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Preparation of heterocyclic phosphorus ylides containing the tetramic acid ring system and seven-membered ring vinylogues

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Abstract—Pyrolysis of amino acid-derived (α-aminoacyl)(ethoxycarbonyl)ylides results in ring closure with extrusion of ethanol to give novel five-, six- and seven-membered ring heterocyclic ylides.

Some time ago we reported that the stabilised α-aminoacyl phosphorus ylides, readily prepared from protected amino acids, underwent extrusion of Ph_3PO under conditions of flash vacuum pyrolysis (FVP) to afford a convenient synthesis of the protected α,β-acetylenic-γ-amino acids **2**.[1] It was believed that the protection of the amino function as the carbamate was only required for synthesis of **1** and not for the pyrolysis step and, since some difficulties were encountered in deprotecting the amino group in the products **2**, we were interested to examine the effect of deprotection prior to pyrolysis in the hope of obtaining the acetylenic amino esters directly. We report here that this leads to a complete change in the pyrolysis behaviour and gives rise to novel stabilised ylides with a tetramic acid ring structure.

The ylides **3**–**5** were readily prepared in moderate to good yield as stable crystalline solids by hydrogenolytic removal of the *N*-benzoxycarbonyl group from the ylides **1**. When they were subjected to FVP at 600°C and 10^{-2} Torr using the previously described conventional flow system,[2] crystalline products were obtained in good yield which still contained phosphorus (Table 1). These showed a characteristic low value for the ^{31}P NMR signals of δ_P +10.8 and analytical and spectroscopic data were in full agreement with the pyrrolidine-2,4-dione(tetramic acid) ylide structures **6**–**8** resulting from loss of ethanol (Scheme 1).[3]

Tetramic acids are of some importance since this function occurs in a wide variety of naturally occurring compounds, many of which display useful biological

Table 1. Formation of aminoacyl ylides and their conversion into cyclic ylides using FVP

Compound	R^1	Yield (%)	δ_P	Product	Yield (%)	δ_P
3	H	37	+17.2	**6**	56	+10.8
4	Me	86	+18.1	**7**	68	+10.8
5	Pr^i	89	+18.7	**8**	72	+10.8
14	–	90	+18.1	**15**	67	+10.1
16	–	–	–	**17**[a]	20	+10.8
	–	–	–	**18**[a]	12	+17.8
20	–	83	+17.9	**21**	42[b]	+14.5
24	H	46	+21.3	**27**	20	+21.0
25	Me	33	+21.3	**28**	13	+21.0
26	Pr^i	40	+21.5	**29**	26	+21.0

[a] Formed spontaneously at room temperature.
[b] Product **22** (19%) also formed.

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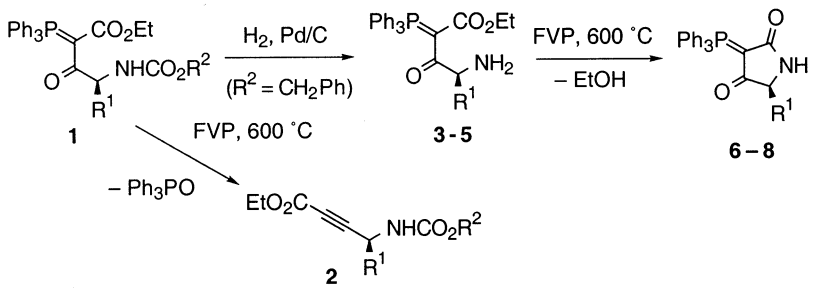
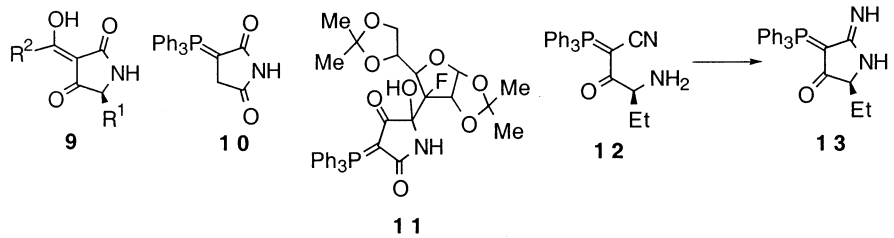


Scheme 1.

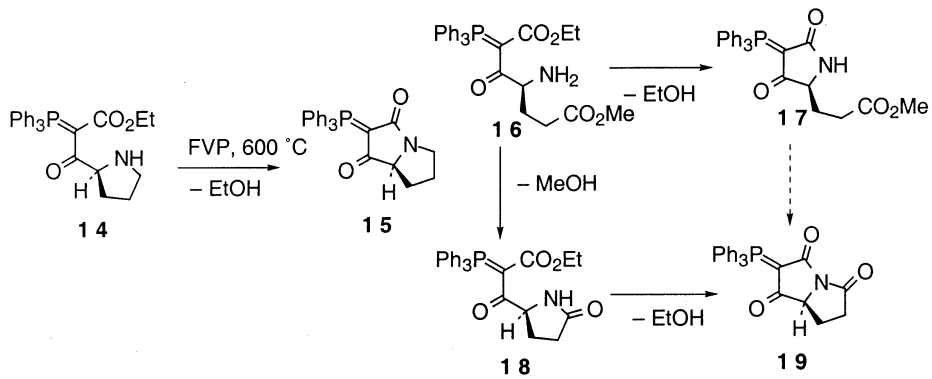
activity.[4] The majority of these have an additional acyl group at the 3-position and exist in the enol form as shown in **9**.



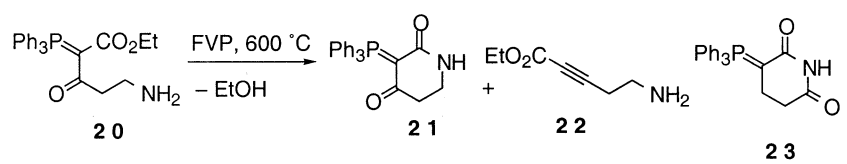
Pyrrolidinedione-containing ylides are rather uncommon among the wide variety of heterocyclic ylides which have been reported. Addition of triphenylphosphine to maleimide gives ylide **10** with the isomeric pyrrolidine-2,5-dione structure[5] and the rather complex 2,4-dione example **11** was obtained as a by-product in the reaction of $Ph_3P{=}CHCONH_2$ with a carbohydrate-derived α-keto ester.[6] Perhaps the result most closely related to the present work is the formation of **13** in low yield by the partial spontaneous cyclisation of the cyano(aminoacyl)ylide **12** recently reported by Wasserman.[7]

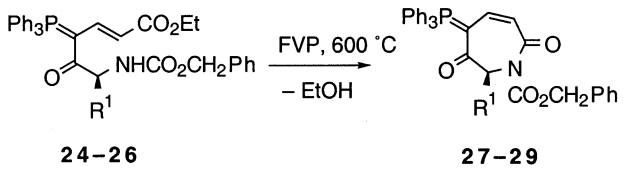
When the proline derived ylide **14** was subjected to the same FVP conditions, the bicyclic ylide **15** was formed in good yield. This inspired us to examine the ylide **16** derived from methyl glutamate in which two competing modes of cyclisation can be envisaged (Scheme 2). In this case, formation of **16** by hydrogenolysis was accompanied by spontaneous cyclisation with competing elimination of ethanol and methanol to give **17** (20%) and **18** (12%) after chromatographic separation. Interestingly, **18** but not **17** was found to undergo further cyclisation upon storage at room temperature for a period of months to give the bicyclic ylide **19** (δ_P +10.0), the oxo analogue of **15**.

The β-aminoacyl ylide **20** was readily prepared in the same way from β-alanine and upon FVP it gave mainly the piperidine-2,4-dione ylide **21**, although this was now accompanied for the first time by the originally expected Ph_3PO extrusion product **22**. The isomeric piperidine-2,6-dione ylide **23** has already been described.[8]



Scheme 2.





24–26 **27–29**

Scheme 3.

In an attempt to extend the conversion of **1** into **2** to obtain more extended amino acid analogues, a series of (α-aminoacyl)(ethoxycarbonylethenyl)ylides **24**–**26** were prepared. Rather surprisingly, subjecting these to FVP as before led to cyclisation with loss of ethanol with the *N*-benzoxycarbonyl group still in place to afford the novel azepine-2,6-dione ylides **27**–**29** (Scheme 3) which are effectively vinylogues of **6**–**8**.[9]

It should be noted that these were recovered in low yield from the residue in the inlet of the pyrolysis system rather than from the cold trap. As far as we are aware, only two seven-membered ring heterocyclic ylides have been described before and these involve 1,3-dithiepane[10] and 1,2,5-trithiepane[11] ring systems. The occurrence of cyclisation in this case is particularly surprising since it requires both *E*/*Z* isomerisation of the double bond and nucleophilic attack by the deactivated carbamate nitrogen.

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2. Aitken, R. A.; Atherton, J. I. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1281–1284.
3. Typical analytical and spectroscopic data:
5 colourless crystals, mp 120–122°C (found: M+H$^+$, 448.2050. $C_{27}H_{30}NO_3P$ requires M+*H*, 448.2042); ν_{max}/cm^{-1} (Nujol) 3380, 1655, 1575, 1300, 1275, 1100, 750, 720 and 690; δ_H 8.09 (2 H, br s, NH_2), 7.81–7.63 (6 H, m, Ph), 7.61–7.48 (9 H, m, Ph), 5.00 (1 H, brs, CH), 3.75 (2 H, m, OCH_2), 2.61 (1 H, m, C*H*Me$_2$), 1.29 (3 H, d, *J* 7, CH*Me*), 0.81 (3 H, d, *J* 7, CH*Me*) and 0.69 (3 H, t, *J* 7, OCH_2*Me*); δ_C 189.1 (d, *J* 5, P=C–*C*O), 166.5 (d, *J* 13, CO_2), 133.3 (d, *J* 10, 6×C-2 of P-Ph), 132.2 (d, *J*<2, 3×C-4 of P-Ph), 128.8 (d, *J* 13, 6×C-3 of P-Ph), 124.9 (d, *J* 94, 3×C-1 of P-Ph), 70.5 (d, *J* 110, P=C), 60.5 (d, *J* 9, NCH), 59.0 (OCH_2), 30.4 (*C*HMe$_2$), 20.4 (CH*Me*), 15.1 (CH*Me*) and 13.7 (OCH_2*Me*); δ_P +18.7; *m*/*z* (CI) 448 (M+H$^+$, 10%) and 402 (100).
8 colourless crystals, mp 240–241°C (found: C, 74.5; H, 6.0; N, 3.4. $C_{25}H_{24}NO_2P$ requires C, 74.8; H, 6.0; N, 3.5%); ν_{max}/cm^{-1} (Nujol) 3310, 1590, 1100, 720 and 690; δ_H 7.72–7.57 (9 H, m, Ph), 7.56–7.45 (6 H, m, Ph), 5.09 (1 H, br s, NH), 3.78 (1 H, dd, *J* 2, 1, NCH), 2.22 (1 H, m, CH), 1.00 (1 H, d, *J* 7, Me) and 0.91 (1 H, d, *J* 7, Me); δ_C 196.6 (d, *J* 7, P=C*C*O), 176.9 (d, *J* 17, NC=O), 134.1 (d, *J* 11, 6×C-2 of P-Ph), 132.9 (d, *J* 2, 3×C-4 of P-Ph), 128.8 (d, *J* 13, 6×C-3 of P-Ph), 123.2 (d, *J* 93, 3×C-1 of P-Ph), 67.4 (d, *J* 13, NCH), 64.6 (d, *J* 122, P=C), 29.8 (CH), 20.1 (Me) and 15.5 (Me); δ_P+10.8; *m*/*z* (CI) 402 (M+H$^+$, 100%), 279 (15), 263 (7) and 187 (15).
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9. Typical analytical and spectroscopic data:
26 yellow oil; ν_{max}/cm^{-1} 3422, 1719, 1664, 1586, 1498, 1439, 1390, 1370, 1331, 1266, 1164, 1104, 736 and 694; δ_H 7.80–7.51 (15 H, m, Ph), 7.35 (5 H, s, Ph), 7.27 (1 H, m, =CH), 6.90 (1 H, m, =CH), 6.04 (1 H, m, C*H*NH), 5.51 (1 H, br d, *J* 7, NH), 5.10 (2 H, s, OCH_2Ph), 4.15 (2 H, m, OCH_2Me), 2.19 (1 H, m, C*H*Me$_2$), 1.22 (3 H, t, *J* 7, CH_2*Me*), 1.02 (3 H, d, *J* 7, CH*Me*$_2$) and 0.74 (3 H, d, *J* 7, CH*Me*$_2$); δ_C 193.3 (P=C–*C*O), 168.8 (*C*O$_2$Et), 156.5 (NHCO), 155.4 (d, *J* 10, =C–), 137.0 (C-1 of Ph), 133.4 (3×C-4 of P-Ph), 133.2 (d, *J* 10, 6×C-2 of P-Ph), 129.3 (d, *J* 12, 6×C-3 of P-Ph), 128.0 (Ph), 127.5 (Ph), 127.4 (Ph), 123.0 (d, *J* 90, 3×C-1 of P-Ph), 101.0 (d, *J* 16, P=C–C=*C*), 74.2 (d, *J* 100, P=C), 65.7 (OCH_2Ph), 60.7 (CHN), 58.3 (O*C*H$_2$Me), 31.8 (*C*HMe$_2$), 20.2 (Me), 15.9 (Me) and 14.2 (CH_2*Me*); δ_P +21.5; *m*/*z* (FAB) 609 (M+2H$^+$, 25%), 401 (30), 302 (32), 154 (100) and 136 (70).
29 brown oil (HRMS: found M+2H$^+$, 563.2261. $C_{35}H_{32}NO_4P$ requires *M*+*2H*, 563.2225); ν_{max}/cm^{-1} 3059, 2964, 1720, 1660, 1582, 1497, 1266, 1166, 1021, 860, 782 and 699; δ_H 7.90–7.50 (20 H, m, Ph), 7.50–6.90 (2 H, 2×m, =CH), 5.30 (2 H, s, OCH_2), 4.08 (1 H, s, CHN), 2.44 (1 H, m, C*H*Me$_2$), 1.16 (3 H, d, *J* 7, Me) and 0.88 (3 H, d, *J* 7, Me); δ_C 192.4 (P=C–*C*O), 171.0 (C=C–*C*O), 152.1 (NCO_2), 147.8 (br, P=C–*C*=), 136.3 (C-1 ofPh), 133.9 (d, *J* 2, 3×C-4 of P-Ph), 133.4 (d, *J* 10, 6×C-2 of P-Ph), 129.7 (d, *J* 12, 6×C-3 of P-Ph), 128.4 (Ph), 127.6 (Ph), 127.5 (Ph), 121.9 (d, *J* 91, 3×C-1 of P-Ph), 101.4 (d, *J* 18, P=C–C=*C*), 79.2 (d, *J* 101, P=C), 66.9 (OCH_2), 66.5 (CHN), 30.0 (*C*HMe$_2$), 18.3 (Me) and 15.9 (Me); δ_P+21.0; *m*/*z* (FAB) 563 (M+2H$^+$, 80%), 519 (20), 454 (25), 428 (32), 384 (30), 277 (100) and 262 (65).
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