Efficient and practical aerobic radical addition of thiophosphites to alkenes

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Abstract—Thiophosphites, but not phosphites, add onto alkenes under very mild conditions when treated with triethylborane and oxygen, and deliver the expected adducts in high isolated yields. This method, featuring a high atom economy, complements those described in literature and can be used to initiate tandem cascade processes. © 2001 Published by Elsevier Science Ltd.

The formation of carbon–phosphorus bonds has been an area of intense investigation for decades due to the implication of organophosphorus compounds as ligands of metals, as close analogues of phosphate esters, and because of their involvement in reactions such as the Wittig (and related) olefination. Thus, these C–P bonds have traditionally been created by nucleophilic substitution of halides (including Arbuzov transformations) or by addition of phosphorus-centered radical onto alkenes (chain process).

In particular, phosphonyl and phosphonothioyl radicals (**3**) and (**4**) have been used to produce phosphonates (**8**) and phosphonothioates (**9**), respectively, which can be considered as non-hydrolyzable analogues of monoesters of the phosphate group. Radical (**3**) or (**4**) have been typically generated (i) from the corresponding phosphites (**1**) or thiophosphites (**2**) in the presence of peroxides (Scheme 1, route A), or (ii) from selenophosphates (**10**) or selenophosphorothioates (**11**) and trialkyltin hydride (**12**) in the presence of a radical initiator (route B).[1,2]
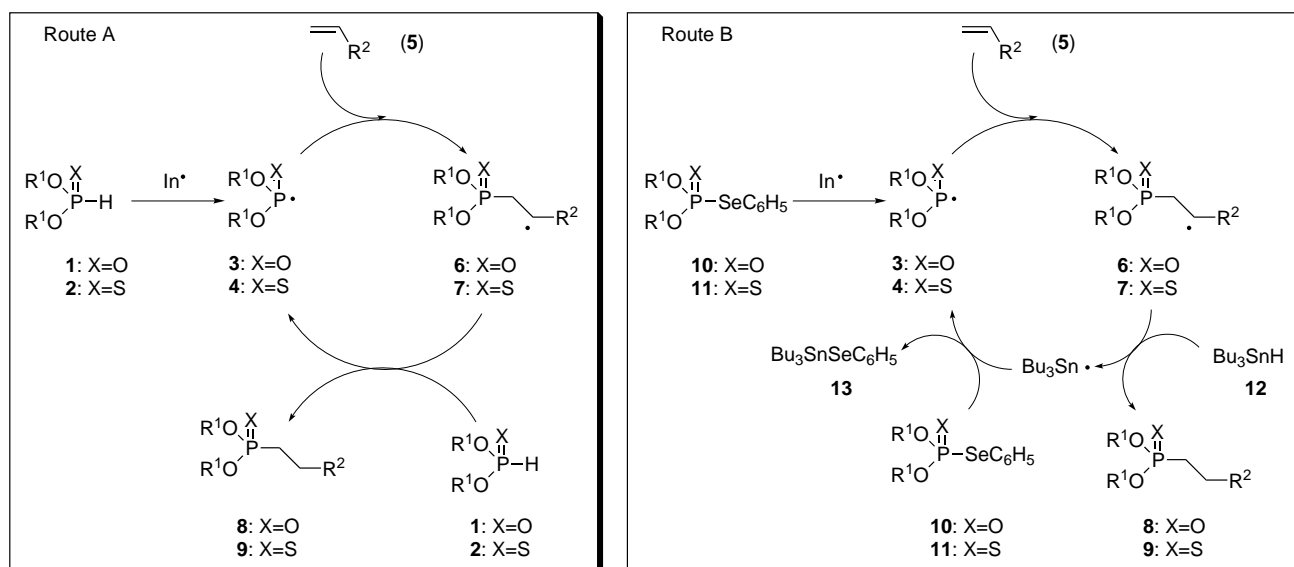

Scheme 1. (R^1 = alkyl; R^2 = alkyl, aryl, …).

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Comparison between the two procedures allows one to rapidly identify two disadvantages of the latter. Thus, the use of tris(*n*-butyl)tin hydride as hydrogen quench produces tin-based by-products that render purification tedious.[3] Furthermore, the use of the selenoether moiety strongly speaks again of the notion of atom economy, since this functional group becomes replaced with a hydrogen atom in the final product.[4] Therefore, route A represents the most direct way to carry out these reactions, the major drawback of the procedure being the use of peroxides as initiators of the chain process. Our own work on the addition of phosphonyl and phosphonothioyl radicals (generated from thiophosphite and *tert*-butyl peroxypivalate) to 1,1-difluoroalkenes clearly demonstrated that phosphites and thiophosphites participate efficiently in the chain process through hydrogen transfer to the carbon-centered radical in the radical-adduct.[1a] This observation led us to speculate that the chain process could be initiated by any alkyl radical. A common procedure to generate

alkyl radicals relies on the interaction between trialkyl-boranes and oxygen.[5] We thus envisioned this system as being potentially able to generate the above-mentioned chain process.

Combining equimolar amounts of diethylphosphite (**1a**) and *n*-octene (**5a**) with triethylborane (**14**) (Et₃B, 1.5 equiv.) under aerobic conditions induced no change, even under forcing conditions. However, replacing diethyl phosphite with diethyl thiophosphite (**2a**) resulted in a clean and complete conversion to diethyl octylphosphonothioate (**9a**) after only 10 min at room temperature, as shown by ^{31}P NMR spectrometry. Decreasing the amount of borane to 1 equivalent did not induce any change in the course of the reaction, but 0.5 equivalents of **14** required 3 h for the reaction to attain completion. The use of 0.25 equivalents of triethylborane resulted in only 50% conversion, the unconsumed phosphite and octene being recovered.
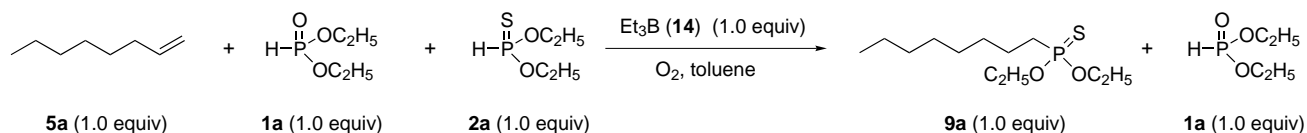
Scheme 2.

Table 1. Reaction between alkenes (**5**) and diethyl thiophosphite (**2a**) in the presence of Et₃B and oxygen

Entry	Alkene (5)		Product (9)		yield (%)[a]
1		5a		9a	95
2		5b		9b	90
3		5c		9c	95
4		5d		9d	79
5		5e		9e	0[b] (0)[c]
6		5f		9f	0[b] (65)[d]
7		5g		9g	0[b] (81)[d]
8		5h		9h	91
9		5i		9i	72 (86)[d] (*cis/ trans*: 70/30)
10		5j		9j	55 (60)[d] (*cis/ trans*: 75/25)

[a] All yields refer to isolated products; all compounds gave analytical data in accordance with the depicted structures.
[b] The formation of a complex mixture is observed; thiophosphite is recovered.
[c] The formation of a complex mixture is observed; thiophosphite is consumed.
[d] Reaction between thiophosphite **2** and the alkene in the presence of *tert*-butyl peroxypivalate, see Ref. 11.

The difference in reactivity between diethylphosphite (**1a**) and diethylthiophosphite (**2a**) was confirmed by conducting the reaction in the presence of *both* reagents. Thus, mixing octene (**5a**) (1.0 equiv.), phosphite **1a** (1.0 equiv.) and thiophosphite **2a** (1.0 equiv.) and submitting the resultant mixture to the above procedure resulted in the exclusive and quantitative formation of product **9a** and the recovery of unconsumed **1a** (1.0 equiv.) (Scheme 2).

Dichloromethane, diethyl ether, tetrahydrofuran, toluene or fluorobenzene were all found to be suitable solvents. The reaction can also be carried out at lower temperatures: complete conversion was observed at −40°C after only 1 h of stirring. This first study allowed us to define the optimal conditions as described in the procedure.[6]

We next investigated the scope and limitation of this procedure by submitting a range of substrates to the reaction (Table 1). Clean additions occurred on mono-, di- and trisubstituted alkenes, resulting in the isolation of the expected pure phosphonothioates (**9**) in yields higher than 90% (entries 1–3 and 8). Electron-enriched alkenes such as *n*-butylvinyl ether (**5d**) also gave the adduct in good yield (entry 4), but ethyl acrylate (**5e**) produced only polymers, the thiophosphite being recovered unchanged. An analogous result was observed with *tert*-butyl peroxypivalate. The presence of ketals in the substrate has a deleterious effect on the course of the reaction: although the thiophosphite is completely consumed, a complex mixture is produced, presumably the result of the Lewis acidity of triethylborane.[7] Interestingly, when *tert*-butyl peroxypivalate was used, the expected adducts (**9f**) and (**9g**) were obtained in 65 and 81% yields, respectively (entries 6 and 7). In the case of (**9g**), hydrogen quenching of the radical adduct by the thiophosphite occurred exclusively from the β-face of the furanoside, due to the shielding effect of the 2,3-acetonide moiety.[2b]

Entries 8–10 depict products resulting from tandem cascade processes: ring opening of the cyclobutane moiety in the radical adduct of (1*R*)-(+)-α-pinene (**5h**) furnished menthene thiophosphonate (**9h**) as a single stereoisomer.[8] Bisallyl sulfonamide (**5i**) produced pyrrolidine (**9i**) in good yield after a *5-exo-trig* cyclization.[9] The reaction occurs even in the presence of chelating groups (entry 10).

In summary, phosphonothioyl radicals can be generated by aerobic decomposition of triethylborane and trapped by alkylsubstituted and electron rich olefins to produce phosphonothioates in good to excellent yields. Even though the intimate mechanism of the reaction requires further studies, this method constitutes a valuable addition to the growing field of tin-free radical reactions.[10] The reaction is easily carried out and can initiate useful tandem processes.

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6. *General procedure*. To a solution of (1*R*)-(+)-α-pinene (136 mg; 1.0 mmol) and diethylthiophosphite (200 mg, 1.3 mmol) in toluene (5 mL) is added dropwise triethylborane (1.0 mL of a 1.0 M solution in hexane) under an air atmosphere. A slightly exothermic reaction ensues and, after 15 min of additional stirring, the reaction mixture is poured into a 2 M aqueous solution of NaOH (15 mL), extracted with ether, dried over sodium sulfate and evaporated under reduced pressure. Kugelrohr distillation (170°C/0.1 mbar) yields 262 mg (91%) of pure **9h**. ^{1}H NMR (CDCl$_3$; external reference: (CH$_3$)$_4$Si; 200 MHz) δ (ppm) 5.6 (s, 1H); 4.1 (m, 4H); 2.6 (dd, $J=23$ Hz and 5.8 Hz, 1H); 2.31 (t, $J=13$ Hz, 1H); 2.0 (m, 1H); 1.7 (m, 5H); 1.3 (m, 8H); 0.8 (dd, $J=6.5$Hz, 6H). ^{13}C NMR (CDCl$_3$; external reference: CDCl$_3$; 50 MHz) δ (ppm) 128.4 (d, $^2J_{\text{C-P}}=9.1$ Hz), 126.6 (d, $^3J_{\text{C-P}}=13.6$ Hz), 62.7 ($^2J_{\text{C-P}}=7.6$ Hz), 61.7 ($^2J_{\text{C-P}}=7.6$ Hz), 46.3 (d, $^1J_{\text{C-P}}=103.0$ Hz), 34.9 (s), 32.3 (s), 29.0 (d, $^2J_{\text{C-P}}=3.0$ Hz), 27.9 (s), 24.0 (s), 19.6 (s), 19.4 (s), 16.2 (s), 16.0 (s). ^{31}P NMR (CDCl$_3$; external reference: H$_3$PO$_4$; 81 MHz) δ (ppm) 100 (s). MS (EI) m/z (%) 290 (26), 155 (41), 137 (50), 136 (92), 121 (72), 92 (100). Exact mass (EI) m/z calcd for C$_{14}$H$_{27}$O$_2$SP: 290.1469. Found: 290.1480.

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10. The reaction between deuterated thiophosphite (D-P(S)(OEt)$_2$) and 4-phenyl-1-butene (**5b**) in conditions identical to those of Table 1 (entry 2) furnished a 1:1 mixture of product **9b** and the analogous 2-deuterated adduct (^{31}P NMR (CDCl$_3$) and mass spectrometries (EI)). Inasmuch as a full half equivalent of triethyl borane is required to obtain a complete conversion, we assume that the relative inefficiency of the chain process might be attributed to the possible role of triethylborane as a chain terminator, with competitive quenching by deuterated thiophosphite and triethylborane. For the action of triethylborane as a chain terminator, see: (a) Miyabe, H.; Ueda, M.; Yoshioka, N.; Naito, T. *Synlett.* **1999**, 465–467; (b) Miyabe, H.; Tanaka, H.; Naito, T. *Tetrahedron Lett.* **1999**, *40*, 8387–8390. For a review on radical chemistry without tin, see: Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3072–3082.

11. A mixture of thiophosphite (1.3 equiv.), alkene (1.0 equiv.) and *tert*-butylperoxypivalate (10 mol%) in degassed toluene (C = 0.2 M) was heated under argon at 80°C for 5 h. Evaporation and purification (SiO$_2$) led to the isolation of the desired, pure product.[1a]