JOC*Note*

Mild and Efficient Chemoselective Deprotection of Anomeric *O*-Methyl Glycosides with Trityl Tetrafluoroborate

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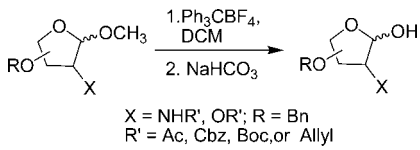
Received March 28, 2008



A facile chemoselective deprotection of anomeric *O*-methyl glycosides has been achieved in good to excellent yields within 10−40 min with use of trityl tetrafluoroborate in dichloromethane at ambient temperatures. The present method is easily implemented and tolerates different functional groups.

One of the crucial steps in organic synthesis, including carbohydrate chemistry, involves selective interconversion of functional groups.[1] In this context changes at the anomeric center are particularly important since it usually plays a key role in the synthesis of oligosaccharides and glycoconjugates[2] as well as in organic synthesis utilizing sugars as chiral synthons.[3,4] The anomeric −*O*Me group in an *O*-methyl glycoside[5] acts as an effective protecting group in carbohydrate chemistry as it is relatively stable under basic conditions. Usually the deprotection of the anomeric *O*-methyl group is carried out by using protic[6] and Lewis acids.[7] However, deprotection under these conditions, sometimes, requires a long reaction time,[6a,g] high temperature,[6a,d,f] and strong acids. Further, selective hydrolysis in the presence of other functional groups is also not easily observed. Hence, there remains a need to develop a mild, neutral, and chemoselective method for deprotecting the anomeric *O*-methyl glycosides especially with highly functionalized molecules that cannot tolerate strong acidic conditions.

In an ongoing project in our laboratory related to the synthesis of glycosidase inhibitors we faced the difficulty of selectively hydrolyzing the anomeric −*O*Me group of molecule **1a** (Table 1), which resulted in the decomposition of the starting material while, using protic acid mediated deprotection. Hence we explored the possibility of using a rather neutral method for this purpose. In this context, it was found from literature that the synthetic use of trityl tetrafluoroborate as a reagent has been widely investigated[8] in various organic transformations particularly in the deprotection of benzyl ethers. However, it was anticipated that in preference to a benzyl ether, the anomeric −*O*Me group should be easily deprotected due to higher nucleophilicity of the anomeric oxygen as well as higher stability of the carbocation at the anomeric center that could result after the hydride transfer. Based on this, in this Note, we report, for the first time, a practical and highly chemoselective method for the deprotection of *O*-methyl glycosides under extremely mild conditions by using trityl tetrafluoroborate as a reagent in good to excellent yields (Table 1). Under these conditions several functional groups such as benzyl, acyl, amide, and carbamates remain unaffected. The reactions were carried out by dissolving anomeric *O*-methyl glycosides in dichloromethane followed by the addition of trityl tetrafluoroborate and stirring the reaction mixture at room temperature. The results are summarized in Table 1. The yields are good to excellent, ranging from 72% to 92% in most cases. The functionalized *O*-methyl furanosides (entries 1−6) were converted to the corresponding lactols within 10−45 min, whereas tetrabenzylated *O*-methyl pyranosides (entries 7−9) took longer reaction times of up to 8−10 h. These results indicate that in the presence of a benzylic ether only anomeric *O*-methyl glycosides are hydrolyzed.

Interestingly, when the same reactions were performed with 2-hydroxy (**10a** and **11a**) as well as *NH*Boc-substituted (**12a**) furanosides (Scheme 1), a dual behavior was observed. Thus, we found that substrates **10a** and **11a** afforded the corresponding epoxides **10a′** and **11a′** whereas compound **12a** gave the bicyclic carbamate **12a′**, respectively (Scheme 1). This indicates that an oxacarbenium ion was formed as an intermediate and the free hydroxy and amide groups at the C-2 position undergo intramolecular nucleophilic substitution reactions as shown in Scheme 2.

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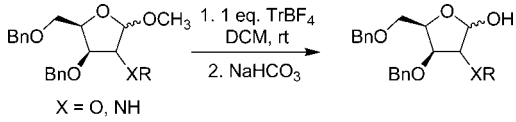
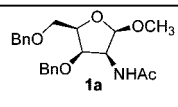
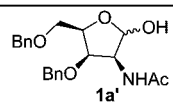
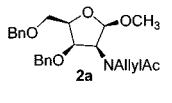
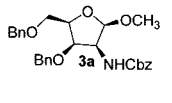
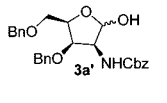
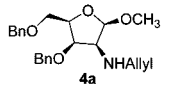
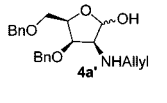
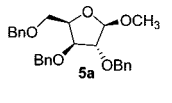
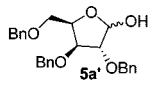
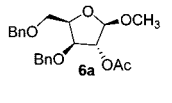
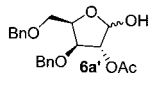
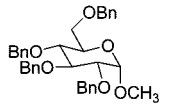
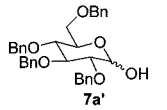
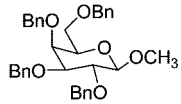
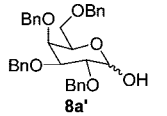
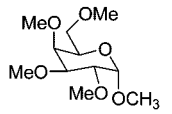
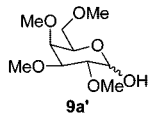
10.1021/jo800693w CCC: $40.75
Published on Web 06/27/2008

TABLE 1. Deprotection of Anomeric *O*-Methyl Glycosides with Trityl Tetrafluoroborate at Room Temperature[a,b]



entry	substrate	product	time (min)	yield (%)	α/β ratio
1	 **1a**	 **1a'**	30	90	1.1:1
2	 **2a**	 **2a'**	10	92	1:1
3	 **3a**	 **3a'**	30	89	1:1
4	 **4a**	 **4a'**	45	89	1.2:1
5	 **5a**	 **5a'**	30	85	1:1
6	 **6a**	 **6a'**	40	82	1:1
7	 **7a**	 **7a'**	8h	78	1.2:1
8	 **8a**	 **8a'**	10 h	75	1:1
9	 **9a**	 **9a'**	10 h	72	1:1

[a] Reactions were performed as described in the general procedure. [b] Substrates and products displayed satisfactory ^{1}H and ^{13}C NMR and HRMS.

The stereochemistry at the ring junctions of compounds **11a′** and **12a′** was confirmed by NOE experiments as shown in Figure-1. For compound **11a′**, no NOE interactions were observed between H-4, H-1, and H-2 indicating that H-1, H-4 and H-2, H-4 are trans to each other. On the other hand,

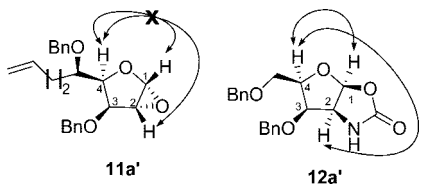
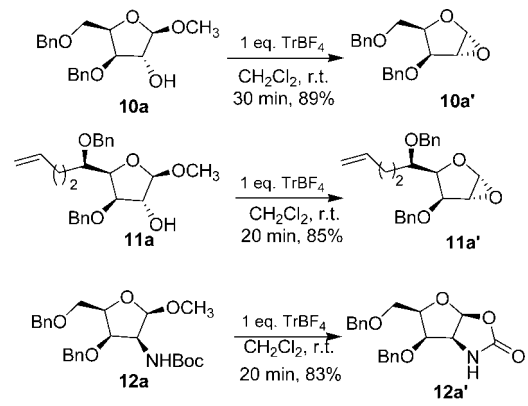
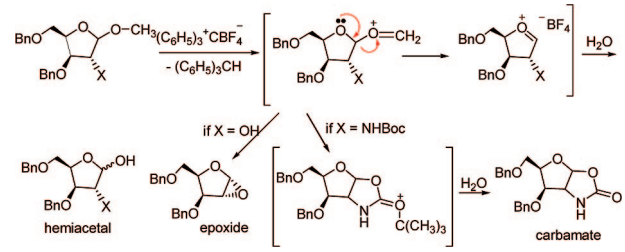


FIGURE 1. NOE correlations of compounds **11a′** and **12a′**.

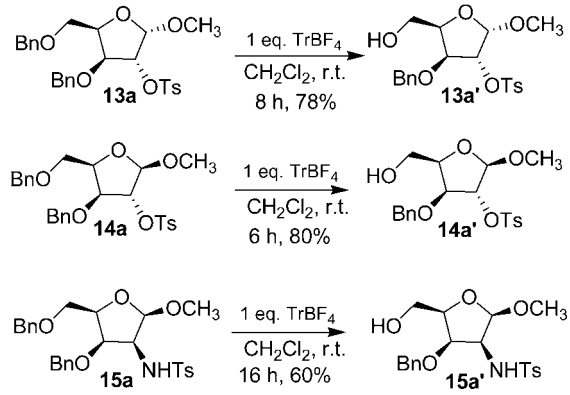
SCHEME 1. One-Pot Synthesis of Epoxide and Bicyclic Carbamate from *O*-Methyl Glycosides



SCHEME 2. Plausible Mechanisim for Anomeric *O*-Methyl Glycosides Hydrolysis and for Epoxide and Carbamate Formation



SCHEME 3



irradiation of the H-4 proton of compound **12a′** enhanced the peaks corresponding to H-3, H-2, and H-1 protons and clearly these are cis to each other

A plausible mechanism along the lines proposed in the literature[8] with use of trityl tetrafuloroborate is depicted in Scheme 2. This involves transfer of a hydride ion from the anomeric −*O*Me group to the trityl cation followed by loss of HCHO, generation of an oxonium ion, and finally hydrolysis.

Surprisingly, with substrates bearing C-2 *O*-tosyl and *NH*-tosyl substituents primary *O*-benzyl groups were debenzylated as depicted in Scheme 3. The products were characterized by functional group interconversions as well as NMR and mass spectral studies.

This peculiar behavior could be attributed to the steric hindrance provided by *O*- and *N*-tosyl groups present adjacent to the anomeric *O*-methyl glycosides which prevent the interaction of the −*O*Me group. Subsequently, the sterically less hindered primary −*O*Bn group is deprotected.

In conclusion, trityl tetrafluoroborate chemistry can be successfully applied to a wide range of functionalized *O*-methyl glycosides, affording the corresponding lactols in good to excellent yields. This method is easy to implement and tolerates several functional groups and is chemoselective in most of the cases. Further expolartion of this methodology is currently under study in our laboratory.

Experimental Section

General Experimental Procedure for Deprotection of Anomeric *O*-Methyl Glycosides. To a solution of an anomeric *O*-methyl glycoside (1 mmol) in dry dichloromethane (3 mL) was added trityl tetrafluoroborate (330 mg, 1 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for the required length of time (Table 1). After completion of the reaction (TLC monitoring), the mixture was quenched with an excess of sodium hydrogen carbonate. The organic phase was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product obtained was further purified by column chromatography on silica gel (100−200 mesh).

***tert*-Butyl (2*R*,3*S*,4*R*,5*R*)-4-(Benzyloxy)-5-(benzyloxymethyl)-2-methoxytetrahydrofuran-3-ylcarbamate (12a).** The amine **2** (200 mg, 1.75 mmol) was dissolved in CH_2Cl_2 (3 mL) and treated with Et_3N (0.33 mL, 2.37 mmol) and $(Boc)_2O$ (518 mg, 2.37) at room temperature then the mixture was stirred for 3 h. The reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL) and the organic layer was washed with water and brine. The usual workup gave a crude product that was purified by column chromatography to give compound **12a**. Yield 85%. R_f 0.50 (hexane:ethyl acetate, 4:6), $[\alpha]_D^{28}$ +88.5 (*c* 1.45, CH_2Cl_2). IR (CH_2Cl_2) ν_{max} 3062, 2823, 1679, 1420 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.25 (m, 10H), 5.18 (d, 1H, J = 4.6 Hz), 4.89 (t, 1H, J = 4.6 Hz), 4.66 (d, 1H, J = 11.7 Hz), 4.60 (s, 1H), 4.54 (d, 1H, J = 10.4 Hz), 4.49 (d, 1H, J = 10.4 Hz), 4.40 (ddd, 1H, J = 10.4, 6.3, 4.2 Hz), 4.30 (dd, 1H, J = 6.3, 4.6 Hz), 3.73 (dd, 1H, J = 10.7, 4.2 Hz), 3.64 (dd, 1H, J = 10.7, 6.6 Hz), 3.41 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (100 MHz) δ 155.8, 137.7, 137.6, 128.3−127.5 (m), 107.5, 79.1, 77.6, 73.7, 73.0, 68.0, 55.3, 55.0, 40.2, 28.3, 27.7, 21.3. HRMS calcd for $C_{25}H_{34}NO_6$ $[M + H]^+$ 444.2386, found 444.2310.

(3a*S*,5*R*,6*R*,6a*S*)-6-(Benzyloxy)-5-(benzyloxymethyl)tetrahydrofuro[3,2-*d*]oxazol-2(1*H*)-one (12a′). Yield 83% (syrup). R_f 0.50 (hexane:ethyl acetate, 6:4), $[\alpha]_D^{28}$ +18.2 (*c* 0.85, CH_2Cl_2). IR (CH_2Cl_2) ν_{max} 3291, 3062, 2923, 1767, 1454 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.26 (m, 10H, Ar), 5.94 (d, 1H, J = 2.6 Hz, H-1), 5.73 (s, 1H, NH), 4.63 (d, 1H, J = 11.7 Hz, $-OCH_2Ph$), 4.59 (d, 1H, J = 11.7 Hz, $-OCH_2Ph$), 4.49−4.44 (m, 3H, 2 × $-OCH_2Ph$ and H-4), 4.16−4.12 (m, 2H, H-3, and H-2), 3.75 (dd, 1H, J = 11.0, 4.1 Hz, H-5), 3.53 (dd, 1H, J = 11.0, 7.3 Hz, H-5′). ^{13}C NMR (100 MHz) δ 157.3, 137.9, 136.7, 128.7−127.5 (m), 120.7, 80.1, 77.8, 73.5, 73.4, 69.4, 56.8. HRMS calcd for $C_{20}H_{22}NO_5$ $[M + H]^+$ 356.1498, found 356.1492.

Acknowledgment. We thank the Department of Science and Technology, New Delhi, for financial support in the form of a Ramanna Fellowship to Y.D.V. (Grant No. SR/S1/RFOC-04/2006). A.K. and D.V.R. thank the CSIR, New Delhi for senior research fellowships.

Supporting Information Available: Compounds **5a**, **5a′**, **7a**, **7a′**, **8a**, **8a′**, **9a**, **9a′**, **10a**, **10a′**, **13a**, and **14a** have been previously characterized and their NMR spectral data were in good agreement with the literature data; experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800693W