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Phosphine-Boranes as Selective Reagents For The Radical Deoxygenation of a Hindered Secondary Alcohol

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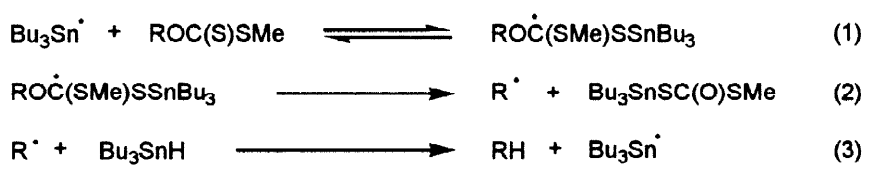
Abstract: **The xanthate of a hindered secondary alcohol can be deoxygenated easily with phosphine-boranes and AIBN in a high yielding radical chain reaction. A similar efficient olefin forming reaction has been seen with a 1,2-dixanthate under the same conditions. In contrast to tin hydride based reagents phosphine-boranes do not reduce chlorides or bromides.**

Radical deoxygenation of alcohols plays an important role in organic synthesis, especially for polyfunctionalized molecules like biologically active carbohydrates.[1] Barton and McCombie demonstrated 20 years ago[2] that secondary alcohols can be deoxygenated in high yield by a radical chain reduction of suitable thiocarbonyl derivatives using tributyltin hydride and AIBN as initiator. The methodology has been extended to primary[3] and tertiary[4] alcohols as well as the dideoxygenation of vicinal diols.[5] Under normal conditions, the Barton-McCombie Reaction proceeds by the radical chain mechanism shown in (eq 1-3).[6]



Although tributyltin hydride and its congeners give high yields in radical reactions there are disadvantages to their use on a practical scale. They are toxic and give residues which are difficult to remove from the product. Their use would not be possible in a manufacturing process in the pharmaceutical industry. Considerable efforts have been expended to overcome these difficulties. The recent report by Fu and his colleagues[7] on the use of a polymeric silicon hydride with a catalytic amount of tin reagent is an important advance. Another alternative which meets the criteria of cost and non-toxicity is the use of hypophosphorous acid, suitably as the ethylpiperidinium salt (Aldrich 43,617-8).[8] There are also other useful hydrogen-donors such as silanes, principally described by Chatgilialoglu[9] and by Roberts.[10]

Besides considerations of cost and toxicity, it is also desirable to produce more selective reagents. We now show that certain readily available phosphine-boranes $R_3P.BH_3$ will carry out the Barton-McCombie reaction efficiently without reducing bromides or chlorides as do tin hydrides. Roberts and his colleagues have already studied the radical chemistry of this class of compounds with EPR spectroscopy.[11] The reactivity of

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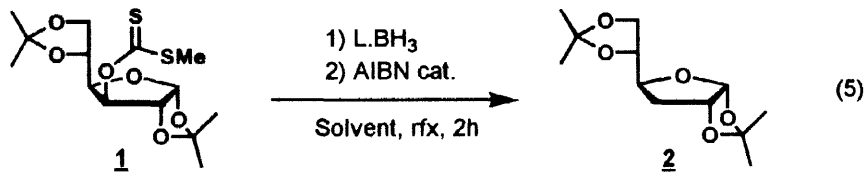
phosphine-boranes towards electrophylic carbon radicals has been used in few synthetically usefull radical chain reactions.[11d,12] One of those was the reaction between $R_3P.BH_2Ph$, an alkyl iodide, and ethyl acrylate according to (eq 4).[11d]

$$Bu_3P.BH_2Ph + RI + H_2C{=}CHCO_2Et \longrightarrow RCH_2CH_2CO_2Et + Bu_3PBHIPh \quad (4)$$

In this paper, we describe the deoxygenation of the xanthate derivative of 1,2:5,6-di-*O*-isopropyliden-α-D-glucofuranose **1** with various phosphine-boranes ($R_3P.BH_3$) in the presence of AIBN as the initiator (eq 5). Certain phosphine-boranes are commercially available and others have been prepared[13] in our laboratory. The results show that all the boranes tested reduced the xanthate. Their reactivity depended on the phosphorus compound ligated to the borane (Table 1). The boranes in Entries 1-4 were not sufficiently reactive in benzene. However, when the solvent was changed to dioxane the triphenylphosphine-borane (Entry 5) gave a good yield of product. In dioxane tris-(trimethylsilyloxy)phosphine-borane also reduced the xanthate well (Entry 6).



1 2 (5)

Table 1. Deoxygenation of 1,2:5,6-di-*O*-isopropyliden-α-D-glucofuranose **1** with various phosphine-boranes in the presence of AIBN.[a]

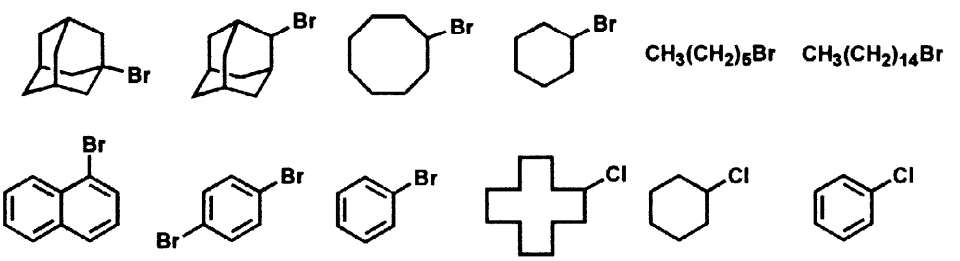
Entry	$R_3P.BH_3$	eq.	AIBN eq.	Solvent	**2** %[b]	**1** (rec.) %[c]
1	$(iPrO)_3P.BH_3$	5	0.4	benzene	23	61
2	$(MeO)_3P.BH_3$	5	0.4	benzene	31	51
3	$(Et_2N)_3P.BH_3$	5	0.4	benzene	44	37
4	$Ph_3P.BH_3$	5	0.4	benzene	42	39
5	$Ph_3P.BH_3$	5	0.4	dioxane	90	n.d.
6[d]	$(Me_3SiO)_3P.BH_3$	5	0.4	dioxane	85	n.d.
7	$nBu_3P.BH_3$	5	0.3	benzene	80[e]	n.d.
8	$nBu_3P.BH_3$	3	0.4	benzene	81	n.d.
9[f]	$nBu_3P.BH_3$	5	0.2	dioxane	89	n.d.
10[g]	$nBu_3P.BH_3$	2	0.3	dioxane	88	n.d.
11	$nBu_3P.BH_3$	3	0	dioxane	0	100
12	$nBu_3P.BH_3$	0	0.4	dioxane	0	100

[a]A typical procedure was as follows unless noted otherwise: The solution of xanthate **1** (0.2 mmol, 1 eq.) and phosphine-borane (2-5 eq.) in refluxing dry benzene (1.5 mL) was treated under argon each 30 min with a solution of AIBN (50 μL, 0.1 eq.) 0.4M in dry benzene. After 2 h the reaction was stopped, the solvent removed under vacuum and the mixture analysed by ^1H NMR. [b]Analysed by ^1H NMR. [c]Starting material recovered and analysed by ^1H NMR. [d]1 mL of dioxane. [e]Starting from 1 mmol of xanthate in 6 mL of dioxane, isolated yield after chromatography on silica gel. [f]Time 60 min and 90% of $nBu_3P.BH_2SC(O)SMe$ was detected by ^{31}P NMR with respect to the starting xanthate. [g]Time 90 min.

The best hydrogen-donor tested for the radical deoxygenation was the tributylphosphine-borane (Entries 7-10). With this borane, we obtained the required product with a good isolated yield (Entry 7). The reaction has been optimized so that with 2 eq. of borane in the presence of AIBN in refluxing dioxane, 88% of deoxygenated compound was obtained (Entry 10). The reaction was a radical chain reaction as only 0.2 eq. of initiator was required (Entry 9). Furthermore, we have isolated for the first time the side product of the radical deoxygenation reaction, $nBu_3P.BH_2SC(O)SMe$,[14] in 85% yield with the conditions describe in Entry 7. Therefore the radical chain reaction follows the same mechanism as that with tributyltin hydride. Entries 11 and 12 are the appropriate blank reactions. The phosphorus derivatives (R_3P) ligated to the borane can be classified by their reactivity as hydrogen-donors in the Barton-Mc Combie Reaction as follows: $(iPrO)_3\ P < (MeO)_3\ P < (Et_2N)_3P < (Me_3SiO)_3P = Ph_3P < nBu_3P$.

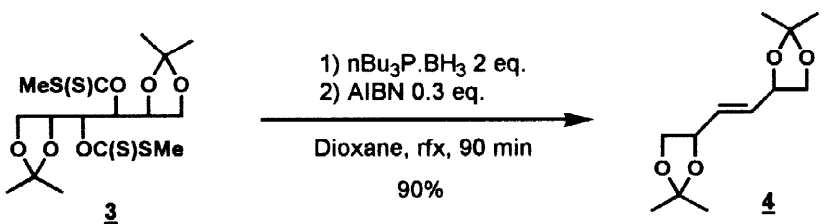
Moreover, the phosphine-boranes showed a specific reactivity towards the xanthate group. In contrast to tributyltin hydride and other hydrogen-donors, the tributylphosphine-borane reacted selectively with the xanthate of alcohol **1** to give 85-90% of deoxygenated product **2** in the presence of various halide derivatives without reduction of the bromide or chloride under our conditions (Scheme 1). However, with various iodide derivatives the deoxygenation did not occur totally. There was an inhibition due to the reaction between the borane and the iodide to give $nBu_3P.BH_2I$ (detected by ^{31}P NMR).

Scheme 1. Bromide and chloride derivatives[a]



[a]The reduction of the xanthate **1** (70 mg, 0.2 mmol, 1 eq.) with tributylphosphine-borane (2 eq.) and AIBN (0.4 eq.) in the presence of halide derivative (1eq. with respect to the xanthate) in refluxing dioxane (1.5 mL) during 2 h gave 85-90% of deoxygenated product **2** (analysed by ^1H NMR and gas chromatography) and no transformation of the bromide or chloride.

The same method can also be used to transform the *bis*-xanthate of vicinal diol **3** to the corresponding olefin **4** in 90% isolated yield (Scheme 2). The borane seems to be the most powerful reagent to date for radical olefin synthesis based on 1,2-dixanthate reduction.



3 **4**

Scheme 2.

In conclusion, the phosphine-boranes and especially tributylphosphine-borane which are readily available, easy to handle, and relatively non-toxic hydrogen-donors have been found to be good selective reagents for the deoxygenation and dideoxygenation of alcohol xanthate's.

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14. $nBu_3P.BH_2SC(O)SMe$ is an oil: Rf = 0.4 (Petroleum Ether/Et_2O : 9/1); IR (film) 2958-2871, 2434, 2380, 1631(CO), 1464, 995, 858 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 0.94 (t, 9 H, CH_3), 1.3-1.8 (m, 18 H, CH_2), 2.33 (s, 3 H, SMe); ^{13}C (50.3 MHz, $CDCl_3$) δ 13.4, 13.7, 20 (d, J_{C-P} = 36 Hz), 24.2 (d, J_{C-P} = 8 Hz), 24.4, 193 (d, J_{C-P} = 3 Hz); ^{31}P (121 MHz, C_6D_6) δ 6 (m); ^{11}B (64.2 MHz, C_6D_6) δ -28 (d, J_{B-P} = 75 Hz); MS m/z (relative abondance, assignment) 322 (10, M), 262 (100, M-COS); Anal. Calcd for $C_{14}H_{32}BOPS_2$: C, 52.17; H, 10.01; S, 19.90. Found: C, 52.32; H, 10.08; S, 20.02.