), 7.25 (s, 20H)
5d	1.88 (m_c, 5H), 3.37 (m_c, 4H), 4.73 (t br, 2H, J = 6), 7.20 (s, 20H)
6a	1.38 (t, 9H, J = 7.0), 1.70 (m_c, 6H), 1.93 (m_c, 9H), 3.31–3.81 (m_c, 10H)
7a	1.03 (t, 6H, J = 7.0), 1.45–2.20 (m, 15H), 2.32–2.78 (m, 6H), 3.30 (m_c, 2H), 6.42 (s br, 1H)
9a	1.31 (t, 3H, J = 7.1), 1.35 (dt, 6H, J = 1.4, J = 7.1), 1.71 (m_c, 6H), 1.83 (m_c, 6H), 1.95–2.35 (m, 5H), 3.00 (ddd, 1H, J = 24.3, J = 9.2, J = 5.1), 3.33 (m_c, 2H), 4.24 (m_c, 6H), 6.16 (t br, 1H, J = 5.4)
9b	1.23 (t, 3H, J = 7.1), 1.31 (dt, 6H, J = 0.8, J = 7.0), 2.28 (m_c, 2H), 3.10 (ddd, 1H, J = 23.3, J = 9.2, J = 4.2), 3.54 (q br, 2H, J = 6), 4.13 (quint br, 6H, J = 7.1), 6.60 (s br, 1H), 7.41 (m_c, 3H), 7.84 (m_c, 2H)
9d	1.23 (t, 3H, J = 7.0), 1.29 (t, 6H, J = 7.0), 1.80–2.50 (m, 2H), 2.96 (ddd, 1H, J = 22.5, J = 8.2, J = 6.0), 3.60 (q, 2H, J = 7), 4.21 (quint, 6H, J = 7), 4.78 (t, 1H, J = 5.5), 7.22 (s, 10H)
10c	1.36 (t, 9H, J = 7.0), 2.23 (m_c, 1H), 2.47 (m_c, 1H), 3.02 (ddd, 1H, J = 22.4, J = 8.6, J = 6.8), 3.76–4.48 (m, 8H)
10d	1.22 (t, 3H, J = 7.0), 1.25 (t, 3H, J = 7.0), 2.18 (m_c, 1H), 2.38 (m_c, 1H), 2.77 (ddd, 1H, J = 22.5, J = 9.0, J = 6.5), 3.88 (m_c, 6H), 7.15 (s, 10H)
10e	1.18 (t, 6H, J = 7.0), 2.05–2.71 (m, 2H), 2.38 (s, 3H), 3.03 (ddd, 1H, J = 22.5, J = 8.7, J = 6.3), 3.71–4.25 (m, 6H), 7.31 (d, 2H, J = 8.9), 7.78 (d, 2H, J = 8.9)
12a	0.90 (t, 3H, J = 6.2), 1.27 (m_c, 4H), 1.38 (m_c, 2H), 1.71 (m_c, 6H), 1.88 (m_c, 6H), 1.97–2.41 (m, 5H), 2.50–2.90 (m, 2H), 3.35 (m_c, 3H), 3.83 (d, 6H, J = 11.0), 6.48 (t br, 1H, J = 6)
12b	0.84 (t, 3H, J = 6.5), 1.22 (m_c, 4H), 1.50 (m_c, 2H), 2.09 (m_c, 1H), 2.34 (m_c, 1H), 2.52 (dt, 1H, J = 18.3, J = 7.1), 2.74 (dt, 1H, J = 18.3, J = 7.1), 3.37 (ddd, 1H, J = 22.5, J = 9.6, J = 3.9), 3.44 (m_c, 2H), 3.74 (d, 6H, J = 10.9), 7.02 (t br, 1H, J = 5.6), 7.30–7.55 (m, 3H), 7.80 (m_c, 2H)
12d	0.88 (t, 3H, J = 6.6), 1.07–1.94 (m, 6H), 2.08 (m_c, 1H), 2.32 (m_c, 1H), 2.62 (m_c, 2H), 3.28–3.51 (m, 3H), 3.75 (d, 6H, J = 11.0), 4.68 (d, 1H, J = 5.5), 7.20 (s, 10H)

Table 5. ^{13}C NMR Data (63 MHz, $CDCl_3$/TMS) of Compounds **9a, b** and **12b**, δ, J (Hz)

9a	13.9, 16.1 (d, J = 5.9), 16.1 (d, J = 5.9), 26.4 (d, J = 4.5), 27.9, 36.3, 38.8 (d, J = 14.2), 38.9, 44.3 (d, J = 131.7), 61.5, 61.7, 62.7 (d, J = 6.3), 62.8 (d, J = 6.3), 168.8 (d, J = 5.1), 178.1
9b	13.8, 16.0 (d, J = 5.9), 16.1 (d, J = 6.0), 26.5 (d, J = 4.4), 38.4 (d, J = 14.0), 43.2 (d, J = 131.5), 61.5, 62.7 (d, J = 6.5), 62.8 (d, J = 6.9), 126.9, 128.2, 131.1, 134.0, 167.3, 168.9 (d, J = 5.8)
12b	13.7, 22.2, 22.8, 26.3 (d, J = 4.6), 30.8, 38.4 (d, J = 14.0), 44.0, 49.6 (d, J = 125.7), 53.2 (d, J = 5.8), 126.8, 128.3, 131.3, 133.9, 167.6, 205.6 (d, J = 4.9)