Bu_3SnH-Catalyzed Barton−McCombie Deoxygenation of Alcohols

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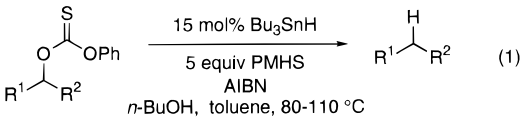
The Barton−McCombie procedure for the deoxygenation of alcohols (Figure 1)[1,2] is an extremely useful method that has found widespread application in synthetic organic chemistry.[3] This radical-mediated process typically employs 1.5−3 equiv of Bu_3SnH as the reducing agent. In this paper, we describe the first catalyzed variant of the Barton−McCombie deoxygenation reaction, using Bu_3SnH as the catalyst and polymethylhydrosiloxane (PMHS; TMSO-$(SiHMeO)_n$-TMS) as the stoichiometric reductant (eq 1).



Bu_3SnH is an extraordinarily versatile reagent for organic synthesis.[4] Unfortunately, some tributyltin-containing compounds are toxic,[5] a fact that has stimulated the development of alternatives to Bu_3SnH.[6] Silicon hydrides have been the primary focus of attention, and in a number of instances they have been shown to serve as suitable substitutes for Bu_3SnH.[7] However, disparate reactivity has also been observed,[8] as would be expected for fundamentally distinct families of compounds.

Rather than forsaking Bu_3SnH due to concerns about toxicity, we are developing processes in which it is employed as a *catalyst* in conjunction with an innocuous stoichiometric reductant.[9,10] This strategy allows us to exploit the well-developed, sometimes unique, chemistry of Bu_3SnH while greatly diminishing the quantity of organotin residue that is generated. The application of this approach to a Bu_3SnH-catalyzed variant of the Barton−McCombie deoxygenation reaction is outlined in Figure 2. The reduction of a thionocarbonate by Bu_3SnH affords COS, the desired alkane, and $Bu_3Sn(OPh)$ (Figure 2, left-hand side; cf. Figure 1);[11] $Bu_3Sn(OPh)$ then reacts with the stoichiometric reductant, M−H, to regenerate the Bu_3SnH catalyst (Figure 2, right-hand side).

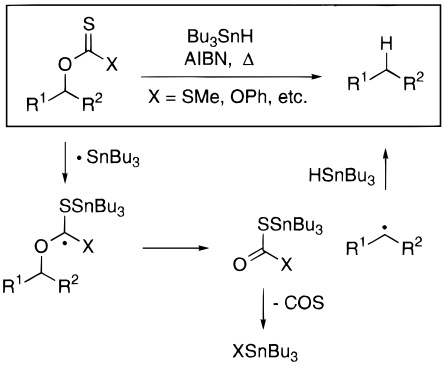


Figure 1. The Barton−McCombie deoxygenation reaction.

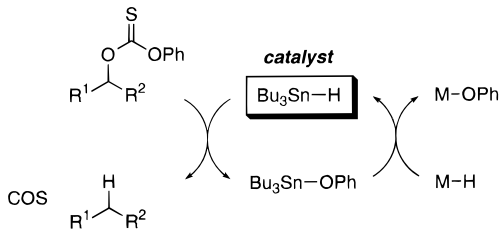


Figure 2. Proposed catalytic cycle for the Bu_3SnH-catalyzed Barton−McCombie deoxygenation reaction.

We chose to focus on the use of PMHS (TMSO-$(SiHMeO)_n$-TMS) as the stoichiometric reductant for our tin-catalyzed Barton−McCombie process, based on the report of Itoi that PMHS can reduce $Bu_3Sn(OPh)$ to Bu_3SnH.[12] Furthermore, PMHS possesses the attributes of being nontoxic,[13] easily handled,[14] and inexpensive.[15]

We have successfully developed a Bu_3SnH-catalyzed, PMHS-mediated Barton−McCombie reaction based on the strategy illustrated in Figure 2. Thus, treatment of a thionocarbonate with 7.5 mol % of $(Bu_3Sn)_2O$, 5 equiv of PMHS,[16] 5.5 equiv of *n*-BuOH, and 2,2′-azobisisobutyronitrile (AIBN) in toluene (80−110 °C) provides the desired reduction product in good yield (eq 1; Table 1, catalyzed),[17,18] comparable to that observed for reactions that employ Bu_3SnH as the stoichiometric reductant (2.0 equiv; Table 1, stoichiometric).[19] Thionocarbonates derived from simple alcohols (entries 1 and 2), as well as from carbohydrates (entries 3 and 4), are smoothly deoxygenated.

(1) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585.

(2) The use of phenyl thionocarbonate esters was pioneered by Robins: (a) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932−933. (b) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059−4065.

(3) (a) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609−2645. (b) McCombie, S. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 8, Chapter 4.2. (c) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413−1432. (d) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: Boston, 1987; Chapter 5.

(4) For reviews of the chemistry of Bu_3SnH, see: (a) Neumann, W. P. *Synthesis* **1987**, 665−683. (b) RajanBabu, T. V. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995.

(5) Boyer, I. J. *Toxicology* **1989**, *55*, 253−298.

(6) For a succinct discussion, see: Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 7200−7201.

(7) For an overview of the use of silanes as reducing agents in the Barton−McCombie deoxygenation, see: Chatgilialoglu, C.; Ferreri, C. *Res. Chem. Intermed.* **1993**, *19*, 755−775. See also: Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *J. Org. Chem.* **1993**, *58*, 6838−6842.

(8) For example, see: (a) Reference 7. (b) Apeloig, Y.; Nakash, M. *J. Am. Chem. Soc.* **1994**, *116*, 10781−10782. (c) Ballestri, M.; Chatgilialoglu, C.; Lucarini, M.; Pedulli, G. F. *J. Org. Chem.* **1992**, *57*, 948−952.

(9) (a) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4−5. (b) Hays, D. S.; Scholl, M.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 6751−6752.

(10) For the work of others, see: (a) Nitzsche, S.; Wick, M. *Angew. Chem.* **1957**, *69*, 96. Lipowitz, J.; Bowman, S. A. *Aldrichim. Acta* **1973**, *6*, 1−6. (b) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554−2555. Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303−304.

(11) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1990**, *31*, 3991−3994.

(12) (a) Itoi, K. Fr. Pat. 1,368,522, 1964. (b) Itoi, K.; Kumano, S. *Kogyo Kagaku Zasshi* **1967**, *70*, 82−86.

(13) Klyaschitskaya, A. L.; Krasovskii, G. N.; Fridlyand, S. A. *Gig. Sanit.* **1970**, *35*, 28−31; *Chem. Abst.* **1970**, *72*, 124864r. LD_{50} of PMHS: 80 g/kg.

(14) In contrast to Bu_3SnH, PMHS is neither air- nor moisture-sensitive.

(15) Prices from Aldrich Chemical Company (Milwaukee, WI), per mole of hydride: PMHS \$6; Bu_3SnH \$250; $(Me_3Si)_3SiH$ \$1300.

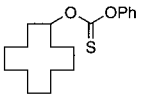
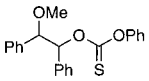
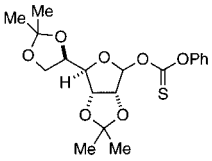
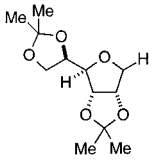
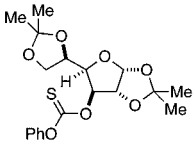
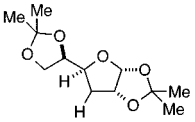
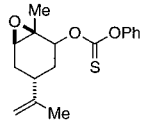
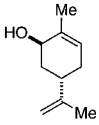
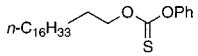
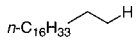
(16) Based on a hydride equivalent weight of 60 g/mol.

(17) Sample experimental (Table 1, entry 2): PMHS (300 mg, 5.00 mmol), *n*-butanol (500 μL, 5.46 mmol), AIBN (25 mg, 0.15 mmol), and $(Bu_3Sn)_2O$ (19 μL, 0.037 mmol) were added to a solution of thionocarbonate (364 mg, 1.00 mmol) in toluene (1.0 mL). The resulting solution was stirred at 80 °C for 8 h, and then more $(Bu_3Sn)_2O$ (19 μL, 0.037 mmol) and AIBN (25 mg, 0.15 mmol) were added. After an additional 16 h of stirring at 80 °C, the reaction mixture was cooled to room temperature and diluted with THF (10 mL). Aqueous 2 N NaOH (10 mL) was added slowly to the rapidly stirring solution. After 8 h, the reaction mixture was extracted with Et_2O (2 × 15 mL), and the combined organic layers were washed (1 N HCl, 2 × 10 mL; brine, 1 × 15 mL), dried, and concentrated. The product was purified by flash chromatography (1% EtOAc/hexanes), affording 165 mg (71%) of a colorless oil.

(18) Notes: (a) These reactions were not individually optimized. (b) In no instance did we experience any difficulty with tin contamination of our products, a problem often encountered in reactions that employ stoichiometric quantities of Bu_3SnH (ref 6 and 19b).

S0002-7863(97)01400-5 CCC: \$14.00

Table 1. Bu_3SnH−Catalyzed Barton-McCombie Deoxygenation of Alcohols (eq 1)

Entry	Substrate	Product	Isolated Yield (%) Catalyzed[a]	Stoichiometric
1			66	68
2			70	65
3			63	72
4			75	79
5			68	61
6			66[b]	68

[a] Average of two runs. [b] Twelve mol % $(Bu_3Sn)_2O$ was used.

Reduction of a 2,3-epoxy alcohol derivative affords an allylic alcohol (entry 5), as expected for a radical-mediated process.[20] We have also effected the Bu_3SnH-catalyzed deoxygenation of a phenylthionocarbonate derived from a primary alcohol, 1-octadecanol (entry 6).[21] In the absence of $(Bu_3Sn)_2O$ under otherwise identical conditions, no reaction (<2% conversion) is observed for any of the substrates illustrated in Table 1.

The use of $(Bu_3Sn)_2O$, rather than Bu_3SnH, and the inclusion of *n*-BuOH in our tin-catalyzed Barton−McCombie reduction (eq 1) warrant explanation. In initial studies, we established that Bu_3SnH itself does indeed serve as an effective deoxygenation catalyst. On the basis of reports that treatment of $(Bu_3Sn)_2O$ with PMHS at 80 °C (neat) affords 1 equiv of Bu_3SnH,[22] we explored the viability of $(Bu_3Sn)_2O$ as a precatalyst in our Barton−McCombie reduction, and we determined that Bu_3SnH and $(Bu_3Sn)_2O$ can in fact be employed interchangeably. Compared with Bu_3SnH, $(Bu_3Sn)_2O$ has advantages from the standpoints of cost[23] and stability.[24] Furthermore, we established that the presence of *n*-BuOH leads to more efficient utilization of $(Bu_3Sn)_2O$: whereas, treatment of $(Bu_3Sn)_2O$ with PMHS at 80 °C in the absence of *n*-BuOH provides 1 equiv of Bu_3SnH, 2 equiv of Bu_3SnH is produced in the presence of *n*-BuOH (eq 2).[25]

$$(Bu_3Sn)_2O\ (1\ \text{equiv}) \quad \text{PMHS dimer (excess)} \xrightarrow[\text{toluene}]{80\ ^\circ\text{C, 4 h}} Bu_3SnH\ (n\ \text{equiv}) \qquad (2)$$

without *n*-BuOH, n = 1
with *n*-BuOH, n = 2

In addition to aiding the initial *generation* of Bu_3SnH from the precatalyst, *n*-BuOH serves a second important function—it facilitates the *regeneration* of Bu_3SnH from Bu_3SnOPh (eq 3; ∼10-fold acceleration versus no *n*-BuOH), which represents the turnover step for the catalytic reaction (Figure 2, right-hand side). Indeed, when the Barton−McCombie reduction of the

$$Bu_3Sn\text{-}OPh\ (1\ \text{equiv}) \quad \text{PMHS dimer (excess)} \xrightarrow[\text{toluene}]{80\ ^\circ\text{C, 1 h}} Bu_3SnH \qquad (3)$$

without *n*-BuOH, < 5% conversion
with *n*-BuOH, 43% conversion

thionocarbonate derived from cyclododecanol (Table 1, entry 1) is run under the standard catalytic conditions,[17] but without *n*-BuOH, less than 10% conversion to cyclododecane is observed.

In summary, we have developed a novel Bu_3SnH-catalyzed, PMHS-mediated variant of the Barton−McCombie deoxygenation reaction; the reduction of Bu_3SnOPh to Bu_3SnH in the presence of *n*-BuOH provides the critical turnover step for the catalytic cycle. Compared with the original procedure, which requires stoichiometric Bu_3SnH, this catalytic process is superior from the standpoints of decreased cost and tin waste, as well as increased ease of product purification. The development of other Bu_3SnH-catalyzed processes is underway.

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Supporting Information Available: Experimental procedures and compound characterization data (13 pages). See any current masthead page for ordering and Internet access instructions.

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(19) Notes: (a) These reactions employed 2 equiv of Bu_3SnH and were not individually optimized. (b) In contrast to the catalyzed reactions (see ref 18b), removing tin-derived impurities from reactions that employed stoichiometric Bu_3SnH was difficult in a few instances (see Supporting Information).

(20) Barton, D. H. R.; Motherwell, R. S. H.; Motherwell, W. B. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2363−2367.

(21) To date we have explored only one other substrate derived from a primary alcohol (1,2;3,4-di-*O*-isopropylidene-6-*O*-(phenoxy(thiocarbonyl))-α-D-galactopyranoside). Under the standard catalytic conditions, the major product of the reaction is the original alcohol. See also: Barton, D. H. R.; Motherwell, W. B.; Stange, A. *Synthesis* **1981**, 743−745.

(22) (a) Reference 12. (b) Hayashi, K.; Iyoda, J.; Shiihara, I. *J. Organomet. Chem.* **1967**, *10*, 81−94. At a higher temperature, additional Bu_3SnH is produced.

(23) Prices from Aldrich Chemical Company (Milwaukee, WI), per mole of tin: $(Bu_3Sn)_2O$ $38; Bu_3SnH $250.

(24) Bu_3SnH is sensitive to light, O_2, and adventitious impurities: (a) Kuivila, H. G. *Adv. Organomet. Chem.* **1964**, *1*, 47−87. (b) Poller, R. C. *The Chemistry of Organotin Compounds*; Logos: London, 1970; pp 105−107. (c) Reference 4b.

(25) To facilitate GC analysis of the reactions illustrated in eqs 2 and 3, "PMHS dimer" (TMSO-$(SiHMeO)_n$-TMS, $n = 2$), rather than PMHS itself ($n \approx 35$), was employed as the reductant. We have established through ^{119}Sn NMR studies that "PMHS dimer" and PMHS have comparable reactivity.