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Highly Efficient and Mild Method for Regioselective De-*O*-benzylation of Saccharides by $Co_2(CO)_8$-Et_3SiH−CO Reagent System

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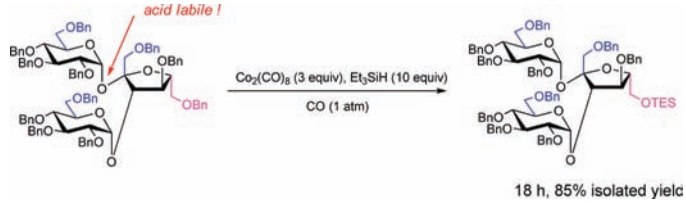
ABSTRACT



A highly efficient and mild method for the de-*O*-benzylation of protected saccharides was developed by transforming terminal benzyl ethers into silyl ethers using $Co_2(CO)_8$-Et_3SiH under 1 atm of CO. The method was successfully used for the de-*O*-benzylation of perbenzylated monosaccharides with various anomeric protecting groups, as well as natural disaccharides and trisaccharides such as sucrose, raffinose, and melezitose in good yields (>80%).

The selective protection and deprotection of hydroxyl groups plays a key role in carbohydrate chemistry owing to the universal presence of multiple hydroxyl groups and the need for controlled unmasking in the multistep chemical synthesis of complex oligosaccharides. The benzyl ether is one of the most widely used hydroxyl protecting groups because of its easy formation, inherent stability, and the large number of deprotection methods available.[1] Various methods have been developed to regioselectively introduce benzyl protecting groups, including the controlled selective benzylation of hydroxyl groups in carbohydrates[2] and the regioselective opening of benzylidene acetal derivatives.[3] Alternatively, an attractive route for the selective benzylation of carbohydrates is provided by the regioselective de-*O*-benzylation of easily available perbenzylated precursors.

Several selective de-*O*-benzylation methods have been studied for monosaccharides, which include acetolysis,[4] catalytic hydrogenolysis,[5] catalytic transfer hydrogenolysis,[6] Lewis acid deprotection (such as $TiCl_4$ and $SnCl_4$,[7] BCl_3,[8] $CrCl_2$/LiI,[9] TMSI[10]), TIBAL/DIBAL-H,[11] or halogenation with NIS.[12] Note that thioglycosides, which are the most

(1) Greene, T. W.; Wuts, P. G. M. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons: Hoboken, NJ, 2007; pp 102−120.

(2) (a) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643–663. (b) Hanessian, S. *Preparative Carbohydrate Chemistry*; Marcel Dekker: New York, 1997; pp 69−83. (c) Bouzide, A.; Sauvé, G. *Tetrahedron Lett.* **1997**, *38*, 5945–5948. (d) Grice, P.; Ley, S. V.; Pietruszka, J.; Priepke, H. W. M.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 351–363. (e) Classon, B.; Garegg, P. J.; Oscarson, S.; Tidén, A. K. *Carbohydr. Res.* **1991**, *216*, 187–196. (f) Wang, C.-C.; Lee, J.-C.; Luo, S.-Y.; Fan, H.-F.; Pai, C.-L.; Yang, W.-C.; Lu, L.-D.; Hung, S.-C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2360–2362.

(3) For recent examples, see: (a) Kumar, P. S.; Baskaran, S. *Tetrahedron Lett.* **2009**, *50*, 3489–3492. (b) Daragics, K.; Fügedi, P. *Tetrahedron Lett.* **2009**, *50*, 2914–2916. (c) Kumar, P. S.; Kumar, G. D. K.; Baskaran, S. *Eur. J. Org. Chem.* **2008**, 6063–6067. (d) Johnsson, R.; Olsson, D.; Ellervik, U. *J. Org. Chem.* **2008**, *73*, 5226–5232. (e) Tani, S.; Sawadi, S.; Kojima, M.; Akai, S.; Sato, K. *Tetrahedron Lett.* **2007**, *48*, 3103–3104.

(4) (a) Allerton, R.; Fletcher, H. G., Jr. *J. Am. Chem. Soc.* **1954**, *76*, 1757–1760. (b) Eby, R.; Sondheimer, S. J.; Schuerch, C. *Carbohydr. Res.* **1979**, *73*, 273–276. (c) Sakai, J.-I.; Takeda, T.; Ogihara, Y. *Carbohydr. Res.* **1981**, *95*, 125–131. (d) Angibeaud, P.; Utille, J.-P. *Synthesis* **1991**, 737–738. (e) Yang, G.; Ding, X.; Kong, F. *Tetrahedron Lett.* **1997**, *38*, 6725–6728. (f) Ganem, B.; Small, V. R., Jr. *J. Org. Chem.* **1974**, *39*, 3728–3730. (g) Brar, A.; Vankar, Y. D. *Tetrahedron Lett.* **2006**, *47*, 5207–5210.

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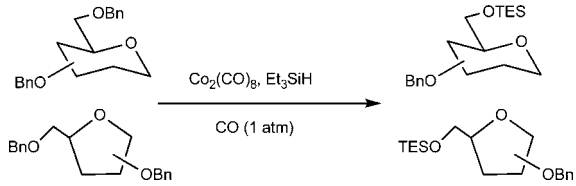
popular building blocks in carbohydrate chemistry, are rarely utilized with the above methods because the sulfur is prone to trap the strong electrophilic reagents.[4g] In addition, for most methods, careful manipulations are needed to obtain good selectivity and yield. Furthermore, there are few methods for selective debenzylation of complex saccharides.[11] The difficulty obviously arises from the presence of more benzyl ethers with similar reactivity. As a consequence, development of mild methods that are compatible with various anomeric protecting groups and that can achieve high selectivity and good yields is necessary.

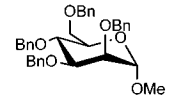
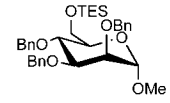
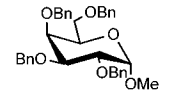
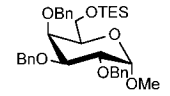
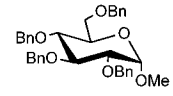
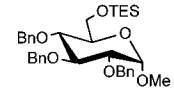
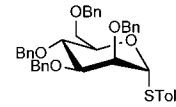
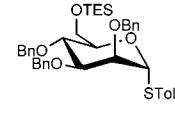
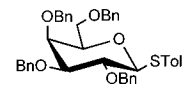
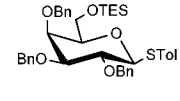
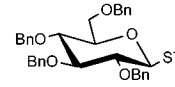
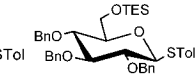
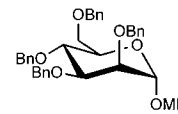
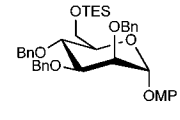
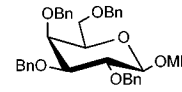
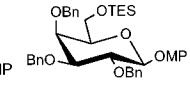
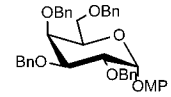
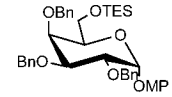
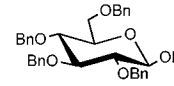
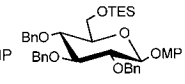
Natural disaccharides or trisaccharides, such as sucrose, raffinose, and melezitose, have attracted considerable interest in the chemical, biological, and material fields due to their easy availability in large quantities and special properties.[13] For example, sucrose can be used for the preparation of biodegradable polymers and surfactants;[13b,14] derivatives of sucrose and raffinose modified at terminal positions possess interesting biological properties;[15] melezitose possesses unique physiological activity and is often used in Chinese medicine.[16] Thus, great efforts have been made to synthesize selectively *O*-benzylated intermediates for the preparation of multifunctional derivatives with tunable properties. However, results are not satisfactory because of the presence of many similar hydroxyl groups and the acid labile properties of glycosidic bonds.[17] Herein we described an efficient method for the selective de-*O*-benzylation of protected sugars that involves transforming the benzyl ethers into silyl ethers, which can be used for the preparation of monosaccharides, natural disaccharides, and trisaccharides with free primary hydroxyl groups (Scheme 1).

Scheme 1. Regioselective De-*O*-benzylation of Saccharides by $Co_2(CO)_8$-Et_3SiH−CO Reagent System



During our experiments with siloxymethylation of glycosides according to Murai's protocol,[18] we accidentally found that when treated with 1.5 equiv of $Co_2(CO)_8$ and 6.0 equiv of Et_3SiH in CH_2Cl_2 at room temperature under 1 atm CO, perbenzylated methyl mannoside **1a** (Table 1) was converted smoothly to the silylated product **1b** (Table 1) in 48 h in a yield of 75%. The reaction rate was greatly improved by carrying out the reaction in benzene at 50 °C while selectivity

Table 1. Regioselective De-O-benzylation of Perbenzylated Monosaccharides[a]

entry	substrates	products	time (h)	yield[b] (%)
1	 **1a**	 **1b**	18	92
2	 **2a**	 **2b**	24	90
3	 **3a**	 **3b**	30	90
4	 **4a**	 **4b**	18	91
5	 **5a**	 **5b**	18	90
6	 **6a**	 **6b**	24	92
7	 **7a**	 **7b**	18	87
8	 **8a**	 **8b**	30	85
9	 **9a**	 **9b**	18	88
10	 **10a**	 **10b**	30	85

[a] Reaction condition: $Co_2(CO)_8$ (1.5 equiv), Et_3SiH (6 equiv), CO (1 atm), benzene, 50 °C. [b] Isolated yields.

(5) (a) Beaupère, D.; Boutbaia, I.; Wadouachi, A.; Fréchou, C.; Demailly, G.; Uzan, R. *New J. Chem.* **1992**, *16*, 405–411. (b) Maryanoff, B. E.; Reitz, A. B.; Tutwiler, G. F.; Benkovic, S. J.; Benkovic, P. A.; Pilkis, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 7851–7853.

(6) Cruzado, M. del, C.; Martín-Lomas, M. *Tetrahedron Lett.* **1986**, *27*, 2497–2500.

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(8) Xie, J.; Ménand, M.; Valéry, J.-M. *Carbohydr. Res.* **2005**, *340*, 481–487.

(9) Falck, J. R.; Barma, D. K.; Venkataraman, S. K.; Baati, R.; Mioskowski, C. *Tetrahedron Lett.* **2002**, *43*, 963–966.

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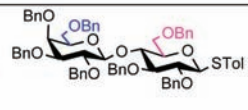
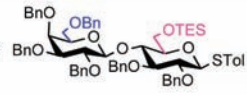
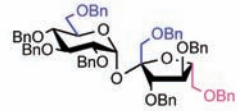
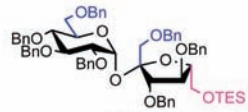
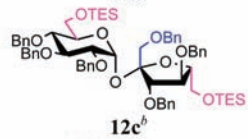
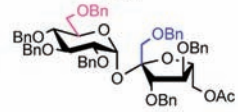
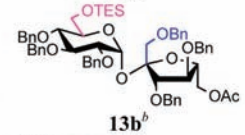
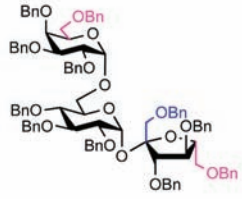
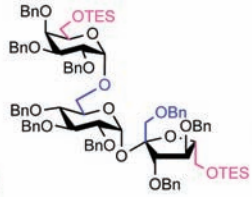
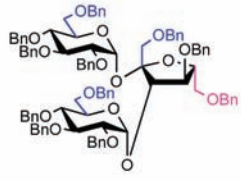
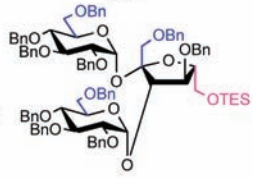
was not influenced (Table 1, entry 1). Under these conditions, all the entries (Table 1) gave excellent yields within 24 h, except that **3a**, **8a**, and **10a** (Table 1, entries 3, 8, and 10) needed longer reaction time. We found that even if excess of reagents were used, the selectivity was not affected but reaction time is shortened.

After the successful application of our procedure to monosaccharides, we investigated the potential selective de-*O*-benzylation of perbenzylated disaccharides (Table 2).

Table 2. Regioselective De-*O*-benzylation of Perbenzylated Disaccharides and Trisaccharides

entry	substrates	products	time (h)	yield[a] (%)
1	 **11a**	 **11b**	24	80
2	 **12a**	 **12b**  **12c**[b]	24 48	85 80
3	 **13a**	 **13b**[b]	48	78
4	 **14a**	 **14b**[b]	24	80
5	 **15a**	 **15b**	18	85

[a] Isolated yield. [b] Additional reagents were added after a period of reaction time.

Indeed, when the perbenzylated *p*-methylphenyl lactoside **11a**, which has two primary and five secondary benzyloxy protecting groups, was treated with 3 equiv of $Co_2(CO)_8$ and 10 equiv of Et_3SiH in benzene under 1 atm CO at 50 °C, it generated the 6-*O*-TES product **11b** in a yield of 80% (Table 2, entry 1). The selective debenzylation and silylation of the 6-OBn of *S*-glucoside over *O*-galactoside indicated that anomeric protecting groups may have a great influence on the reactivity of the 6-OBn. Then we carried out this selective reaction in more complex substrates. Under the same condition, the perbenzylated sucrose **12a**[19] afforded 6′-*O*-TES derivative **12b** in 85% yield. With additional reagents, 6,6′-di-*O*-TES product**12c** was obtained in 80% yield under prolonged time (Table 2, entry 2). The TES group in **12b** and **12c** could be readily cleaved to afford 6′-OH and 6,6′-diol derivatives, which are very important versatile building blocks in sucrose chemistry.[20] The traditional approach to 6′-OH compound was achieved by selective protection of the 6′-OH of sucrose with bulky ether-forming reagents, benzylation, and selective deprotection of the bulky ether.[13c,21] The main difficulty comes from the complexity of hydroxyl groups in sucrose. For example, a 49−85% yield of the 6′-*O*-TBDPS derivative was obtained by treatment of sucrose with 1.1 equiv of TBDPSCl, while equal amount of 6′-*O*-Tr and 6-*O*-Tr derivatives were formed in yield of 20% when 1.2 equiv TrCl was used. The use of excess of reagents will lead to multiple protection and it was reported that 1,6′,6-triprotected derivative was obtained with about 4 equiv of reagents.[20h,22] In addition, perbenzylation of TBDPS-protected sucrose requires a large amount of base and a long reaction time, and a small fraction of TBDPS is usually cleaved because it is slightly unstable under the basic reaction condition.[20h] Moreover, the deprotection of Tr is a delicate process because of the high sensitivity of the glycosidic bond in acidic media. For the preparation of 6,6′-diol derivatives, the traditional procedure provided a 48% overall yield in four steps.[23] By comparison, our procedure provides a more

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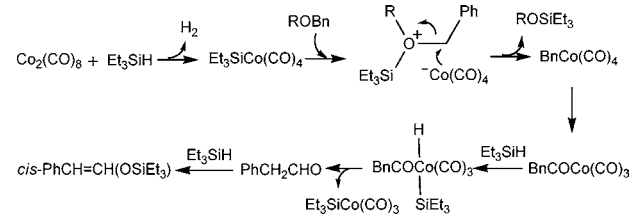
convenient preparation of sucrose derivatives with free primary hydroxyl groups in high selectivity and yield. Usually, the differentiation between 6-OH and 6′-OH was achieved by selective protection of 6,6′-diol compound with TBDPSCl in a yield of 60%.[20f] Using our procedure, 6′-OAc derivative **13a** was easily prepared from **12b**, which was further modified to afford the orthogonally protected 6-*O*-TES derivative **13b** in 78% yield (Table 2, entry 3).

After the successful selective de-*O*-benzylation of disaccharides, we investigated the selective deprotection of more challenging natural saccharides such as melezitose and raffinose, which have more primary hydroxyl groups. The reported selective chemical modifications of primary hydroxyl groups in melezitose and raffinose, by using Mitsunobu reaction,[24] selective protection with trityl chloride or sulfuryl chloride[16,25] or acetalization,[26] produce complex mixtures and the isolated yields are low.

Using our procedure, the perbenzylated raffinose **14a**[19] was converted to 6,6″-di-*O*-TES derivative **14b** in 80% yield (Table 2, entry 4). We were unable to control the reaction to achieve monosilylation in good yield because of the competing de-*O*-benzylation at 6″ position. To our surprise, for perbenzylated melezitose **15a**,[19] which has four primary and seven secondary benzyloxy protecting groups, the reaction was very clean and gave the 6′-*O*-TES product **15b** in a yield of 85% after SiO_2 chromatographic separation (Table 2, entry 5). The reaction can be readily performed on a 0.5 g scale in our hands with yield and selectivity not being affected.

The active intermediate involved in the transformation of benzyl ethers to silyl ethers may be $Et_3SiCo(CO)_4$, which is easily prepared by mixing $Co_2(CO)_8$ with Et_3SiH in situ. $Et_3SiCo(CO)_4$ was first developed by Chalk,[27] and it has found wide applications in organometallic chemistry.[28] The silicon atom in $Et_3SiCo(CO)_4$ is strongly Lewis acidic and electrophilic, so it acts to transform benzyl ethers to silyl ethers, and the resultant $BnCo(CO)_4$, via insertion of CO, oxidative addition with triethylsilane and reductive elimination, generates $PhCH_2CHO$, which reacts with triethylsilane to produce *cis*-PhCH=CH(OTES) separated by SiO_2 chromatography and identified by NMR (Scheme 2). The process is similar to Murai's mechanism.[28a]

Scheme 2. Proposed Mechanism



In conclusion, a highly selective, efficient, and mild de-*O*-benzylation method has been developed. The method can be applied to the selective de-*O*-benzylation of various per-*O*-benzylated monosaccharides and more complex natural oligosaccharides. The method is complementary to past selective protection strategies and provides a short-cut for the rapid preparation of saccharides with free primary hydroxyl groups, which can be used for further modification or construction of more complex natural products.[29]

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Supporting Information Available: All experimental procedures and data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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