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Radical cyclisation reactions involving phosphonyl radicals: the use of phosphites and phosphine oxides as alternatives to tributyltin hydride

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Abstract—Free radical cyclisation of a variety of 1,6-dienes using CCl_4 in the presence of diethyl phosphite or diphenylphosphine oxide has been investigated. These reactions involve addition of the trichloromethyl radical to the diene followed by a 5-*exo*-*trig* cyclisation reaction. The resultant cyclic primary radical can abstract a chlorine atom from CCl_4 or alternatively, abstract a hydrogen atom from the solvent or the organophosphorus compound. © 2001 Elsevier Science Ltd. All rights reserved.

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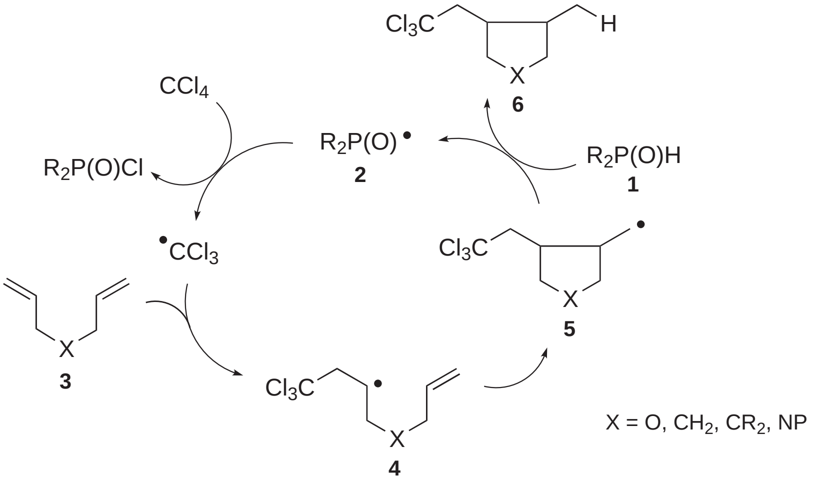
1. Introduction

Free-radical reactions, particularly cyclisations, have been extensively studied over the past twenty years and the most common method of radical initiation involves reaction of halide or related precursors with organotin hydrides.[1] Unfortunately, this method is far from ideal and the toxicity and difficulty of removing tin-containing byproducts has led to the development of alternative reagents for radical generation.[2] Notable examples include tris(trimethylsilyl)silane, cobaloximes, manganese(III) acetate and samarium(II) iodide but the use of organotin hydrides, which provide a flexible and mild method of radical generation, still dominates. This has restricted the use of radical chemistry in the pharmaceutical and fine chemical industries, which is unfortunate because radical reactions offer a number of advantages over ionic reactions (e.g. no solvation, abil-



Scheme 1.

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

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ity to assemble hindered centres, flexible tandem and cascade sequences, and mild, neutral reaction conditions).

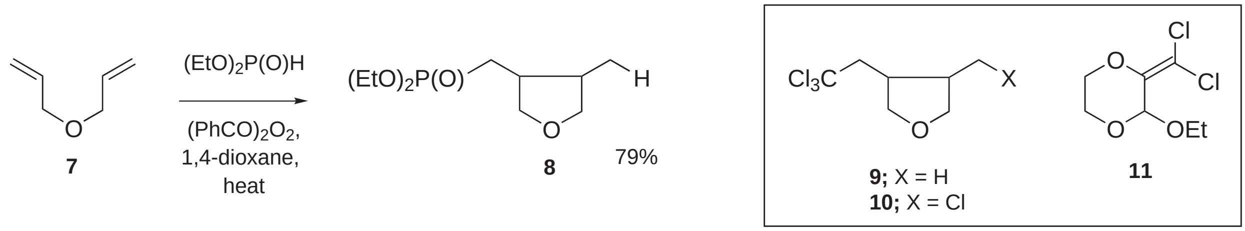
As part of a programme to develop alternative and more versatile free-radical initiators to organotin hydrides (and related compounds), we have recently been investigating the use of phosphorus-centred radicals in carbon–carbon bond formation. This area has largely been neglected, although recent work by Murphy and co-workers, for example, has shown that hypophosphorous acid or 1-ethylpiperidine hypophosphite can be used to initiate radical cyclisation reactions.[3] We now report the novel use of diethyl phosphite or diphenylphosphine oxide in radical cyclisation reactions of the type shown in Scheme 1. It is known that phosphonyl radicals of type **2** can be formed from heating phosphites **1** with peroxides[4] and that these types of radicals can abstract a halogen atom from organohalides, including carbon tetrachloride, which have a weak carbon–halogen bond.[5] The resulting (electrophilic) trichloromethyl radical was then expected[6] to add to one of the (electron-rich) double bonds of diene **3** to form radical **4**. Following 5-*exo-trig* cyclisation, it was envisaged that primary radical **5** would abstract a hydrogen atom from phosphite **1** to continue the chain reaction.[7]

2. Results and discussion

One potential problem to the formation of **6**, was the fact that phosphorus-centred radicals are known to add rapidly to alkenes.[4,7] Phosphonyl radical **2** could therefore add to diene **3** rather than abstract a chlorine atom from CCl_4. In order to probe this competitive reaction, our studies began by heating diethyl phosphite (5 equiv.), diallyl ether **7** (1 equiv.) and benzoyl peroxide (0.2 equiv.) in 1,4-dioxane (Scheme 2).[8] This did indeed produce the cyclic organophosphorus adduct **8** in good yield, thus establishing the efficient addition of the phosphonyl radical to the diene.

Having established the formation and addition of the phosphonyl radical to **7**, the reaction of **7** with diethyl phosphite was investigated in the presence of varying amounts of CCl_4 (Table 1, entries 1–4). It was pleasing to see that the major compound from each of these reactions was the desired trichlorotetrahydrofuran **9** in 47–64% yield. All reactions gave predominantly the *cis*-diastereoisomer of **9** (as indicated by the NMR spectra[9]), as expected from a chair-like transition state. These reactions also produced two further products derived from diene **7**; the organophosphorus adduct **8** in <29% yield, and the tetrachloride **10** (derived from a chlorine-atom transfer reaction)[6] in 7–27%. As anticipated the higher the concentration of CCl_4, the higher the yield of tetrachloride **10**. Unexpectedly, these reactions also produced small quantities of the dioxane derivative **11** (ca. 2% yield based on CCl_4). One mechanism for the formation of **11** could involve an initial hydrogen atom abstraction from 1,4-dioxane. In order to probe this reaction, **7** was heated in 1,4-dioxane with CCl_4 and benzoyl peroxide in the *absence* of diethyl phosphite (entry 5). This gave rise to **9** and **10** in 41 and 21% yield, respectively, the formation of **9** thereby confirming the ability of 1,4-dioxane to act as a hydrogen atom donor in this type of reaction.[10] However, as **9** was isolated in a greater yield in the presence of diethyl phosphite, this suggested that the phosphite was also acting as a hydrogen atom donor in these reactions.

This then led us to investigate the use of alternative solvents to 1,4-dioxane, so as to develop a method in



Scheme 2.

Table 1. Radical cyclisation of diene **7** using CCl_4 under a variety of conditions

Entry	Reaction conditions[a]	% Yield **9** (d.r.[b])	% Yield **10** (d.r.[b])
1	**7** (1), CCl_4 (3), $(EtO)_2P(O)H$ (5), $(PhCO)_2O_2$ (0.2), 1,4-dioxane	47 (3.0:1)	7 (2.3:1)
2	**7** (1), CCl_4 (4), $(EtO)_2P(O)H$ (5), $(PhCO)_2O_2$ (0.4), 1,4-dioxane	64 (3.2:1)	11 (3.1:1)
3	**7** (1), CCl_4 (5), $(EtO)_2P(O)H$ (5), $(PhCO)_2O_2$ (0.4), 1,4-dioxane	59 (2.8:1)	22 (2.1:1)
4	**7** (1), CCl_4 (6), $(EtO)_2P(O)H$ (5), $(PhCO)_2O_2$ (0.3), 1,4-dioxane	64 (3.4:1)	27 (1.7:1)
5	**7** (1), CCl_4 (4), $(PhCO)_2O_2$ (0.3), 1,4-dioxane	41 (3.7:1)	21 (1.4:1)
6	**7** (1), CCl_4 (4), $(EtO)_2P(O)H$ (5), $[CH_3(CH_2)_{10}CO]_2O_2$ (0.2), cyclohexane	56 (2.9:1)	9 (1.2:1)
7	**7** (1), CCl_4 (4), $(EtO)_2P(O)H$ (10), $(PhCO)_2O_2$ (0.2), *tert*-butylbenzene	54 (3.6:1)	8 (1.9:1)

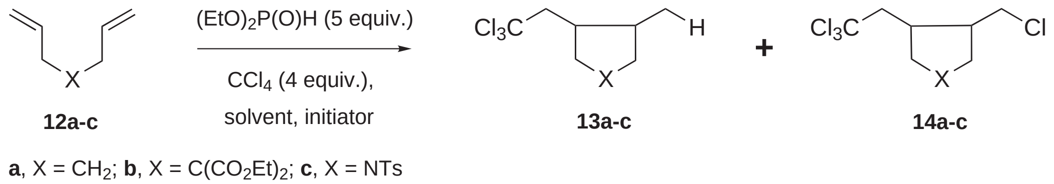
[a] The number of equivalents of reagents are given in brackets.

[b] *cis*:*trans* ratio determined from the ^1H and ^{13}C NMR spectra.

which the phosphite (and not the solvent) was the exclusive (or predominant) hydrogen atom donor. Hence, reaction of **7** and CCl_4 in cyclohexane using lauroyl peroxide as the initiator gave **9** and **10** in 56 and 9% yield, respectively (entry 6). A similar result was obtained using *tert*-butylbenzene and benzoyl peroxide to give **9** and **10** in 54 and 8% yield, respectively (entry 7).

The cyclisation of related dienes **12a–c** was also attempted using a variety of reaction conditions (Scheme 3, Table 2). Thus, cyclopentane **13a** was isolated as the major product from cyclisation of **12a** when using 1,4-dioxane, cyclohexane or *tert*-butylbenzene as the solvent (entries 1–3). Similar results were obtained for the cyclisation of diester **12b** in the presence of diethyl phosphite (entries 4, 5 and 8). For the cyclohexane reaction (entry 5), however, the solvent was shown to act as a hydrogen atom donor: GCMS showed the presence of cyclohexyl chloride in the crude product, while a control reaction showed the formation of **13** in 46% yield in the absence of phosphite (entry 6). In contrast, the use of *tert*-butylbenzene reduces the yield of **13** to only 6% in the absence of diethyl phosphite (entry 7). When the same reaction was repeated in the presence of 10 equiv. of diethyl phosphite, the yield of **13** improved to a respectable 56% (entry 8). This clearly shows that it is the diethyl phosphite, which is acting as the predominant hydrogen atom donor in the *tert*-butylbenzene reactions (entries 3, 8, 9 and 12).

In order to investigate the effect of a different organophosphorus reagent, the cyclisation of diene **12b** using CCl_4 in the presence of diphenylphosphine oxide, rather than diethyl phosphite, was investigated. Hence after heating **12b** with 4 equiv. of CCl_4, 3–5 equiv. of diphenylphosphine oxide and benzoyl peroxide in *tert*-butylbenzene, trichloride **13b** and tetrachloride **14b** were isolated in similar yields to the diethyl phosphite reaction (i.e. 52–55 and 11–13%, respectively). The use of diphenylphosphine oxide was however, shown to be advantageous for the cyclisation of **12b** in the presence of $Cl_3C–CCl_3$ (Scheme 4). When **12b** (1 equiv.) was heated with $Cl_3C–CCl_3$ (4 equiv.) and diethyl phosphite (10 equiv.) in *tert*-butylbenzene, this gave pentachloride **15** in 19% and hexachloride **16** in 20% yield. In con-



Scheme 3.

Table 2. Radical cyclisation of dienes **12a–c** using CCl_4 under a variety of conditions

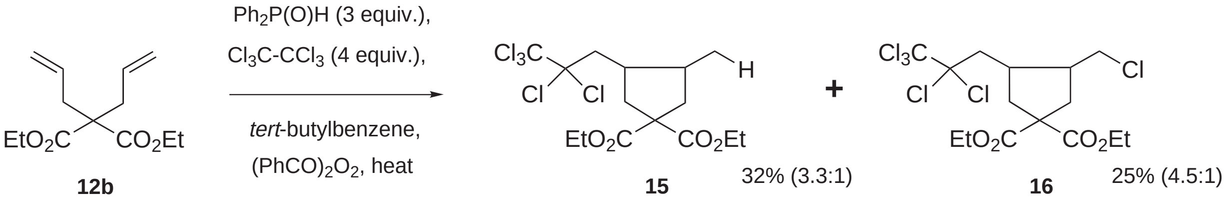
Entry	12	Reaction conditions	% Yield **13** (d.r.[d])	% Yield **14** (d.r.[d])
1	**a**	$(PhCO)_2O_2$, 1,4-dioxane	54 (4.6:1)	44 (3.9:1)
2	**a**	$[CH_3(CH_2)_{10}CO]_2O_2$, cyclohexane	66 (4.6:1)	20 (2.4:1)
3	**a**	$(PhCO)_2O_2$, *tert*-butylbenzene[a]	50 (3.4:1)	22 (2.5:1)
4	**b**	$(PhCO)_2O_2$, 1,4-dioxane	72 (4.6:1)	18 (2.6:1)
5	**b**	$[CH_3(CH_2)_{10}CO]_2O_2$, cyclohexane	59 (5.5:1)	5 (6.8:1)
6	**b**	$(PhCO)_2O_2$, cyclohexane[b]	46 (7.0:1)	45 (5.3:1)
7	**b**	$(PhCO)_2O_2$, *tert*-butylbenzene[b]	6 (3.7:1)	55 (1.4:1)
8	**b**	$(PhCO)_2O_2$, *tert*-butylbenzene[a]	56 (4.8:1)	19 (2.4:1)
9	**b**	AIBN, *tert*-butylbenzene[c]	52 (3.9:1)	19 (3.3:1)
10	**c**	$(PhCO)_2O_2$, 1,4-dioxane	60 (3.6:1)	4 (1.8:1)
11	**c**	$[CH_3(CH_2)_{10}CO]_2O_2$, cyclohexane	57 (3.4:1)	6 (1.4:1)
12	**c**	$(PhCO)_2O_2$, *tert*-butylbenzene[a]	55 (2.7:1)	11 (1.5:1)

[a] Reaction carried out using 10 equiv. of diethyl phosphite.

[b] Reaction carried out in the absence of diethyl phosphite.

[c] Reaction carried out using 15 equiv. of diethyl phosphite and 5 equiv. of CCl_4.

[d] *cis*:*trans* ratio determined from the ^1H and ^{13}C NMR spectra.



Scheme 4.

trast, when diphenylphosphine oxide (3 equiv.) was used in place of diethyl phosphite the pentachloride **15** was isolated in 32% yield after column chromatography.

3. Summary

This work has shown for the first time that diethyl phosphite or diphenylphosphine oxide can be used to mediate the cyclisation of a variety of 1,6-dienes in the presence of, for example, CCl_4. These radical addition–cyclisation reactions are shown to be strongly influenced by the solvent. The use of *tert*-butylbenzene rather than 1,4-dioxane, for example, leads to predominant hydrogen atom transfer by the organophosphorus reagent. These reactions have also shown that halogen-atom abstraction by the phosphonyl radical is in competition with direct addition of the phosphonyl radical to the diene. Indeed, organophosphorus byproducts (of type **8**) were isolated in variable yields from all of the reactions investigated. In comparison, this is less of a problem for tin- or silicon-centred radical reactions because these radicals react more rapidly than phosphonyl radicals with organohalides (e.g. typically three to four orders of magnitude faster for silyl radicals). However, the use of CCl_4, with weak C–Cl bonds, ensures that halogen-atom abstraction by the phosphonyl radical can take place at a competitive rate. This work suggests that alternative organohalides, with particularly weak C–X bonds, could undergo similar transformations.

The use of these reagents has a number of advantages over tributyltin hydride. For example, these compounds are considerably less toxic than organotin compounds and the polar phosphorus chloride byproducts are easily removed on column chromatography. Reactions using diethyl phosphite are particularly attractive because this reagent is considerably less expensive than tributyltin hydride. The lower reactivity of these organophosphorus reagents towards halogen-atom abstraction, when compared to tin- or silicon-centred radicals, also allows the formation of novel carbo- and heterocyclic compounds bearing a versatile trichloro group. Thus, no over-reduction to dichloro- or monochlorinated products was observed. It should also be noted that these cyclisations do not require slow addition of the organophosphorus reagent. This is presumably due to the relatively slow rate of hydrogen atom transfer, to the intermediate primary radical, compared to tributyltin hydride.[7]

Finally, the reactions involving hexachloroethane have demonstrated the different reactivity of diethyl phosphite and diphenylphosphine oxide. We are currently investigating how the substituents affect the reactivity of a variety of organophosphorus derivatives containing a P–H bond.

Acknowledgements

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