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LETTERS

Cyclisation of dienes using phosphorus-centred radicals to form organophosphorus adducts

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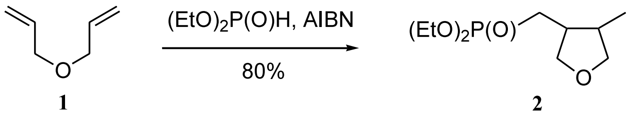
Abstract—Reaction of various dienes with phosphites or related phosphorus hydrides, under free radical cyclisation conditions, affords cyclic organophosphorus adducts. This quick, mild and technically clean approach affords 5- and 6-ring carbocycles and heterocycles in good to excellent yield. © 2002 Elsevier Science Ltd. All rights reserved.

The use of free-radical cyclisation reactions has been extensively investigated in recent years and by far the most common method of initiation involves the use of tributyltin hydride.[1] Cyclisation is usually achieved by reaction of tributyltin hydride with unsaturated organohalide precursors, although cyclisation of dienes or enynes to form cyclic products bearing versatile stannane or vinyl stannane functional groups is also known.[2] Recently, the problems associated with the toxicity and difficulty of removing tin-containing by-products has led to the development of alternative non-metal hydrides for radical generation.[3] Recent examples include cyclohexadienes,[4] silylated cyclohexadienes[5] and hypophosphorous acid (and its salts)[6] although the use of tributyltin hydride still dominates.[7] As part of a programme to develop alternative and more versatile free-radical initiators we have recently investigated the use of phosphites in organic synthesis. This work has shown that reaction of CCl_4 with an alkene or diene in the presence of diethyl phosphite $[(EtO)_2P(O)H]$ produces polychlorinated products in good yields.[8] These reactions involve the formation of an intermediate phosphonyl radical $[(EtO)_2P(O)^\bullet]$ which abstracts a chlorine atom from CCl_4 to form the $^\bullet CCl_3$ radical. This radical then adds to the alkene or diene. An important side reaction was also observed and organophosphorus by-products were isolated from some of these reactions. These by-products were formed from direct addition of the phosphonyl radical to the alkene or diene[9] as illustrated by the reaction of diallyl ether **1** with diethyl phosphite and AIBN to give tetrahydrofuran **2** in 80% yield (Scheme 1).[10,11] This efficient carbon–carbon bond forming reaction suggested that the addition of phosphonyl radicals to dienes could provide a mild and general approach to cyclic organophosphonates, so offering an attractive alternative to the Arbusov (Michaelis–Arbuzov) reaction.[12]

Our initial studies investigated the formation of carbocycles by reaction of 1,6-dienes **3** and **5** with diethyl phosphite (5 equiv.) and AIBN (0.3 equiv.) in refluxing cyclohexane (Table 1, entries 1 and 2). This afforded the desired cyclopentanes **4** and **6** in excellent 87% yields as inseparable mixtures of *cis*-:*trans*-diastereoisomers.[13] In both cases only the five-membered ring products were isolated[14] and the predominant formation of the *cis*-diastereoisomers is consistent with chair-like (Beckwith–Houk) transition states. A variety of alternative dienes were also reacted with diethyl phosphite (5 equiv.) under the same reaction conditions (entries 3–8). Hence, reaction of benzamide **7** with diethyl phosphite gave pyrrolidine **8** in 73% yield when using AIBN as the initiator, or 75% yield when using Et_3B/O_2[15] at room temperature (entry 3). Bicyclic oxygen and nitrogen heterocycles could also be prepared as illustrated



Scheme 1.

Keywords: cyclisation; dienes; phosphorus compounds; radicals and radical reactions.

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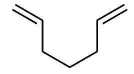
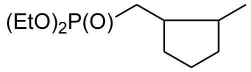
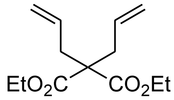
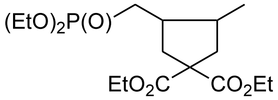
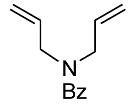
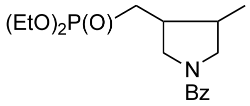
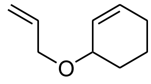
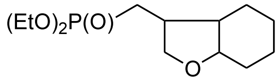
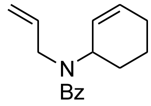
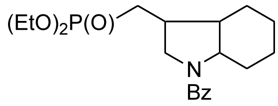
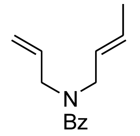
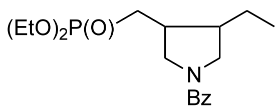
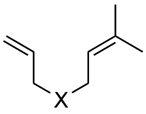
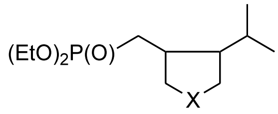
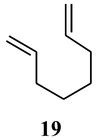
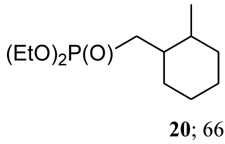
Table 1.

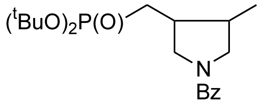
Entry	Diene	Product/% yield
1	 **3**	 **4**; 87% (3:1)[a]
2	 **5**	 **6**; 87% (5.9:1)[a]
3	 **7**	 **8**; 73%[b] (75%)[c]
4	 **9**	 **10**; 56%[b]
5	 **11**	 **12**; 66%[b]
6	 **13**	 **14**; 68%[b]
7	 **15**; X = NBz **16**; X = O	 **17**; X = NBz, 40%[b] **18**; X = O, 35%[b]
8	 **19**	 **20**; 66% (1:1)[a]

[a] Diastereoisomer ratio determined from the ^{1}H NMR spectrum.

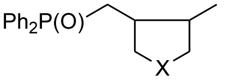
[b] The diastereoisomer ratio could not be determined from the ^{1}H NMR spectrum due, for example, to the presence of amide conformers which complicated the spectrum.

[c] Reaction initiated by Et_3B/O_2 (rt) rather than AIBN (80°C) in cyclohexane

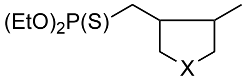
by the formation of **10** and **12** in 56 and 66% yield from dienes **9** and **11**, respectively (entries 4 and 5). It should be noted that the cyclisation of **9** and **11** involves reaction of diethyl phosphite with intermediate *secondary* (rather than primary) carbon-centred radicals. A similar reaction was also observed to give pyrrolidine **14** from diene **13** in 68% yield (entry 6). Following successful cyclisations involving intermediate primary and secondary carbon-centred radicals, our attention turned to the reaction of diethyl phosphite with tertiary carbon-centred radicals. Hence, reaction of prenyl derivatives **15** and **16** with diethyl phosphite gave the desired cyclic products in modest yields of 40 and 35%, respectively (entry 7). The lower yields of **17** and **18** can be explained by the greater stability of tertiary carbon-centred radicals, which results in lower rates of hydro-



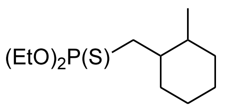
21; 66%



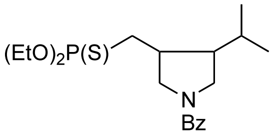
22; X = CH_2; 93% (3.9:1)
23; X = NBz; 88%



24; X = CH_2; 95% (3.6:1)
25; X = NBz; 90%



26; 75% (1:1)



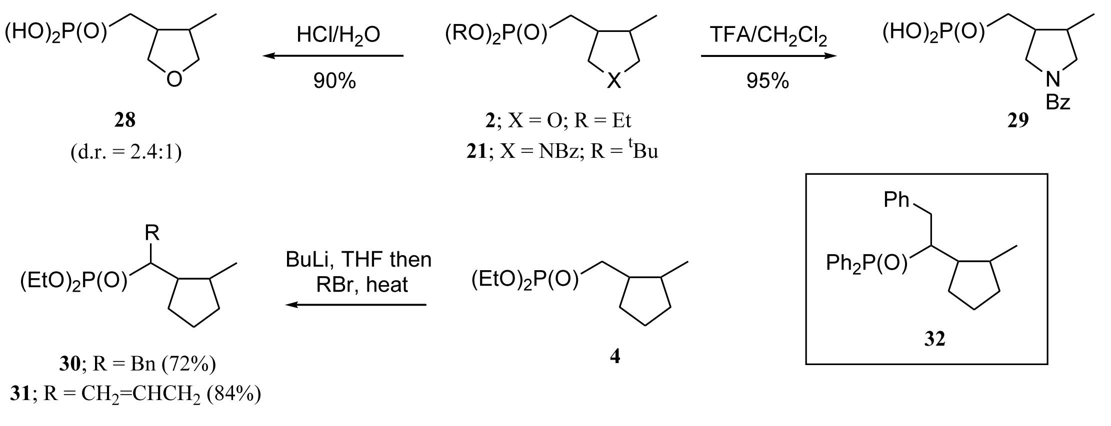
27; 70%

gen-atom transfer from diethyl phosphite.[16] This method of cyclisation can also be extended to the formation of six-membered rings as shown by the formation of cyclohexane **20** from 1,7-diene **19** (entry 8).

For comparison, some of the dienes were reacted with alternative phosphorus hydrides. Reaction of benzamide **7** with di-*tert*-butyl phosphite (5 equiv.) gave phosphonate **21** in good yield, while excellent yields for phosphine oxides **22** and **23** were observed on reaction of 1,6-heptadiene **3** and benzamide **7** with 5 equiv. of diphenylphosphine oxide [$Ph_2P(O)H$]. Reaction with diethyl thiophosphite [$(EtO)_2P(S)H$, 1.1 or 5 equiv.] was also successful and on heating with diene **3** or **7** and AIBN (in boiling THF or cyclohexane) this resulted in the efficient formation of thiophosphonates **24** and **25**.[17] Diethyl thiophosphite has been shown to be a more effective hydrogen-atom donor than diethyl phosphite in other radical additions[18] and this was confirmed by the formation of thiophosphonate **26** in 75% yield (as a 1:1 mixture of diastereoisomers) when using only 1.5 equiv. rather than 5 equiv. of diethyl thiophosphite. The thiophosphite (5 equiv.) can also be used to efficiently trap tertiary carbon-centred radicals as illustrated by the cyclisation of prenyl derivative **15** to give thiophosphonate **27** in 70% yield (cf. 40% with diethyl phosphite).

The phosphonate products derived from these radical cyclisation reactions are useful synthetic intermediates as shown in Scheme 2. Acid hydrolysis of phosphonates **2** and **21** can be used to prepare phosphonic acids **28** and **29**, respectively, in excellent yield. α-Alkylation reactions are also possible as illustrated by the benzylation of **4** to give **30** in 72% yield (as a mixture of diastereoisomers using 1.7 equiv. of BuLi and benzyl bromide) while reaction of **4** with butyllithium (1.7 equiv.) followed by allyl bromide (1.7 equiv.) gave **31** in 84% yield (as a mixture of isomers). These types of reactions can also be carried out in one-pot. Hence reaction of 1,6-heptadiene **3** with diphenylphosphine oxide (1.1 equiv.) and AIBN in THF, followed by addition of butyllithium (1.7 equiv.) and then benzyl bromide (1.7 equiv.), gave cyclopentane **32** in 30% overall yield (as a mixture of isomers).

This work has shown that radical cyclisation of 1,6- or 1,7-dienes using phosphorus hydrides affords a mild, efficient and general approach to organophosphorus derivatives. In comparison to tin hydrides, phosphorus hydrides such as diethyl phosphite are inexpensive, non-toxic and it is also much easier to change the substituents on phosphorus. For example, alternative phosphites including **33** can be easily prepared (from L-menthol and PCl_3)[19] and reaction of **33** with benzamide **7** afforded the expected pyrrolidine phosphorus adduct in 58% yield. Indeed, substitution is shown to influence the reactivity of the phosphorus hydrides in hydrogen-atom transfer reactions. Thus, diphenylphosphine oxide and diethyl thiophosphite are more effective hydrogen-atom donors than diethyl phosphite. This was further evidenced by the reaction of hydrazone **34**



28 (d.r. = 2.4:1)

2; X = O; R = Et
21; X = NBz; R = ^tBu

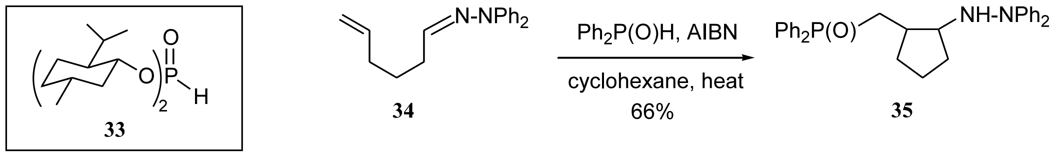
29

30; R = Bn (72%)
31; R = CH_2=$CHCH_2$ (84%)

4

32

Scheme 2.



Scheme 3.

to give hydrazine **35** (in 66% yield) when using diphenylphosphine oxide (5 equiv.), but this reaction was unsuccessful when using diethyl phosphite (5 equiv.) (Scheme 3). The formation of organophosphorus adducts under such mild reaction conditions is of particular note and this method offers a flexible approach to these types of compounds, which have been shown to undergo synthetically important hydrolysis and α-alkylation reactions.

Acknowledgements

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13. *Experimental procedure*: Diethyl phosphite (1.73 g, 12.5 mmol) and AIBN (0.12 g, 0.75 mmol) were added to a stirred solution of 1,6-heptadiene **3** (0.24 g, 2.5 mmol) in degassed cyclohexane (20 cm^3) under an atmosphere of nitrogen and heated at 80°C. After 6 h, further AIBN was added (0.12 g, 0.75 mmol) and the mixture stirred at 80°C for 12 h. The mixture was then concentrated in vacuo and ethyl acetate (150 cm^3) and aqueous sodium hydroxide (150 cm^3, 2.5% w/w) was added. The combined organic layer was dried ($MgSO_4$), filtered and concentrated to afford crude product. Purification by column chromatography on silica (ethyl acetate) afforded diethyl (2-methyl-cyclopentylmethyl)phosphonate **4** (0.51 g, 87%) as a colourless oil as a 3:1 mixture of diastereoisomers as indicated by the ^{1}H NMR spectrum. R_f 0.4 (ethyl acetate); ν_{max} (CH_2Cl_2) 2982 (s), 2957 (s), 2908 (s), 1270 (s), 1054 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 4.21–4.00 (4H, m, $2\times OC\underline{H}_2CH_3$), 2.20–2.02 (2H, m, $2\times CH$), 1.95–1.22 (8H, m, $4\times CH_2$), 1.31 (6H, t, *J* 7.0 Hz, $2\times OCH_2C\underline{H}_3$), 0.97 (3H, d, *J* 7 Hz, *trans*-$CHC\underline{H}_3$), 0.79 (3H, d, *J* 7 Hz, *cis*-$CHC\underline{H}_3$); δ_C (67.5 MHz, $CDCl_3$) (*cis*-diastereoisomer) 61.8 (d, J_{CP} 6.7 Hz, $O\underline{C}H_2$), 37.6 (d, J_{CP} 4.0 Hz, $\underline{C}HCH_2P$), 37.1 (d, J_{CP} 12 Hz, $\underline{C}HCH_3$), 33.1, 30.6 ($2\times \underline{C}H_2$), 26.8 (d, J_{CP} 140.5 Hz, P-$\underline{C}H_2$), 22.4 ($\underline{C}H_2$), 16.7 (d, J_{CP} 6.7 Hz, $OCH_2\underline{C}H_3$), 15.4 ($CH\underline{C}H_3$); (*trans*-diastereoisomer) 61.8 (d, J_{CP} 6.7 Hz, $O\underline{C}H_2$), 42.3 (d, J_{CP} 17.5 Hz, $\underline{C}HCH_3$), 42.1 (d, J_{CP} 5.4 Hz, $\underline{C}HCH_2P$), 34.0,

33.4 ($2\times\underline{C}H_2$), 30.3 (d, J_{CP} 140.5 Hz, P-$\underline{C}H_2$), 23.3 ($\underline{C}H_2$), 18.7 ($CH\underline{C}H_3$), 16.7 (d, J_{CP} 6.7 Hz, $OCH_2\underline{C}H_3$); *m*/*z* (CI, NH_3) 235 $M+H^+$, 100% (Found: $M+H^+$, 235.1462. $C_{11}H_{23}O_3P$ requires for $M+H^+$, 235.1463).

14. This contrasts with the cyclisation of ethyl diallylacetate (1 equiv.) using diethyl phosphite (1 equiv.), which has been reported to give a mixture of cyclopentane (minor) and cyclohexane (major) products. See: Cadogan, J. I. G.; Hey, D. H.; Hock, A. O. S. *Chem. Ind. (London)* **1964**, 753. The predominant formation of the 6-*endo* product, in the presence of only 1 equiv. of diethyl phosphite, may be explained by a reversible 5-*exo* cyclisation. However, in our hands, no organophosphorus adducts were detected when using only 1 equiv. of diethyl phosphite and 5×0.3 equiv. of AIBN.
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