A Mild, Highly Efficient, and Chemoselective Deprotection of Trityl Ethers of Carbohydrates and Nucleosides Using Iodine Monobromide[1]

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Abstract: Iodine monobromide in dichloromethane–methanol or acetonitrile constitutes an effective reagent for the deprotection of *O*-trityl and *O*-dimethoxytrityl ethers of carbohydrates and nucleosides. Acid-labile functionalities (acetals, *O*-*p*-methoxybenzyl ethers, etc.) as well as base-labile groups (esters and amides) are stable under these conditions; and the method has been found to be superior to the hitherto known literature methods.

Key words: interhalogen, iodine monobromide, trityl ether, carbohydrate, nucleoside, chemoselective deprotection

Trityl (Tr) and the dimethoxytrityl (DMTr) groups continue to be two of the most frequent favourites for the protection of primary hydroxyl groups in carbohydrate and nucleoside chemistry.[2] These groups have traditionally been removed using strong protic acids (such as HBr in AcOH,[3] HCOOH,[4] or TFA[5]), Lewis acids (such as $BiCl_3$,[6] $Ce(OTf)_4$,[7] BCl_3,[8] $InBr_3$,[9] or $MgBr_2$[10]) or others.[11] Recently while synthesizing a trisaccharide intermediate **1** towards one of our targeted oligosaccharides using iodine as promoter[12] in CH_2Cl_2, we observed the competing 6′-de-O-tritylation of the donor **2** during its reaction with the acceptor substrate (Figure 1).

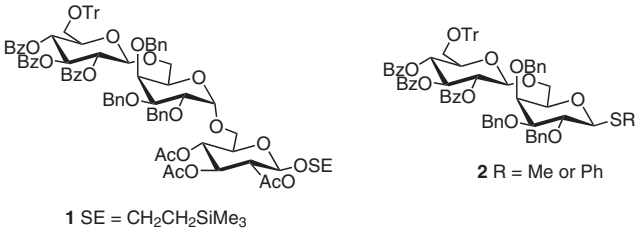

Figure 1

A literature search revealed precedence for the detritylation of carbohydrates and nucleosides using solutions of I_2 in MeOH, which was reasoned to be due to an acid-catalysed reaction.[13] Although formation of methyl glycosides has been noted to be a limitation of this method, no studies have been reported using alternative solvents. The TBDMS group is another example of an acid-labile group whose deprotection has been reported using I_2/MeOH,[14] as well as by IBr in various solvents.[15] Removal of *O*-alkylidene acetals using I_2/MeOH has also been reported wherein, again, the formation of methyl glycosides has been a serious limitation.[16] In the light of the above observations, and based on the increased electrophilicity of iodine in IBr/ICl compared to molecular I_2, an investigation of the application of IBr as a promoter for the deprotection of trityl ethers was carried out.

Using the 6-*O*-trityl glucoside **3** the de-O-tritylation reaction conditions were first optimized. Thus, treatment of **3** in MeOH with IBr gave the alcohol **4** in 75–90% isolated yield. The efficiency of the reaction was dependent on the IBr concentration employed (see Table 1, entries 1–4).

Moving away from neat methanol as a solvent, MeCN proved more effective for the reaction (entries 5–7, Table 1) than either THF or CH_2Cl_2 (entries 8 and 9, Table 1). As the efficacy of the I_2/MeOH system for the removal of TBDMS ethers and isopropylidene acetals was at least in part attributed to HI produced in situ, the de-O-

Table 1 Deprotection of Trityl Ether **3** Using IBr[a]

3 **4**

Entry	Solvent	IBr (mol equiv)	Time (min)	Yield (%, **4**)[b]
1	MeOH	0.5	8 h	75
2	MeOH	1.2	1 h	85
3	MeOH	1.5	45	90
4	MeOH	2.0	45	90
5	MeCN	1.2	30	90
6	MeCN	1.5	<15	95
7	MeCN	2.0	<15	95
8[c]	THF	1.2	3 h	45
9[d]	CH_2Cl_2	1.2	6 h	47
10	CH_2Cl_2–MeOH (9:1)	1.2	5	92

[a] Substrate (0.25–1.0 mmol) dissolved in the desired solvent (1–2 mL/100 mg **3**) was treated with IBr (commercially available 1 M soln in CH_2Cl_2).
[b] Yield calculated after aq workup and column chromatography.
[c] Reaction was complete but byproduct from acetyl migration was significant.
[d] Reaction was incomplete and unchanged **3** was isolated.

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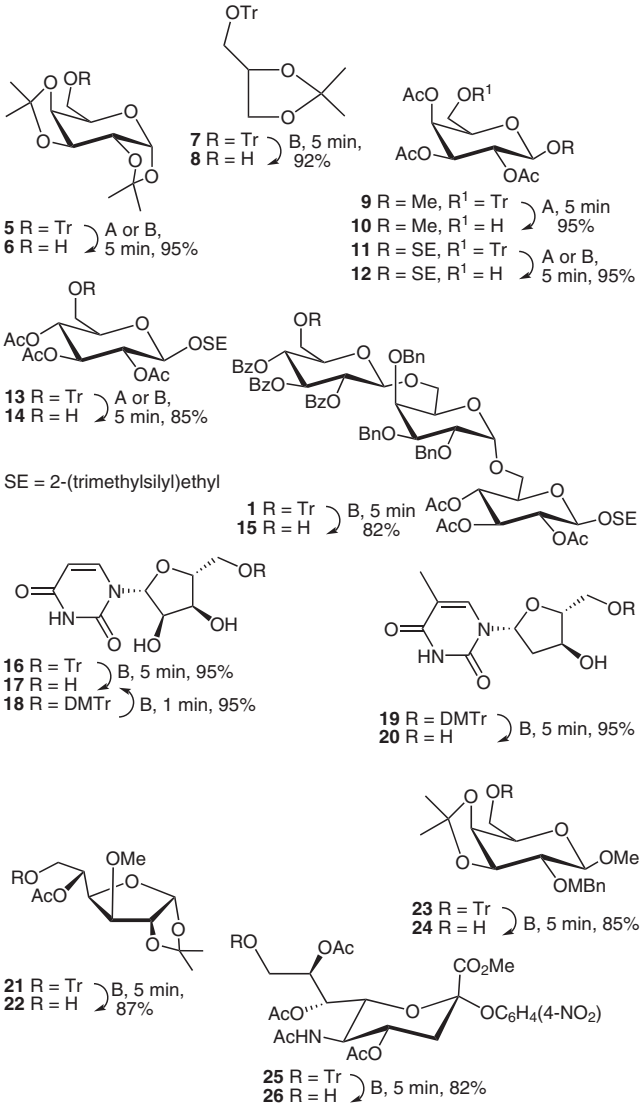
tritylation reaction was also conducted in CH_2Cl_2 containing a small portion of MeOH. Interestingly, the reaction under these conditions was found to be almost instantaneous, and it was judged to be clean by ^1H NMR spectroscopy (entry 10, Table 1). Thus, our contention that if HBr, produced in situ by the reaction of IBr with MeOH, had indeed been the main causative agent for the deprotection, it must be more available for the deprotection reaction in CH_2Cl_2 than in MeOH. To further verify this point, when the trityl ether **3** (56 mg, 0.1 mmol) was treated with a solution of HBr–AcOH reagent (50 μL, 33% w/v) in anhydrous CH_2Cl_2 (1 mL) the deprotection reaction was complete nearly instantaneously, again giving the desired alcohol **4** in excellent yield (92%, isolated).[17] As *O*-isopropylidene acetals are known to be susceptible to protic acids, a galactopyranosyl derivative **5**, bearing both trityl and isopropylidene acetal groups, was subjected to the above deprotection conditions. This reaction allowed evaluation of the relative advantages of the two methods in terms of the scope for achieving chemoselectivity. Indeed, it was found that while the IBr method gave the desired chemoselectivity, resulting in the deprotected diacetonide **6** (5 min, 95% isolated yield), the same reaction performed in the presence of HBr–AcOH led to the instantaneous removal of the trityl group along with partial loss[18] of the isopropylidene protecting groups (Scheme 1). The distinct advantage of employing IBr for the reaction thus became evident.

In addition, treatment of the glycerol derivative **7**, bearing a trityl ether as well as an isopropylidene acetal group, with IBr in CH_2Cl_2 led to the chemoselective formation of 1,2-*O*-isopropylidene glycerol (**8**; 5 min, 92% isolated). In contrast, the same reaction in the presence of HBr–AcOH in CH_2Cl_2 resulted in the formation of glycerol, confirming the clear advantage of using IBr for the chemoselective deprotection of the trityl ether functionality of acid-sensitive substrates such as **5** and **7**.

The scope of the IBr method was then evaluated by subjecting various other substrates bearing common protecting groups that are sensitive to different reaction conditions. The results show that functional groups that are typically susceptible to acidic (Lewis/protic acid; see **9**, **11**, **13**, **21**, **23**, and **25**) or basic (see **1**, **9**, **11**, **13**, **21**, and **25**) conditions are well tolerated. Also, the method is equally suited for the deprotection of the trityl/dimethoxytrityl groups in nucleosides (see **16**, **18**, and **19**). The current method is thus superior to literature methods, and its novelty lies in the fact that it is simple to perform, it requires short time periods, it avoids the formation of by-products, and is high-yielding.

In summary, we have demonstrated that IBr in MeCN and IBr in CH_2Cl_2–MeOH are excellent reagent systems for the deprotection of *O*-Tr and *O*-DMTr ethers. These reagent systems represent improved, practical alternatives to many of the reagents that are currently available for the purpose.[19]



Scheme 1 Deprotection of trityl ethers using IBr.[19] Method A: IBr/MeCN (1.2 mol equiv), r.t. Method B: IBr (1.2 mol equiv) in CH_2Cl_2–MeOH (9:1), r.t.

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(17) The workup and isolation of the product are also a lot more convenient in the present case as the literature method[3] makes use of glacial AcOH as the solvent for the reaction.
(18) Treatment of **5** with HBr/AcOH reagent in CH_2Cl_2 as described for **3** led to the formation of a mixture of 1,2-*O*- and 3,4-*O*-isopropylidene-D-galactoses and D-galactose as judged by TLC and ^1H NMR spectroscopy.
(19) **Typical Procedure for Conversion of 3 → 4**
Method A
IBr (1.2 mL of a 1 M soln in CH_2Cl_2, 1.2 mmol) was added to a soln of **3** (562 mg, 1 mmol) in MeCN (10 mL) and was stirred until TLC (EtOAc–hexanes, 2:3) showed completion of the reaction. The reaction mixture was then diluted with CH_2Cl_2 and was washed successively with dilute aq $Na_2S_2O_3$ and Na_2CO_3 soln, dried (Na_2SO_4), concentrated to dryness under reduced pressure and was purified by column chromatography (silica gel; EtOAc–hexanes, 2:3) to yield crystals (308 mg, 95%) of **4**.
Alternatively, after the completion of the reaction, the workup can also be carried out by stirring the reaction mixture with Amberlite IRA-400 (hydroxide form) resin to get a colourless solution. Filtration, concentration of the filtrate under reduced pressure, and chromatography as described above afforded **4**.
Method B
The reaction was carried out by the same procedure as described above but CH_2Cl_2–MeOH (9:1) was used as the solvent instead of MeCN. The product was obtained in practically the same yield.