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Efficient and Selective Removal of Methoxy Protecting Groups in Carbohydrates

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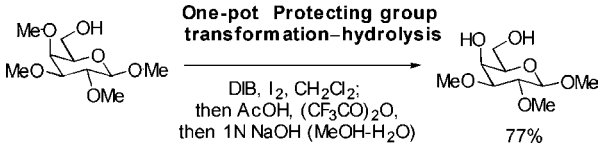
ABSTRACT



The selective removal from carbohydrate substrates of methoxy protecting groups next to hydroxy groups is reported. On treatment with $PhI(OAc)_2$–I_2, the methoxy group is transformed into an easily removable acetal. The mild conditions of this methodology are compatible with many functional groups, and good to excellent yields are usually achieved.

The methoxy group can be readily formed and is stable to a wide range of reaction conditions. Hence, it has been frequently used as a protecting group in carbohydrates and many other substrates.[1] On the other hand, the removal of this robust ether is often difficult, requiring conditions not compatible with other functional groups. Moreover, if several methoxy groups are present in the same molecule (as in product **1**, Scheme 1), the selective removal of one of them is challenging. These problems are especially important in carbohydrate systems where mild, selective deprotection conditions are usually required.

We report now on an efficient methodology to selectively remove methoxy groups next to hydroxy functions (Scheme 1). The methoxy group is transformed, under mild conditions, into an acetal **2** or **3**, which can be hydrolyzed in the presence of many functional groups, including other acetals.

The transformation is achieved using a tandem radical hydrogen abstraction−oxidation reaction. Thus, on treatment with (diacetoxyiodo)benzene (DIB) and iodine, the hydroxy group generates an alkoxyl radical (as in intermediate **4**, Scheme 1), which abstracts nearby hydrogen atoms within a suitable distance (2.3−2.8 Å).[2,3] The intramolecular H-abstraction (IHA) from a methoxy group gives a C-radical **5** stabilized by the adjacent oxygen atom. Under the reaction conditions, the C-radical is oxidized to an oxycarbenium ion **6**,[4] which is trapped intra- or intermolecularly by nucleophiles such as hydroxy groups (route a) or acetate ions from the reagent (route b).

Several carbohydrate substrates were prepared to study the scope of this methodology. The galactose anomers **7** and **8** (Table 1), the glucose derivatives **9**−**12**, and the rhamnose derivative **13** were obtained from commercial sugars.[5]

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons: New York, 1991.

(2) IHA. Reviews: (a) Cekovic, Z. *Tetrahedron* **2003**, *59*, 8073−8090. (b) Feray, L.; Kuznetsov, N.; Renaud, P. In *Radicals in Organic Synthesis;* Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 246−278. (c) Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, *30*, 94−103. (d) Majetich, G.; Wheless, K. *Tetrahedron* **1995**, *51*, 7095−7129, and references therein.

(3) For recent examples of hydrogen abstraction reaction, see: (a) Jastrzebska, I.; Morzycki, J. W.; Trochimowicz, U. *Tetrahedron Lett*. **2004**, *45*, 1929−1932. (b) Sartillo-Piscil, F.; Vargas, M.; Anaya-de-Parrodi, C.; Quintero, L. *Tetrahedron Lett*. **2003**, *44*, 3919−3921. (c) Lee, J. S.; Fuchs, P. L. *Org. Lett.* **2003**, *5*, 2247−2250. (d) Aubele, D. L.; Floreancig, P. E. *Org. Lett.* **2002**, *4*, 3443−3446. (e) Crich, D.; Huang, X.; Newcomb, M. *J. Org. Chem.* **2000**, *65*, 523−529. (f) Chatgilialoglu, C.; Gimisis, T.; Spada, G. P. *Chem.—Eur. J.* **1999**, 2866−2876. (g) Allen, P. A.; Brimble, M. A.; Prabaharan, H. *Synlett* **1999**, 295−298. (h) Petrovic, G.; Saicic, R. N.; Cekovic, Z. *Synlett* **1999**, 635−637. (i) Frey, B.; Wells, A. P.; Rogers, D. H.; Mander, L. N. *J. Am. Chem. Soc.* **1998**, *120*, 1914−1915. (j) Tsunoi, S.; Ryu, I.; Okuda, T.; Tanaka, M.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1998**, *120*, 8692−8701. (k) Allen, P. R.; Brimble, M. A.; Fares, F. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2403−2411. (l) Dorta, R. L.; Martín, A.; Salazar, J. A.; Suárez, E.; Prangé, T. *J. Org. Chem.* **1998**, *63*, 2251−2261.

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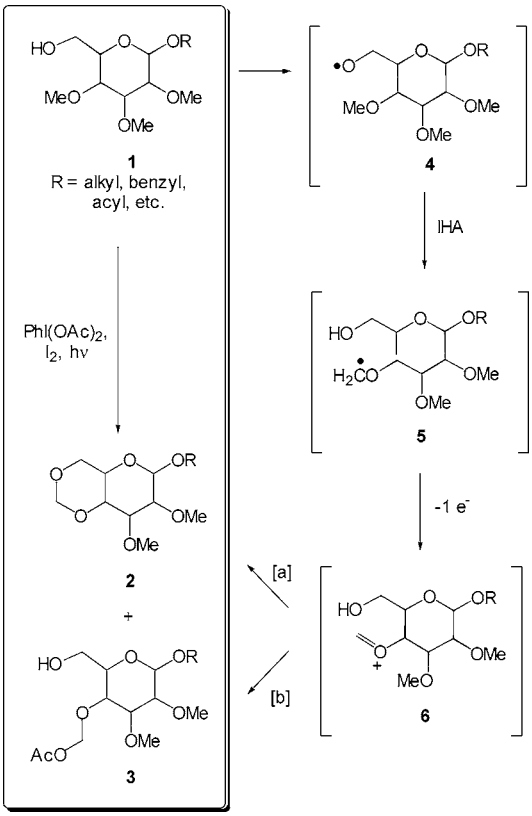
Scheme 1. Selective Methoxy Protecting Group Transformation



Substrate **7** underwent reaction with DIB and iodine after irradiation with visible light in CH_2Cl_2 to give methylenedioxy acetal **14**[6] as the major product (entry 1, Table 1), and the *O*-methyl acetate **15** as the minor product, in 82% overall yield. The other galactose anomer **8** gave similar results (entry 2).

The 1α-benzylglucose derivative **9** yielded a cyclic acetal **18** as the sole product under identical conditions (entry 3). A similar yield was obtained with the 1*β*-*O*-benzyl epimer **10** (entry 4). Interestingly, no hydrogen abstraction was observed from the benzylic position.[4a]

The hydrogen abstraction was then studied with the glucose substrate **11**, which presented a secondary hydroxy group (entry 5). Although the MM2 calculations[7] suggested that the distance between the oxygen at C-4 and the 3-OMe hydrogens was suitable for *H*-abstraction (2.5−2.9 Å), the *β*-fragmentation could be an important side-reaction. In fact, it is known that secondary O-radicals usually give scission as the main reaction when the resulting C-radical is stabilized by oxygen functions.[4,8]

To our satisfaction, the hydrogen abstraction was the main reaction, and the mixed acetal **20** was obtained in satisfactory yield. The other expected product, the cyclic acetal **21**, could not be isolated as a pure compound. Observing that it was a volatile product, the protecting group transformation was repeated with the 1-*O*-benzyl analogue **12**. In this case, both the mixed acetal **22** and the cyclic acetal **23** could be isolated, as the major and minor product, respectively.

The rhamnose substrate **13** also presented a secondary hydroxy group. As in the previous case, the calculated distance $C_2-\boldsymbol{O\cdots H}-CH_2O-C_4$ (about 2.4−2.8 Å) was suitable for the abstraction. According to this, the abstraction products **24** and **25** were obtained in excellent overall yield (entry 7). Again, the major product was the *O*-methyl acetate **24** and not the methylene dioxy acetal **25**.

The cleavage of the cyclic and the acetoxy acetals was then studied via acetolysis. As seen before, the functionalization of substrate **8** gave the acetals **16** and **17** (Scheme 2). When the methylenedioxy acetal **16** was treated with acetic acid and trifluroacetic anhydride (TFAA),[9] the mixed acetals **26** and **27** were obtained in 52 and 45% yield, respectively (97% global yield). In both compounds, the oxygen functions on C-4 and C-6 are differently protected, and hence further selective manipulation of the molecule is possible.

In case that the 4,6-diol **28**[10] is required, it can be obtained in excellent yield by treatment of products **26**, **27**, or **17** with methanolic NaOH.

The possibility of obtaining the diol **28** directly from substrate **8**, avoiding the purification of the acetal intermediates, was tempting. To study the feasibility of the one-pot H-abstraction−cleavage process, the substrate **8** was treated under hydrogen abstraction conditions; then, the solvent was

(4) (a) It has been reported that the primary alkoxy radicals derived from carbohydrates in the furanose form gave a mixture of fragmentation and intramolecular hydrogen abstraction (IHA): Boto, A.; Hernández, D.; Hernández, R.; Suárez, E. *J. Org. Chem.* **2003**, *68*, 5310−5319. Under appropriate conditions, the fragmentation predominated over the IHA. In contrast, the pyranose substrates described in this communication gave IHA as the sole reaction. (b) For other related works, see: Francisco, C. G.; Herrera, A. J.; Suárez, E. *J. Org. Chem.* **2002**, *67*, 7439−7445. (c) Francisco, C. G.; Freire, R.; Herrera, A. J.; Pérez-Martín, I.; Suárez, E. *Org. Lett.* **2002**, *11*, 1959−1961. (d) Madsen, J.; Viuf, C.; Bols, M. *Chem.—Eur. J.* **2000**, *6*, 1140−1146. (e) Francisco, C. G.; Herrera, A. J.; Suárez, E. *Tetrahedron Lett.* **2000**, *41*, 7869−7873.

(5) (a) Compound **7**: Valangenhove, H.; Reinhold: V. N. *Carbohydr. Res.* **1985**, *143*, 1−20. (b) Compound **8**: Vries, N. K.; Buck, H. M. *Carbohydr. Res.* **1987**, *165*, 1−16. (c) Compounds **9** and **10**: Francisco, C. G.; González, C. C.; Suárez, E. *J. Org. Chem.* **1998**, *63*, 2099−2109. (d) Compound **11**: Reuben, J. *Carbohydr. Res.* **1986**, *157*, 201−213. (e) Compound **12**: See Supporting Information. (f) Compound **13**: Monneret, C.; Gagnet, R.; Florent, J. C. *Carbohydr. Res.* **1987**, *6*, 221−229.

(6) All compounds were completely characterized by ^1H and ^{13}C NMR, MS, HRMS, IR, and elemental analysis. Two-dimensional COSY, HSQC, and NOESY experiments were also carried out.

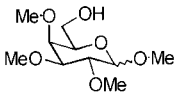
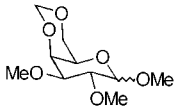
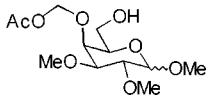
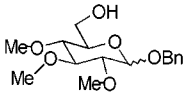
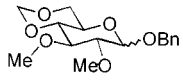
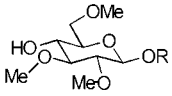
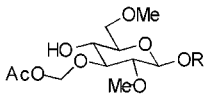
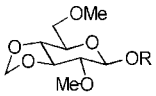
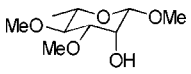
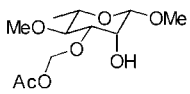
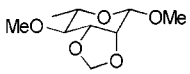
(7) Calculations using a MM2 force field model implanted in ChemBats3D ultra 6.0 from CambridgeSoft (www.cambridgesoft.com).

(8) For reviews on *β*-fragmentation, see: (a) Hartung, J.; Gottwald, T.; Spehar, K. *Synthesis* **2002**, 1469−1498. (b) Zhdankin, V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523−2584. (c) Togo, H.; Katohgi, M. *Synlett* **2001**, 565−581. (d) Zhang, W. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 234−245. (e) Suárez, E.; Rodríguez, M. S. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 440−454. (f) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224−2248. (g) Wirth, T.; Hirt, U. H. *Synthesis* **1999**, 1271−1287. (h) Yet, L. *Tetrahedron* **1999**, *55*, 9349−9403. (i) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: New York, 1997. (j) Brun, P.; Waegell, B. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1983; Vol. 3, pp 367−426. (k) See also: Wilsey, S.; Dowd, P.; Houk, K. N. *J. Org. Chem.* **1999**, *64*, 8801−8811 and references therein.

(9) Different deprotection procedures were studied. The best results were obtained with the $AcOH-(CF_3CO)_2O$ system: Gras, J. L.; Pellissier, H.; Nouguier, R. *J. Org. Chem.* **1989**, *54*, 5675−5677.

(10) Evtushenko, E. V. *Carbohydr. Res.* **1999**, *316*, 187−200.

Table 1. Selective Transformation of Methoxy Protecting Groups into Acetals Using Carbohydrate Substrates

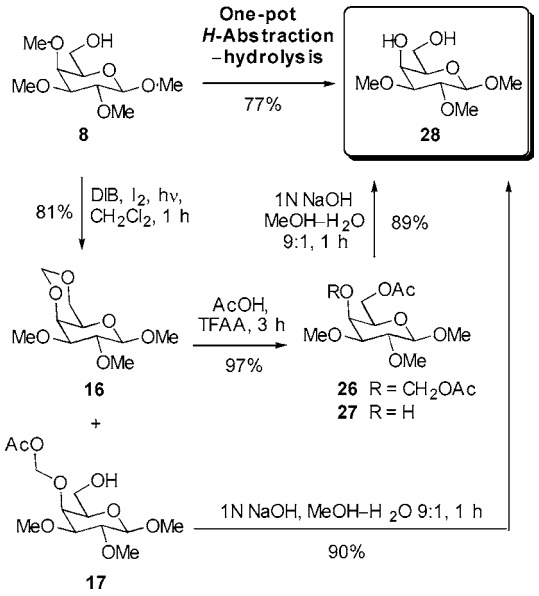
Entry	Substrate	Products (%)[b]		Overall Yield
				
1	**7** 1α-OMe	**14** 1α-OMe (68)	**15** 1α-OMe (14)[c]	82%
2	**8** 1β-OMe	**16** 1β-OMe (70)	**17** 1β-OMe (11)	81%
				
3	**9** 1α-OBn	**18** 1α-OBn (66)		66%
4	**10** 1β-OBn	**19** 1β-OBn (51)		51%
				
5	**11** R = Me	**20** R = Me (54)	**21** R = Me (–)[d]	54%
6	**12** R = Bn	**22** R = Bn (52)	**23** R = Bn (17)	69%
				
7	**13**	**24** (80)	**25** (10)[c]	90%

[a] Conditions: DIB (1.5 equiv), I_2 (1 equiv), CH_2Cl_2, 25 °C, irradiation with two 80 W tungsten filament lamps. [b] Yields are given for products purified by chromatography on silica gel. [c] Minor product **15** could not be separated from the major product **14**. The product ratio was calculated by NMR. [d] Product **21** proved to be volatile. [e] Minor product **25** could not be separated from the major product **24**. The product ratio was calculated by NMR.

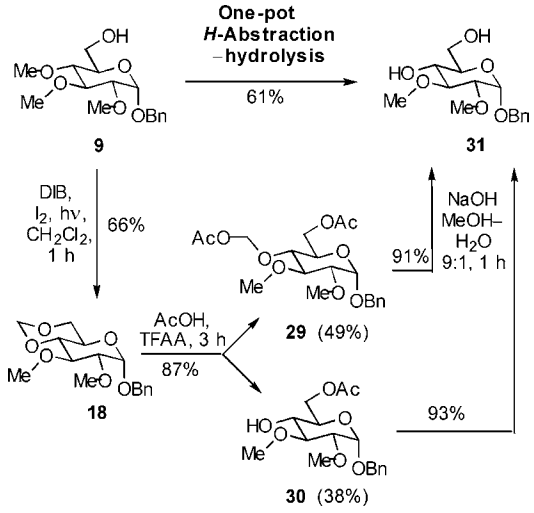
removed under vacuum, and glacial acetic acid and trifluroacetic anhydride were added at 0 °C. After the mixture was stirred for 2 h at room temperature, the solvent was evaporated and 4% NaOH in MeOH−H_2O (9:1) was added, affording the 4,6-diol **28** in good overall yield (77%).

Similarly, treatment of the 1α-benzyl-4,6-methylene glucose derivative **18** (Scheme 3), formed from substrate **9**, with acetic acid and trifluroacetic anhydride afforded the *O*-methyl

Scheme 2. One-Pot Transformation of Substrate **8** into Diol **28**



Scheme 3. One-Pot Transformation of Substrate **9** into Diol **31**

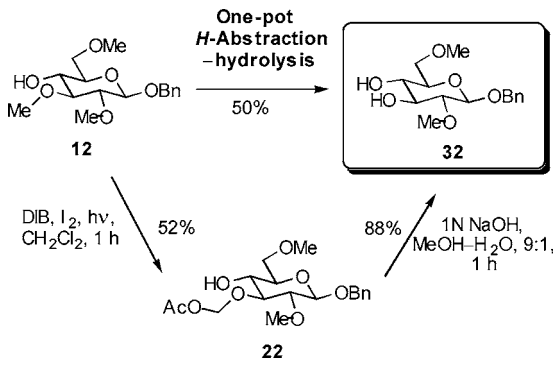


acetate **29** and the acetate **30** in excellent global yield. It must be noted that the 1-*O*-benzyl group was not affected by the cleavage process conditions. Both products **29** and **30** released the 4,6-diol **31** by saponification.

The sequential H-abstraction−hydrolysis process was also carried out on **9**, under the previously described conditions, affording the diol **31** in 61% yield (Scheme 3).

As seen in the previous cases, the *O*-methyl acetates can be easily removed by basic hydrolysis. Also, as shown in the Table 1, in the selective deprotection of substrates **11**, **12**, and **13**, the major products were the *O*-methyl acetates **20**, **22**, and **24**, respectively. To exemplify the hydrolysis of these substrates, the acetoxy acetal **22** underwent treatment with methanolic NaOH (Scheme 4), affording the diol **32** in good yield (88%).

Scheme 4. One-Pot Transformation of Substrate **12** into Diol **32**



Moreover, when the glucose precursor **12** underwent the tandem protecting group transformation−cleavage reaction, the diol **32** was obtained in 50% yield.

In summary, a mild and efficient methodology to selectively cleave methoxy protecting groups next to hydroxy functions is described. The reaction was carried out with galactose, glucose, and rhamnose substrates. In the first step, the methoxy protecting group was transformed into a methylenedioxy acetal or an *O*-methyl acetate, using a tandem radical hydrogen abstraction−oxidation reaction. These acetal groups were then removed in good to excellent yields. To simplify this methodology, an efficient one-pot protecting group transformation−cleavage reaction was developed. The resulting diols were easily purified, and the yields were similar to those obtained in the multistep process.

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Supporting Information Available: Synthesis of substrate **12** and General Procedure for the one-pot protecting group transformation−hydrolysis. ^{1}H and ^{13}C NMR spectra and spectroscopic data for compounds **12**, **14**−**20**, **22**−**27**, and **29**−**32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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