ORGANIC LETTERS

2002
Vol. 4, No. 13
2141−2144

Facile Cleavage of Triethylsilyl (TES) Ethers Using *o*-Iodoxybenzoic Acid (IBX) without Affecting *tert*-Butyldimethylsilyl (TBS) Ethers

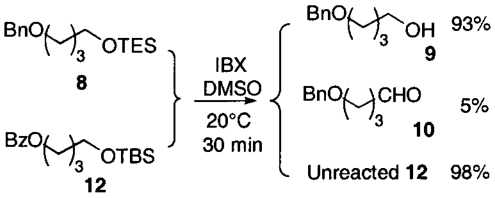
Yikang Wu,* Jia-Hui Huang, Xin Shen, Qi Hu, Chao-Jun Tang, and Liang Li

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

yikangwu@pub.sioc.ac.cn

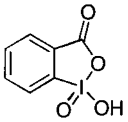
Received March 29, 2002

ABSTRACT



In DMSO cleavage of triethylsilyl (TES) ethers by *o*-iodoxybenzoic acid (IBX) was significantly faster than cleavage of *tert*-butyldimethylsilyl (TBS) ethers or further oxidation into carbonyl compounds. In most cases, TES protecting groups could be removed in good to excellent yields within 1 h, whereas similar TBS protecting groups remained intact under the same conditions. The procedure also could be adapted for direct one-pot conversion of TES ethers into carbonyl compounds.

Although it was discovered[1] in 1893, *o*-iodoxybenzoic acid (1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide, usually abbreviated as IBX) remained almost "forgotten" until the 1980s when Dess and Martin[2] used it to prepare the now broadly employed mild oxidant Dess−Martin periodinane. Use of IBX itself as oxidant in organic synthesis was not known until 1994, when Frigerio and Santagostino[3] reported the first successful oxidations. Since then, IBX has received increasing attention[4] in the chemical community. Herein we wish to report a novel use of IBX as a highly effective and selective desilylation agent, which allows for the facile cleavage of triethylsilyl ethers (TES). Under the same conditions similar *tert*-butyldimethylsilyl ethers (TBS) were very slow to react.



o-Iodoxybenzoic acid (IBX)

Silyl protecting groups have played increasingly important roles in the synthesis of complicated molecules, because they may be cleaved under conditions that do not affect, for example, acetal/ketal and thioacetal/thioketal types of protecting groups. Among the silyl protecting groups, TES ethers hold a special position. Compared with TMS ethers, TES

---

[1] Hartman, C.; Meyer, V. *Chem. Ber.* **1893**, *26*, 1727−1732.

[2] (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4145. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7278. (c) Ireland, R. E.; Liu, L.-B. *J. Org. Chem.* **1993**, *58*, 2899−2899. (d) Stevenson, P. J.; Treacy, A. B.; Nieuwenhuyzen, M. *J. Chem. Soc., Perkin Trans. 2* **1997**, 589−591.

[3] (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019−8022. (b) De Munari, S.; Frigerio, M.; Santagostino, M. *J. Org. Chem.* **1996**, *61*, 9272−9279. (c) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537−4538.

[4] (a) For a recent review, see: Wirth, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 2812−2814. (b) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993−995. (c) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 996−1000. (d) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233−2244. (e) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245−2258.

10.1021/ol025946n CCC: $22.00

ethers are remarkably more stable and thus can survive many more synthetic transformations and chromatographic purifications. At the same time, the TES ethers do not introduce as much steric bulkiness as the *tert*-butyldimethylsilyl (TBS) or *tert*-butyldiphenylsilyl (TBDPS) ethers. In some particular situations, such as protection of the hydroxyl in Evans' aldols, masking the OH as a TES ether is often much more feasible and practical than protection as a TBS ether.

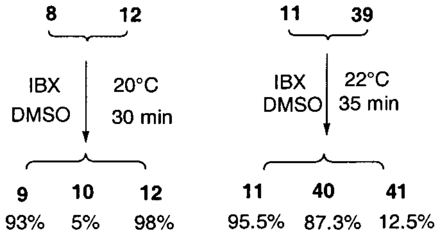
Selective removal of TES protecting groups in the presence of TBS ethers or other even more stable silyl protecting groups has been documented in the literature. However, in most instances, successful cases[5] were only one step in the multistep synthesis of a complex molecule, and the limits and scope of the recipe were unexplored or unreported. To our knowledge, there is only one systematic study[6] that was directed toward selective deprotection of TES protecting groups in the presence of TBS ethers, where mesoporous silica[7] MCM-41 (probably not readily accessible to most organic chemists) was used as the reagent. The reaction was run in a heterogeneous system, and essentially no information about functional group compatibility was provided therein.

In executing an ongoing project involving reactions using IBX, we noticed that a TES protecting group was unexpectedly cleaved, giving an alcohol (rather than a carbonyl compound) as the main product. This inspired us to further examine the reaction of IBX with other TES and TBS ethers. Preliminary results[8] are summarized in Table 1.

It can be seen from Table 1 that unhindered primary TES ethers were cleaved in high yields within less than 1 h. The closely related TBS ethers, however, remained untouched under the same conditions, as shown by TLC monitoring and the high-yield recovery of the starting materials by column chromatography. Some commonly employed protecting groups such as ketal, thioacetal, pivaloyl, benzyl, and benzoyl groups were not affected to a detectable degree.

In the beginning, IBX caught synthetic chemists' attention mainly as an oxidizing agent. The immediate products of desilylation in this work were alcohols. Therefore, it is not surprising that the resulting alcohols could be further oxidized into corresponding carbonyl compounds (in high yields if excess IBX was present and the reaction time was prolonged). What deserves to be noted here is that the rates at which the alcohols were oxidized were apparently much lower than those for the silicon−oxygen bond cleavage. Such significant rate differences between desilylation and oxidation made it possible in most cases to isolate the alcohols as the predominant products.

Scheme 1



Cleavage of sterically hindered TES ethers such as those in **1** and **4** (entries 1 and 2, Table 1) required longer reaction times. In the case of deprotection of **1**, full consumption of the starting TES ether took 5 h at 23 °C. Workup and chromatographic separation gave the alcohol **2** in 65.6% yield, along with a small amount of ketone **3** (8.1%). Cleavage of the TES protecting group in **4** was similar. After 4.5 h of reaction at 20 °C, alcohol **5** and aldehyde **6** were isolated from the product mixture in 60% and 28% yields, respectively (together with 4.5% of unreacted starting **4**).

The reaction with geranyl TES ether (entry 21) was somewhat peculiar, where oxidation of alcohol **37** appeared to be more easily oxidized than most other alcohols tested in this work, giving aldehyde **38** as the main product.

To investigate the large differences in cleavage rates between TES ethers and TBS ethers using parallel runs with various individual pairs of TES/TBS ethers, we also performed two intermolecular competition experiments (Scheme 1). Starting with an equimolar mixture of the TES ether **8** and the TBS ether **12**,[9] the reaction with 1.5 molar equiv of IBX at 20 °C for 30 min led to alcohol **9** in 93% yield (and 5% of aldehyde **10**), with the TBS ether **12** recovered in 98% yield. Switching the functional groups in the two substrates (using **11** and **39** in place of **8** and **12**) did not change the selectivity. Similar preferential cleavage of TES ether was also observed with a compound containing both TES and TBS funtionalities within the same molecule (entry 19, Table 1; because of a solubility problem a 3:4 v/v mixture of THF and DMSO was used instead of neat DMSO). Again, the TES was fully cleaved,[10] whereas the TBS remained intact. We note that under Swern oxidation conditions the same substrate (**32**) gave[11] only aldehyde **34** (rather than alcohol **33**) in 85% yield.

The IBX appeared to be substantially consumed with the desilylation process. The λ_{max} (259 nm) of IBX in the run with **8** (starting with 1.0 mmol of **8** and 1.1 mmol of IBX) decreased by 37% over 35 min (mostly within 15−20 min), whereas in the absence of **8** (under otherwise identical

---

(5) See the examples in a recent review: Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031−1069.

(6) Itoh, A.; Kodama, T.; Masaki, Y. *Synlett* **1999**, 357−359.

(7) Kresge, C. T.; Leonowicz, M. E.; Roth, W. J.; Vartuli, J. C.; Beck, J. S. *Nature* **1992**, *359*, 710−712.

(8) **General Procedure.** IBX (1.1 mmol) was added to a solution of the silyl ether (1 mmol) in DMSO (5 mL) containing added water (90 μL, 5 mmol). The mixture was stirred at 20 °C (TLC monitoring) for the indicated time (Table 1) before being partitioned between diethyl ether and water. The organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. The solvents were removed by rotary evaporation, and the products were obtained by flash chromatography on silica gel (eluting with ethyl acetate/hexanes).

(9) We chose this compund instead of structurely more closely related TBS ether **11** just for unambiguous identification of the origin of the alcohol in the product mixture.

(10) It is noteworthy that Dess−Martin periodinane (structurally closely related to IBX) did not cleave TES while oxidizing alcohols into carbonyls. See, e.g.: Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998−3017.

(11) Tolstikov, G. A.; Miftakhov, M. S.; Vostrikov, N. S.; Komissarov, N. G.; Alder, M. E.; Kuznetsov, O. M. *Zh. Org. Khim*. **1988**, *24*, 224−225 (in Russian); *Chem. Abstr.* **1989**, *110*, 7162.

Table 1. IBX-Mediated Cleavage of Silyl Ethers[a]

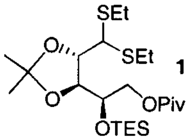
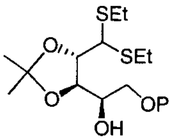
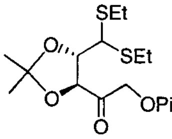
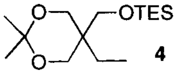
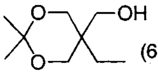
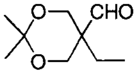
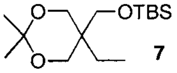
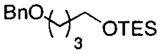
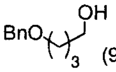
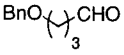
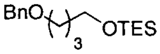
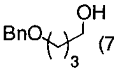
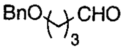
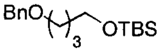
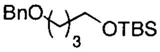
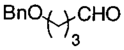
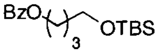
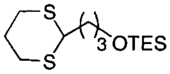
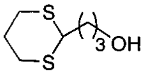
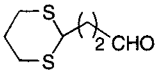
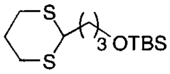
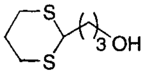
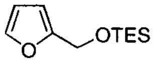
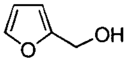
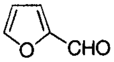
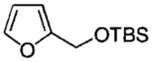
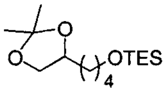
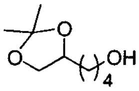
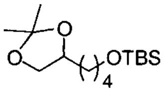
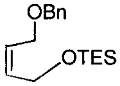
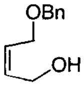
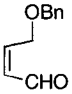
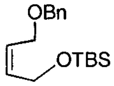
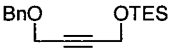
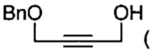
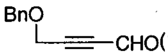
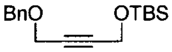
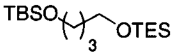
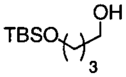
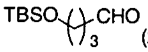
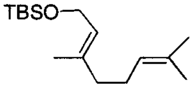
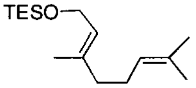
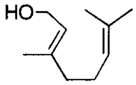
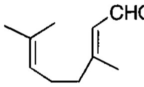
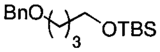
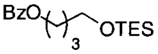
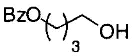
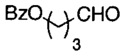
Entry	Substrate	Conditions	Products (Yield)
1[b]	 **1**	5h / 23°C	 **2** (65.6%)  **3** (8.1%)
2	 **4**	4.5 h / 20°C	 **5** (60%)  **6** (28%) Unreacted **4** (4.5%)
3	 **7**	4.5 h / 21°C	No reaction[c] (96% recovery)
4[d]	 **8**	30 min / 20°C	 **9** (93%)  **10** (5%)
5[e]	 **8**	45 min / 20°C	 **9** (73.9%)  **10** (18%) Unreacted **8** (4.8%)
6	 **11**	30 min / 25°C	No reaction[c]
7[b]	 **11**	48 h / 25°C	 **10** (85.6%)
8[d]	 **12**	30 min / 20°C	No reaction[c] (98% recovery)
9	 **13**	35 min / 20°C	 **14** (72%)  **15** (13.6%)
10	 **16**	35 min / 20°C	 **14** (6%) Unreacted **16** (89%)
11	 **17**	45 min / 20°C	 **18** (78%)  **19** (9%)
12	 **20**	1 h / 20°C	No reaction[c] (95% recovery)
13[f]	 **21**	45 min / 20°C	 **22** (79.3%)
14	 **23**	45 min / 20°C	No reaction[c] (95% recovery)
15	 **24**	30 min / 20°C	 **25** (62%)  **26** (8%)
16	 **27**	30 min / 25°C	No reaction[c]
17	 **28**	75 min / 20°C	 **29** (74%)  **30** (18%) Unreacted **28** (4.7%)
18[g]	 **31**	75 min / 20°C	 **29** (12%) Unreacted **31** (84%)

Table 1. (Continued)

Entry	Substrate	Conditions[a]	Products (Yield)
19[h]	 **32**	45 min / 20°C	 **33** (73%)  **34** (21%) Unreacted **32** (2.9%)
20	 **35**	45 min / 20°C	No reaction[c] (96.3% recovery)
21	 **36**	45 min / 20°C	 **37** (24.4%)  **38** (73.6%) Unreacted **36** (1.9%)
22[d]	 **11**	35 min / 22°C	No reaction[c] (95.5 % recovery)
23[d]	 **39**	35 min / 22°C	 **40** (87.3%)  **41** (12.5%)

[a] For general procedure, see ref 8. [b] 1.5 mmol of IBX was used in the reaction. [c] As shown by TLC (yield by column chromatography). [d] Intermolecular competition experiment. [e] 0.5 mmol of IBX was used in the reaction. [f] The small amount of corresponding aldehyde was not isolated, probably because of hydrolysis of the acetonide protecting group on silica gel during column chromatography. [g] The weight of aldehyde **30** was negligible. [h] A mixture of DMSO/THF (4 mL/3 mL) was used as solvent because of poor solubility of **32** in neat DMSO.

conditions) only <5% decrease in the λ_{max} was recorded over the same time period. This observation suggests that the desilylation process mediated by IBX is probably not a simple acid-catalyzed hydrolysis.[12] It is noteworthy that the cleavage of the oxygen−silyl linkage does not require equal molar amounts of IBX, because, for example, treatment of **8** (entry 5, Table 1) with 0.5 (instead of 1.1) molar equiv of IBX at 20 °C for 45 min led to **9** and **10** in 73.9% and 18% yields, respectively (along with 4.8% of unreacted **8**).

In brief, we have conducted a systematic investigation on cleavage of TES vs TBS in homogeneous systems and developed a facile detriethylsily protocol that does not rely on acid-catalyzed hydrolysis. As a result of its mildness and different profile of functional group compatibility, this method may serve as a useful complement to the existing methodologies and find applications in the synthesis of complicated molecules.

Acknowledgment. This work was supported by the National Natural Science Foundation of China (20025207, 29832020), the Major State Basic Research Development Program (G2000077502), the Chinese Academy of Sciences (CAS), and the Life Science Special Fund of CAS Supported by the Ministry of Finance of China (Stz 98-3-03).

Supporting Information Available: Preparation of the silyl ethers, spectroscopic data for the new compounds, and the references for the known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL025946N

---

[12] Note that most of the known cases (in moderate to good yields) of selective removal of TES without significantly touching TBS relied on hydrolysis in a mixture reaction medium of carefully tuned acidity. See, for example, those examples cited in ref 5.