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Radical deoxygenation of alcohols and intermolecular carbon–carbon bond formation with surfactant-type radical chain carriers in water

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Abstract—An efficient and mild method is developed for radical deoxygenation of alcohols and formation of carbon–carbon bonds in water without adding additives such as surfactants. The reaction was applied to synthesis of 2′,3′-didehydro-2′,3′-dideoxynucleosides that are potent anti-HIV agents. The reaction afforded environmentally benign reaction conditions.

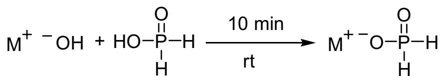
Applications of radical reactions in organic synthesis have attracted much attention in the area of new carbon–carbon bond formation and modification of polyfunctionalized compounds in recent years because they afford neutral reaction conditions in which sensitive polyfunctionalized molecules can remain intact.[1]

Organotin hydrides, especially $^{n}Bu_3SnH$, have been widely employed in radical reactions. It is notorious, however, that organotin hydrides are toxic, expensive, and difficult to remove, and that they often contaminate products. These reasons have limited the use of organotin hydrides in industrial applications. Research effort on finding ideal alternatives to organotin hydrides has been made.[2] And it has been found that phosphorus hydrides are efficient substitutes for organotin hydrides in radical reactions from the viewpoints of cost-effectiveness, toxicity, and work-up process.[3]

Recently, water has drawn considerable attention as a reaction solvent in organic synthesis.[4] Compared with organic solvents generally used for organic reactions, water is cheap, safe, and environmentally benign showing unique solvent effects. Although radical reactions, which were performed in aqueous media have been developed,[5] it is quite difficult to accomplish radical reactions in water without using organic co-solvents. Reactions reported in the literature in fully water required a surfactant,[6] which may form a micellar system to obtain high yields of the desired products. Herein, we report on radical deoxygenation of alcohols and intermolecular carbon–carbon bond formation with a surfactant-type radical chain carrier in water.

Tetraalkylammonium hypophosphites (TAHPs) were readily prepared by mixing the corresponding tetraalkylammonium hydroxide with aqueous H_3PO_2 (Table 1). We then examined the reactivity of the prepared TAHPs as radical chain carriers as well as surfactants. *O*-Cyclododecyl-*S*-methyl dithiocarbonate (**1a**) has been chosen as the model compound. The reaction of the xanthate **1a** with TAHP-1 in the presence of water-soluble radical initiator, ABCVA (4,4′-azobis(4-cyanovaleric acid)), in water yielded 94% of the deoxy product **1b**

Table 1. Synthesis of tetraalkylammonium hypophosphites



$$M^+\ {}^-OH + HO\!-\!\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle H}{|}}{P}}\!-\!H \xrightarrow[\text{rt}]{\text{10 min}} M^{+}\,{}^{-}O\!-\!\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle H}{|}}{P}}\!-\!H$$

M^+	Product
$(CH_3)_3N^+(CH_2)_{15}CH_3$	TAHP-1
Bu_4N^+	TAHP-2
$Bu_3N^+CH_3$	TAHP-3
$(CH_3)_4N^+$	TAHP-4

Keywords: Radical water; Phosphorus hydride; Deoxygenation; Surfactant; C–C bond formation.

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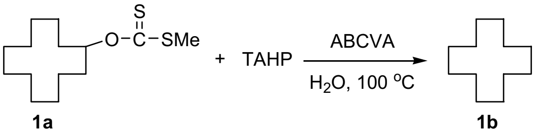
Table 2. Deoxygenation of *O*-cyclododecyl *S*-methyl dithiocarbonate with tetraalkylammonium hypophosphites in H_2O



Entry	TAPH (equiv)	ABCVA (equiv)	Time (h)	Yield (%)[a]
1	TAHP-1 (3)	0.5	5	94
2	TAHP-1 (2)	0.5	8	84
3	TAHP-2 (3)	0.75	7	90
4	TAHP-3 (3)	0.75	8	62 (29)[b]
5	TAHP-4 (3)	0.75	8	45 (52)[b]

[a] Isolated yields.

[b] Recovered starting material.

after 5 h (Table 2, entry 1). With TAHP-2, 90% of the deoxy product **1b** was obtained (entry 3). It is noteworthy that radical deoxygenation of alcohols is possible to perform in water without adding external additives such as surfactants. We performed the reaction with TAHPs having short alkyl chains such as TAHP-3 and TAHP-4 giving moderate yields of the deoxy product with the recovered starting material (entries 4 and 5). The longer the alkyl chains are, the more efficient TAHPs are as radical chain carriers in water. As expected, the long alkyl chain promoted the solubility of the substrates and the formation of a micellar system to accelerate the reaction.

To find out the most suitable initiator, we screened a series of water-soluble radical initiators. ABCVA were found to be the most effective initiator among the initiators we employed (Table 3).

We then investigated the generality of the deoxygenation of alcohols using TAHP-1 and ABCVA, which was the most efficient conditions. Under these conditions, xanthate derivatives of secondary alcohols, **2a** and **3a** were readily transformed into the deoxy products in high yields (Table 4, entries 1 and 2).[8] Hydrophobic substrate such as cholestanyl derivative **4a** gave poor yield (entry 3). Next, we performed the dideoxygenation of bis-xanthates. The bis-xanthate of α-D-glucose derivative **5a** was converted into the corresponding dideoxy product **5b** in 80% yield (entry 4). Then, the reaction was applied to synthesis of 2′,3′-didehydro-2′,3′-dideoxynucleosides that are potent anti-HIV agents. The bis-xanthate of N^3-methyluridine derivative **6a** was subjected to the radical reaction conditions in water, which gave the corresponding olefin **6b** in 82% yield (entry 5). A similar result was obtained with an adenosine derivative **7a** (entry 6).

Table 3. Deoxygenation of *O*-cyclododecyl *S*-methyl dithiocarbonate with TAHP-1 in boiling H_2O in the presence of various radical initiators

Entry	Initiator[b]	Time (h)	Yield (%)[a]
1	ABCVA	5	94
2	VA-057	8	20
3	V-50	8	15
4	VA-061	8	21
5	V-70	24	NR[c]

[a] Isolated yields.

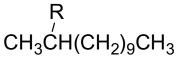
[b] ABCVA = 4,4′-azobis(4-cyanovaleric acid), VA-057 = 2,2′-azobis[*N*-(2-carboxyethyl)-2-methylpropionamidine], V-50 = 2,2′-azobis(2-amidinopropane) dihydrochloride, VA-061 = 2,2′-azobis(2-imidazolinylpropane), V-70 = 2,2′-azobis(2,4-dimethyl-4-methoxy valeronitrile).

[c] At room temperature.

Table 4. Deoxygenation of various alcohols via *S*-methyl dithiocarbonate derivatives with TAHP-1 in H_2O at 100 °C

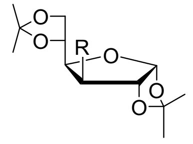
Entry	Substrate	TAHP-1 (equiv)	ABCVA (equiv)	Time (h)	Product	Yield (%)[a]
1	**2a**	3	0.5	5	**2b**	90
2	**3a**	3	0.5	7	**3b**	88
3	**4a**	3	0.75	12	**4b**	7
4	**5a**	3	0.5	7	**5b**	80
5	**6a**	3	0.5	6	**6b**	82
6	**7a**	3	0.5	6	**7b**	76

[a] Isolated yields.

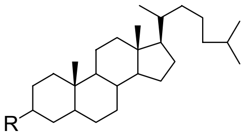


$$\overset{R}{CH_3CH}(CH_2)_9CH_3$$

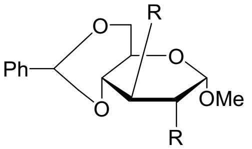
2a : R = O(C=S)SMe
2b : R = H



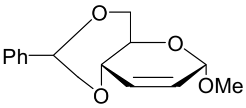
3a : R = O(C=S)SMe
3b : R = H



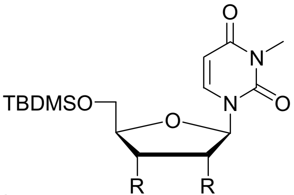
4a : R = O(C=S)SMe
4b : R = H



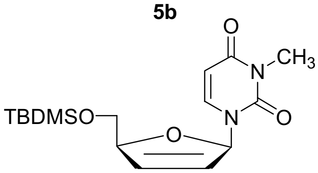
5a : R = O(C=S)SMe



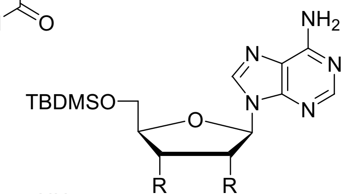
5b



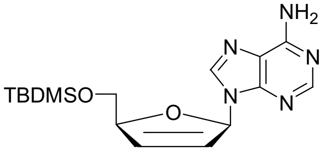
6a : R = O(C=S)SMe



6b



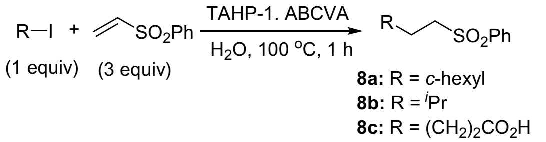
7a : R = O(C=S)SMe



7b

To expand the utility of our methodology, we subsequently investigated radical carbon–carbon bond forming reactions, which generally required a large excess

Table 5. Radical addition reactions of alkyl iodides to phenyl vinyl sulfone (3 equiv) with TAHP-1 (3 equiv) in the presence of ABCVA (0.25 equiv) in H_2O



Entry	R	Product	Yield (%)[a]
1	*c*-Hexyl	**8a**	89
2	*c*-Hexyl	**8a**	57[b]
3	^{i}Pr	**8b**	76[c]
4	$(CH_2)_2CO_2H$	**8c**	70
5	1-Adamantyl		0 (70)[d]

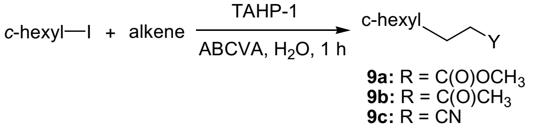
[a] Isolated yields.
[b] Using 1 equiv of phenyl vinyl sulfone.
[c] At 80 °C.
[d] 1-Adamantanol.

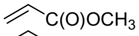
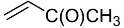
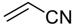
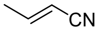
of alkenes to trap radicals when $^nBu_3SnH$ was employed.[7] The reaction of 1 equiv of cyclohexyl iodide with 3 equiv of vinylsulfone in the presence of TAHP-1 and ABCVA in water produced the addition adduct **8a** in 89% yield (Table 5, entry 1).[9] With 1 equiv of phenyl vinyl sulfone, the yield was decreased to 57% (entry 2). Similar results were obtained with isopropyl iodide and 3-iodopropionic acid (entries 3 and 4). Tertiary iodide was readily hydrolyzed to give alcohol under these conditions (entry 5).

Next, we examined a series of alkenes to uncover the reactivity as radical acceptors (Table 6). α,β-Unsaturated ester, ketone, and nitrile were found to be good radical acceptors affording high yields of addition adducts. As expected, β-substituted alkene did not proceed under these conditions.

In conclusion, we have discovered that the combination of surfactant-type radical chain carrier, TAHP, and water-soluble radical initiator, ABCVA, is an ideal reaction system to accomplish deoxygenation of alcohols and carbon–carbon bond formation in water. This method has no need to add external additives such as surfactants to promote the reaction. The reagents used for the reaction are non-toxic and inexpensive, and the method offers mild and neutral reaction conditions and an easy work-up process. Therefore, the reaction may find an application in an environmentally benign procedure in a large scale.

Table 6. Radical addition reactions of cyclohexyl iodide (1 equiv) to various alkenes (3 equiv) with TAHP-1 (3 equiv) in the presence of ABCVA (0.25 equiv) in H_2O



Entry	Alkene	Temp (°C)	Product	Yield (%)[a]
1		80	**9a**	77
2		80	**9b**	84
3		70	**9c**	83
4		80		0

[a] Isolated yields.

Acknowledgments

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8. Typical procedure for deoxygenation of alcohols with TAHP-1: A solution of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(methylthio)thiocarbonyl-α-D-glucofuranose (**3a**) (100 mg, 0.29 mmol) and TAHP-1 (1.26 mL, 0.86 mmol, 0.68 M solution in H_2O) in degassed water (20 mL) under argon was treated with ABCVA (27 mg, 0.072 mmol) twice (2.5 h interval) at 100 °C for 7 h. After the reaction was completed, the reaction mixture was diluted with EtOAc, then washed with water, dried over $MgSO_4$, and evaporated the solvent in vacuo. The residue was purified by flash column chromatography over silica gel (*n*-hexane/EtOAc, 8:2) to furnish 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**3b**) (61 mg, 88%).
9. Typical procedure for carbon–carbon bond formation with TAHP-1: A solution of cyclohexyl iodide (50 μL, 0.38 mmol), phenyl vinyl sulfone (191 mg, 1.14 mmol) and TAHP-1 (1.67 mL, 1.14 mmol, 0.68 M solution in H_2O) in degassed water (20 mL) under argon was treated with ABCVA (35 mg, 0.095 mmol) at 100 °C for 1 h. After the reaction was completed, the reaction mixture was diluted with EtOAc, then washed with water, dried over $MgSO_4$, and evaporated the solvent in vacuo. The residue was purified by flash column chromatography over silica gel (*n*-hexane/EtOAc, 10:1) to furnish (2-cyclohexyl) ethyl phenyl sulfone (**8a**) (85 mg, 89%).