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Phosphonyl radical addition to enol ethers. The stereoselective synthesis of cyclic ethers

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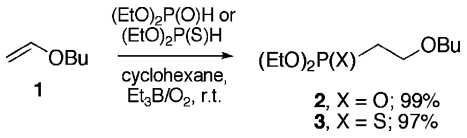
Abstract—Addition of diethyl phosphite or diethyl thiophosphite to enol ethers, in the presence of a radical initiator, results in the regioselective synthesis of organophosphonate or phosphonothioate derivatives, respectively, under mild conditions. This method can be applied to the stereoselective formation of substituted tetrahydrofurans and tetrahydropyrans, on cyclisation of vinyl ethers bearing unsaturated side chains.

One useful method for preparing organophosphorus derivatives involves the regioselective addition of phosphonyl ($R_2P(O)^{\cdot}$) or thiophosphonyl ($R_2P(S)^{\cdot}$) radicals to alkenes.[1] Diethyl phosphite ($(EtO)_2P(O)H$) and particularly diethyl thiophosphite ($(EtO)_2P(S)H$), have been shown to add efficiently to a variety of electron-rich alkenes and dienes[2] in the presence of a radical initiator. The requirement for an electron-rich alkene can be explained by the electrophilicity of the phosphorus-centred radicals, while the higher yields obtained when using diethyl thiophosphite presumably reflects a weaker P–H bond in this compound.

In contrast to reactions with alkenes, addition of phosphonyl and particularly thiophosphonyl radicals, to the electron-rich double bond of enol ethers has not been widely studied.[3] This is surprising because of the mild conditions employed and the range of important biological properties associated with β-alkoxy phosphonates.[4] As a consequence, the addition of diethyl phosphite and diethyl thiophosphite to various enol ethers, including enol ethers with unsaturated side chains, was investigated for the first time.

Initially, diethyl phosphite (10 equiv) was reacted with *n*-butyl vinyl ether **1** (1 equiv) in the presence of triethylborane (4 × 0.3 equiv) at room temperature (Scheme 1).[5,6] This afforded phosphite **2** in quantitative yield, following addition of the intermediate phosphorus-centred radical to the least hindered end of the vinyl ether. A similar result was obtained on reaction of **1** with 5 equiv of diethyl thiophosphite to give adduct **3**.[3a] In both cases, 1.5 equiv of the initiator triethylborane was added, which reflects the short chain length in these reactions. Also, a greater excess of the phosphite, compared to thiophosphite, was required for efficient addition—the excess phosphite or thiophosphite was removed from the crude product by distillation and could be recycled.

Addition of diethyl phosphite and diethyl thiophosphite to other enol ethers is also possible. Hence reaction of diethyl thiophosphite (4.8–5 equiv) with vinyl acetate, 3,4-dihydro-2*H*-pyran, tri-*O*-acetyl-D-glucal and 1-(trimethylsilyloxy)cyclohexene, in the presence of triethylborane (1.2–1.5 equiv) at rt, afforded adducts **4–7** in 63–99% yield (Fig. 1). Whereas **7** was isolated as an equal mixture of diastereoisomers (from the NMR



Scheme 1. Addition of diethyl phosphite and diethyl thiophosphite to *n*-butyl vinyl ether **1**.

Keywords: Cyclisation; Phosphorus compounds; Radicals and radical reactions.

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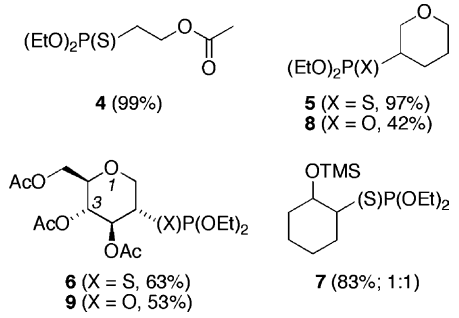
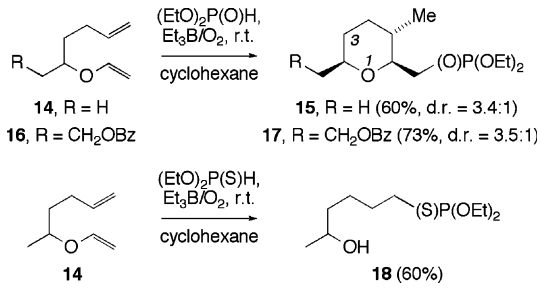


Figure 1. Organophosphorus adducts prepared by addition of diethyl thiophosphite or diethyl phosphite to various enol ethers.

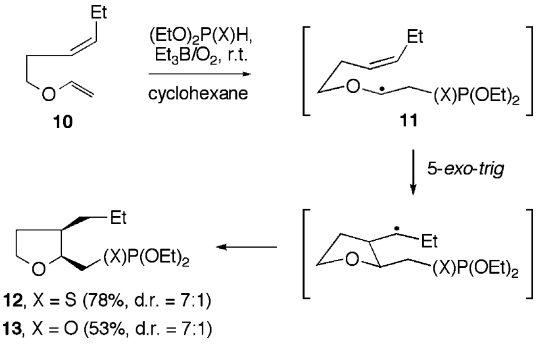


Scheme 3. Addition of diethyl phosphite and diethyl thiophosphite to 1-methyl-4-pentenyl vinyl ether **14** and 3-vinyloxy-6-heptenyl benzoate **16** (the relative stereochemistry of the major isomers of **15** and **17** is shown).

spectra), selective *anti*-addition of the thiophosphonyl radical to the double bond of tri-*O*-acetyl-D-glucal was observed to give **6** as a single diastereoisomer. The relative stereochemistry of **6** was assigned as all-*trans* on the basis of a J_{4-5} value of 11 Hz in the ^{1}H NMR spectrum together with a positive correlation between H-3 and H-5 in the NOESY NMR spectrum. Reaction of 5 and 20 equiv of diethyl phosphite with 3,4-dihydro-2*H*-pyran and tri-*O*-acetyl-D-glucal was found to afford reasonable yields of phosphonates **8** and **9**, respectively. However, the yields were lower than those observed when using diethyl thiophosphite even when using a large excess of the phosphite.

Following these preliminary studies, our attention turned to the reaction of diethyl phosphite and diethyl thiophosphite with enol ethers bearing alkene side chains. For these substrates, the intermediate phosphorus-centred radical could add to the double bond of the alkene and/or the enol ether and it was of interest to explore the chemoselectivity of these novel reactions.

Our studies focused on the reaction of phosphorus hydrides with vinyl ether **10** as shown in Scheme 2. This precursor was prepared in 75% yield by reaction of *Z*-hexen-3-ol with excess ethyl vinyl ether in the presence of the catalyst mercury(II) trifluoroacetate.[7] Reaction of **10** with diethyl thiophosphite (5 equiv) or diethyl phosphite (10 equiv) afforded disubstituted tetrahydrofurans **12** or **13**, respectively, as predominately the *cis*-diastereoisomer (from the NMR spectra). The formation of **12** and **13** can be explained by chemo- and regioselective addition of the phosphorus-centred radical to the enol ether double bond followed by 5-*exo trig* radical cyclisation, which is expected to proceed via a chair-like (Beckwith–Houk) transition state **11**.[8]



Scheme 2. Addition of diethyl phosphite and diethyl thiophosphite to (*Z*)-1-(vinyloxy)-3-hexene **10** (the relative stereochemistry of the major isomers of **12** and **13** is shown).

The stereoselective formation of tetrahydropyrans is also possible as illustrated by the reaction of vinyl ethers **14** and **16** with diethyl phosphite (10 equiv) (Scheme 3). Even though a terminal alkene is present in both **14** and **16**, the phosphonyl radical prefers to add to the vinyl ether double bond. This may be explained by polarity and the fact that the electrophilic phosphorus radical prefers to add to the more electron-rich double bond. Tetrahydropyrans **15** and **17** were isolated as mixtures of inseparable diastereoisomers. The assignment of stereochemistry of the major isomers, shown in Scheme 3, was made on the basis of the NMR spectra and NOESY experiments. This stereochemistry is consistent with a chair-like transition state for the 6-*exo trig* radical cyclisation, while the minor diastereoisomers of **15** and **17** were assigned the all-*cis* stereochemistry.[9]

Surprisingly, when vinyl ether **14** was reacted with diethyl thiophosphite (3 equiv), only secondary alcohol **18** was isolated after column chromatography (Scheme 3). The thiophosphonyl radical prefers to undergo simple addition to the alkene double bond of **14** and this is presumably followed by vinyl ether hydrolysis (on column chromatography) to give the secondary alcohol. This change in chemoselectivity could reflect the greater electrophilicity of the phosphonyl radical, $(EtO)_2P(O)^{\cdot}$, compared to the thiophosphonyl radical, $(EtO)_2P(S)^{\cdot}$.

There are a number of natural and biologically active five- and six-ring ethers that could be prepared using this novel cyclisation methodology. This includes ionophore antibiotics such as tetronomycin **19**, which is active against several Gram-positive bacteria (Fig. 2).[10] Yoshii and co-workers have reported the only total synthesis of **19**.[11] This approach involves the elaboration of trisubstituted tetrahydropyran **20**, which was prepared in 17 steps from L-ascorbic acid (in ~10% overall yield). As shown in Scheme 4, our initial work has concentrated on the development of a shorter racemic synthesis of the related silyl ether **21**, using a phosphonyl radical cyclisation in the key step.

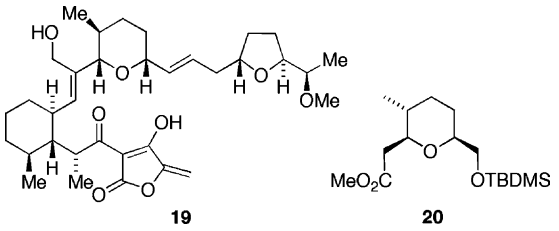
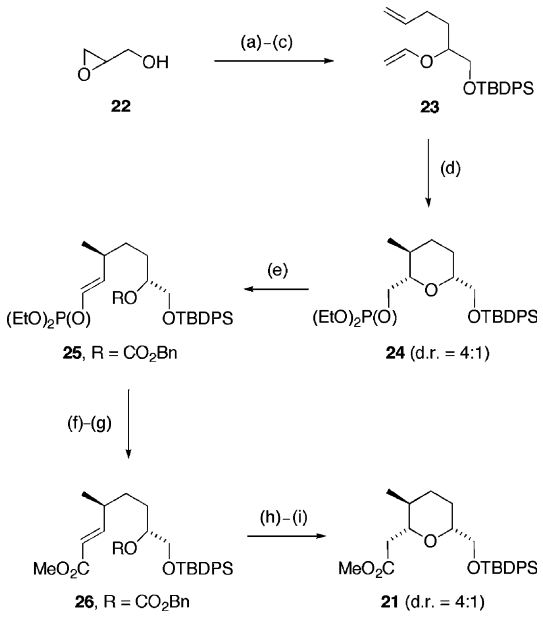
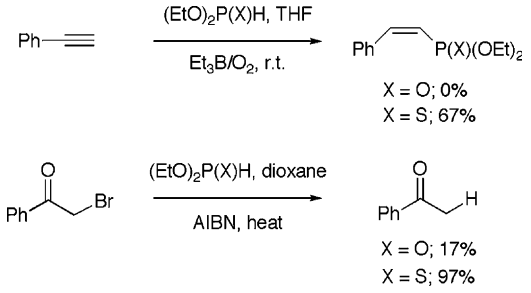


Figure 2. Tetronomycin **19** and tetrahydropyran **20**.



Scheme 4. Synthesis of trisubstituted tetrahydropyran **21** (the relative stereochemistry of the major isomer is shown). Reagents and conditions: (a) TBDPSCl, imidazole, CH_2Cl_2, rt (90%); (b) CuI, $H_2C{=}CHCH_2MgBr$, THF, 0 °C to rt (77%); (c) $EtOCH{=}CH_2$, $Hg(O_2CCF_3)_2$, rt (75%); (d) $(EtO)_2P(O)H$, Et_3B/O_2, cyclohexane, rt (57%); (e) ^{s}BuLi, then $ClCO_2Bn$, −78 °C to rt, THF (78%); (f) O_3, CH_2Cl_2, −78 °C then PPh_3; (g) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, rt (65% over two steps); (h) Pd/C, 1,4–cyclohexadiene, MeOH, rt (90%); (i) KOH, MeOH, rt then ^{t}BuOK, THF, rt (60%).

The synthesis of **21** started by *O*-silylation of glycidol **22** followed by regioselective ring opening of the epoxide[12] and vinyl ether formation (Scheme 4). Reaction of **23** with diethyl phosphite, using Et_3B as initiator, resulted in the formation of tetrahydropyran **24** in 57% yield as a 4:1 mixture of inseparable diastereoisomers. A similar yield of **24** (50%) was obtained when the cyclisation was carried out at 80 °C using AIBN as the initiator, although the diastereoselectivity was reduced to 2:1. Deprotonation of phosphonate **24**, at low temperature, followed by addition of benzyl chloroformate and warming to rt, resulted in an efficient β-elimination reaction[13] and the formation of carbonate **25**. Only the *E*-alkene isomer was isolated (after chromatography) as indicated by the ^{1}H NMR spectrum. Deprotonation of **24** in the absence of benzyl chloroformate resulted in the quantitative formation of the corresponding vinyl phosphonate bearing a secondary alcohol.[14] Oxidative cleavage of vinyl phosphonate **25** was then followed by a Wittig reaction to afford the *E*-alkene **26**. Finally, transfer hydrogenation resulted in efficient deprotection of the benzyl carbonate[15] to afford the corresponding secondary alcohol. Michael-type cyclisation with KOH followed by equilibration using ^{t}BuOK[11] afforded the desired tetrahydropyran **21** (as a 4:1 mixture of diastereoisomers[16]). The nine-step synthesis from glycidol **22** resulted in the formation of **21** in an overall yield of 8%.



Scheme 5. Reaction of phosphorus hydrides with phenylacetylene and 2-bromoacetophenone.

As both *R*- and *S*-enantiomers of glycidol **22** are commercially available, the preparation of either enantiomeric series of **21** is possible. The synthesis of tetronomycin **19** will require the *S*-enantiomer, while the *R*-enantiomer could be used as a starting material for the synthesis of the alternative ionophore, tetronasin (M139603).[17]

This work has shown that inexpensive and nontoxic phosphorus hydrides can add efficiently to a variety of enol ethers. Slow (syringe-pump) addition of the phosphorus hydride is not required for good product yields due to the relatively slow rate of hydrogen atom abstraction (in comparison to tin hydrides), although this means that an excess of the phosphorus hydride is desirable. Of particular synthetic interest is the regio- and stereoselective formation of tetrahydrofuran and tetrahydropyran ring systems. These cyclisation studies clearly illustrate the different reactivity of phosphonyl and thiophosphonyl radicals towards double bonds, which can be explained by radical polarity. Further evidence to support the fact that diethyl thiophosphite is a more effective hydrogen-atom donor than diethyl phosphite is also provided through this work. This is consistent with other phosphorus hydride radical reactions we have recently investigated, including addition to phenylacetylene and reduction of 2-bromoacetophenone (Scheme 5). In both cases, reduced products were isolated in higher yields when using diethyl thiophosphite.

Acknowledgements

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5. All new compounds gave consistent spectral and high resolution mass spectroscopic data.
6. *Typical experimental procedure*: To a stirred solution of diethyl phosphite (1.38 g, 10.0 mmol) in cyclohexane (15 cm^3) was added *n*-butyl vinyl ether **1** (100 mg, 1.0 mmol) and a 1 M solution of triethylborane in hexanes (0.3 cm^3, 0.3 mmol) at ambient temperature. After 6 h, further triethylborane (0.3 cm^3, 0.3 mmol, 1 M solution in hexanes) was added and the mixture stirred for 48 h while adding triethylborane (3×0.3 cm^3, 3×0.3 mmol, 1 M solution in hexanes) over this period. The mixture was then concentrated in vacuo. Excess diethyl phosphite was removed by kugelrohr distillation (75 °C, 2 mmHg). Purification by column chromatography on silica (ethyl acetate) afforded *O,O*-diethyl 2-butoxyethyl-phosphonate **2** (235 mg, 99%) as a colourless oil. R_f 0.4 (ethyl acetate); ν_{max} (CH_2Cl_2) 2983 (s), 2962 (s), 2873 (s), 1245 (s, P=O), 1099 (s, P–O), 962 (s) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.18–4.05 (4H, m, 2×POCH_2), 3.66 (2H, dt, *J* 11.6, 7.3, PCH_2CH_2O), 3.43 (2H, t, *J* 6.4, OCH_2), 2.11 (2H, dt, *J* 18.6, 7.6, PCH_2), 1.55 (2H, quintet, *J* 6.4, OCH_2CH_2), 1.40–1.30 (2H, m, CH_2CH_3), 1.30 (6H, t, *J* 7.0, 2×$POCH_2CH_3$), 0.91 (3H, t, *J* 7.3, CH_2CH_3); δ_C (67.9 MHz, $CDCl_3$) 70.6 (PCH_2CH_2O), 64.4 (OCH_2), 61.5 (d, J_{CP} 6, $POCH_2$), 31.6 (OCH_2CH_2), 28.9 (d, J_{CP} 138, PCH_2), 19.1 (CH_2CH_3), 16.3 (d, J_{CP} 7, 2×$POCH_2CH_3$), 13.7 (CH_3); *m/z* (CI, NH_3) 239 ($M+H^+$, 100%); Found 239.1405. $C_{10}H_{24}O_4P$ requires for $M+H^+$, 239.1412.
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