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Chemoselective TBS deprotection of primary alcohols by means of pyridinium tribromide (Py·Br_3) in MeOH

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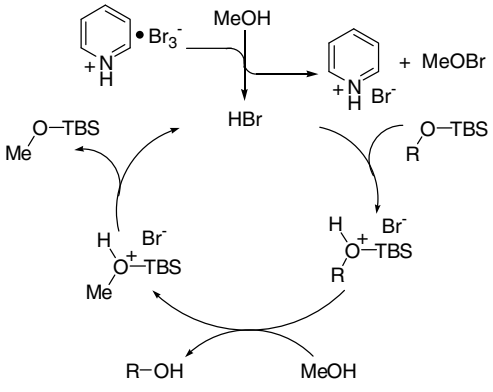
ABSTRACT

A catalytic amount of pyridinium tribromide (Py·Br_3) in MeOH chemoselectively deprotects primary TBS ethers in the presence of a variety of other protecting and common functional groups in modest to excellent yields when performed at 0 °C.

The usage of protecting groups in modern organic chemistry, more specifically, in multi-step natural product synthetic chemistry has become quite ubiquitous over the past 30 years.[1] While the selective masking and un-masking of precious functional groups plays an important role in many areas of organic synthesis, there remains a great need for the ability to chemoselectively introduce and remove orthogonal protecting groups in multi-functionalized molecules.[2] Since the introduction of the TBS group for the protection of the alcohol moiety by Corey, virtually every polyketide and/or polypropionate natural product synthesis has utilized this or a similar silicon masking group.[3,4] With the usage of such protecting groups, numerous reagents have been developed for the chemoselective unmasking of a given silyl ether dependent upon its acid or base lability.[5] For example, the fluoride anion (i.e., TBAF, aq HF, HFpyridine, etc. has been utilized under both acidic and basic conditions for the cleavage of a variety of silyl ethers. In addition, silyl protecting groups can be cleaved under either Lewis or Brönsted acidic conditions. One of the major drawbacks in both of these cases lies in the potential inability to chemoselectively remove silyl ethers in the presence of other protecting groups or functionalities.

In one of our on-going synthetic projects, we had the need to chemoselectively remove a primary TBS ether in the presence of a secondary TES group. We initially investigated the typical desilylation methods (TBAF, aq HCl, PPTS in MeOH, etc., but unfortunately these reaction conditions failed to furnish the desired primary alcohol in workable yields. We next focused our attention on the report of Patel, that tetrabutyl ammonium tribromide (TBATB) in MeOH removed a primary TBS ether within minutes as opposed to hours for the secondary TBS ether counterparts.[6] Based on this observation, we adopted their protocol for our chemoselective deprotection and found that TBATB did indeed remove the primary TBS ether in the presence of a secondary TES group, however, the yield was modest (~45%) due to a competing side reaction, which ultimately led to dead-end material. Based on this observation, we decided to investigate if a catalytic amount (5 mol %) of pyridinium tribromide (Py·Br_3) in MeOH at lower temperatures (−20 °C) would mimic the same chemoselectivity as TBATB, but be devoid of the unwanted side-product.

Our initial working catalytic cycle is highlighted in Scheme 1. It has been reported that tertalkylammounium tribromides generate HBr in the presence of MeOH.[6,7] Based on these observations, we assumed that Py·Br_3 would mirror that of the afore mentioned aliphatic tribromides, provide a small amount of HBr, and enter into a catalytic process. Subsequent to the HBr formation, protonation of the TBS ether should provide the oxonium cation, followed by a nucleophilic displacement with MeOH should cleave the silyl ether and furnish the desired alcohol. A final deprotonation (or disproportionation) of the secondary oxonium cation derived from



Scheme 1.

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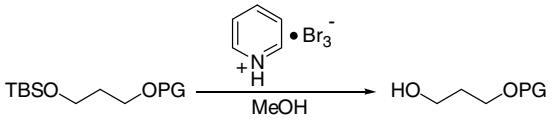
MeOTBS with Br^- should regenerate the acid catalyst, hence making the protocol catalytic in HBr.

With this idea in mind, we decided to investigate the chemoselective deprotection of a TBS ether in the presence of other protecting groups derived from 1,3-propane diol. A series of orthogonally TBS- protected diols were synthesized and subjected to differing amounts of Py·Br_3 in MeOH as shown in Table 1.

Initially, we chose to investigate the catalyst loading of Py·Br_3 on the chemoselective deprotection of the TBS ether in the presence of the quite robust TBDPS silyl moiety (**1a**). Thus, treatment of **1a** with a full molar equivalent of Py·Br_3 at 0 °C in MeOH led to a 40% yield of the TBDPS- protected diol **1b**, while the remaining material balance was the bis-desilylated-1,3-propane diol. Lowering the molar equivalents of Py·Br_3 from 50→5 mol %, while maintaining the reaction temperature at 0 °C for **1a**, afforded **1b** in increased yield (from 48 to 77%) as the catalyst loading decreased as shown in Table 1. Likewise, a similar trend is also observed when cooling the reaction of **1a** down to −20 °C. The optimal yield of **1b** (89%) for the chemoselective TBS deprotection of **1a** with Py·Br_3 occurred at −20 °C with 5 mol % catalyst loading. Similar to that of **1a**, we next investigated the TIPS- protected 1,3-propane diol variant **2a**. It is well known that the TIPS ether resident in **2a** is more labile to acidic conditions when compared to the TBDPS group of **1a**.[8] Thus, we initially envisioned that the yield for deprotection of **2a** might be inferior to that of **1a**. After scanning a variety of reaction conditions with respect to catalyst loading and temperature, the maximum yield for the chemoselective TBS ether cleavage in the presence of the TIPS group was 86% for the desired compound **2b**. Interestingly, these conditions furnished nearly identical yields (89% vs 86%) for both **1b** and **2b**, respectively. With the standardized reaction condition in hand (5 mol % Py·Br_3 at −20 °C), we chose to investigate the scope and limitations of the selective TBS ether removal in the presence of a variety of other orthogonal protecting groups. Hence, the TES–TBS- protected 1,3-propane diol variant (**3a**) unfortunately did not afford the mono-protected TES diol **3b**. Not surprising due to the instability of the TES moiety under acidic conditions, the catalytic amount of HBr formed from Py·Br_3 in MeOH at −20 °C cleaved both the TBS and TES ethers, and provided 1,3-propane diol as the quantitative product. Similar to that of **3a**, the THP–TBS compound **8a** did not furnish the desired THP- protected diol **8b**, but afforded 1,3-propane diol as the sole product due to the lability of the THP moiety under reaction conditions. Much to our delight other orthogonally protected 1,3-propane diol derivatives did undergo chemoselective TBS removal with Py·Br_3 in MeOH at −20 °C. Thus, the Bz (**6a**) and Ac (**7a**)-TBS -protected diols underwent silyl ether cleavage and provided the corresponding desired products **6b** and **7b** in very goods yields of 94% and 82%, respectively. Likewise, the acyclic acetal MOM-TBS 1,3-propane diol (**4a**) readily afforded the MOM- protected alcohol **4b** in 93% yield by means of the chemoselective removal of the silyl ether under the standard reaction conditions. Lastly, the Bn ether derivative **5a** smoothly underwent selective silyl group removal to provide the desired product **5b** in 80% yield.

While Table 1 provided us with an appropriate standardized condition for chemoselective removal of the TBS group and provided some insight into the scope and limitations of the reaction, we decided to shift the focus of our investigation to examining selective silyl group (TES and TBS) removal in the presence of other common function groups as described in Table 2. Thus, the removal of both secondary TBS and TES ethers of **9a** and **10a** in the presence

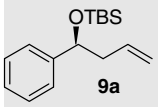
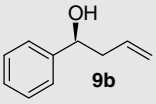
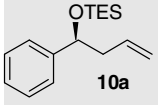
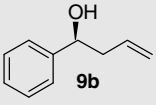
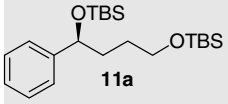
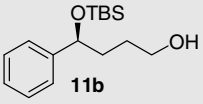
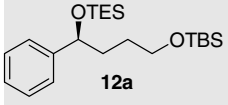
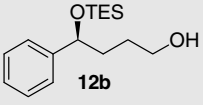
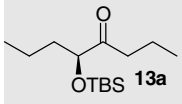
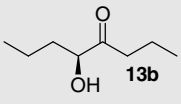
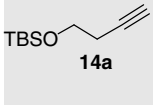
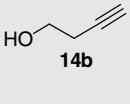
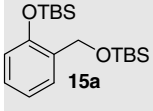
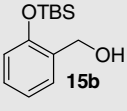
Table 1
Chemoselective pyridinium tribromide (Py·Br_3) deprotection of primary TBS ethers in the presence of other protecting groups



1a-8a **1b-8b**

sm #	PG	mol %	Temp.	*T* (h)	Prod. #	Yield %
1a	TBDPS	100	0	1.5	**1b**	40
1a	TBDPS	50	0	1.5	**1b**	48
1a	TBDPS	30	0	1.5	**1b**	52
1a	TBDPS	10	0	1.5	**1b**	66
1a	TBDPS	5	0	1.5	**1b**	77
1a	TBDPS	100	−20	1.5	**1b**	60
1a	TBDPS	50	−20	1.5	**1b**	60
1a	TBDPS	10	−20	1.5	**1b**	52
1a	TBDPS	5	−20	1.5	**1b**	89
2a	TIPS	30	0	2.0	**2b**	36
2a	TIPS	10	0	2.0	**2b**	70
2a	TIPS	100	−20	2.0	**2b**	36
2a	TIPS	50	−20	2.0	**2b**	41
2a	TIPS	30	−20	2.0	**2b**	35
2a	TIPS	10	−20	2.0	**2b**	81
2a	TIPS	5	−20	2.0	**2b**	86
3a	TES	5	−20	1.5	**3b**	0
4a	MOM	5	−20	1.5	**4b**	93
5a	Bn	5	−20	1.5	**5b**	80
6a	Bz	5	−20	1.5	**6b**	94
7a	Ac	5	−20	1.5	**7b**	82
8a	THP	5	−20	1.5	**8b**	0

Table 2
Py·Br_3 catalyzed deprotection of the silyl groups in the presence of a variety of functional groups[a]

Silyl ether	Product	Yield (%)
 **9a**	 **9b**	78[b]
 **10a**	 **9b**	76[b]
 **11a**	 **11b**	74
 **12a**	 **12b**	72
 **13a**	 **13b**	55[b,c]
 **14a**	 **14b**	81
 **15a**	 **15b**	93

[a] Reactions were run with 5 mol % of Py·Br_3 and 0.15 mmol of substrate in 2 mL of MeOH at 0 °C until complete by TLC analysis.
[b] 10 mol % of Py·Br_3 was employed.
[c] Reaction run at rt.

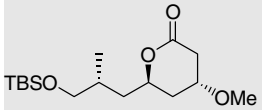
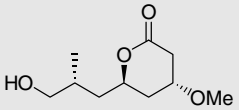
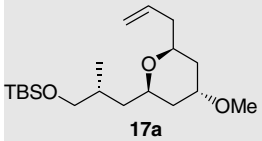
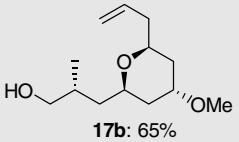
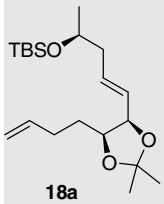
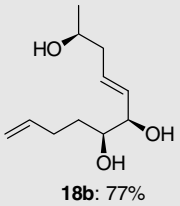
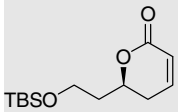
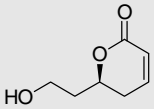
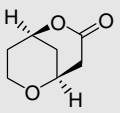
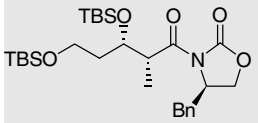
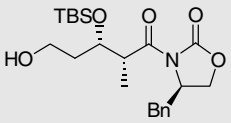
of a terminal alkene proceeded with Py·Br_3 in MeOH to provide the corresponding homoallylic alcohol **9b** in nearly identical yields of 78% and 76%. However, the catalyst loading was increased from 5 to 10 mol % and the reaction temperature was warmed from −20 to 0 °C to help facilitate the protecting group removal within a few hours. It should be noted that one could utilize the standardized conditions from Table 1 for silyl ethers **9a** and **10a**, although the reactions times were much longer (>24 h) for appreciable conversion to **9b**. Based on this observation, we envisioned that lower catalyst loading might allow for a chemoselective removal of a primary TBS (or TES) ether in the presence of a secondary one. Much to our delight, treatment of the bis-TBS ether compound **11a** with 5 mol % of Py·Br_3 in MeOH at 0 °C did indeed undergo chemoselective cleavage of the primary TBS ether in the presence of the secondary one and afforded the mono-protected alcohol **11b** in 74% yield. Likewise, chemoselective removal of the primary TBS moiety resident in **12a** in the presence of a secondary TES ether was also accomplished under the exact reaction conditions for that of **11a** to provide alcohol **12b** in a virtually identical yield of 72% with respect to **11b**.

We also examined the chemoselectivity of the TBS ether cleavage in the presence of other typical functional moieties. Thus, the TBS- protected α-hydroxy ketone **13a** did undergo silyl cleavage without affecting the carbonyl group to furnish the keto-alcohol **13b** in a modest yield of 55%. However, the reaction was quite sluggish at 0 °C and required warming to rt to drive the reaction to significant conversion with 10 mol % of Py·Br_3. Likewise, selective deprotection of the TBS group resident in **14a** at 0 °C readily afforded 3-butyn-1-ol (**14b**) in an 81% yield. Similar to that of **10a**, chemoselective removal of the primary TBS ether of **15a** in the presence of a phenolic TBS protecting group furnished the free benzylic alcohol **15b** in an exceptional 93% yield under the standard reaction conditions as described in Table 2.

As the final component of our investigation, we chose to examine the efficiency of Py·Br_3 in MeOH for the chemoselective removal of TBS ethers in the presence of other function groups resident in fairly complex organic synthons and/or natural product intermediates as delineated Table 3.

Thus, treatment of the primary TBS ether β-hydroxy lactone **16a** with 5 mol % of Py·Br_3 in MeOH at 0 °C swiftly removed the TBS protecting group, while not disturbing either the lactone or the β-methoxy moiety and provided the desired free primary alcohol **16b** in 70% yield. We were initally concerned that the reaction conditions might promote β-elimination of the methoxide anion to provide the corresponding α,β-unsaturated lactenone. However, we were quite pleased that only TBS ether cleavage was observed. Similar to **16a**, Py·Br_3-mediated chemoselective TBS cleavage of the protected β-C-glycoside compound **17a** readily proceeded to afford the free hydroxyl group of **17b** with a modest yield of 65%. We also examined the selective removal of a secondary TBS ether in the presence of an acetonide protecting. Unfortunately, treatment of **18a**[9] with Py·Br_3 in MeOH at 0 °C led to concomitant removal of both the acetonide and silyl ether after 24 h to provide the triol **18b** with a 77% yield. Similar to lactone **16a**, the TBS- protected α,β-unsaturated lactenone **17a** was subjected to standard reaction conditions and furnished two products **17b** and **17c** in a combined yield of 90%. The predicted desilylated lactenone **17b** was produced in 41% yield, whereas the bicyclic pyran-lactone **19c** was formed in 49% yield via an intramolecular cyclization of the free hydroxyl moiety onto the Michael acceptor.[10,11] Not surprisingly, longer reaction times led selectively to the bicyclic lactone **19c** (via **19 b**) in nearly quantitative yields. Thus, Py·Br_3 in MeOH can catalyze TBS group removal and also facilitate intramolecular Michael additions as well. Lastly, the bis-TBS-protected β-hydroxy carbonyl **20a**, derived from an Evans' oxazolidinone aldol reaction,[12] readily underwent primary silyl group cleavage to afford the free hydroxy compound **20b** in an 89% yield without forming any appreciable amount of the cyclized lactone product. Interestingly, the reaction of **20a** with TBATB not only chemoselectively removed the TBS moiety, but also promoted cyclization to afford the corresponding lactone in approximately 50% yield.

Table 3
Py·Br_3 catalyzed deprotection of the TBS group resident in complex organic synthons[a]

Silyl ether	Product, Yield
 **16a**	 **16b**: 70%
 **17a**	 **17b**: 65%
 **18a**	 **18b**: 77%
 **19a**	 **19b**: 41%
	 **19c**: 49%
 **20a**	 **20b**: 89%

[a] Reactions were run with 5 mol % of Py·Br_3 and 0.15 mmol of substrate in 2 mL of MeOH at 0 °C until complete by TLC analysis.

In conclusion, we have shown that Py·Br_3 in MeOH chemoselectively deprotects primary TBS (and TES) ethers in the presence of a variety of other protecting and common functional groups in modest to excellent yields when performed at 0 °C and 5 mol % catalyst loading. Based on the various substrates investigated, the described mild and straightforward protocol should be quite useful in the stereoselective synthesis of natural product subunits and/or the production of valuable organic synthons.[13]

Acknowledgement

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References and notes

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13. *A general procedure is as follows:* To a solution of bis-TBS- protected diol **15a** (67 mg, 0.20 mmol) dissolved in methanol (2.0 ml) was added $Py{\cdot}Br_3$ (3.0 mg, 0.01 mmol, 0.05 equiv) at 0 °C. The reaction mixture was left under stirring until the starting material was consumed according to TLC analysis (1.5 h). The reaction mixture was then quenched with sodium bicarbonate (1 ml). The aqueous layer was then extracted (3×10 ml) with EtOAc. The combined organic extracts were dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography (silica, 10% ethyl acetate in hexanes) afforded the product **15b** as a yellowish oil (42 mg, 93%).