Table I
Yields and Physical Data for Gla Derivatives[a]

Compd	Yield, %[b]	Mp, °C[c]
2a	82	Oil
2b	30	Oil
2c	60	82–83.5
2d[d]	56	Oil
2e[e]	43	122.5–123.5 dec[e]
3	63[f]	91.5–93
4a	75[g]	108.5–110
4b	73	82–83
5[e]	80[h] (60[g])	97.5–99[e]

[a] All new compounds gave satisfactory NMR spectra and combustion analysis, except as noted. [b] Isolated yields of purified products; not maximized. [c] Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. [d] Combustion analysis was not obtained for this compound; the substance was characterized as the hydrazide, 4b. [e] Characterized as the monohydrate. [f] Overall yield from 2b. [g] Overall yield from 1a, without purification of 2b. [h] Overall yield from 4a.

in the following manner: hydrogenation of **2b,** followed by coupling to *N*-benzyloxycarbonylglycine using the mixed anhydride procedure,[11] afforded dipeptide **3** in 63% yield. The total yield for the conversion from *N*-benzyloxycarbonyl-L-serine methyl ester tosylate to the dipeptide derivative was 53%. Selective hydrazinolysis of either methyl ester **2b** or **2d** provided the corresponding hydrazides, **4a** and **4b,** and thus a convenient means of coupling at the COOH terminus. Conversion of **4a** to the acyl azide, and reaction with ethyl glycinate using a modified Honzl–Rudinger[12] procedure, afforded the dipeptide **5** in 80% yield. The total yield for the conversion from *N*-benzyloxycarbonyl-L-serine methyl ester tosylate was 60%.

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References and Notes

(1) (a) The following abbreviations have been used in the text: Gla,[1b] γ-carboxyglutamic acid; Z, benzyloxycarbonyl; Boc, *tert*-butyloxycarbonyl; Bzl, benzyl; *t*-Bu, *tert*-butyl; Tos, *p*-toluenesulfonyl. (b) There is no international symbol for this entity; both Glx[2b,c] and Gla[2d,3] have been used previously.
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(7) H. R. Morris, M. R. Thompson, and A. Dell, *Biochem. Biophys. Res. Commun.*, **62,** 856 (1975), reported the synthesis of Gla via *N*-benzyloxycarbonyl-DL-chloroalanine benzyl ester and dibenzyl malonate. The product was characterized by mass spectrometry, paper electrophoresis, and comparison with natural Gla obtained by mild hydrolysis of prothrombin.
(8) Displacement reactions were run under similar conditions: 15 ml of solvent, ambient temperature, 20 hr. Sodium malonates were formed by adding 1 equiv of the malonic ester to a stirred suspension of sodium hydride in dimethylformamide. Lithium malonates were generated by reaction of 1 equiv of lithium diisopropylamide (prepared by *n*-butyllithium and diisopropylamine in THF) with the malonic ester in THF. The metal malonate (2 equiv) was then added dropwise to stirred solutions of the tosylate in the same solvent. Starting tosylates were prepared according to published procedures.[4,5]
(9) Beckman Model 116 amino acid analyzer; Beckman custom spherical ion exchange resin, type VR-30.
(10) Reaction of *N*-benzyloxycarbonyl-*O*-tosyl-L-serine methyl ester under any of the following conditions results largely in elimination: diisopropylamine, THF, 20 hr; sodium malonate (1 equiv), methanol, 20 hr; sodium malonate (1 equiv), DMF, 20 hr; diethylamine, 50:50 ether–ethyl acetate, 7 hr or 20 hr; lithium malonate (1 equiv), THF, 20 hr.
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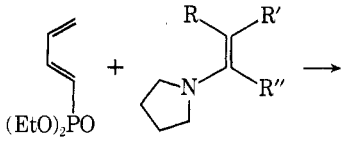
Cycloaddition Reactions of Enamines and Diethyl 1,3-Butadienephosphonate. The Formation of β-Aminophosphonates via a Mannich Reaction[1,2]

Summary: Cycloaddition of 1-diethylphosphinyl-1,3-butadiene and enamines proceeds in good yield to give β-aminophosphonates which deaminate to yield cyclohexadienephosphonates.

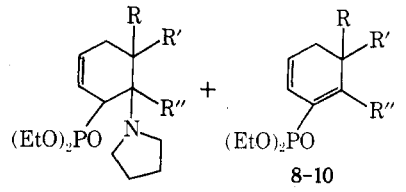
Sir: We wish to report the first observed cycloaddition reaction of a phosphonate activated butadiene to an enamine.

The diene **1** was prepared from triethyl phosphite and 1,4-dichloro-2-butene in two steps, with an overall yield of 74%, by using a procedure for the formation of diethyl vinylphosphonate.[3] The reaction of 0.1 mol of diene **1** with an equal amount of 1-pyrrolidinocyclohexene(**2**), 1-pyrrolidino-2-methylpropene (**3**), or 1-pyrrolidinopropene (**4**) was carried out under nitrogen in a solution containing 100 ml of benzene and refluxed for 24–48 hr. Water was added to the refluxing solution, in the work-up, to hydrolyze any enamine. The major products were β-aminophosphinates (**5, 6,** or **7**) and the cyclohexadienyl phosphonates (**8, 9,** or **10**). The yields of the cyclohexadienephosphonates were increased at the expense of the β-aminophosphonates by further heating of the reaction mixture. The latter were never completely transformed. The products were separated and isolated from the organic layer with dilute hydrochloric acid solution. The acid layer was neutralized to recover the amine.



1 2-4

2 (R = H; R′R″ = $-CH_2CH_2CH_2CH_2-$)
3 (R, R′ = CH_3; R″ = H)
4 (R = CH_3; R′, R″ = H)



5-7 8-10

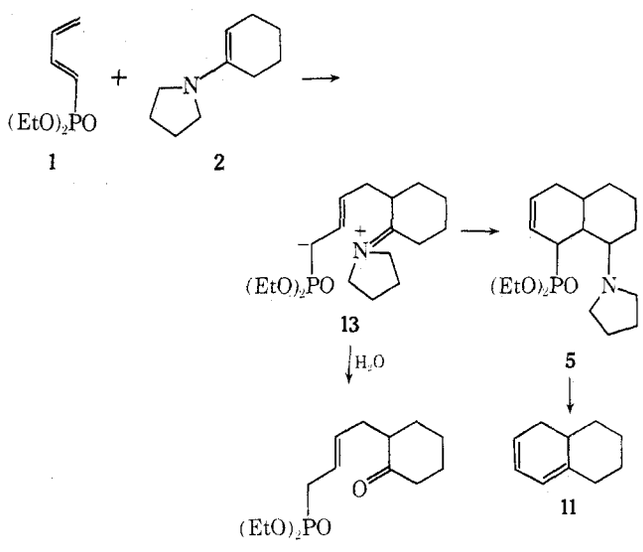
Products	
5	8
6	9
7	10

The respective products isolated follow. **5:** 30%; bp 155–156° (0.3 mm); δ ($CDCl_3$) 1.2–2.9 (m, 26 H), 4.2 (ABX pentet, 4 H), 5.5 (m, 2 H). **8:** 35%; bp 131–132° (0.3 mm); λ_{max}^{EtOH} 278 nm (ε 21.0 × 10^3); δ ($CDCl_3$) 1.2–2.8 (m, 17 H), 4.0 (ABX pentet, 4 H), 5.5–6.1 (m, 2 H); mass spectrum for $C_{14}H_{23}O_3P$, *m/e* 270. **6:** 35%; bp 150–153° (0.5 mm); δ ($CDCl_3$) 1.0 (s, 6 H), 1.3 (t, 6 H), 1.4–3.3 (m, 12 H), 4.0 (ABX pentet, 4 H), 5.2–5.8 (m, 2 H). **9:** 36%; bp 110–112° (0.5 mm); λ_{max}^{EtOH} 260 nm (ε 28.8 × 10^3); δ ($CDCl_3$) 1.0 (s, 6 H), 1.2 (t, 6 H), 2.1 (d, J = 3 Hz, 2 H), 4.1 (ABX pentet, 4 H), 5.7 (m, 2 H), 6.2 (d, J = 19 Hz, 1 H); mass spectrum for $C_{12}H_{21}O_3P$, *m/e* 244. **7:** 46.5%; bp 135–137° (0.4 mm); δ ($CDCl_3$) 1.0 (d, J = 7.5 Hz, 3 H), 1.2 (t, 6 H), 1.5–3.2 (m, 13 H), 4.1 (ABX pentet, 4 H), 5.8 (m, 2 H). **10:** 10.5%; bp 110–112° (0.5 mm); λ_{max}^{EtOH} 265 nm (ε 27.2 × 10^3); δ ($CDCl_3$) 1.2 (d, J = 7.5 Hz, 3 H), 1.3 (t, 6 H), 1.5–2.8 (m, 3 H), 4.0 (ABX pentet, 4 H), 5.7–6.1 (m, 2 H), 6.5 (d, J = 19 Hz, 1 H); mass spectrum for $C_{11}H_{19}O_3P$, *m/e* 230.

From the reaction of **1** and **2** there was also isolated <1% 4,4a,5,6,7,8-hexahydronaphthalene (**11**), bp 44–45° (0.1 mm), and <1% uncyclized ketone (**12**). The latter was removed with Girard-T reagent from the neutral organic fraction. The ketone **12** was obtained in 10.4% yield when the reaction was refluxed only 12 hr: bp 135–137° (0.05 mm); $\lambda_{max}^{CCl_4}$ 5.85 μm; δ ($CDCl_3$) 1.2 (t, 6 H), 1.3–2.8 (m, 13 H), 4.1 (ABX pentet, 4 H), 5.5 (m, 2 H); mass spectrum for $C_{14}H_{25}O_4P$, *m/e* 288.

The isolation of this ketone clearly indicates that the reaction between diene **1** and an enamine is a two-step process. Each cycloaddition reaction above is terminated by the addition of water to the refluxing solution to hydrolyze unreacted enamine and immonium salts. The yield of ketone **12** is higher for the 12-hr reaction than for the 48-hr reaction. The yield of **5** and **8** are lower for the former reaction than for the latter reaction. This would preclude the aminophosphonate **5** as the source of **12.** In addition, when **5** was refluxed in benzene solution with triethylamine, followed by the addition of water, the only other product isolated along with **5** was the deaminated product **8.** No evidence was found to suggest that the β-aminophosphonates underwent a reverse Mannich reaction.

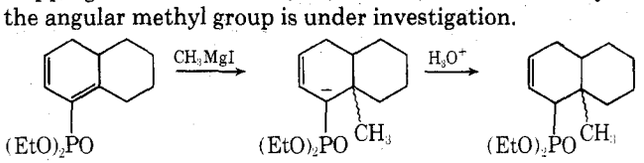
All previous reports on enamine cycloadditions are ambiguous on the reaction mechanisms, giving the impression of a concerted process.[4] We propose here that the mechanism is a *nonconcerted* two-step process involving, first, Michael addition to the activated diene to give the intermediate (**13**), followed by a Mannich reaction of the phosphinyl carbanion on the immonium ion to give **5.** Such a mechanism is consistent with the reported Michael additions to **1**[5] and in accord with other observations on activated butadienes.[6] We do not imply here that all cycloadditions of **1** are nonconcerted. The diene **1** has been shown to undergo typical Diels–Alder reactions with itself and standard dienophiles.[7] Hydrolysis of the reaction mixture would be expected to convert intermediate **13** into ketone **12.** The geometry of this alkene **12** is shown to be trans from the ir absorption at 965 cm^{-1}. Isomerization of the allylic carbanion **13** would be expected to occur during the prolonged reaction. Presumably the hydrocarbon **11** is derived from the aminophosphonate **5** by a nitrogen analog of the Emmons–Wittig reaction.[8]



Deamination of aminophosphinates **5, 6,** or **7** occurred when 0.1 mol of the amine in 100 ml of benzene was refluxed under nitrogen for 24 hr. The dienes obtained were identical with those isolated previously. The yields were 86% **8,** 60% **9,** and 63.5% **10.**

The dienephosphonates, **8** and **9,** underwent ozonolysis to give 2-oxocyclohexaneacetic acid and 2,2-dimethylsuccinic acid, respectively. Catalytic hydrogenation of dienes **8** or **9** in ethyl acetate over 19% Pd/C resulted in the uptake of 1 mol of hydrogen to give the corresponding cyclohexenylphosphonates.[9] **14:** 77%; bp 133–135° (0.3 mm); δ ($CDCl_3$) 0.75–3.2 (m, 21 H) 4.1 (ABX pentet, 4 H). **15:** 97%; bp 114–115° (0.5 mm); δ ($CDCl_3$) 0.9 (s, 6 H), 1.25 (t, 6 H), 1.1–2.4 (m, 6 H), 4.0 (ABX pentet, 4 H), 6.7 (d, J = 22 Hz, 1 H).

The reactivity of cycloalkadienephosphonates may be illustrated by the following sequence. When **8** is added to an ethereal solution of methylmagnesium iodide, a white precipitate is formed. Acidification and isolation of the product gave **17:** 51%; bp 135–137° (0.3 mm); δ ($CDCl_3$) 1.0–3.0 (m, 21 H), 4.1 (ABX pentet, 4 H), 5.7 (m, 2 H). The improved yield of the Grignard addition product over previous reports[10] may be ascribed to the greater stabilization of the phosphinyl carbanion through allylic resonance. The trapping of the carbanion, **16,** and the stereochemistry of the angular methyl group is under investigation.



8 **16** **17**

We have shown that the cycloaddition of a butadienephosphonate and an enamine is a general method for obtaining varied cyclohexadienylphosphonates. These compounds are not an end product but may be considered potentially useful synthetic intermediates.

References and Notes

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