Cleavage of N−O Bonds Promoted by Samarium Diiodide: Reduction of Free or N-Acylated *O*-Alkylhydroxylamines

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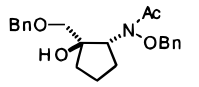
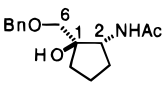
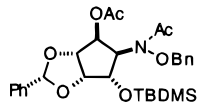
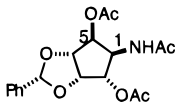
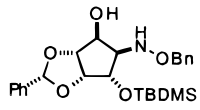
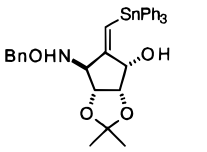
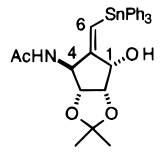
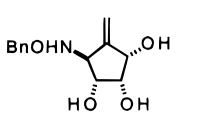
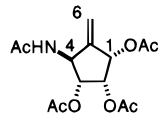
Received August 28, 1995

In our current work on the tributyltin hydride[1] -mediated cycloisomerizations of conveniently functionalized *O*-alkyl oxime ethers derived from carbohydrates, we were usually confronted with the necessary transformation of the resulting *O*-alkylhydroxylamines into the corresponding free amino derivatives. A detailed survey of the methods currently available for effecting this N−O bond cleavage[2] in our polyfunctionalized substrates proved in some cases inappropriate and, in practice, resulted in low yielding processes.[3,4] Obviously, a new and milder method was desired in order to overcome these unexpected difficulties.

Although samarium diiodide is known to promote some N−O reductive cleavage reactions,[5] to our knowledge this reagent has never been exploited for the chemoselective reduction of *O*-alkylhydroxylamines to amines. We have recently shown[6] that samarium diiodide is a convenient and efficient reagent for effecting this particular transformation in densely functionalized aminocyclopentitols such as **3**[6a] and **5**.[6b] A recent report from Keck's laboratory describing a similar process using samarium diiodide[7] prompted us to report here in full our experimental conditions for the synthesis of amines from *O*-alkylhydroxylamines. Additional examples (compounds **1**,[8] **2**,[6a] and **4**[8]) have been included in order to test the scope and extent of the new methodology. For the sake of simplicity, only the corresponding free or N-acetylated *O*-benzylhydroxylamines have been studied, but in principle these conditions can be easily applied to other *O*-alkylhydroxylamines or *O*-alkylhydroxamic acids.[7]

General and reliable conditions (see Experimental Section) were found for the successful implementation of the desired transformation. The results are shown in Table 1. These results deserve some comments. All reductions have been performed at room temperature either by adding the substrate to samarium diiodide in THF or by reverse addition, with no significant change in chemical yield. The reductive cleavage is strongly accelerated in the presence of a proton source. Water (20−25 equiv with respect to substrate) has proven to be most effective.[9,10] Compounds with free hydroxyl groups (e.g., **4** and **5**) are reduced reasonably fast in the absence of added water, except if the hydroxyl group is tertiary (as in **1**) or hindered (as in **4**[11]). The reduced products derived from **3**-**5** have been transformed in situ into the corresponding acetamides to ease isolation and characterization. Due to the highly functionalized nature of our precursors, we had the opportunity to test the stability of different functional groups to the reaction conditions: esters, acetals, silyl[12] or benzyl ethers, double bonds, and vinylstannylidene functions remain unaltered and the hydroxyl groups do not need to be protected. Finally, it is also important to emphasize the very simple workup manipulation required for the isolation of the final products.

Table 1. Reduction of *O*-Benzylhydroxylamines and *N*-Acetyl-*O*-benzylhydroxylamines 1−5 with SmI_2

Substrate	Product	Time[a](h)	Yield[b](%)
 **1**	 **6**	0.7	48[c]
 **2**	 **7**	2	69[c,d]
 **3**	**7**	7	76[d,e]
 **4**	 **8**	48	85[e,f]
 **5**	 **9**	3	79[e,g]

[a] Time required for the N−O reductive cleavage step. [b] Isolated yields. [c] Method A. [d] See ref 12. [e] Method C. [f] See ref 11. [g] Reference 6b.

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(2) Gilchrist, T. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 8, pp 394−395.
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(4) Marco-Contelles, J.; Ruiz, P.; Martínez. L.; Martínez-Grau. A. *Tetrahedron* **1993**, *49*, 6669.
(5) For recent reviews on reductions with samarium diiodide, including examples of N−O reductive cleavage, see: (a) Imamoto, T. *Lanthanides in Organic Synthesis*; Academic Press: London, 1994; p 38−39. (b) Molander, G. A. *Org. React.* **1994**, *46*, 211.
(6) (a) Chiara, J. L.; Marco-Contelles, J.; Khiar, N.; Gallego, P.; Destabel, C.; Bernabé, M. *J. Org. Chem.* **1995**, *60*, 6010. (b) Marco-Contelles, J.; Destabel C.; Chiara, J. L.; Bernabé, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1547.
(7) (a) Keck, G. E.; McHardy, S, F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289. (b) Keck, G. E.; McHardy, S. F. ; Wager, T. T. *Tetrahedron Lett.* **1995**, *36*, 7419.
(8) The synthesis of these compounds will be reported elsewhere.
(9) For previous reports on SmI_2-promoted reactions in the presence of water, see: Hanessian, S.; Girard, C. *Synlett* **1994**, 861 and references cited therein.
(10) Other proton sources are not as efficient. Thus, treatment of **2** with excess SmI_2 in THF and *t*-BuOH (10 equiv) at room temperature for 16 h produced only 21% of the reduced product (as a mixture with a silyl-migrated analogue, see ref 12), and unreacted **2** was recovered in 57% yield.
(11) The hydroxyl group at C-1 in **4** was not acetylated after prolonged treatment with Ac_2O, pyridine, and cat. DMAP at rt, due to the strong steric hindrance introduced by the $SnPh_3$ group.
(12) In the reduction of **2** and **3**, a nonseparable mixture of two compounds (5.4:1 and 4:1 ratio, respectively, as determined by ^1H NMR) was obtained in 67% (75% taking into account recovered **2**) and 83% yield, respectively, due to partial silyl group migration to nitrogen. Reaction of this mixture with tetra-*n*-butylammonium fluoride in THF followed by standard acetylation in situ provided the pure compound **7** in ∼90% yield.

0022-3263/96/1961-0359$12.00/0

In summary, we have shown that the samarium diiodide-mediated reduction of free or N-acylated *O*-benzylhydroxylamines is a new, chemoselective, and high-yielding process for the synthesis of the corresponding amines or amides, respectively, representing an advantageous alternative to previously described methods.

Experimental Section

General Methods. See ref 1.

General Procedure for the Samarium Diiodide Reduction of *O*-Benzylhydroxylamines. Method A. A solution of the substrate in THF (0.05−0.2 M) was added dropwise to a stirred solution of SmI_2 in THF (0.1 M, 3 equiv) and deoxygenated water (20−25 equiv) at 23 °C. When TLC analysis showed the disappearance of the starting material (see Table 1), the crude reaction mixture was partitioned between EtOAc and aqueous saturated $NaHCO_3$. The aqueous phase was extracted with EtOAc (3×), and the combined organic extracts were washed successively with aqueous 10% $Na_2S_2O_3$ and brine, dried over anhyd Na_2SO_4, and concentrated at reduced pressure. The residue was purified by flash column chromatography (EtOAc/hexane or CH_2Cl_2/MeOH mixtures). Alternatively, if the final compound was water soluble, a simple nonaqueous workup procedure was performed as follows. The crude reaction mixture was filtered through Celite, rinsing the filter cake with THF, the filtrate was concentrated at reduced pressure, and the residue was purified by flash column chromatography.

Method B. Following method A, when TLC analysis showed that the starting material had been consumed (see Table 1), the reaction mixture was cooled to 0 °C, and pyridine (1 mL per mmol of substrate) and acetic anhydride (0.5 mL per mmol of substrate) were added. The mixture was stirred at rt for 16 h, diluted with EtOAc, and quenched with aqueous saturated $NaHCO_3$. Extractive workup as in method A and flash chromatography of the residue (EtOAc/hexane or CH_2Cl_2/MeOH mixtures) afforded the pure products.

Method C. Same as method B, but the reduction was performed in the absence of added water.

***trans*-2-Acetamido-1-*C*-((benzyloxy)methyl)cyclopentanol (6).** *trans*-2-((Benzyloxy)acetamido)-1-*C*-((benzyloxy)-methyl)cyclopentanol (**1**)[8] (0.038 g, 0.10 mmol) was treated following method A, affording, after flash column chromatography (MeOH/CH_2Cl_2, 0:100−4:96), compound **6** (0.013 g, 48%) as a colorless oil: R_f = 0.46 (6% MeOH/CH_2Cl_2); ν_{max} (liquid film) 3300, 1650, 1550, 1455, 1375 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.53 (m, 1 H), 1.68 (m, 1 H), 1.78 (m, 1 H), 1.80 (m, 1 H), 1.83 (s, 3 H), 1.95 (m, 1 H), 2.08 (m, 1 H), 3.37 (d, J = −9.4 Hz, 1 H), 3.45 (d, J = −9.4 Hz, 1 H), 3.87 (s, 1 H), 4.09 (dt, J = 10.8, 7.1 Hz, 1 H), 4.46 (d, J = −11.9 Hz, 1 H), 4.56 (d, J = −11.9 Hz, 1 H), 5.96 (d, J = 7.1 Hz, 1 H), 7.31 (m, 5 H); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 171.7 (s), 138.0 (s), 128.5 (d), 127.9 (d), 127.8 (d), 80.1 (s), 74.3 (t), 73.7 (t), 62.1 (d), 35.2 (t), 31.3 (t), 22.8 (q), 20.6 (t).

Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.66; H, 7.90; N, 5.26.

(1*R*,2*S*,3*R*,4*S*,5*S*)-1-Acetamido-2,5-di-*O*-acetyl-3,4-*O*-benzylidenecyclopentane-2,3,4,5-tetrol (7). From Compound 2. Following method A, compound **2** (0.069 g, 0.13 mmol) afforded, after flash column chromatography (EtOAc/hexane, 30:70−80:20), recovered **2** (0.008 g, 12%) and a nonseparable 5.4:1 mixture of 1-acetamido-5-*O*-acetyl-3,4-*O*-benzylidene-2-(*tert*-butyldimethylsilyl)cyclopentane-2,3,4,5-tetrol and a silyl-migrated analogue[12] 0.037 g, 48%) as a white solid: R_f = 0.52 (EtOAc/hexane 4:1); ν_{max} (KBr) 3320, 2940, 2860, 1760, 1750, 1655, 1560, 1380, 1230, 1165, 1145, 1065, 835, 780 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) (for the major component) δ 0.13 (s, 6 H), 0.91 (s, 9 H), 2.00 (s, 3 H), 2.10 (s, 3 H), 4.05 (dd, J = 4.9, 10.5 Hz, 1 H), 4.39 (d, J = 6.1 Hz, 1H), 4.47 (dd, J = 4.9, 6.1 Hz, 1 H), 4.80 (ddd, J = 5.0, 9.0, 10.3 Hz, 1 H), 5.06 (d, J = 5.0 Hz, 1 H), 5.52 (d, J = 8.8 Hz, 1 H), 5.75 (s, 1 H), 7.40 (m, 3 H), 7.55 (m, 2 H); ^{13}C NMR (50.32 MHz, $CDCl_3$) (for the major component) δ 169.6 (s), 169.2 (s), 135.6 (s), 129.6 (d), 128.3 (d), 127.0 (d), 105.4 (d), 81.1 (d), 77.6 (d), 75.4 (d), 73.6 (d), 53.6 (d), 25.6 (q), 23.3 (q), 20.9 (q), 18.1 (s), −4.5 (q), −4.9 (q); MS (70 eV) m/z 379 (11), 378 (45), 273 (18), 272 (97), 230 (7), 212 (9), 188 (11), 171 (13), 170 (27), 158 (25), 138 (10), 129 (39), 117 (10), 116 (24), 115 (10), 105 (32), 96 (23), 91 (15), 80 (11), 79 (9), 78 (10), 77 (22), 75 (56), 74 (10), 73 (66), 72 (15), 59 (19), 57 (12), 43 (100), 42 (14).

Anal. Calcd for $C_{22}H_{33}NO_6Si$: C, 60.66; H, 7.64; N, 3.22. Found: C, 60.42; H, 7.38; N, 3.09.

This mixture (0.016 g, 0.037 mmol) was dissolved in THF (1 mL) and treated with TBAF (1 M in THF, 0.11 mL, 0.11 mmol) at rt for 3 h and then with acetic anhydride (0.1 mL) and pyridine (0.2 mL). After being stirred overnight at rt, the reaction mixture was concentrated at reduced pressure and the crude product was purified by flash column chromatography (EtOAc), affording **7** (0.012 g, 90%) as a white foam: R_f = 0.33 (EtOAc); mp 65−67 °C; $[\alpha]^{25}_D$ −63.0 (c 1.00, EtOH); ν_{max} (KBr) 3300, 1750, 1660, 1550 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.99 (s, 3 H), 2.12 (s, 3 H), 2.13 (s, 3 H), 4.49 (d, J = 6.1 Hz, 1 H), 4.77 (dd, J = 4.8, 6.1 Hz, 1 H), 5.02 (ddd, J = 4.6, 8.2, 10.8 Hz, 1 H), 5.11 (dd, J = 4.8, 10.8 Hz, 1 H), 5.19 (d, J = 4.6 Hz, 1 H), 5.83 (d, J = 8.2 Hz, 1 H), 5.75 (s, 1 H), 7.40 (m, 3 H), 7.55 (m, 2 H); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 171.5 (s), 169.9 (s), 169.1 (s), 134.9 (s), 130.0 (d), 128.5 (d), 127.0 (d), 105.8 (d), 81.1 (d), 75.7 (d), 74.7 (d), 73.1 (d), 51.8 (d), 23.2 (q), 20.8 (q), 20.8 (q); MS (70 eV) m/z 362 (M^+ − 1, 2), 257 (10), 214 (12), 198 (8), 156 (9), 155 (12), 148 (11), 143 (9), 139 (20), 138 (19), 115 (15), 105 (22), 101 (38), 97 (8), 96 (9), 91 (13), 84 (17), 77 (12), 73 (8), 60 (12), 59 (15), 43 (100).

Anal. Calcd for $C_{18}H_{21}NO_7 \cdot H_2O$: C, 56.68; H, 6.08; N, 3.67. Found: C, 56.80; H, 5.64; N, 3.70.

From 3. Following method C, compound **3** (0.065 g, 0.142 mmol) afforded a nonseparable 4:1 mixture of 1-acetamido-5-*O*-acetyl-3,4-*O*-benzylidene-2-(*tert*-butyldimethylsilyl)cyclopentane-2,3,4,5-tetrol and a silyl-migrated analogue,[12] as above, 0.051 g, 83%). This mixture was desilylated and acetylated to give **7**, following the same procedure indicated above.

(*Z*)-(1S,2S,3R,4S)-4-Acetamido-2,3-*O*-isopropylidene-6-(triphenylstannyl)-5-methylenecyclopentane-1,2,3-triol (8). Following method C, (*Z*)-(((benzyloxy)amino)methylene)cyclopentane triol (**4**)[8] (0.039 g, 0.06 mmol) afforded, after flash column chromatography (EtOAc/hexane, 2:1), **8** (0.030 g, 85%) as a colorless oil: $[\alpha]^{25}_D$ −54.9 (c 0.83, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 and 1.37 (2 s, 6 H), 1.98 (s, 3 H), 2.32 (d, J = 10.1 Hz, 1 H), 4.34 (d, J = 5.4 Hz, 1 H), 4.60 (m, 3 H), 5.69 (d, J = 5.4 Hz, 1 H), 6.66 (s, 1 H), 7.36 (m, 15 H), 7.60 (m, 5 H); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 170.0 (s), 160.0 (s), 140.7 (s), 137.0 (s), 137.2 (d), 136.8 (d), 136.4 (d), 129.1 (d), 128.9 (d), 128.7 (d), 128.6 (d), 128.5 (d), 128.4 (d), 128.2 (d), 127.9 (d), 127.3 (d), 111.4 (s), 92.1 (d), 77.9 (d), 73.7 (d), 60.4 (d), 26.1 (q), 24.6 (q), 23.2 (q). Correct microanalytical data could not be obtained for this compound.

(1*S*,2*S*,3*R*,4*S*)-4-Acetamido-1,2,3-tri-*O*-acetyl-5-methylenecyclopentane-1,2,3-triol (9). Following method C, (((benzyloxy)amino)methylene)cyclopentanetriol (**5**)[6b] (0.310 g, 1.23 mmol) gave, after flash column chromatography (CH_2Cl_2/MeOH, 0:100 to 4:96), **9** (0.304 g, 79%) as a white foam: R_f = 0.35 (4% MeOH/CH_2Cl_2); mp 142 144 °C; $[\alpha]^{25}_D$ −30.2 (c 0.83, $CHCl_3$); ν_{max} (KBr) 3400, 1750, 1650, 1540, 1380, 1230 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.01, 2.05, 2.07, 2.10 (4 s, 12 H), 5.08 (dd, J = 4.0, 9.5 Hz, 1 H), 5.18 (m, J = 2.7, 8.5, 9.5 Hz, 1 H), 5.30 (t, J = 2.7 Hz, 1 H), 5.36 (t, J = 2.7 Hz, 1 H), 5.51 (t, J = 4.3 Hz, 1 H), 5.68 (m, J = 2.5 Hz, 1 H), 5.73 (d, J = 8.5 Hz, 1 H); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ 170.4, 170.3, 170.0, 169.9, 144.0, 113.8 (6 s), 73.5, 70.7, 70.2, 53.8 (4 d), 22.9, 20.4 (2 q); MS (70 EV) m/z 254 (M^+ − 59, 2), 151 (12), 110 (20), 43 (100).

Anal. Calcd for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.11; N, 4.47. Found: C, 53.95; H, 6.01; N, 4.59.

Acknowledgment. We thank Professor Gary E. Keck for informing us of his similar procedure (ref 7b) prior to publication. Financial support provided by DGICYT (grant nos. SAF94-0818-C02-02 and PB93-0127-C02-01), CICYT (grant no. CE93-0023), Comunidad Autónoma de Madrid-Consejería de Educación y Cultura (grant no. AE-0094/94), and EU (Human Capital and Mobility Program; Contract ERBCHRXCT 92-0027) is also gratefully acknowledged.

JO951571Q