Pergamon

Tetrahedron Letters 43 (2002) 5921–5924

TETRAHEDRON LETTERS

Radical deoxygenation of alcohols and vicinal diols with *N*-ethylpiperidine hypophosphite in water

Doo Ok Jang* and Dae Hyan Cho

Department of Chemistry, Yonsei University, Wonju 220-710, Republic of Korea

Received 1 June 2002; accepted 28 June 2002

Abstract—Radical deoxygenation of alcohols and vicinal diols with *N*-ethylpiperidine hypophosphite both in alcohols and in water is described. *S*-Methyl dithiocarbonate and bis-*S*-methyl dithiocarbonate of carbohydrates and nucleosides were deoxygenated efficiently under reaction conditions.

Radical deoxygenation of alcohols is a very important reaction for preparing polyfunctionalized compounds such as biologically important carbohydrates and nucleoside derivatives.[1] Although various methodologies for deoxygenation of alcohols have been reported, the Barton–McCombie reaction is the most suitable for this purpose.[2] It affords mild reaction conditions in which sensitive polyfunctionalized molecules can remain intact.

Organotin hydrides, especially tributyltin hydride, have played a major role as hydrogen sources and radical chain carriers in radical reactions.[3] It is well known, however, that organotin compounds are toxic, expensive, and difficult to remove from the desired end products. Therefore, the use of organotin hydrides is not suitable for synthesizing drugs and medicines. Several attempts have been made to find ideal alternatives to organotin hydrides.[4] Among them, hypophosphorous acid has proven to be the most promising substitute for organotin hydrides in various radical reactions from the viewpoints of cost-effectiveness, toxicity, and work-up process.[5–7]

Water is a very attractive solvent in organic reactions as it is economic, safe, and shows unique solvent effects. Although various organic reactions in water have been reported in the literature recently,[8] works on radical reactions in water are relatively rare.[6,9]

There have been research efforts in which alcohols were used to reduce the toxicity of the solvent employed in the radical deoxygenation of alcohols with hypophosphorous acid.[7] However, there is no report on water being used as a sole solvent in radical deoxygenation of alcohols. As part of our ongoing effort to expand the synthetic utility of hypophosphorous acid in water,[6a,c] we are reporting the results of deoxygenation of alcohols and vicinal diols that has been accomplished efficiently with *N*-ethylpiperidine hypophosphite (EPHP) in water.

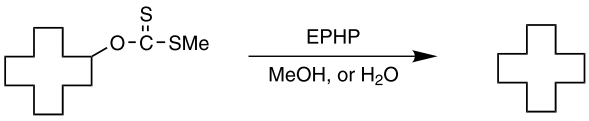
We chose *S*-methyl dithiocarbonate of cyclododecanol for a model compound and investigated optimal reaction conditions for the deoxygenation of alcohols (Table 1). Treatment of *S*-methyl dithiocarbonate of cyclododecanol with EPHP and Et_3B in MeOH at room temperature produced cyclododecane in 89% yield. No new thiocarbonate by-product was detected from competing hydrolysis of thiocarbonates (entry 1).[10] When the reaction was carried out in aqueous methanol (MeOH:H_2O, 1:1) at room temperature, half of the starting material remained even after being stirred for 10 h (entry 2). The observation implies that solubility of the substrates is the main factor in obtaining high yields of the desired products in this reaction. It is presumed that a phase–transfer agent is necessary to improve the solubility of the substrate in water. The reaction of *S*-methyl dithiocarbonate of cyclododecanol with EPHP in water in the presence of a phase-transfer agent, cetyltrimehtylammonium bromide (CTAB), and

Keywords: radical reactions; deoxygenation; alcohol; *N*-ethylpiperidine hypophosphite.

* Corresponding author. Tel.: +82-33-760-2261; fax: +82-33-760-2182; e-mail: dojang@dragon.yonsei.ac.kr

0040-4039/02/$ - see front matter
PII: S0040-4039(02)01247-9

Table 1. Deoxygenation of *O*-cyclododecyl *S*-methyl dithiocarbonate with EPHP (10 equiv.)



Entry	Solvent	Initiator (equiv.)	CTAB (equiv.)	Temp (°C)	Time (h)	Yield (%)
1	MeOH	Et_3B (10)	0	rt	2.4	89
2	MeOH/H_2O, 1:1	Et_3B (10)	0	rt	10	48 (49)[a]
3	H_2O	Et_3B (10)	2	rt	10	42 (37)[a] (19)[b]
4	H_2O	ABCVA (0.75)	2	80	8	73
5	H_2O	AIBN (1.0)	0	80	8	0

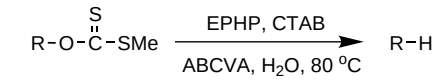
[a] Yields in parentheses are for the recovered starting material.
[b] The corresponding alcohol was obtained.

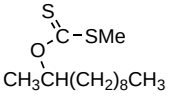
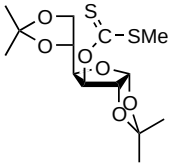
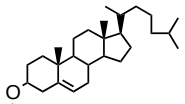
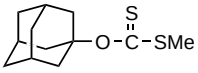
an initiator, Et_3B, provided a moderate yield of the deoxy product along with 19% of the corresponding alcohol (entry 3). It is assumed that Et_3B played a role as a Lewis acid hydrolyzing the substrate. Enhancement of solubility of the substrate was also limited at room temperature giving 37% of the recovered starting material. We finally optimized the reaction conditions for deoxygenation of alcohols in water, using CTAB for a surfactant and 4,4′-azobis(4-cyanovaleric acid) (ABCVA), a water-soluble initiator, at 80°C affording high yield of the deoxy product (entry 4). In the absence of the phase-transfer reagent, the reaction in water at 80°C gave cyclododecanol, the hydrolyzed product, without giving the deoxy product (entry 5).

The reaction was applied to the deoxygenation of a series of substrates (Table 2). A high yield of the deoxy product was obtained from *S*-methyl dithiocarbonate of a secondary alcohol (entry 1). The carbohydrate derivative was also a good substrate for the reaction (entry 2), while the hydrophobic steroid derivative gave a low yield of deoxy product accompanied with the recovered starting material (entry 3), although the reaction in EtOH proceeded efficiently (entry 4). *S*-Methyl dithiocarbonate of tertiary alcohol was readily hydrolyzed under the conditions to generate the corresponding alcohol (entry 5).

We next applied our method to transform vicinal diols into corresponding olefins with EPHP, which has been possible only by adding an excessive amount of terminal olefins to prevent phosphorus radical from being added to the product olefin (Table 3).[5b,11] The conversion of the bis-*S*-methyl dithiocarbonate of cyclododecan-1,2-diol into cyclododecene in water was accomplished efficiently in the absence of extra terminal olefins (entry 1). The reaction was also performed in EtOH at room temperature with efficiency (entry 2). The bis-*S*-methyl dithiocarbonate of D-mannitol and α-D-glucose derivatives were converted smoothly into the corresponding olefins in high yields under reaction conditions (entries 3–5). The reaction was also applicable to dideoxygenation of nucleoside derivatives for preparation of 2′,3′-dihydro-2′,3′-dideoxynucleosides that are potent anti-HIV agents.[12] The bis-*S*-methyl dithiocarbonate of an N^3-methyluridine derivative was subjected to the radical reaction in water at 80°C, which produced the corresponding olefin in 95% yield (entry 6). A similar result was obtained with an adenosine derivative (entries 7–8).

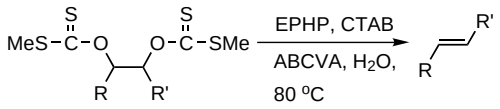
Table 2. Deoxygenation of various alcohols via their *S*-methyl dithiocarbonate derivatives with EPHP (5 equiv.) in the presence of CTAB (2 equiv.) in H_2O at 80°C

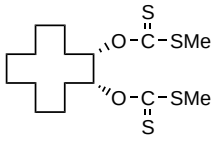
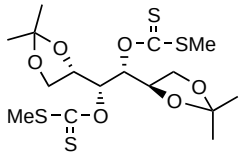
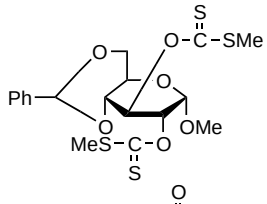
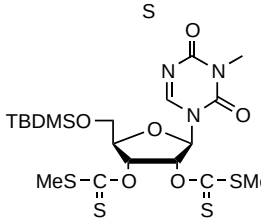
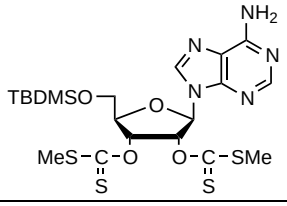


Entry	Substrate	ABCVA (equiv)	Time (h)	Yield (%)
1		0.75	9	88
2		0.75	9	81
3		1.0	12	28(70)[a]
4		-[b]	1	91
5		0.5	5	14(75)[c]

[a]Yields in parentheses are for the recovered starting material. [b]Reaction was carried out in EtOH with Et_3B (5 equiv) at room temperature. [c]The corresponding alcohol, hydrolyzed product.

Table 3. Synthesis of olefins from bis-*S*-methyl dithiocarbonates of vicinal diols with EPHP (10 equiv.) in H_2O in the presence of CTAB (2 equiv.) at 80°C[12]



Entry	Substrate	ABCVA (equiv)	Time (h)	Yield (%)
1		0.75	8	92
2		-[a]	1.5	71
3		0.75	9	85
4		-[a]	3	79
5		0.75	8	83
6		0.75	9	95
7		1.25	15	58
8		-[a]	2	76

[a]Reaction was carried out in EtOH with Et_3B (5 equiv) at room temperature.

In conclusion, we have developed a useful radical process for deoxygenation and dideoxygenation of various alcohols in water or in non-toxic alcohol. It is worth noting that dideoxygenation of bis-*S*-methyl dithiocarbonate of vicinal diols with EPHP can be accomplished without adding terminal olefins. The reagents and solvents used in this reaction are non-toxic and inexpensive. The reaction can also be carried out under mild reaction conditions, and it offers an easy work-up process. Therefore, the process can be used economically for deoxygenation of various alcohols on a large scale.

Acknowledgements

This work was supported by grant (R05-2002-000-00036-0) from the basic research program of the Korea Science and Engineering Foundation.

References

1. (a) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609; (b) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992.
2. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
3. (a) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, p. 715; (b) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React*. **1996**, *48*, 301.
4. For recent reviews: (a) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 3072; (b) Studer, A.; Amrein, S. *Synthesis* **2002**, 835.
5. (a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett*. **1992**, *33*, 5709; (b) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *J. Org. Chem*. **1993**, *58*, 6838; (c) McCague, R.; Pritchard, R. G.; Stoodley, R. J.; Williamson, D. S. *J. Chem. Soc., Chem. Commun*. **1998**, 2691; (d) Tokuyama, H.; Yamashita, T.; Reding, M. T.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc*. **1999**, *121*, 3791; (e) Graham, S. R.; Murphy, J. A.; Coates, D. *Tetrahedron Lett*. **1999**, *40*, 2415; (f) Graham, S. R.; Murphy, J. A.; Kennedy, A. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3071; (g) Jang, D. O.; Song, S. H. *Tetrahedron Lett*. **2000**, *41*, 247; (h) Concepcion, G. M.; Murphy, J. A.; Christopher, R. S. *Tetrahedron Lett*. **2000**, *41*, 1833; (i) Takamatsu, S.; Katayama, S.; Hirose, N.; Naito, M.; Izawa, K. *Tetrahedron Lett*. **2001**, *42*, 7605; (j) Jang, D. O.; Cho, D. Y.; Chung, C.-M. *Synlett* **2001**, 1923.
6. (a) Jang, D. O. *Tetrahedron Lett*. **1996**, *37*, 5367; (b) Kita, Y.; Nambu, H.; Ramesh, N. G.; Anikumar, G.; Matsugi, M. *Org. Lett*. **2001**, *3*, 1157; (c) Jang, D. O.; Cho, D. Y. *Synlett* **2002**, 631.
7. (a) Graham, A. E.; Thomas, A. V.; Yang, R. *J. Org. Chem*. **2000**, *65*, 2583; (b) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Chem. Lett*. **2000**, 105; (c) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn*. **2001**, *74*, 225.
8. (a) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley and Sons: New York, 1997; (b) Grieco, P. A. *Organic Synthesis in Water*; Blackie Academic and Professional: London, 1998; (c) Lubineau, A.; Auge, J. In *Modern Solvents in Organic Synthesis*; Knochel, P., Ed.; Springer-Verlag: Berlin, 1999.
9. (a) Minisci, F. *Synthesis* **1973**, 1; (b) Breslow, R.; Light, J. *Tetrahedron Lett*. **1990**, *31*, 2957; (c) Yamazaki, O.; Togo, H.; Nogami, G.; Yokoyama, M. *Bull. Chem. Soc. Jpn*. **1997**, *70*, 2519; (d) Maitra, U.; Sarma, K. D. *Tetrahedron Lett*. **1994**, *35*, 7861; (e) Nambu, H.; Hata, K.; Matsugi, M.; Kita, Y. *J. Chem. Soc., Chem. Commun*. **2002**, 1082. For a recent review (f) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **2002**, 674.

10. The reaction in refluxing ^{n}PrOH gave a solvolysis product of starting thionocarbonate (Ref. 7a).
11. (a) Typical reaction procedure for dideoxygenation of vicinal diols in water: A solution of 1,2:5,6-di-*O*-isopropylidene-3,4-bis-*O*-[(*S*-methylthio)thiocarbonyl]-D-mannitol (98 mg, 0.22 mmol), EPHP (397 mg, 2.22 mmol) and CTAB (162 mg, 0.44 mmol) in degassed water (5 mL) under argon was treated with ABCVA (20 mg, 0.06 mmol) three times (3 h interval) at 80°C. After the reaction was completed, the reaction mixture was diluted EtOAc, then washed with water, dried over anhydrous $MgSO_4$, and evaporated the solvent in vacuo. The residue was purified by flash column chromatography over silica gel (hexane/EtOAc, 9:1) to furnish 1,2:5,6-di-*O*-isopropylidene-hex-3-(*E*)-ene-D-*threo*-1,2:5,6-tetraol (44 mg, 85%). (b) Typical reaction procedure for dideoxygenation of vicinal diols in alcohol at room temperature: To a solution of 1,2:5,6-di-*O*-isopropylidene-3,4-bis-*O*-[(*S*-methylthio)thiocarbonyl]-D-mannitol (110 mg, 0.25 mmol), EPHP (446 mg, 2.49 mmol) and Et_3B (1.25 mL, 1.25 mmol, 1 M solution in THF) in degassed EtOH (5 mL) was added air (10 mL/h) at room temperature with syringe pump until the reaction was completed by TLC. The reaction mixture was diluted EtOAc, then washed with water, dried over anhydrous $MgSO_4$, and evaporated the solvent in vacuo. The residue was purified by flash column chromatography over silica gel (hexane/EtOAc, 9:1) to give 1,2:5,6-di-*O*-isopropylidene-hex-3-(*E*)-ene-D-*threo*-1,2:5,6-tetraol (45 mg, 79%).
12. (a) Chu, C. K.; Bhadti, V. S.; Doboszewski, B.; Gu, Z. P.; Kosugi, Y.; Pullaiah, K. C.; Van Roey, P. *J. Org. Chem.* **1989**, *54*, 2217; (b) Palmer, S.; Russell, J. D.; Pallansch, L. A.; Driscoll, J. S.; Buckheit, R. W., Jr. *Antiviral Res.* **1999**, *41*, LB4.