Single-Step Process for the Reductive Deoxygenation of Unhindered Alcohols

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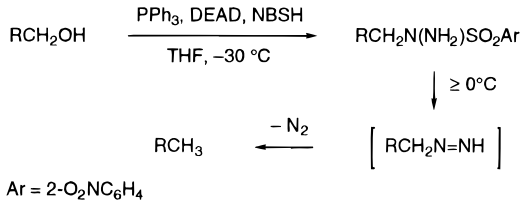
Received May 30, 1997

The importance of methodology for the reductive deoxygenation of alcohols can be gauged by the widespread use of the Barton deoxygenation reaction in synthetic organic chemistry.[1] This two-step procedure involves initial acylation of an alcohol with a reagent such as thiocarbonyldiimidazole followed by reductive cleavage of the resultant thiocarbonyl compound with tri-*n*-butyltin hydride. As an outgrowth of recent methodological studies,[2] we report the development of a process for the reductive deoxygenation of unhindered primary and secondary alcohols that proceeds in a single step without using metal hydride reagents.

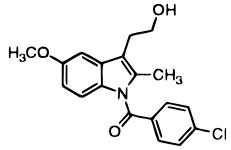
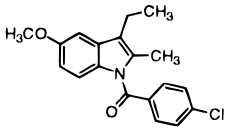
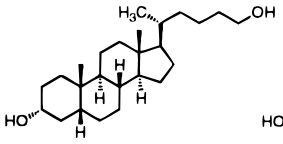
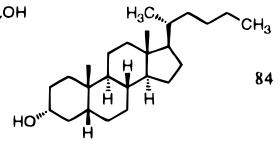
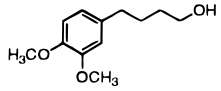
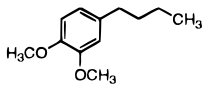
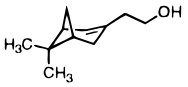
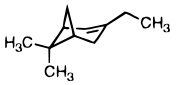
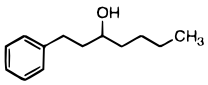
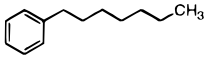
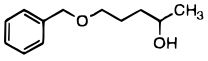
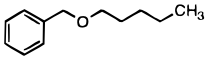
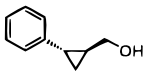
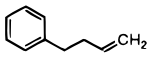
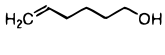
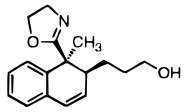
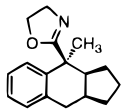
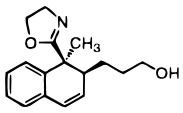
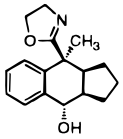
The new method involves the transformation of an alcohol to a monoalkyl diazene[2,3] and proceeds by Mitsunobu displacement[4] of the alcohol with *o*-nitrobenzenesulfonylhydrazine (NBSH)[5] followed by in situ elimination of *o*-nitrobenzenesulfinic acid. In prior work, displacement by NBSH was shown to lead to efficient reductive transposition of allylic and propargylic alcohols to form alkenes and allenes, respectively, by a sigmatropic elimination reaction.[2] The present study



concerns the transformation of non-allylic (non-propargylic) alcohols, for which literature precedent, most notably the work of Kosower et al.,[6] suggested that the proposed monoalkyl diazene intermediates would decompose by a free-radical mechanism to form deoxygenated products. This expectation was realized experimentally, as demonstrated by the examples of Table 1, and represents a valuable new method for the reductive deoxygenation of alcohols. The following experimental procedure is illustrative: diethylazodicarboxylate (DEAD, 183 μL, 1.16 mmol, 2.00 equiv) was added to a deoxygenated solution of triphenylphosphine (304 mg, 1.16 mmol, 2.00 equiv) and *N*-(4-chlorobenzoyl)-3-(2-hydroxyethyl)-5-methoxy-2-methylindole (Table 1, entry 1, 200 mg, 0.58 mmol, 1 equiv) in anhydrous tetrahydrofuran (THF, 4.0 mL) at −30 °C. After 20 min, a solution of NBSH (378 mg, 1.74 mmol, 3.00 equiv) in THF (2.0 mL) was added. The reaction mixture was stirred at −30 °C for 2 h and then warmed to 23 °C to induce diazene formation. After 2 h, the orange reaction mixture was concentrated. Purification of the residue by flash column chromatography on silica gel (5% ethyl acetate in hexanes) afforded the deoxygenated product as an off-white solid (165 mg, 87%, mp 70−71 °C).[7]

The method is found to work well for unhindered alcohols, but sterically encumbered and β-oxygenated alcohols (diisopropylidene-D-galactopyranose, glycerol acetonide, thymidine)

Table 1. Deoxygenation of Primary and Secondary Alcohols

Entry	Substrate	Product	Yield (%)[a]
1			87
2			84
3[b]			86
4[b]			73
5[b,c]			80
6[b,c]			76
7[b]			71
8[b,d]			(66)
9			65
10[e]			84

[a] Isolated yields; yield in parentheses obtained by gas chromatography. [b] NMM used as the solvent. [c] Neopentyl alcohol (2.0 equiv) was added. [d] Mitsunobu product (−30 °C) added to a solution of toluene at reflux. [e] Dioxygen was introduced prior to diazene formation at 23 °C; methyl sulfide workup.

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(6) (a) Kosower, E. M. *Acc. Chem. Res.* **1971**, *4*, 193. (b) Tsuji, T.; Kosower, E. M. *J. Am. Chem. Soc.* **1971**, *93*, 1992.

(7) The indicated stoichiometries are recommended, as fewer equivalents of reagents may lead to incomplete conversion of substrate.

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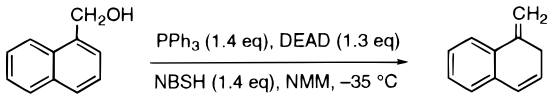
fail to undergo the Mitsunobu displacement and are recovered unchanged from the reaction mixture. The sensitivity of the new method to steric effects can be used to one's advantage, as exemplified in entry 2 of Table 1 where the primary alcohol of the steroidal diol is deoxygenated selectively. Acyclic secondary alcohols can be deoxygenated (entries 5 and 6) if neopentyl alcohol (2.0 equiv)[8] is incorporated in the reaction medium and *N*-methylmorpholine (NMM)[2b] is used as the solvent; both modifications improve the efficiency of the Mitsunobu displacement reaction.

There can be little doubt that the deoxygenation is ultimately a free-radical process, for the cyclopropyl carbinol of entry 7 fragments to form 4-phenyl-1-butene and 5-hexen-1-ol forms methylcyclopentane (entry 8). The ratio of cyclized to noncyclized product in the latter case was optimal when a cold (−30 °C) solution of the Mitsunobu adduct was added to a solution of toluene at reflux. Failing this, appreciable amounts of 1-hexene were obtained, suggesting that the rate of hydrogen atom transfer from the monoalkyl diazene intermediate to the alkyl radical is quite rapid.[9] The proposed monoalkyl diazene intermediate was observed spectroscopically for the deoxygenation of 2-naphthaleneethanol. Monitoring of this reaction, conducted in THF-d_8, by variable-temperature ^{1}H NMR spectroscopy revealed that displacement with NBSH occurred within 1.5 h at −30 °C and that the resultant 1-alkyl-1-sulfonylhydrazine was stable at temperatures below −15 °C.[10] Warming to 0 °C induced slow elimination of *o*-nitrobenzenesulfinic acid ($t_{1/2}$ > 1 h) with formation of a diazene intermediate, as evidenced by a peak for the diazenyl proton at δ 15.6 ppm with a characteristic long-range coupling to the adjacent methylene group of 2.2 Hz.[3h,6] Formation of the diazene was much more rapid at 20 °C and occurred concomitantly with its decomposition to form 2-ethylnaphthalene. After 10 min at 20 °C, the reaction mixture contained equal parts of 2-ethylnaphthalene and the Mitsunobu adduct and half as much of the diazene intermediate; the deoxygenation reaction was complete within 40 min at 20 °C.

Hydrogen atom transfer to the alkyl radical was suppressed almost completely when an oxygen atmosphere was introduced prior to diazene formation. For example, displacement of 2-naphthaleneethanol with NBSH at −30 °C, as described above, followed by introduction of $^{18}O_2$ and warming to 23 °C afforded 2-naphthaleneethanol (following a methyl sulfide workup to reduce the hydroperoxide intermediate) in 90% yield with ≥96% incorporation of ^{18}O. A similar procedure conducted with the unsaturated alcohol of entry 10 (Table 1) led to the novel sequence of C−O bond cleavage, C−C bond formation, and C−O bond (re-)formation to provide the cyclic carbinol product in 84% yield[11] after a methyl sulfide workup.

Although it is evident that the free-radical decomposition of monoalkyl diazenes is a facile process, the concerted sigmatropic elimination of dinitrogen will occur preferentially, where possible, as established by stereospecific transformations of allylic and propargylic alcohols.[2,12] In light of the present findings it was of interest to probe the deoxygenation chemistry of aryl carbinols, where the barrier to free-radical decomposition is lower (benzylic radical stabilization) and the barrier to sigmatropic elimination is presumably raised (loss of arene resonance). These considerations notwithstanding, the experimental evidence established that the sigmatropic elimination pathway is greatly favored even with benzylic substrates, providing a synthetic route to interesting and perhaps valuable polyenes. For example, deoxygenation of 1-naphthalenemethanol, as above, afforded the unstable hydrocarbon shown below in 65% yield;[13] simple benzylic alcohols reacted in a similar manner to afford the corresponding isotoluene derivatives.[14]



65%

The chemistry described herein provides valuable methodology for the deoxygenation of unhindered alcohols, not only by abbreviating the process from two steps to one and by avoiding toxic reagents but also for its ability to bring about unique transformations such as that in the equation above and in entry 10 (Table 1).

Acknowledgment. Financial support from the National Science Foundation is gratefully acknowledged.

Supporting Information Available: Listings of analytical data and reaction conditions for all transformations in Table 1 (3 pages). See any current masthead page for ordering and Internet access instructions.

JA971768V

(8) Walker, M. A. *J. Org. Chem.* **1995**, *60*, 5352.

(9) Myers, A. G.; Movassaghi, M.; Zheng, B. *Tetrahedron Lett.* In press.

(10) 1-Alkyl-1-sulfonylhydrazine assignment was supported by the absence of the characteristic downfield sulfonamide NH signal and by the presence of a two-proton singlet (δ 4.71) for the amino group in the ^{1}H NMR spectra.

(11) For free-radical cyclizations conducted in the presence of dioxygen, see: (a) Nakamura, E.; Inubushi, T.; Aoki, S.; Machii, D. *J. Am. Chem. Soc.* **1991**, *113*, 8980. (b) Mayer, S.; Prandi, J. *Tetrahedron Lett.* **1996**, *37*, 3117.

(12) The sigmatropic elimination of dinitrogen from a *trans*-propargylic diazene intermediate has been observed to occur at −70 °C ($t_{1/2} \approx$ 2.5 h, proposed to involve rate-limiting trans → cis isomerization); sigmatropic elimination from the corresponding *cis*-diazene was proposed to occur rapidly below −95 °C (ref 3h).

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