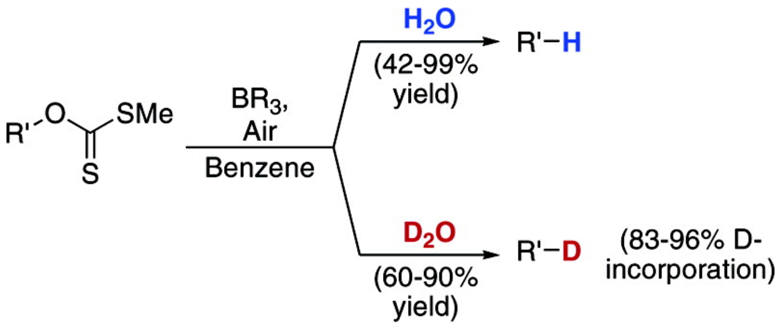
Communication

Deoxygenation of Alcohols Employing Water as the Hydrogen Atom Source

David A. Spiegel, Kenneth B. Wiberg, Laura N. Schacherer, Matthew R. Medeiros, and John L. Wood

J. Am. Chem. Soc., **2005**, 127 (36), 12513-12515• DOI: 10.1021/ja052185l • Publication Date (Web): 18 August 2005



Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

J|A|C|S
COMMUNICATIONS

Deoxygenation of Alcohols Employing Water as the Hydrogen Atom Source

David A. Spiegel, Kenneth B. Wiberg, Laura N. Schacherer, Matthew R. Medeiros, and
John L. Wood*

Sterling Chemistry Laboratory, Department of Chemistry, Yale University, New Haven, Connecticut 06520-8107

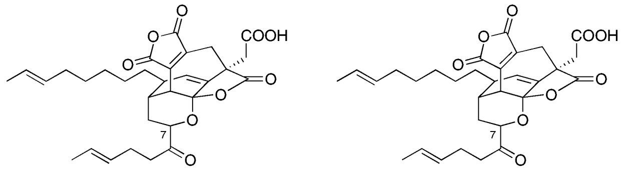
Received April 5, 2005; E-mail: john.wood@yale.edu

Since its initial disclosure in 1975,[1] the Barton−McCombie reaction has proven to be widely useful in the deoxygenation of alcohols.[2] This process has been shown to involve the radical decomposition of an *O*-alkyl thiocarbonate (xanthate) ester to the corresponding alkyl radical, followed by hydrogen atom transfer from an organotin hydride to provide an alkane product.[3−8] A substantial drawback associated with this method is that organotin hydrides are costly, often difficult to separate from desired reaction products, and highly toxic.[9−11] Therefore, a variety of methods have been reported for replacing stoichiometric tin in deoxygenation processes.[12] In the course of an ongoing effort directed toward a synthesis of the phomoidrides (**1**−**4**, Figure 1), we discovered that water could replace toxic metal hydrides as the source of hydrogen in trialkylborane-mediated variants of the Barton−McCombie process. Herein, we describe the events surrounding this discovery and provide insight into the factors underlying this remarkable and previously overlooked mode of reactivity for water.

During the course of our synthetic studies, we prepared complex isotwistane **5** (Scheme 1) in anticipation of accessing olefin **7** through the intermediacy of radical **6**. Initial attempts to effect fragmentation employing traditional Barton−McCombie conditions resulted predominantly in the formation of **8**,[13] presumably owing to the rapid rate of H-transfer from the metal hydride species.[1] In an effort to avoid rapid reduction, we sought alternative conditions for the generation of **6** and became intrigued by an isolated example from Barton and co-workers wherein the treatment of a secondary xanthate ester with triethylborane/air appeared to furnish products arising from the slow reduction of an intermediate alkyl radical.[3,14] Although this study did not address the origin of the H-atom in reduction products, we reasoned that BEt_3 might have been involved either through a disproportionation pathway involving ethyl radicals[15] or via the homolysis of the α-boryl C−H bond.[16] Since our goal was to impede radical reduction altogether and produce olefin **7**, we reasoned that using BMe_3 in place of BEt_3 might accomplish the desired result. Thus, we explored the ability of BMe_3 to promote the fragmentation of **5**.

Astonishingly, under these conditions, **5** undergoes conversion to **8** in quantitative yield and high purity following simple solvent evaporation. Intrigued by this discovery, we decided to explore its generality by applying these tin-free, workup-free conditions to a series of simple xanthate test substrates. In these initial studies, the corresponding deoxygenated products were formed in irreproducible yields that were uniformly lower than those reported for the metal-hydride-mediated protocols (data not shown).[17] Clearly, optimization of the process was required; it therefore became critical to establish the hydrogen atom source.

To this end, the deuterium-labeling studies listed in Table 1 were initiated. Initially, each hydrogen-containing reagent was substituted with its deuterated counterpart (entries 1−3). However, ^1H NMR analysis of **8** revealed no detectable levels of D-incorporation.[19] Unexpectedly, when all H-containing reagents were simultaneously replaced with their deuterated variants (entry 4), only a minimally deuterated sample of **8** was isolated.



Phomoidride A (**1**): C-7 = *S* (CP-225,917)
Phomoidride C (**3**): C-7 = *R*

Phomoidride B (**2**): C-7 = *S* (CP-263,114)
Phomoidride D (**4**): C-7 = *R*

Figure 1. The phomoidrides.

Scheme 1

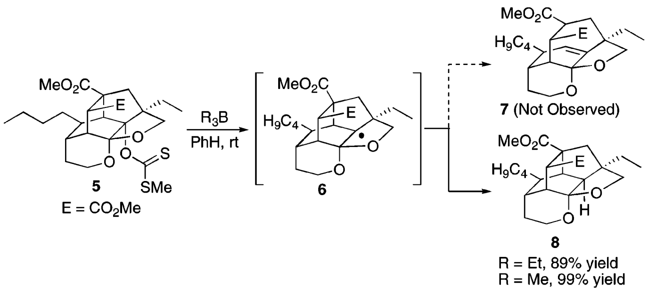
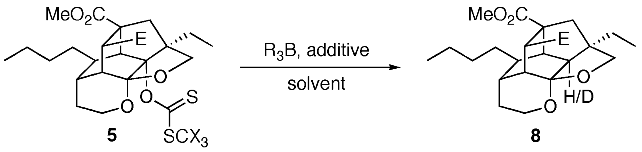


Table 1. Deuterium-Labeling Studies[18]



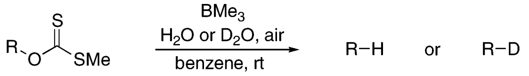
Entry[a]	X	R	additive	solvent	D-incorp (%)[b]
1	D	CH_3	None	PhH	<5
2	H	CD_3	None	PhH	<5
3	H	CH_3	None	PhH-d_6	<5
4	D	CD_3	None	PhH-d_6	4
5	D	CD_3	D_2O	PhH-d_6	85
6	D	CD_3	H_2O	PhH-d_6	3
7	H	CH_3	D_2O	PhH	94

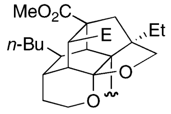
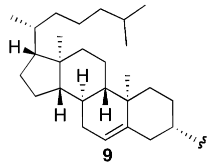
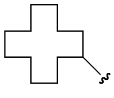
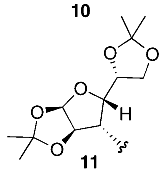
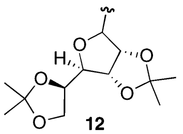
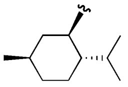
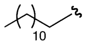
[a] For all entries, xanthate **1** (3 mg, 0.006 mmol, 1.0 equiv) was dissolved in benzene (0.2 mL) with or without additive (20 equiv), and trialkylborane (20−50 equiv) was bubbled through reaction mixtures until TLC analysis indicated completion. [b] Values in entries 1−3 were obtained from integration of ^1H NMR spectra, and those in entries 4−7 were calculated from isotopic ratios in electrospray ionization mass spectra.

Since the above reductions were conducted on relatively small scales, we reasoned that adventitious water could have been present as a contaminant. However, since the BDE of an O−H bond in water is greater even than that of a C−H bond in the reaction solvent benzene (117.6 versus 113.5 kcal/mol),[20] we considered water an unlikely H-atom source. Nevertheless, we addressed the issue by exploring the deoxygenation of **3** using BMe_3-d_9 in the presence

10.1021/ja052185l CCC: $30.25 © 2005 American Chemical Society

Table 2. Trialkylborane/H_2O/D_2O-Mediated Xanthate Reductions



Entry[a]	R	H/D Source	Yield R-H or R-D (%)	D-incorp (%)
1[b]	 **5**, E = CO_2Me	H_2O	99	
2[b]		D_2O	90	94
3	 **9**	H_2O	71	
4		D_2O	67	95
5	 **10**	H_2O	99	
6		D_2O	67	86
7	 **11**	H_2O	63	
8		D_2O	60	83
9	 **12**	H_2O	91	
10		D_2O	68	93
11	 **13**	H_2O	77[c]	
12		D_2O	72[c]	96
13	 **14**	H_2O	42[c]	
14		D_2O	51[c]	94

[a] Unless otherwise indicated, substrates (90−106 mg, 0.19−0.39 mmol, 1.0 equiv) were dissolved in benzene (0.03 M) in the presence of either H_2O (5.0 equiv) or D_2O (20 equiv) as indicated. Air (0.8 equiv of O_2) was then added at a rate of 1.3 mL/h. [b] See Supporting Information, Scheme 1, and/or Table 1 for experimental details. [c] Yield determined by gas chromatographic (GC) analysis.

of D_2O (entry 5) and were surprised to observe very high deuterium incorporation in the product (**6**). Taken together with control experiments conducted in parallel (entries 6 and 7), these data clearly indicated that H_2O or D_2O was serving as the source of hydrogen or deuterium.

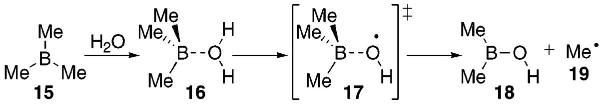
This observation enabled the development of optimized reaction conditions, which were surveyed on the substrates listed in Table 2. As shown, introduction of trimethylborane gas into a solution of water or deuterium oxide in benzene, followed by the addition of air, converted the methyl xanthate esters of tertiary (entries 1 and 2), secondary (entries 3−12), and primary (entries 13 and 14) alcohols into the corresponding protio- and deuterioalkanes in good to excellent yields. These compared favorably with metal-hydride-based protocols, and in some cases, proved better than existing methods (e.g., entries 1 and 9).[13,21] Conveniently, the formation of C−H versus C−D bonds depended solely upon whether H_2O or D_2O was added to reaction mixtures. Furthermore, as with the examples depicted in Table 1, reactions employing BMe_3 did not require aqueous workup; products were obtained in high purity following simple low-pressure removal of volatile byproducts.[19]

Table 3. Generality of Reduction Reactions[a]

Entry	Substrate	Trialkyl-borane	H/D Source	Yield R-H or R-D (%)	D-incorp (%)
1[b]	**5**	BEt_3	H_2O	89	
2	**9**	BBu_3	D_2O	19[c]	88
3	**10**	BEt_3	D_2O	63[c]	88
4	**10**	BBu_3	D_2O	83[c]	92
5	**12**	BBu_3	D_2O	66	97
6	**13**	BBu_3	D_2O	52[d]	95
7	**14**	BEt_3	D_2O	3[d]	N/D

[a] Reactions conducted as in Table 2, except for reaction scale (30−145 mg, 0.06−0.53 mmol in substrate), and the indicated trialkylborane was added in place of BMe_3. [b] See Supporting Information for experimental details. [c] With 5.0 equiv of D_2O added. [d] Yields determined by GC analysis.

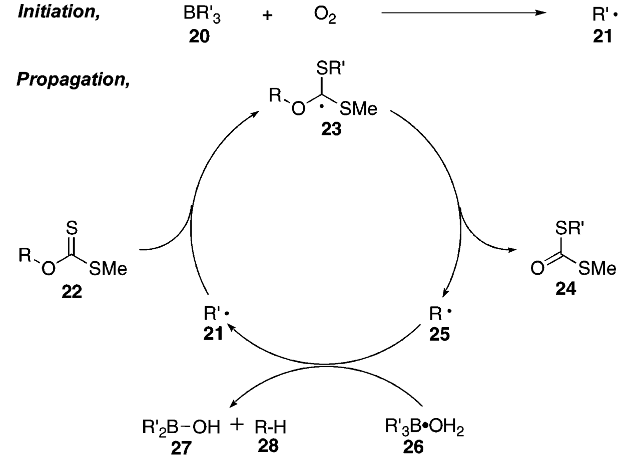
Scheme 2. Results of Ab Initio Calculations[22]



When BMe_3 was replaced by BEt_3 or BBu_3 (Table 3), deoxygenation products were also obtained in good yields with high levels of deuterium incorporation. In general, however, these reductions were not found to be as efficient as those with BMe_3. These results indicated that the observed patterns of reactivity were general, at least for simple primary trialkylboranes. To rationalize the unexpected behavior of water in these reactions,[23] we considered the known Lewis acidity of trialkylboranes[24] and postulated that complexation of water to the trialkylborane might furnish a species activated for O−H bond homolysis. We therefore turned to the Gaussian 3 (G3) model chemistry developed by Pople et al.[22] to determine the enthalpies of formation for several relevant intermediates. Calculation of reaction enthalpies using these data indicated a dramatic decrease in the O−H BDE for the $Me_3B{\bullet}OH_2$ complex (endothermic by 86 kcal/mol compared to 116 kcal/mol for uncomplexed water derived through the same method).[19] Importantly, these results indicated that the derived C_s symmetric radical (**17**) was a transition structure that upon geometry optimization underwent dissociation into methyl radical (**19**) and Me_2BOH (**18**). The latter process was determined to be exothermic by 13 kcal/mol. Overall, the computations indicated that homolysis of the O−H bond in **16** to provide **18** and **19** was endothermic by 73 kcal/mol—a value 43 kcal/mol lower than the BDE predicted for the O−H bond in uncomplexed water—and slightly lower than the Sn−H bond in tributyltin hydride.[25] Interestingly, analogous calculations performed on the $Me_3Al{\bullet}OH_2$ complex (not shown)[19] yielded an O−H BDE of 116 kcal/mol, implying that the observed trend may be unique to trialkylborane−water systems.

On the basis of these calculations, along with experimental observations,[26] the mechanism in Scheme 3 is proposed. Here, the process begins with air oxidation of the trialkylborane (**20**) to liberate an alkyl radical (**21**). This reacts with the xanthate (**22**) to provide intermediate **23**, which rapidly decomposes to *S*-alkyl-*S*-methyl dithiocarbonate (**24**) and substrate-derived alkyl radical **25**.[2−8] This species is then reduced by $R_3B{\bullet}OH_2$ (**26**) to provide the observed product (**28**), dialkyl borinic acid **27**, and an equivalent of alkyl radical **21** capable of propagating the radical chain. While this mechanism is consistent with the results of experiments and calculations, alternative pathways, including the intermediacy of the hydroperoxy radical (HOO•)[27] and/or thiol-mediated proton transfer, could not be ruled out. However, with regard to the latter, the observation of deuterated butane production upon exposure of tributylborane/water/benzene mixtures to air suggests that thiol-

Scheme 3. Proposed Mechanism for Xanthate Reductions



mediated hydrogen transfer is not a necessary step in the reaction mechanism.[17]

In summary, this report provides evidence that water−trialkylborane solvent mixtures, in the absence of metal hydrides, are capable of mediating the deoxygenation of xanthate esters, perhaps through the intermediacy of trialkylborane−water complexes. These results not only represent a potentially useful alternative to available methods for replacing alcohols with hydrogen, deuterium, or potentially tritium but also suggest more broadly the existence of a novel mode of reactivity for water. In this regard, the analogy of trialkylborane−water complexes to metal−water complexes seen in biological systems (e.g., photosystem II)[28−31] is particularly intriguing. Further investigations into the mechanistic details of this deoxygenation and other uses of triakylborane aqua complexes are currently in progress.

Acknowledgment. The authors wish to thank Professors Glenn C. Micalizio, Jerome A. Berson, David A. Evans, and John Hartwig for helpful discussions, as well as Dr. Joshua Lawrence for helpful discussions and use of reagents. We also acknowledge Dr. TuKiet Lam (W. M. Keck Foundation, Biotechnology Resource Laboratory, New Haven, CT) for assistance in obtaining FTICR mass spectra. D.A.S. thanks the Yale Medical Scientist Training Program and the NIH Cancer Education Program for funding. J.L.W. acknowledges the NIH (Grant No. 1 RO1 CA/GM 93591-01A), Bristol-Myers-Squibb, Eli Lilly, GlaxoSmithKline, Yamanouchi, and AstraZeneca for financial support through their Faculty Awards Programs, and the Henry Dreyfus Foundation for a Teacher−Scholar Award.

Supporting Information Available: Experimental details and compound characterization (13 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Barton, D. H. R.; McCombie, S. W., *J. Chem. Soc., Perkin Trans. 1* **1975**, *16*, 1574−1585.
(2) For reviews, see: (a) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413−1432. (b) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609−2645.
(3) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1990**, *31*, 3991−3994.
(4) Barton, D. H. R.; Crich, D.; Lobberding, A.; Zard, S. Z. *Tetrahedron* **1986**, *42*, 2329−2338.
(5) Barton, D. H. R.; Crich, D.; Lobberding, A.; Zard, S. Z. *Chem. Commun.* **1985**, *10*, 646−647.
(6) Bachi, M. D.; Bosch, E.; Denenmark, D.; Girsh, D. *J. Org. Chem.* **1992**, *57*, 6803−6810.
(7) Crich, D. *Tetrahedron Lett.* **1988**, *29*, 5805−5806.
(8) Bachi, M. D.; Bosch, E. *J. Chem. Soc., Perkin Trans. 1* **1988**, *6*, 1517−1519.
(9) Appel, K. E. *Drug. Metab. Rev.* **2004**, *36*, 763−786.
(10) Boyer, I. J. *Toxicology* **1989**, *55*, 253−298.
(11) Dopp, E.; Hartmann, L. M.; Florea, A. M.; Rettenmeier, A. W.; Hirner, A. V. *Crit. Rev. Toxicol.* **2004**, *34*, 301−333.
(12) For reviews, see: (a) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3073−3082. (b) Studer, A.; Amrein, S. *Synthesis* **2002**, *7*, 835−849. (c) Gilbert, B. C.; Parsons, A. F. *J. Chem. Soc., Perkin Trans. 2* **2002**, *2*, 367−387. For lead references on stoichiometric tin hydride substitutes, see: for silanes (a) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188. For phosphites: (b) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *J. Org. Chem.* **1993**, *58*, 6838−6842. For functionalized cyclohexadienes: (c) Studer, A.; Amrein, S.; Schleth, F.; Schulte, T.; Walton, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 5726−5733 and references contained therein. For phosphine−boranes: (d) Barton, D. H. R.; Jacob, M. *Tetrahedron Lett.* **1998**, *39*, 1331−1334. For cyclohexane: (e) Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **1996**, *118*, 9190−9191. For catalytic tin: (f) Lopez, R. M.; Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 6949−6950.
(13) Reduction of **5**, as described in ref 1, provided **8** in 78% yield.
(14) The reduction product was isolated in 62% yield versus 90% in reactions containing tributyltin hydride (ref 3). Further evidence for slow reduction under tin-free conditions was the isolation of products from radical recombination (9%) and disproportionation (12%).
(15) Kochi, J. K. *Free Radicals*; Wiley: New York, 1973.
(16) Walton, J. C.; McCarrroll, A. J.; Chen, Q.; Carboni, B.; Nziengui, R. *J. Am. Chem. Soc.* **2000**, *122*, 5455.
(17) The full details of these studies will be disclosed at a later date.
(18) Since compound **8** obtained upon BMe_3 treatment followed by solvent evaporation was pure by ^1H and ^{13}C NMR analysis, and neither workup or flask transfer was necessary for product purification, the possibility that a C−H bond in **5** or **8** was providing the H-atom in these reactions was discounted.
(19) For full details of these studies, please refer to the Supporting Information.
(20) For the BDE of water (H−OH), see: (a) Ruscic, B.; Wagner, A. F.; Harding, L. B.; Asher, R. L.; Feller, D.; Dixon, D. A.; Peterson, K. A.; Song, Y.; Qian, X.; Ng, C.-Y.; Liu, J.; Chen, W.; Schwenke, D. W. *J. Phys. Chem. A* **2002**, *106*, 2727. For the BDE of benzene ($H−C_6H_5$), see: (b) Davico, G. E.; Bierbaum, V. M.; DePuy, C. H.; Ellison, G. B.; Squires, R. R. *J. Am. Chem. Soc.* **1995**, *117*, 2590.
(21) To the best of our knowledge, the highest yield that has been reported for the deoxygenation of **12** is 86% (Togo, H.; Matsubayashi, S.; Yamazaki, O.; Yokoyama, M., *J. Org. Chem.* **2000**, *65*, 2816−2819).
(22) Curtiss, L. A.; Raghavachari, K.; Reforn, P. C.; Rassolov, V.; Pople, J. A. *J. Chem. Phys.* **1998**, *109*, 7764.
(23) Indeed, many reactions reported to involve free-radical intermediates have been conducted in water−BEt_3−air mixtures. Substantial kinetic and/or mechanistic differences between these methods and the reductions reported herein are likely operating. For more detail on aqueous radical reactions, see: Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **2002**, *5*, 674−686.
(24) Larson, J. W.; McMahon, T. B. *J. Am. Chem. Soc.* **1985**, *107*, 766.
(25) The BDE for $Bu_3Sn−H$ bond has been reported at 78 kcal/mol (Laarhoven, L. J. J.; Mulder, P.; Wayner, D. D. M. *Acc. Chem. Res.* **1999**, *32*, 342−349).
(26) Many of the examples in Table 2 required only substoichiometric oxygen, implying that a chain mechanism is operating. However, the uncontrolled entry of additional oxygen through rubber septa cannot be excluded at this time. Furthermore, the slow introduction of air was critical to achieving high yields in these reactions, as observed in other trialkylborane-mediated free-radical processes. See, for example: (a) Brown, H. C.; Kabalka, G. W. *J. Am. Chem. Soc.* **1970**, *92*, 714−716. (b) Yoshimitsu, T.; Arano, Y.; Nagaoka, H. *J. Org. Chem.* **2003**, *68*, 625−627. (c) Yoshimitsu, T.; Tsunoda, M.; Nagaoka, H. *Chem. Commun.* **1999**, *17*, 1745−1746. The further observation that the reaction of xanthate **11** was completely inhibited by galvinoxyl suggests that the initial generation of alkyl radicals from trialkylboranes (Onak, T. *Organoborane Chemistry*; Academic Press: New York, 1975; p 360) is critical to the mechanism. The isolation of **24** ($R' = Bu$) in 97% yield also supports the proposed mechanism.
(27) If formed upon interaction of water with the dialkylborane peroxy radical ($R_2BOO•$), this species, based upon its BDE (47.6 kcal/mol), would be capable of delivering hydrogen atom. See: Flowers, B. A.; Szalay, P. G.; Stanton, J. F.; Kállay; Gausss, J.; Császár, A. G. *J. Phys. Chem. A* **2004**, *108*, 3195.
(28) For a review, see: Tomos, C.; Babcock, G. T. *Acc. Chem. Res.* **1998**, *31*, 18−25.
(29) Hoganson, C. W.; Babcock, G. T. *Science* **1997**, *277*, 1953−1956.
(30) McEvoy, J. P.; Brudvig, G. W. *Phys. Chem. Chem. Phys.* **2004**, *6*, 4754−4763.
(31) For a review, see: Cukier, R. I. *Biochem. Biophys. Acta* **2004**, *1655*, 37−44.

JA052185L