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# Hypophosphorous Acid and its Salts: New Reagents for Radical Chain Deoxygenation, Dehalogenation and Deamination

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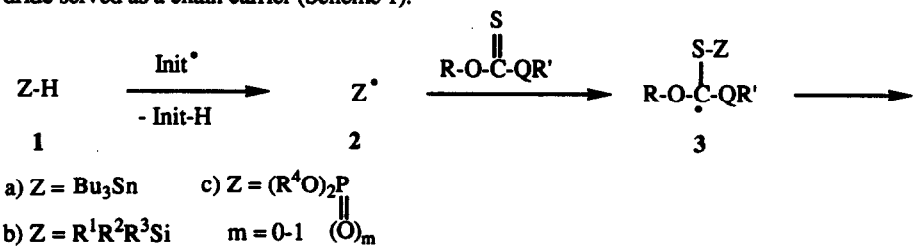
*Abstract:* Thionocarbonates and xanthates of alcohols, bromides, iodides and isonitriles can be transformed to the corresponding hydrocarbons with hypophosphorous acid or its salts in radical chain reactions.

Functional group transformations, such as decarboxylations, deoxygenations, deaminations and dehalogenations are all important in the synthesis of organic molecules. These reactions can be carried out effectively by mild radical methods that are more applicable to sensitive biomolecules then the relatively more drastic ionic processes.[1] Based on the chemistry involved in the radical chain deoxygenation of alcohols by the Barton-McCombie reaction,[2] numerous modifications were reported up till now.[1] In the original Barton-McCombie method tributyltin hydride **1a** was the hydrogen atom source and the tributyltin radical **2a**, generated from the hydride served as a chain carrier (Scheme 1).




**Scheme 1**

Although the method gave good yields and found many applications, the problems associated with the price, toxicity and removal of tin residues prompted a search for other hydrogen atom sources.[1,3] We have explored a wide variety of compounds. We have shown recently, that in addition to tris(trimethylsilyl)silane,[4] and tri-*n*-

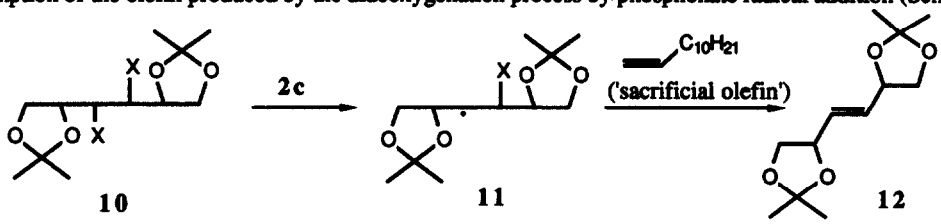
propylsilane,[5] other silanes e.g. triethylsilane,[6] phenylsilane,[7] diphenylsilane,[8] triphenylsilane,[8,9] (general structure **1b**), as well as dialkyl phosphites[10] **1c**, ($R^4$ = alkyl, m = 1) are applicable in deoxygenations, dideoxygenations, as well as dehalogenations. We have also proven by VT $^{29}Si$ NMR experiments[11] that the silanes follow the deoxygenation pathway assumed and proven to operate in the case of $Bu_3SnH$[12] (Scheme 1).

Dialkyl phosphites are almost ideal as hydrogen atom sources and chain-carrier radical precursors. However, the reaction requires the use of benzoyl peroxide as initiator. This is not a problem in small scale reactions, but we attempted to find a method applicable on any scale for deoxygenations, deaminations and dehalogenations. The reagent - we assumed - should be cheap (generally, and also on a per mole basis), effective and non-toxic. We report herein the best method to date.

Radical chain deoxygenations, deaminations and dehalogenations can be carried out with phosphorus-centered radicals, generated from hypophosphorous acid or its salts.[13] The added advantage is that these reactions can be initiated with α,α'-azo*bis*isobutyronitrile (AIBN), thence the use of benzoyl peroxide can be avoided.

Thus, when treated with hypophosphorous acid (**1c**, $R^4$ = H, m = 0) and a tertiary nitrogen base (*e.g.* triethylamine) in boiling dioxane, a series of alcohol thiocarbonyl derivatives were deoxygenated. The tertiary nitrogen base protected the thionocarbonate moiety, as well as acid-labile protecting groups from acidic hydrolysis during the reaction. The method was applicable to primary, secondary and tertiary alcohols. Bromides and iodides also furnished the corresponding hydrocarbons in high yielding radical reactions. Deamination of a primary amine was also achieved *via* the corresponding isonitrile[14] (Table I).

A vicinal diol was dideoxygenated to the corresponding olefin *via* the bis-xanthate **10** (X = O-C=S(SMe)). In this reaction, however, a so-called 'sacrificial olefin' was needed in order to protect the product olefin **12** from an attack by the phosphorus-centered reagent radical **2c**. The presence of an excess of a terminal olefin prevents the consumption of the olefin produced by the dideoxygenation process by phosphonate radical addition (Scheme 2).




**10** **11** **12**

**Scheme 2**

We have also observed this reactivity of phosphorus-centered radicals towards olefins in the case of dialkyl phosphites. Thus, the dimethyl phosphite-generated radical added to the carbon-carbon double bond of cholesterol acetate to give the 6α-phosphonate of cholestanol acetate (m.p. 141-143°C, $[\alpha]_D^{26}$ = - 20.60° (c 1.15, $CHCl_3$), yield: 79%). Cholestanol (4-fluorphenyl)thionocarbonate was deoxygenated in 93% (isolated) yield with $H_3PO_2$.

Although the commercial hypophosphorous acid (50% aqueous solution) can be used for the radical reaction 'as is', the water can also be removed by distillation, evaporation or azeotropic distillation. The pure acid, thus obtained can be transformed to various salts (DABCO, triethylamine, DBU, N-ethylpyperidine, etc), but these salts can also be produced *in situ* in the reaction flask. These salts can then be used in non-aqueous systems for the radical reaction. The excess reagent and and phosphorus-containing side-products are washed out easily from the reaction mixture after the radical reaction. The organic base can then be recovered and recycled.

**Table I** Radical Chain Deoxygenation of Alcohol Thionocarbonates and Xanthates, Dehalogenation of Halides and Deamination *via* the Primary Amine Derived Isonitrile.

| Starting compound | Reagent eq/ (Base) & eq/ Initiator eq[d] | Time (hr) | Yield (%) | Notes |
|---|---|---|---|---|
| X: -O-C(=S)-S-Me | 5/(B1)[e] 5.5/0.4* | 2/3 | 84[a] | [a]by NMR +16% DAG |
| -O-C(=S)-S-Me | 5/(B1) 11/0.4* | 2/3 | 91[a,b] | [b]+ 9% di-acetone-glucose (DAG) |
| | 5/(B1) 11/0.5 | 3/4 | 91[c] | [c]isolated (+ 5% DAG) |
| -O-C(=S)-O-C6H4-F | 5/(B1) 5.5/0.4* | 2/3 | 100[a] | |
| -O-C(=S)-O-C6H4-F | 5/(B2) 5.5/0.33 | 1 | 98[a] | |
| -O-C(=S)-O-C6H4-F | 5/(B3) 2.75/0.5 | 1.5 | 100[a] | |
| **7** | | | | |
| -O-C(=S)-O-C6H4-F | 10/(B1) 11/0.66 | 2 | 91[a] | |
| **8** | 5/(B2) 5/1.16 | 3.5 | 96[a] | |
| X = I | 5/(B1) 5.5/0.5* | 1 | 100[h] | [h]by glc |
| X = Br | 5/(B1) 5.5/1.33* | 2 2/3 | 95[h] | |
| X = O-C=S(SMe) | 5/(B4) 5/0.3 | 1 | 100[h] | |
| **9** | | | | |
| X = NC | 10/ (B1) 15/0.5 | 1.5 | 97[h,f] | [f]+ 3% *N*-formyl cpd. |
| **10** X = -O-C(=S)-S-Me | 5/(B1) 5.5/0.33 | 1 | 78[a,g] | [g]1.5 eq. 1-dodecene was added to protect the olefin product **12**. |

[d]equivalents relative to 1 eq. starting material. [e]B1 = triethylamine, B2 = tri-n-butylamine, B3 = DABCO, B4 = N-ethylpiperidine. The reactions were carried out in boiling dioxane.

*Initiator added in 20 min intervals (150 mL, of a solution of 0.2176 g AIBN (4 mmol) in dioxane).

It appears that hypophosphorous acid and its salts are excellent, low molecular weight, non-toxic hydrogen atom sources in the AIBN-initiated radical chain deoxygenation, dehalogenation and deamination reactions. It is reasonable to assume that these compounds will also find application in other functional group transformations based on radical chain chemistry.

**Typical procedure:** The solution of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose-6-*O*-(4-fluorophenyl) thionocarbonate[15] (0.166 g, 0.4 mmol) and the N-ethylpiperidine salt of hypophosphorous acid (0.72 g, 4.0 mmol) in dioxane (3 mL) under argon was treated with 150 μL of AIBN solution (0.2176 g of AIBN in 3 mL of dioxane) seven times (at every 30 min) during reflux. The solution was washed with water and dried over anhydrous $MgSO_4$. After evaporation of the solvent the residue was analyzed by NMR to give 91 % of the deoxy product 1,2:3,4-di-*O*-isopropylidene-6-deoxy-D-galactopyranose.

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