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Radical Deoxygenations and Dehalogenations with Dialkyl Phosphites as Hydrogen Atom Source

Derek H. R. Barton*, Doo Ok Jang and Joseph Cs. Jaszberenyi

Department of Chemistry, Texas A&M University, College Station, Texas 77843

Abstract: Thionocarbonates and xanthates of alcohols, and various halides and phenylselenides can be transformed to the corresponding hydrocarbons with alkyl phosphites and benzoyl peroxide in most cases in high-yielding radical reactions.

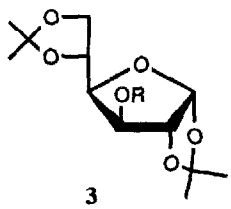
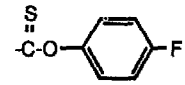
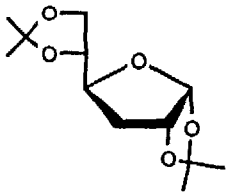
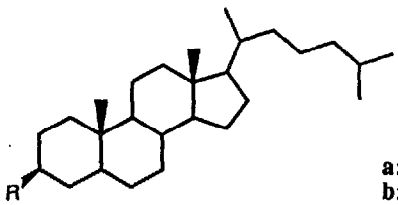
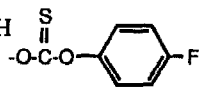
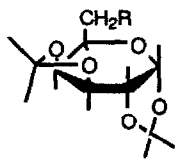
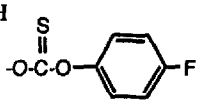
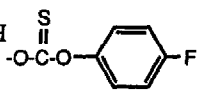
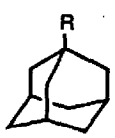
Deoxygenation of alcohols and dehalogenation of certain organic compounds is of synthetic importance. This was the driving force behind the invention of the Barton-McCombie reaction for the radical deoxygenation of secondary alcohols.[1] The principle has found applications later in the radical deoxygenation of primary[2] and tertiary[3] alcohols and the reaction became a widely used synthetic method.[4]

In recent years, however, there have been several known attempts to replace the most widely employed tributyltin hydride with other hydrogen atom donors. This was prompted by stability and toxicity problems, work-up difficulties, environmental concerns, etc. A cheap, non-toxic alternative would be applicable both on laboratory and industrial scale for the preparation of deoxygenated carbohydrates, antibiotics, nucleosides of importance in modern chemotherapy.

One group of compounds, silanes could be good candidates for this purpose. It has indeed been demonstrated recently that tris(trimethylsilyl)silane[5], triethylsilane[6], phenylsilane[7], diphenylsilane[8] and triphenylsilane[9] are all good hydrogen atom sources in radical reactions. The Si-H bond strength is very different in these silanes[10], but depending on the reaction conditions even the silanes with strong Si-H bonds can be used successfully in deoxygenations and dehalogenations. Silanes are much less toxic than tin compounds, or non-toxic, but the group cannot be considered a cheap alternative to tin hydrides. Consequently, large-scale application of these reagents could be costly.

In a search for alternative hydrogen sources and chain carriers for radical reactions we have studied a range of possible reagents. We have found that commercially available dialkyl phosphites can be used efficiently instead of tributyltin hydride. Dimethyl phosphite **1a** or diethyl phosphite **1b** work equally well. The only remaining drawback is that benzoyl peroxide **2** initiation is required, which could prevent the scale-up. Consequently, other, new initiators are being sought. These reactions, when initiated with benzoyl peroxide in boiling dioxane or toluene furnished the deoxygenated products normally in higher than 90% yield. The radical deoxygenation worked equally well with xanthates and 4-fluorophenyl thionocarbonates.[11, 12] Dialkyl phosphites were applicable for the deoxygenation of both primary and secondary alcohols (Table I). Thus, the model compound protected

Table I. Starting materials and products of the radical deoxygenation or dehalogenation with dialkyl phosphites and benzoyl peroxide.

Starting compounds		Products
 **3**	**a:** R = H **b:** R =  **c:** R = 	 **4**
 **5**	**a:** R = OH **b:** R = 	**c:** R = H
 **6**	**a:** R = OH **b:** R = 	**c:** R = H
$CH_3(CH_2)_{16}CH_2R$ **7**	**a:** R = OH **b:** R = 	**c:** R = H
 **8**	**a:** R = OH **b:** R = I **c:** R = Br **d:** R = SePh **e:** R = Cl	**f:** R = H

glucose derivative **3b** was treated with diethyl phosphite **1b** (5.0 equivalents) and benzoyl peroxide (0.4 equivalent) in boiling dioxane for 60 minutes to furnish the deoxygenated product **4** in a 91% yield (^{1}H NMR).

Table II. Radical Deoxygenation of Primary and Secondary Alcohol Thionocarbonates and Xanthates and Dehalogenation of Adamantane Derivatives with Dialkyl Phosphites.

Starting compound	Product	Reagent (eq.) / Initiator (eq.) $(PhCOO)_2$	Time (hr)	Solvent (boiling)	Yield (%)	Notes
3b	**4**	5.0 $(EtO)_2PHO$ / 0.4	1.0	dioxane	91[a]	a: by NMR
		5.0 $(MeO)_2PHO$ / 0.6	1.5	dioxane	92[a]	
3c	**4**	5.0 $(EtO)_2PHO$ / 0.4	1.0	dioxane	90[a]	
		5.0 $(MeO)_2PHO$ / 0.6	1.5	dioxane	97[a]	
		5.0 $(MeO)_2PHO$ / 1.0	2.5	toluene	92[a]	
3b	**4**	2.0 $(MeO)_2PHO$ / 2.0	5.0	dioxane	82[a]	
		0.0 / 0.4	1.0	dioxane	18[a]	+ 82% **3b**
5b	**5c**	5.0 $(MeO)_2PHO$ / 0.8	2.0	dioxane	91[b]	b: isolated yield
6b	**6c**	5.0 $(MeO)_2PHO$ / 0.6	1.5	dioxane	90[a]	
7b	**7c**	5.0 $(MeO)_2PHO$ / 0.8	2.0	dioxane	93[c]	c: by glc
8b	**8f**	10 $(MeO)_2PHO$ / 1.2	3.0	dioxane	98[c]	
8c	**8f**	10 $(MeO)_2PHO$ / 1.0	2.5	dioxane	92[c]	
8d	**8f**	10 $(MeO)_2PHO$ / 2.0	5.0	dioxane	41[c]	+ 13% **8d**

In the blank experiment (without diethyl phosphite) 82% of the starting thionocarbonate **3b** remained unchanged and only 18% deoxygenated product was observed, indicating the contribution of the benzoyloxy and/or phenyl radical. The yield of **4** (91%) remained essentially unchanged when diethyl phosphite was used as a solvent

and hydrogen source. The experimental conditions and yields of deoxygenations and dehalogenations shown in Table I are in Table II. ^{1}H NMR or glc was used for the yield determination but the isolated yields were also high. Various adamantane derivatives **8b-e** were prepared (mostly from **8a**) and transformed to the hydrocarbon **8f**. While the removal of the iodo- or bromo- substituents is relatively easy, the phenylselenyl group was removed only in a moderate yield (41%). The corresponding chloro-compound **8e**, however, remained unchanged in the attempted radical dehalogenation reaction. These findings indicate that the dialkyl phosphite/benzoyl peroxide reagent system in boiling dioxane or boiling toluene is useful for the radical deoxygenation of primary or secondary alcohols or for dehalogenation of iodo- or bromo- compounds.

Typical procedure: To the solution of the starting thionocarbonate **5b** (217 mg, 0.4 mmol) in dry dioxane (3 ml), dimethyl phosphite (180 µl, 2.0 mmol) was added under argon. Then the solution was brought to the boil and treated with 150 µl portions of a solution of benzoyl peroxide (387 mg was dissolved in 3.0 ml dry dioxane) at 30 minutes intervals. The reaction was monitored by tlc. When the reaction was complete (Table II) the solvent was removed in vacuum and the product was isolated by column chromatography on silica gel (eluent: hexanes) giving 135 mg (91%) of cholestane **5c**.

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12. The 4-fluorophenyl chlorothionoformate is commercially available from Aldrich (Cat. # 37,481-4). For the first use of 4-fluorophenyl chlorothionoformate in radical chemistry see ref. 8b, for the synthesis and use in deoxygenation of primary alcohols see ref. 2b.

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