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Radical deoxygenation and dehalogenation of nucleoside derivatives with hypophosphorous acid and dialkyl phosphites

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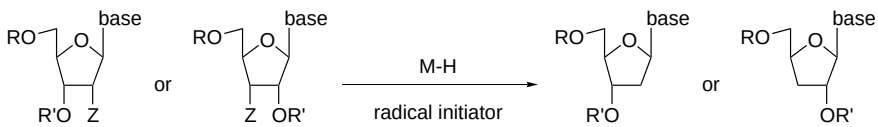
Abstract—Hypophosphorous acid and dialkyl phosphites are effective radical reducing agents for *O*-thiocarbonyl groups or halides at the sugar part of nucleoside derivatives and give the corresponding hydrocarbons in high yield. © 2001 Elsevier Science Ltd. All rights reserved.

The transformation of functional groups is of considerable interest in nucleoside chemistry. Thus far, transformations such as deoxygenation and dehalogenation of nucleoside derivatives have been carried out effectively by free radical reduction (Scheme 1).[1] In the original Barton–McCombie method for deoxygenation, thiocarbonates (-OC(=S)-OAr) or xanthates (-OC(=S)-SMe) were reduced with tri-*n*-butyltin hydride ($^{n}Bu_3SnH$).[2] This reaction has been used not only for the reduction of alcohols at the sugar part of nucleoside derivatives, but also for general organic synthesis.[3]

In the course of our study[4] concerning the synthesis of an anti-HIV agent, 9-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)adenine (**1**, FddA),[5] dehalogenation of **8**[4d] (Fig. 1) was carried out by free radical reduction with $^{n}Bu_3SnH$. However, this tin reagent is not ideal from the perspective of pharmaceutical production because it is toxic, expensive, and produces organotin waste in large quantities, and more importantly it is difficult to completely remove tin byproducts and unreacted $^{n}Bu_3SnH$ from the reaction product.

Therefore, various attempts have been made to identify alternatives. Silanes[6] can be used successfully in radical deoxygenation and dehalogenation. We have also used various silanes for deoxygenation of the 3′-hydroxyl group in **5**.[4a,b] However, although they are much less toxic than tin hydride, they cannot be considered an inexpensive and easily accessible alternative to tin hydride.

Barton et al. reported that the commercially available and inexpensive dialkyl phosphites[7] and hypophosphorous acid[8] could be used for an efficient radical reaction instead of $^{n}Bu_3SnH$. These phosphorous reagents can be considered an almost ideal hydrogen atom source and chain carrier for a radical reaction because of their low cost and safety. Since Barton et al. used these reagents for rather simple substrates, we were interested in using them for deoxygenation and dehalogenation of various nucleoside derivatives such as **2**, **5**, **8**, and **10** (Fig. 1).[9] All of these compounds require a safe and economical deoxygenation or dehalogenation for the synthesis of various nucleoside-related pharmaceuticals.



Z = OC(=S)-OAr, OC(=S)-SMe, halogen, ...
base = adenine, hypoxanthine, guanine, ...

M = $^{n}Bu_3Sn$, $R^1R^2R^3Si$, $(R^4O)_2P(=O)$, $(HO)_2P$, ...
radical initiator = azo compound, peroxide, ...

Scheme 1. Radical deoxygenation and dehalogenation of nucleoside derivatives.

Keywords: dehalogenation; deoxygenation; nucleic acid analogues; nucleosides; radicals and radical reactions.

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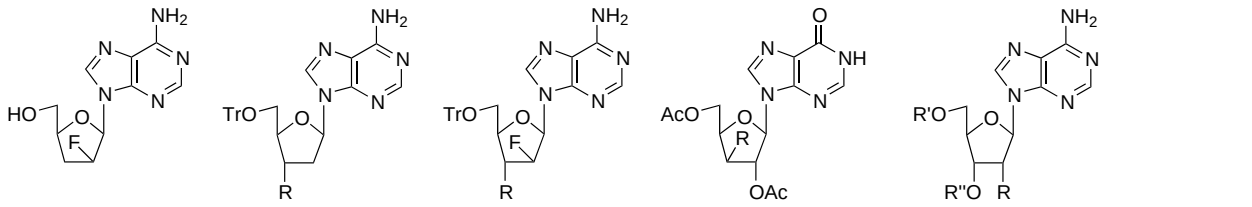


1: FddA

2: R = OH
3: R = OC(=S)-SMe
4: R = H

5: R = OH
6: R = OC(=S)-SMe
7: R = H

8: R = Br
9: R = H

10: R = OH, R'-R'' = -Si(^{i}Pr)$_2$-O-Si(^{i}Pr)$_2$-
11: R = OC(=S)-imidazole,
R'-R'' = -Si(^{i}Pr)$_2$-O-Si(^{i}Pr)$_2$-
12: R = H, R' = R'' = H

Figure 1.

Thus, 9-(5-*O*-trityl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine (**5**) was synthesized,[4a,b] which requires further deoxygenation of the 3′-hydroxyl group to obtain the anti-HIV nucleoside FddA (**1**). Since there was some risk of dehalogenation of the fluorine in **5**, compound **2** was also synthesized and its deoxygenation was examined. Prior to the radical deoxygenation of **2** and **5**, the 3′-hydroxyl group was treated to give xanthates by sequential reaction with carbon disulfide (CS_2) in the presence of sodium hydroxide, and with methyl iodide (MeI). The yields of **3** and **6** were 96 and 87%, respectively.[10]

Xanthates **3** and **6** were then reduced to the corresponding deoxygenated compounds **4** and **7** by the radical reaction with hypophosphorous acid (H_3PO_2) and dialkyl phosphites such as dimethyl phosphite ($(MeO)_2P(O)H$) and diethyl phosphite ($(EtO)_2P(O)H$) in the presence of a catalytic amount of 2,2′-azobisisobutyronitrile (AIBN) as an initiator (Table 1). Hypophosphorous acid is usually available as a 50% aqueous solution, which can be used as such in water-miscible solvents like 1,2-dimethoxyethane (DME). The reactions were conducted in the presence of triethylamine (Et_3N) as a base to avoid damaging the acid-labile substrate and product. High-performance liquid chromatography (HPLC) analysis showed that, after the reaction, the yield of **4** was 79%, while that of **7** varied from 82 to 93%. Both the non-fluorinated (**3**) and fluorinated (**6**) compounds gave a deoxygenated product in good yield (runs 1 and 2). However, C2′-β fluorinated nucleoside is noted for its stability in acid,[11] while 2′,3′-dideoxy-didehydro nucleoside is acid-labile. Decomposition of the product, owing to the acidity of the medium, may have affected the different yield of non-fluorinated and fluorinated compounds (runs 1 and 2). The yield of product was better when a little excess amount of base was added (runs 3 and 4). The best result was obtained when 10 equivalents of H_3PO_2 and 0.6 equivalents of AIBN were used (run 4);[12] however, the amounts of these reagents can be minimized to 2.5 equivalents and 0.2 equivalents, respectively, without substantially reducing the yield (run 6). Barton et al. reported[7,8b] that benzoyl peroxide must be used as an initiator when dialkyl phosphite is used as a hydrogen donor. Interestingly, deoxygenation with dialkyl phosphite proceeded well with a catalytic amount of AIBN in our study, as with H_3PO_2 (runs 7 and 8).[13]

Debromination of 9-(2,5-di-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)-1,9-dihydro-6*H*-purine-6-one (**8**) to obtain 2′,5′-di-*O*-acetyl-3′-deoxyinosine (**9**) was also examined (Table 2). Compound **9** is also an intermediate in the synthesis of FddA.[4d] H_3PO_2 and sodium hypophosphite (NaH_2PO_2) were used as a hydrogen atom source. Since radical debromination carried out in aqueous acetonitrile (CH_3CN) produce hydrogen bromide, the reaction medium becomes strongly acidic during the reaction. Prior to the reaction, base was added to the solution to prevent the decomposition of acid-labile substrate and product. In the case of the reaction with H_3PO_2, triethylamine (Et_3N) was used as a base, while sodium hydroxide (NaOH) was used as a base in the reaction with NaH_2PO_2.

Table 1. Deoxygenation of xanthate (**3** and **6**)

Run	Substrate	Solvent	M–H	P–H (equiv.)	Et_3N (equiv.)	AIBN (equiv.)	Temp. (°C)	Time (h)	Yield (%)[a]
1	**3**	DME	H_3PO_2	5.0	10	0.3	Reflux	1.0	79
2	**6**	DME	H_3PO_2	5.0	10	0.3	Reflux	1.0	84
3	**6**	DME	H_3PO_2	10	20	0.6	Reflux	1.8	86
4	**6**	DME	H_3PO_2	10	11	0.6	Reflux	1.8	93
5	**6**	DME	H_3PO_2	5.0	5.5	0.1	Reflux	1.2	90
6	**6**	DME	H_3PO_2	2.5	2.8	0.2	Reflux	1.3	90
7	**6**	DME	$(MeO)_2P(O)H$	10	–	0.6	Reflux	2.0	84
8	**6**	DME	$(EtO)_2P(O)H$	10	–	0.6	Reflux	2.0	82

[a] The yield is calculated from the results of HPLC analysis.

Table 2. Dehalogenation of brominated nucleoside derivative (**8**)

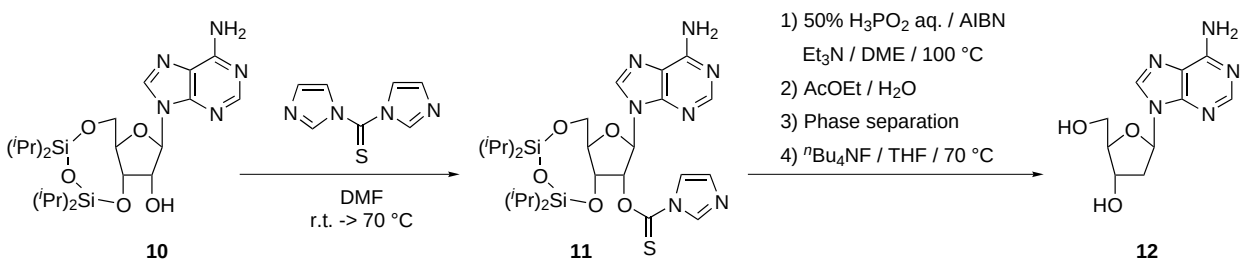
Run	Solvent	P–H (equiv.)	Base (pH[a])	Initiator (equiv.)	Temp. (°C)	Time (h)	Yield (%)[b]
1[c]	Toluene	(^{n}Bu$_3$SnH) (3.0)	None (–)	AIBN (0.1)	90	2.0	92
2	CH_3CN/H_2O	H_3PO_2 (4.0)	Et_3N (pH 7.0)	AIBN (0.1)	70	1.0	97
3	CH_3CN/H_2O	NaH_2PO_2 (4.0)	NaOH (pH 7.0)	AIBN (0.1)	70	2.0	76
4	CH_3CN/H_2O	H_3PO_2 (3.0)	Et_3N (pH 8.0)	V-50 (0.1)	60	3.0	82
5	CH_3CN/H_2O	NaH_2PO_2 (2.0)	NaOH (pH 8.5)	V-50 (0.1)	60	2.0	70
6	CH_3CN/H_2O	H_3PO_2 (3.0)	Et_3N (pH 8.0)	VA-044 (0.1)	50	2.0	99
7	CH_3CN/H_2O	NaH_2PO_2 (2.0)	NaOH (pH 8.5)	VA-044 (0.1)	60	1.0	89
8	CH_3CN/H_2O	NaH_2PO_2 (2.0)	NaOH (pH 8.5)	VA-046B (0.1)	60	1.0	85

[a] pH of the medium when the reaction was started.
[b] The yield is calculated from the results of HPLC analysis.
[c] Ref. 4d.

Although the reaction of brominated compound **8** with ^{n}Bu$_3$SnH in toluene in the presence of AIBN gave **9** in 92% yield (Table 2, run 1),[4d] the reaction with H_3PO_2 or NaH_2PO_2 also gave the product in high yield (runs 2–8). When we used H_3PO_2 in the reaction, the yield was always higher than that with NaH_2PO_2 (runs 2–3, 4–5, 6–7). We assume that decomposition of the product decreased the yield because the pH of the medium after the reaction with NaH_2PO_2 was always much lower than in the reaction with H_3PO_2. Since the reaction was implemented in aqueous medium, the contamination of obtained crystals with hydrophobic AIBN (runs 2–3) was a problem due to its toxicity. Therefore, hydrophilic azoamidine compounds were tested as a radical initiator (runs 4–8) to facilitate the purification of the product. 2,2′-Azobis(2-methylpropionamide) dihydrochloride (V-50™), 2,2′-azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride (VA-044™), and 2,2′-azobis[2-(2-imidazolin-2-yl)propane] disulfate dihydrate (VA-046B™) are all known as azo polymerization initiators, and are available from Wako Pure Chemical Industries, Ltd. When hydrophilic azoamidine compounds were used (runs 4–8), the initiators did not remain in separated crystals, while the yield of the product was at least as high as that with AIBN (runs 2–3). The reaction with a combination of H_3PO_2 and VA-044 gave the product in almost quantitative yield (run 6).[14]

2′-Deoxynucleosides, including 2′-deoxyadenosine and 2′-deoxyguanosine, are currently produced in limited amounts from salmon milt, and it is difficult to satisfy the growing need for these compounds in the production of new diagnostic reagents such as a DNA chip and pharmaceuticals such as antisense oligonucleotides. Although chemical transformation from the corresponding ribose to 2′-deoxynucleoside by radical deoxygenation is known,[1] toxic tin reagents are required for this reaction. To demonstrate the further applicability of this system, an economical synthesis of 2′-deoxynucleoside from readily available ribonucleoside by radical deoxygenation with H_3PO_2 was attempted.

The 3′- and 5′-hydroxyl groups of adenosine were protected by a 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl (TIPDS) group to give the corresponding nucleoside **10** in good yield.[15] Deoxygenation of the 2′-hydroxyl group of **10** was explored to obtain the 2′-deoxynucleoside **12** (Scheme 2), using conditions similar to those mentioned above. First, conversion of the 2′-hydroxyl to its thiocarbonylimidazolyl derivative was accomplished by treatment of **10** with thiocarbonyldiimidazole in DMF, to give **11** in 82% yield. Deoxygenation of **11** in DME with aqueous H_3PO_2 in the presence of Et_3N and a catalytic amount of AIBN gave the 2′-deoxyadenosine **12** after deprotection of the TIPDS group by tetra-*n*-butylammonium fluoride (^{n}Bu$_4$NF). The yield was rather low under the above conditions, which might be due to hydrolysis of the thiocarbonylimidazolyl derivative **11** back to **10**. This is partly because of the liberation of imidazole in the reaction mixture. This argument is supported by the finding that 27% of adenosine was recovered after the reduction and deprotection of **11**. If we exclude this hydrolysis, the yield of the 2′-deoxyadenosine **12** from **11** was 45%. Radical deoxygenation with more stable *O*-thiocarbonyl derivatives is now under investigation in our laboratories.



Scheme 2.

In conclusion, hypophosphorous acid and dialkyl phosphites are effective radical reducing agents for *O*-thiocarbonyl groups, as in xanthates and thiocarbonates, or halides at the sugar part of nucleoside derivatives to give the corresponding hydrocarbons in high yields. The present method is useful for the synthesis of various 2′-deoxy or 3′-deoxynucleoside derivatives, including FddA and 2′-deoxyadenosine.

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10. A representative experimental procedure is as follows: **5** (6.60 g, 12.9 mmol) was dissolved in DMSO (52.4 ml) and cooled to 12°C. To this were added 5M sodium hydroxide (2.84 ml, 14.2 mmol) and carbon disulfide (3.09 ml, 51.6 mmol) at 15°C. After stirring for 15 min at 15°C, methyl iodide (1.60 ml, 25.7 mmol) was added to the mixture. The resulting mixture was poured into water (80 ml) and ethyl acetate (80 ml) with vigorous stirring. The reaction mixture was separated into layers, and the organic layer was washed with water (80 ml). The organic layer was concentrated under reduced pressure to give an oily residue. The residue was crystallized from acetonitrile (50 ml). The resulting crystals were filtered and dried at 50°C under reduced pressure to give the desired product (7.32 g, 91.8% purity, 11.2 mmol, 86.6% yield).
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12. A representative experimental procedure is as follows: To a solution of **6** (102 mg, 98.0% purity, 0.166 mmol) in DME (0.83 ml) were added Et_3N (0.255 ml, 1.83 mmol) and 50% aqueous H_3PO_2 (0.172 ml, 1.66 mmol). This mixture was heated until reflux and AIBN (16.4 mg, 0.0997 mmol) dissolved in DME (0.49 ml) was added in three portions. After stirring for 1.8 h at reflux, the reaction mixture was cooled to room temperature, treated with dichloromethane (5 ml) and water (5 ml), and separated into layers. The organic layer was concentrated under reduced pressure to give a solid residue. HPLC analysis showed that the desired product was obtained in 93.0% yield (76.5 mg, 0.154 mmol).
13. A representative experimental procedure is as follows: To a solution of **6** (61.4 mg, 98.0% purity, 0.100 mmol) in DME (1.0 ml) was added $(MeO)_2P(O)H$ (110 mg, 1.00 mmol). This mixture was heated until reflux, and AIBN (10.0 mg, 0.0600 mmol) dissolved in DME (0.60 ml) was added in three portions. After stirring for 2 h at reflux, the reaction mixture was cooled to rt and concentrated under reduced pressure to give a solid residue. HPLC analysis showed that the desired product was obtained in 84.1% yield (41.7 mg, 0.0841 mmol).
14. A representative experimental procedure is as follows: To a solution of 50% aqueous H_3PO_2 (15.5 ml, 150 mmol) in water (104 ml) was added Et_3N (21.0 ml, 151 mmol) at 16°C. The resulting solution was added to a solution of **8** (20.8 g, 50.0 mmol) in CH_3CN (38.7 ml). This mixture was heated to 43°C, and added Et_3N (3.82 ml, 27.4 mmol) to raise the pH value from 3.8 to 8.0. This mixture was heated to 50°C and VA-044™ (1.62 g, 5.00 mmol) dissolved in water (8.3 ml) was added. After stirring for 30 min at 50°C, the reaction mixture was neutralized to pH 4.0 with 25% aqueous sodium hydroxide (3.54 g, 22.1 mmol). After additional stirring for 1.5 h at 50°C, the reaction mixture was cooled to 10°C, and neutralized to pH 6.0 with 25% aqueous sodium hydroxide (5.94 g, 37.1 mmol). HPLC analysis showed that the desired product was obtained in 99.2% yield (16.7 g, 49.6 mmol).
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