Addition of Trichloromethyl Radicals to Alkenes: The Use of Phosphites as Hydrogen-Atom Donors in Intermolecular Radical Reactions

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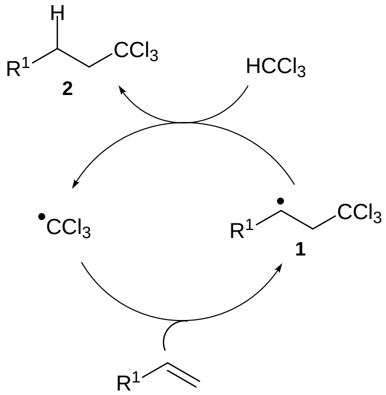
Abstract: Addition of trichloromethyl radicals (generated from $BrCCl_3$ or CCl_4) to a variety of alkenes in the presence of hydrogen-atom donors has been explored. The use of phosphites as hydrogen-atom donors was shown to provide a mild, novel and technically clean approach to trichloroalkanes.

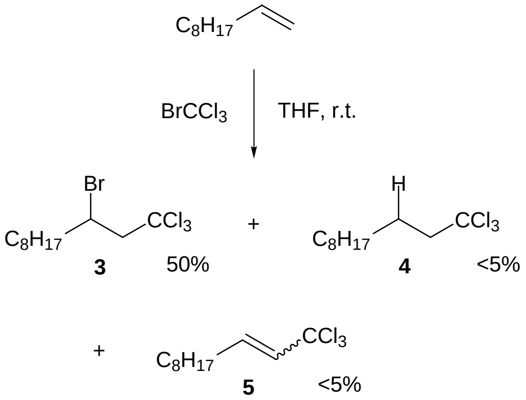
Key words: addition reactions, alkenes, phosphorus, radicals, radical reactions

The formation of polyhalogenated alkanes has attracted the attention of synthetic chemists for many years. This is principally because these compounds have a variety of medicinal and industrial applications including use as anaesthetics, insecticides and organic solvents. One important approach to trihalogenated compounds involves the addition of polyhalomethanes to alkenes using anionic or free radical methods. For example, the trichloromethyl anion has been shown to add to a variety of electron-poor alkenes (in a Michael-type addition) to form trichlorinated adducts.[1,2] Unfortunately, not only are these reactions limited to electron-poor alkenes but they are generally complicated by the formation of dichlorocarbene, which reacts with alkenes to form cyclopropane by-products.[3] In contrast, the trichloromethyl radical has been shown to add regioselectively to a variety of electron-rich alkenes (Scheme 1).[4] This radical, which is often prepared by heating chloroform with a peroxide, adds to the least hindered end of the alkene to form an intermediate carbon-centred radical **1**, which can abstract the hydrogen atom from chloroform to continue the chain reaction. These reactions generally require high temperatures (often >100 °C) and the yields of 1,1,1-trichlorinated adducts **2** are usually very low. This is because the intermediate carbon-centred radical **1** undergoes competitive reactions, such as addition to a further molecule(s) of alkene, to ultimately form oligomer or polymer by-products. As a consequence, alternative approaches to the synthesis of **2** have been reported including, for example, photo-irradiation of polychlorinated compounds in the presence of semiconductor particles[5] and palladium-catalysed oxidation of allylic alcohols in the presence of CCl_4.[6] At present, however, there is still no mild, efficient and technically clean method to trichloroalkanes. This is in stark contrast to the large number of metal-catalysed methods, which can be used to form tetrachlorinated products (in excellent yield) from CCl_4 and alkenes.[7]



Scheme 1

One extremely mild method of adding polyhalogenated compounds to alkenes was reported by Nedelec and coworkers.[8] This work showed that $BrCCl_3$ could add to 1-decene in a THF solution stirred at room temperature (Scheme 2). GLC analysis of the crude reaction mixture showed the formation of the bromine-atom transfer adduct **3** in 50% yield together with less than 5% yield of the non-brominated products **4** and **5**. This simple method of



Scheme 2

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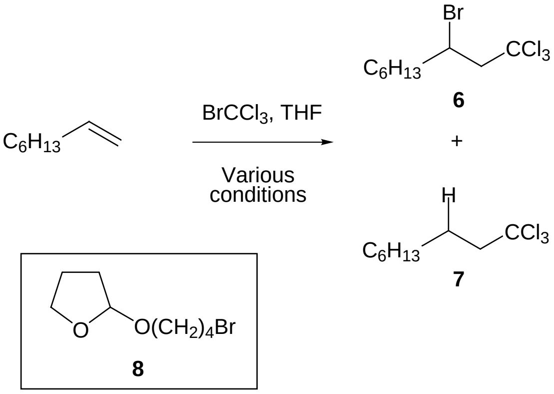
generating the trichloromethyl radical attracted our attention, and we sought to re-investigate this reaction with a view to modifying the conditions so that trichloroalkanes (of type **4**) were the major products.



Scheme 3

Our initial experiments involved addition of $BrCCl_3$ to 1-octene in THF under a variety of reaction conditions (Scheme 3, Table).[9] When $BrCCl_3$ (2 equiv.) and 1-octene (1 equiv.) were stirred in THF at room temperature, bromide **6** was formed in 20% yield while 1,1,1-trichlorononane **7** was formed, somewhat surprisingly, in a reasonable 18% yield (Table, entry 1). Similar reactions at room temperature in an ultrasonic bath (300 W, 30–40 kHz) or at reflux gave almost exclusively bromide **6** (Table, entries 2–5). With a view to increasing the yield of 1,1,1-trichlorononane **7**, potential hydrogen-atom donors (with weak C-H bonds) were introduced so as to trap the intermediate carbon-centred radical of type **1** (Table, entries 6–9). Unfortunately, however, the use of hydrogen-atom donors including 1,4-cyclohexadiene, cumene or isopropanol, under a variety of reaction conditions, did not improve the yield of **7**. Indeed, the introduction of these reagents tended to decrease the yield of **7** although the reason for this is not clear.[10] It should also be noted that all of the above reactions formed varying amounts of bromoacetal **8**, which is derived from a competitive (ionic) reaction between THF and $BrCCl_3$.[11] This bromoacetal is not an efficient hydrogen-atom donor as reaction of 1-octene and $BrCCl_3$ in the presence of **8** gave **7** in only 8% yield (Table, entry 10).

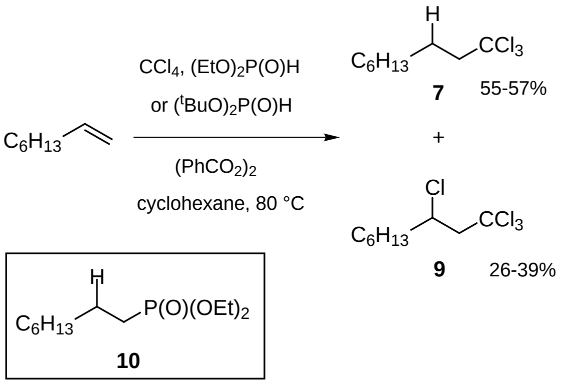
Having established that trichloroalkanes cannot be isolated in good yield when compounds bearing weak C-H bonds are added, our attention turned to the use of phosphites as potential hydrogen-atom donors. These compounds possess relatively weak P-H bonds and our previous work had shown that diethyl phosphite [$(EtO)_2P(O)H$] could be used to form substituted 5-membered rings from reaction of 1,6-dienes with CCl_4 in 1,4-dioxane, *tert*-butylbenzene or cyclohexane.[12,13] Hence, reaction of $(EtO)_2P(O)H$ with CCl_4 in the presence of an initiator produces the trichloromethyl radical, which can react with dienes to form cyclic *primary* radicals capable of abstracting a hydrogen atom from $(EtO)_2P(O)H$. For the desired intermolecular reactions, however, $(EtO)_2P(O)H$ would be required to trap *secondary* radicals of type **1**. The intermolecular reactions were expected to be slower and therefore more difficult to achieve, because of the lower reactivity of secondary versus primary radicals (due to steric and electronic effects).[14] However, if hydrogen-atom transfer from $(EtO)_2P(O)H$ to secondary radicals is possible, then this would be converted to the phosphonyl radical [$(EtO)_2P(O)\cdot$], which could abstract a chlorine atom from CCl_4 to continue the chain reaction. It should also be noted that the use of CCl_4, rather than $BrCCl_3$, would lower the rate of halogen-atom transfer leading to undesired tetrahalogenated products. This is due to the C-Cl bonds (297 kJ mol^{-1}) being stronger than the C-Br bond (234 kJ mol^{-1}).

Table Reaction of $BrCCl_3$ and 1-Octene in THF

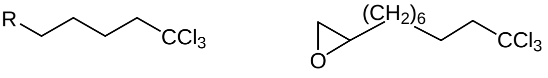
Entry	$BrCCl_3$: 1-octene	Reaction Conditions	Yield of **6** (%)	Yield of **7** (%)
1	2:1	r.t.	20	18
2	3:1	r.t., ultrasound	73	3
3	3:1	heat, slow addition of $BrCCl_3$ (4 h)	38	<3
4	3:1	heat, NaOAc[a] (0.1 equiv.), slow addition $BrCCl_3$ (2 h)	65	<3
5	3:1	heat, slow addition of THF (4 h)	64	14
6	3:1	r.t., 1,4-cyclohexadiene (5 equiv.)	21	<3
7	6:1	r.t., cumene (2 equiv.)	70	3
8	2:1	r.t., isopropanol (5 equiv.)	25	5
9	3:1	heat, isopropanol (10 equiv.), slow addition of $BrCCl_3$ (3 h)	60	<3
10	3:1	heat, bromide **8** (10 equiv.)	65	8

[a] Introduced to neutralise any hydrogen bromide that is produced.

Our first experiments involving reaction of CCl_4 (4 equiv.), 1-octene (1 equiv.) and diethyl phosphite (20 equiv.) in THF did not produce any of the desired trichlorinated product and so reactions in cyclohexane were investigated using benzoyl peroxide (2 × 0.3 equiv.) as the initiator (Scheme 4). Under these conditions, the use of 10 equivalents of diethyl phosphite in cyclohexane was found to produce the desired 1,1,1-trichlorononane **7** in a good yield of 55% after column chromatography; the chloride **9** was also formed but only in 26% yield.[15] This can be compared to the reaction of 1-octene, benzoyl peroxide and $CHCl_3$, which gave **7** in only 22% yield after heating the mixture for 14 h at 80–92 °C under pressure.[4] Trichloride **7** was also isolated in 55% yield when 20 equivalents of diethyl phosphite was used, although the organophosphorus adduct **10**, derived from addition of the phosphonyl radical $[(EtO)_2P(O)\cdot]$ to the double bond, now became a major by-product. It is very interesting to note however, that **7** and **9** were still the major products of the reaction despite the well-known propensity of phosphonyl radicals to add to alkenes.[12,16] Alternative phosphites can also be used and reaction of CCl_4 (4 equiv.) and 1-octene (1 equiv.) in the presence of di-*tert*-butyl phosphite (10 equiv.) gave trichloride **7** in 57% yield and tetrachloride **9** in 39% yield. The importance of the phosphites as hydrogen-atom donors in these reactions was clear from the results of a control reaction, carried out in the absence of phosphite, which gave trichloride **7** in only 3% yield.



Scheme 4

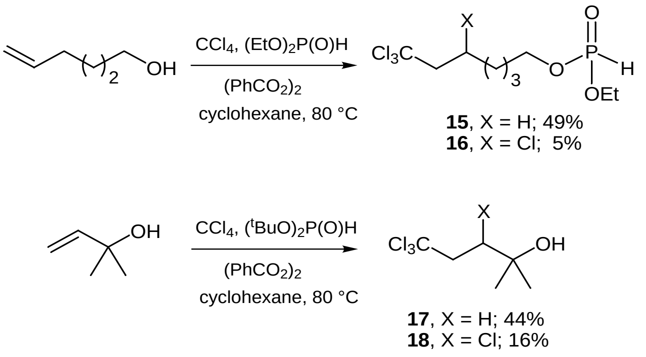


11, R = CH_2OCOCH_3
12, R = CO_2Et
13, R = $COCH_3$

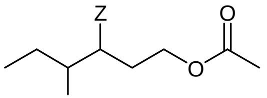
14

Figure 1

Addition to alternative alkenes was also investigated. Hence, reaction of CCl_4, diethyl phosphite and 5-acetoxy-1-pentene, ethyl 4-pentenoate or 5-hexen-2-one yielded trichlorides **11**–**13** (Figure 1) in 56-68% yield; the corresponding tetrachlorides were all isolated in 14% yield. In contrast, reaction with 1,2-epoxy-9-decene gave trichloride **14** (Figure 1) in a lower yield of 35% together with minor products derived from ring opening of the epoxide. Interestingly, when the same reaction was carried out using 5-hexen-1-ol, trichlorophosphite **15** was isolated as the major product in 49% yield (Scheme 5). The primary alcohol had therefore reacted with diethyl phosphite in a nucleophilic acyl substitution (or transesterification) reaction before, or after, radical addition to the alkene double bond.[17,18] It should be noted, that no phosphate products derived from reaction of the alcohol with $(EtO)_2P(O)Cl$ were isolated. A similar result was obtained on reaction of CCl_4 and diethyl phosphite (10 equiv.) with 2-methyl-3-buten-2-ol, although transesterification could be avoided by using di-*tert*-butyl phosphite (5 equiv.), which gave alcohols **17** and **18** in a combined 60% yield.[19] Finally, addition to disubstituted alkenes is also possible and reaction of *cis*-hex-3-enyl ethanoate with CCl_4 and diethyl phosphite gave a 1:1.2 mixture of trichloride regioisomers **19** and **20** (Figure 2), respectively, in a combined yield of 54%.



Scheme 5



19, X = CCl_3, Z = H
20, X = H; Z = CCl_3

Figure 2

This work has shown for the first time, that phosphites can be used to form trichloroalkanes from intermolecular reactions of alkenes with CCl_4. The phosphonyl radical prefers to abstract a chlorine atom from CCl_4 to generate the $\cdot CCl_3$ radical, rather than add directly to the alkene. Regioselective addition of the $\cdot CCl_3$ radical to various alkenes forms secondary carbon-centred radicals, which can abstract a hydrogen atom from the phosphite to continue the chain reaction. The use of phosphites has a number of practical advantages over well-established organometallic hydrogen-atom donors including tributyltin hydride. For example, these compounds are considerably less toxic than organotin compounds and the polar phosphorus chloride by-products 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-centred radicals also means that no over-reduction to dichloro- or monochlorinated products was observed.

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(10) We would like to thank a referee who pointed out that the trichloromethyl radical could prefer to abstract a hydrogen atom from 1,4-cyclohexadiene (and related compounds) rather than add to the alkene double bond. This is certainly possible although we expected competitive alkene addition because reaction of 1,4-cyclohexadiene with $BrCCl_3$ (in THF in the absence of an alkene) produced halogenated products (albeit in ~15% yield) derived from addition of the trichloromethyl radical to a double bond of the diene.

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(15) General experimental procedure. A stirred solution of benzoyl peroxide (0.3 equiv.), carbon tetrachloride (4 equiv.), diethyl phosphite (10–20 equiv.) or di-*tert*-butyl phosphite (5 equiv.), and the alkene (2–2.5 mmol, 1 equiv.) in degassed cyclohexane (20 cm^3) was heated at reflux under a nitrogen atmosphere. After 12–15 h, the solvent was evaporated and saturated aqueous potassium carbonate (20 cm^3) was added. The mixture was then extracted with diethyl ether, washed with brine, dried ($MgSO_4$) and evaporated. Purification by column chromatography (silica) afforded tri- and tetra-chlorinated adducts as colourless oils.

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(17) Heating 1-octanol (1 equiv.) with diethyl phosphite (1.5 equiv.) in cyclohexane for 20 h also led to transesterification and the formation of ethyl octyl phosphite in 60% yield (after column chromatography).

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(19) The reaction of CCl_4 and di-*tert*-butyl phosphite with allyl alcohol was less efficient and the tri- and tetrachloro-alcohols were formed in 18% and 9% yield, respectively. This may be explained by competitive hydrogen atom abstraction at the allylic position.