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Substituted Benzyl Ethers as Radical Stable Protecting Groups

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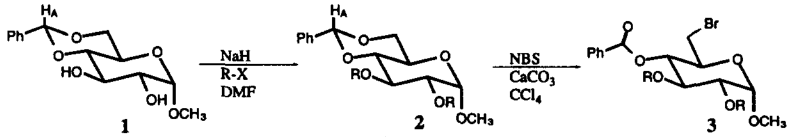
Abstract: Sixteen substituted benzyl ethers were studied for their potential to serve as hydroxyl protecting groups with the ability to withstand radical brominating conditions using N-bromosuccinimide during the conversion of benzylidene **2** into bromobenzoate **3**. © 1997 Elsevier Science Ltd.

While developing a general method to synthesize all possible stereoisomers of polyhydroxylated pyrrolidines from common hexoses, we needed to protect the 2- and 3-hydroxyl groups of the hexoses with a group which was stable to nucleophilic conditions and to both hydride and zinc reductive conditions. In addition, the efficiency of our synthetic strategy hinged on the conversion of a 2,3-O-diprotected-4,6-O-benzylidenehexo-pyranoside **2** into the corresponding 4-O-benzoate-6-bromo-hexopyranoside **3** by treatment with NBS (Scheme 1).[1] Since this reaction begins with the radical abstraction of the benzylidene hydrogen (H_A),[1] the protecting group must also be stable to NBS radical brominating conditions. We initially tried using simple unsubstituted benzyl ethers, hoping that H_A would be more reactive than the benzyl hydrogens of the ethers towards this radical process. Not surprisingly, however, a mixture of products was obtained. The product mixture indicated that hydrogen atom abstraction had occurred not only from the benzylidene, but also from the benzyl ethers. In this work a series of substituted benzyl ethers were studied for their ability to withstand these radical conditions. Based on linear free energy studies on the bromination of substituted toluenes ($\rho = -1.46$),[2] we predicted electron-withdrawing substituents should make the ethers more capable of withstanding the radical conditions. However, the ability of the ether oxygen to stabilize the carbocation-like transition state might have substantially diminished this effect.



Scheme 1

Sixteen different substituted benzyl ethers were selected for this study as indicated in Table 1 (entries 3-18). 4,6-O-Benzylidene-α-D-methylglucopyranoside **1** was converted to the desired 2,3-O-dibenzoxygluco-pyranoside **2** by treatment with NaH and the corresponding benzyl halide in DMF. The resulting protected glucopyranosides were purified by chromatography on silica gel and then were treated with NBS and $BaCO_3$ in CCl_4 under reflux according to the procedure described by Hanessian.[1] Yields of the corresponding 6-deoxy-6-bromo-4-O-benzoylpyranosides were estimated by NMR before purification by chromatography on silica.

Table 1. Protection and Bromination Results

entry	R	2	3 NMR	3 isolated	entry	R	2	3 NMR	3 isolated
1	H	—	85%	48%	10	4-fluorobenzyl	68%	26%	15%
2	benzyl	68%	23%	13%	11	2,4-difluorobenzyl	67%	42%	24%
3	4-nitrilebenzyl	0%	—	—	12	2,5-difluorobenzyl	98%	45%	26%
4	2,4-bis(trifluoromethyl)benzyl	0%	—	—	13	3,5-difluorobenzyl	82%	44%	25%
5	3-nitrobenzyl	0%	—	—	14	3,4-difluorobenzyl	100%	28%	16%
6	4-nitrobenzyl	12%	40%	23%	15	4-trifluoromethylbenzyl	100%	28%	16%
7	4-methoxybenzyl	57%	0%	0%	16	2-trifluoromethylbenzyl	94%	58%	33%
8	3-fluorobenzyl	100%	34%	19%	17	3-trifluoromethylbenzyl	58%	41%	28%
9	2-fluorobenzyl	82%	26%	15%	18	3,5-bis(trifluoromethyl)benzyl	64%	45%	26%

With the exception of benzyl groups with very strong electron-withdrawing character (entries 3-6), the benzyl ethers were formed in high yields. When the benzyl groups had strong electron withdrawing character it appeared that the benzyl halide self-condensed, since compound **1** could be reisolated in quantitative yield from a complex mixture of colored compounds. Two points of reference are used to determine the effectiveness of the substitution on the benzyl group. Since only the benzylidene hydrogen of the unprotected glucoside (entry 1) is susceptible to radical abstraction, there are no competing reactions in this case. Whether particular substituents reduce or enhance the hydrogen abstractions is determined by comparison to the unsubstituted benzyl group (entry 2). For the most part, the results support the prediction that electron-withdrawing substituents on the benzyl ethers will stabilize them against radical bromination while electron-donating substituents will destabilize. The 4-methoxybenzyl (entry 7) led to the radical abstraction occurring only on the ethers. Adding a single fluoro group increased the yield from 23% for the unsubstituted benzyl group to between 26 and 34% (entries 8-10). Adding a second fluoro group increased the yield even further (entries 11-14). The most interesting results were for trifluoromethylbenzyl ethers (entries 15-18). The trifluoromethyl group has a high σ value but is not susceptible to reduction or nucleophilic attack as are the nitro and nitrile substituents. In addition, unlike the fluoro substituent, the trifluoromethyl group provides steric hindrance when in the *meta-* and (especially) the *ortho*-positions. When the glucoside protected with the *2*-trifluoromethylbenzyl ether (the ether most resistant to hydrogen abstraction) was treated with H_2, Pd/C methylglucopyranoside was recovered in quantitative yield, thus demonstrating that the protecting group is easily removable.

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