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Consecutive Approach to Alkenes that Combines Radical Addition of Phosphorus Hydrides with Horner–Wadsworth–Emmons-Type Reactions

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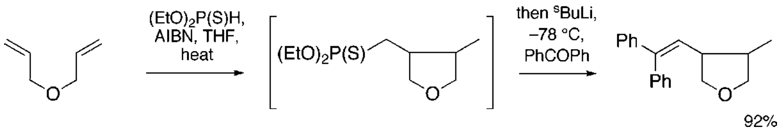
ABSTRACT



Addition of diethyl thiophosphite to terminal alkenes, in the presence of a radical initiator, followed by deprotonation of the phosphonothioate and reaction with a ketone, offers a concise one-pot approach to substituted alkenes. This novel method, which can incorporate alkylation or acylation steps, can be applied to the stereoselective formation of sterically hindered tri- and tetrasubstituted alkenes.

The use of phosphorus hydrides as alternative reagents to tributyltin hydride, for application in radical transformations, has attracted significant attention in recent years.[1] For example, phosphorus hydrides, including hypophosphorous acid (and its salts),[2] diethylphosphine oxide,[3] and diethyl phosphite,[4] have been used to reduce organohalides and xanthates. These reactions involve the formation of intermediate phosphorus-centered radicals, which are also known to add to alkenes to form organophosphorus adducts. Examples of addition of phosphines,[5] diphenylphosphine oxide (Ph$_2$P(O)H),[6] hypophosphites,[7] diethyl phosphite ((EtO)$_2$P(O)H),[8] and diethyl thiophosphite ((EtO)$_2$P(S)H)[8] to a range of alkenes are known.

Research within our own group has recently utilized the radical addition of dialkyl phosphites and thiophosphites in

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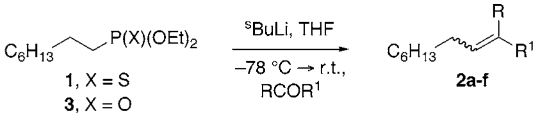
the synthesis of a range of cyclic and acyclic organophosphonates and phosphonothioates under mild conditions.[9] Reactions involving diethyl thiophosphite were shown to be particularly efficient, presumably because of the weaker P−H bond in the thiophosphite. Following the efficient formation of organophosphorus adducts, our attention has now turned to the elaboration of these products to afford alkenes in Horner−Wadsworth−Emmons (HWE)-type reactions.[10] Of particular interest is the development of a novel and flexible one-pot method for preparing alkenes.

Our initial studies concentrated on the preparation and reaction of *O*,*O*-diethyl octylphosphonothioate (**1**) as shown in Scheme 1. This was prepared in quantitative yield by reaction of diethyl thiophosphite (3 equiv) with 1-octene (1 equiv) and triethylborane (5 × 0.3 equiv) in cyclohexane at rt. Nonstabilized phosphonates (without an anion stabilizing group α- to phosphorus) are rarely used in HWE reactions[11] but an isolated report by Corey has shown that nonstabilized phosphonothioates can be converted into alkenes by deprotonation (with ^{n}BuLi at −78 °C) and reaction with aldehydes or ketones (at rt or above).[12] Under these conditions, we found that phosphonothioate **1** gave alkenes **2a**−**f** in higher yields when using ^{s}BuLi (rather than ^{n}BuLi)[13] as the base, and ketones gave higher yields of alkenes than aldehydes.[14] Interestingly, the (*E*)-isomers of alkenes **2b**, **2d**, and **2f** were formed selectively, and raising the temperature of the reaction from −78 to 60 °C did not significantly affect the yields or change the ratio of isomers of the alkenes.

Scheme 1. Synthesis of Di- and Trisubstituted Alkenes **2a**−**f**



(**a**) R = R^1 = Ph, 80%; (**b**) R = Me, R^1 = $C_{11}H_{23}$, 69% (*E*-:*Z*- = 2.4:1);
(**c**) R = R^1 = (CH$_2$)$_5$, 88%; (**d**) R = Me, R^1 = Ph, 81% (*E*-:*Z*- = 6:1);
(**e**) R = R^1 = Et, 53%^{a}; (**f**) R = Ph, R^1 = H, 33% (only *E*-)

[a] **2e** was formed in 40% yield when using LDA as the base.

For comparison, the corresponding phosphonate **3** was prepared by reacting diethyl phosphite (10 equiv) with 1-octene (1 equiv) and triethylborane (5 × 0.3 equiv) in cyclohexane at rt. A quantitative yield of **3** was obtained, although it should be noted that 10 equiv of diethyl phosphite was used, whereas only 3 equiv of diethyl thiophosphite was required for the quantitative formation of **1**. On HWE reaction of phosphonate **3** with benzophenone, under the same conditions as for phosphonothioate **1**, 1,1-diphenylnon-1-ene **2a** was isolated in 56% yield. This compares with an 80% yield from phosphonothioate **1**, which supports the view that phosphonothioates are not only formed more efficiently than phosphonates in radical additions but are also converted into alkenes in higher yields in HWE-type reactions.[12]

The formation of 1,1-diphenylnon-1-ene **2a** was then attempted in one pot by a consecutive reaction of 1-octene with diethyl thiophosphite and AIBN (in THF at reflux) followed by ^{s}BuLi and benzophenone (at −78 °C to rt). This resulted in an excellent 88% yield of the desired alkene **2a** after column chromatography. A similar one-pot transformation using diethyl phosphite (1.2 equiv) in place of diethyl thiophosphite gave **2a** in <5% yield.

Further applications of this novel one-pot approach to alkenes, via intermediate phosphonothioates, were then investigated. For example, reaction of 1-nonene with diethyl thiophosphite followed by deprotonation and reaction with 2-decanone gave 9-methyloctadec-9-ene (**4**) in an excellent yield of 89% (as a 2.55:1 ratio of inseparable alkene isomers) (Figure 1). This alkene has been isolated from the veld grape plant (*Cissus quadrangulariz*), which is an indigenous medicinal plant of India.[15]

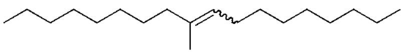


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Figure 1. 9-Methyloctadec-9-ene (**4**) is prepared from 1-nonene in 89% yield.

A similar reaction sequence, involving addition of diethyl thiophosphite to 4-methyl-1-pentene (**5**), followed by deprotonation and reaction with *O*-benzyl pregnenolone (**6**), gave the steroid derivative **7** in 77% yield (as a 4:1 mixture of double-bond isomers) (Scheme 2). Subsequent hydrogenation of **7** (using 10% Pd/C/H$_2$ at 10 atm) resulted in reduction of the two C=C bonds and cleavage of the benzyl ether to afford the naturally occurring steroid cholestanol (in 75% yield).[16] This one-pot approach offers a short and flexible route to analogues of cholestanol, which are of interest because of their biological activities, e.g., high levels of cholestanol are associated with cerebrotendinous xanthomatosis.[17]

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(13) Alkene **2a** was formed in 33% yield when ^{n}BuLi was used in place of ^{s}BuLi.

(14) All new compounds gave consistent spectral and high-resolution mass spectrometry data.

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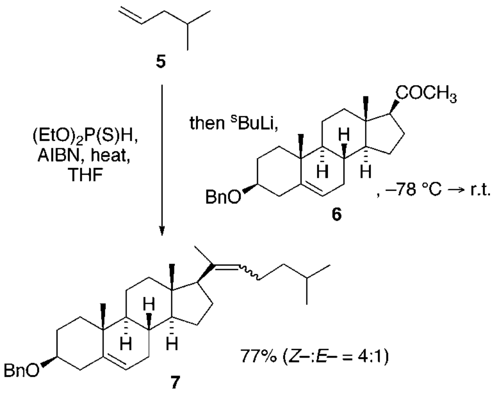
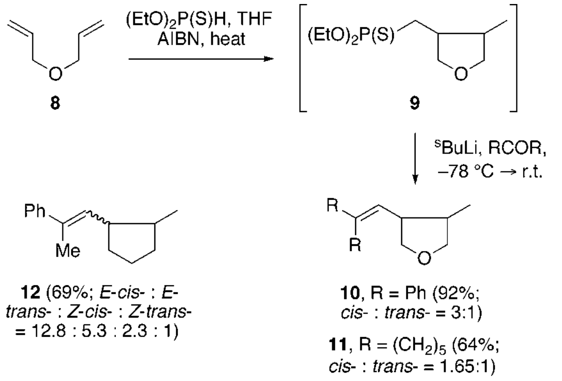
(17) Moghadasian, M. H.; Salen, G.; Frohlich, J. J.; Scudamore, C. H. *Arch. Neurol.* **2002**, *59*, 527−529.

Scheme 2. Consecutive Intermolecular Radical Addition−HWE Reaction

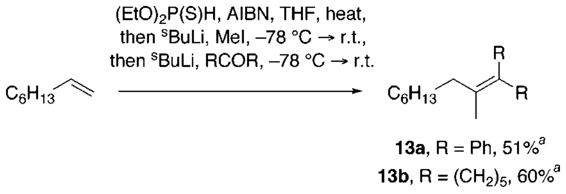


One-pot radical cyclization/intermolecular HWE reactions are also possible (Scheme 3). For example, reaction of diallyl ether (**8**) with diethyl thiophosphite and AIBN produced phosphonothioate **9**, which was immediately deprotonated and reacted with benzophenone to give trisubstituted alkene **10** (as an inseparable 3:1 mixture of cis/trans isomers, respectively) in an excellent 92% yield over the two steps. A similar reaction using cyclohexanone gave the related alkene **11** in 64% yield. This approach can also be used to prepare cyclopentane derivatives, and reaction of hepta-1,6-diene with diethyl thiophosphite, followed by deprotonation and addition of acetophenone, gave trisubstituted alkene **12** in 69% yield (as a mixture of four isomers). For tetrahydrofurans **10** and **11** and cyclopentane **12**, the cis diastereomers were the major products isolated as expected for radical cyclization via a chairlike transition state.

Scheme 3. Consecutive Radical Cyclization−HWE Reactions



Scheme 4. Consecutive Radical Addition−Alkylation−HWE Reaction

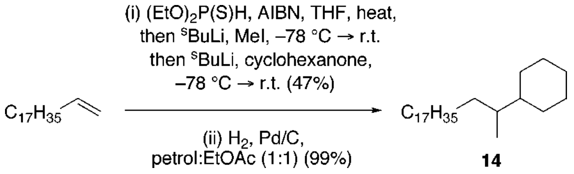


[a] Yields based on the ^{1}H NMR spectra.

To extend the methodology to the preparation of tetrasubstituted alkenes, the incorporation of an alkylation step was investigated. The aim was to alkylate the intermediate phosphonothioate prior to reaction with a ketone. As shown in Scheme 4, radical addition of diethyl thiophosphite to 1-octene, followed by alkylation with methyl iodide and a subsequent HWE reaction, afforded the tetrasubstituted alkenes **13a**,**b** in ≥50% yield (this equates to ≥80% yield for each of the three steps in the sequence). Byproducts **2a** ($\sim$24%) and **2c** ($\sim$5%) (formed by consecutive radical addition/HWE reactions) were also isolated from these reactions, although they could not be separated (using column chromatography) from **13a** and **13b**, respectively. The yields of **13a** and **13b** are therefore based on the ^{1}H NMR spectra.

This methodology was used in a short synthesis of 2-cyclohexyl-eicosane (**14**), a natural product isolated from the plant *Aeonium lindleyi* (Scheme 5).[18]

Scheme 5. Short Synthesis of 2-Cyclohexyl-eicosane (**14**)



Combined radical addition/acylation reaction sequences are also possible. This is illustrated by the formation of ester **15a** (in 86% yield) in one-pot, by radical addition of diethyl thiophosphite to 1-octene, followed by immediate acylation adjacent to phosphorus using diethyl carbonate (1.5 equiv) and LDA (3 equiv) as the base (Figure 2).

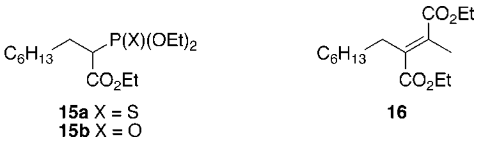


Figure 2. Phosphorus adducts **15a**,**b** and tetrasubstituted alkene **16**.

Stabilized phosphonothioate **15a** is converted into the corresponding phosphonate **15b** in quantitative yield by reaction with *m*CPBA. Phosphonate **15b** could then react in HWE reactions to afford alkenes as reported in the literature.[19] Alternatively, phosphonothioate **15a** can be deproto-

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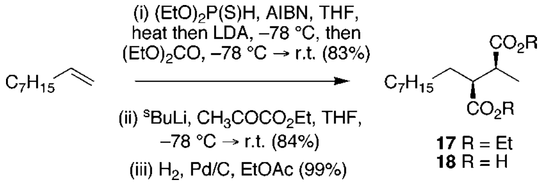
(18) Eglinton, G.; Hamilton, R. J.; Kelly, W. B.; Reed, R. I. *Phytochemistry* **1966**, *5*, 1349−1352.

nated and reacted with aldehydes or ketones to form alkenes. For example, reaction of **15a** with LDA (2 equiv), followed by ethyl pyruvate (2 equiv) at −78 °C to rt in THF, gave (*E*)-alkene **16** in 87% yield.

This methodology was applied to the synthesis of (±)-diethyl sphaeroate (**17**) (Scheme 6). Diester **17** was isolated in an excellent overall yield of 69% from 1-nonene. Sphaeric acid (**18**) has recently been isolated from the fermentation broth of a fungus (*Sphaeropsis* sp.) because of its positive result in a brine shrimp toxicity assay.[20]

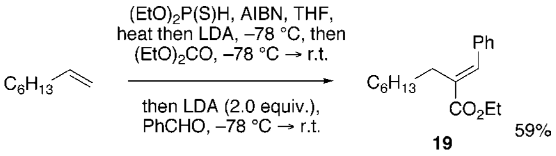
Scheme 6. Concise Synthesis of (±)-Diethyl Sphaeroate **17**



Although consecutive radical addition/α-acylation/HWE reactions using ethyl pyruvate were unsuccessful, one-pot transformations of this type are possible as shown by the formation of the α,β-unsaturated ester **19** (as a single stereoisomer) in Scheme 7. To our knowledge, these are the first examples of ester-stabilized phosphonothioates undergoing HWE-type reactions.

This work has shown that combining thiophosphite radical addition with HWE-type reactions offers a flexible synthetic approach to alkenes. In comparison to related methods,[21] this novel one-pot approach offers a more direct and efficient synthesis of variously substituted alkenes. Even sterically hindered tetrasubstituted alkenes are prepared in good yield from readily available terminal alkenes. We propose the name "radion reaction" to describe these types of one-pot transformations, which involve an initial radical reaction followed by a reaction involving ions.[22]

Scheme 7. Consecutive Radical Addition−Acylation−HWE Reaction



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Supporting Information Available: Representative experimental procedures together with spectroscopic data for compounds **1**, **2b**, **10**, **13b**, **15a**, **16**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Rein, T.; Pedersen, T. M. *Synthesis* **2002**, 579−594.

(20) Wilkinson, R. A.; Strobel, G.; Stierle, A. *J. Nat. Prod.* **1999**, *62*, 358−360.

(21) Reichwein, J. F.; Pagenkopf, B. L. *J. Org. Chem.* **2003**, *68*, 1459−1463.

(22) Tandem reactions that combine radical and anionic reactions are known. For example: Tsunoi, S.; Ryu, I.; Yamasaki, S.; Tanaka, M.; Sonoda, N.; Komatsu, M. *Chem. Commun.* **1997**, 1889−1897.