

A Tin-Free Regioselective Radical De-*O*-benzylation by an Intramolecular Hydrogen Atom Transfer on Carbohydrate Templates**

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Dedicated to the Bayer company on the occasion of its 150th anniversary

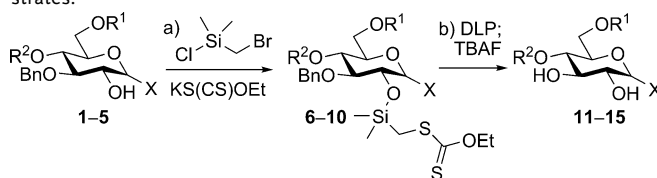
Intramolecular hydrogen atom transfer (HAT) has emerged as a powerful tool in organic synthesis for the functionalization of unreactive C–H bonds.^[1] Notably, carbon-centered radicals have been used as intermediate species to trigger the most common 1,5-HAT, thus affording a new alkyl radical, involved in further transformations.^[2] In contrast, HAT through seven- or higher-membered transition states are generally disfavored in flexible systems because of entropic effects.^[3] Consequently, these free-radical chain reactions have been mainly reported either as minor pathways competing with the 1,5 hydrogen shift^[4] or in rare occasions.^[5] On carbohydrate templates, interesting and unusual 1,6- or 1,8-HAT reactions triggered by conveniently disposed alkoxy radicals have been ingeniously developed by Suarez and co-workers.^[6] Most of these approaches use stoichiometric tributyltin hydride or oxidizing systems (O,N-centered radicals).

We now report a novel, selective mono-de-*O*-benzylation of hydroxy benzyl ethers based on a xanthate-mediated intramolecular 1,7-HAT from a benzylic position to a silylmethylene radical^[7] as the key step. Dilauroyl peroxide serves as the radical initiator and as the stoichiometric oxidant in the overall transformation. To the best of our knowledge, this 1,7-transfer from a C_{sp}³–H to a silylmethylene radical is extremely rare.^[8] This example complements the extremely rich and useful peroxide-mediated chemistry of xanthates or related dithiocarbonyl derivatives extensively developed by Zard and co-workers.^[9]

The one-pot xanthate approach described herein offers a supplementary option for the preparation of selectively protected building blocks, which remains an essential challenge in organic chemistry, especially with carbohydrates. Regioselective protection, notably benzylation, is the most atom-economic strategy and we^[10] and others^[11] have recently proposed one-pot protection procedures on mono- and disaccharides. The regioselective de-benzylation of partially or fully protected substrates is the alternative with recent attractive developments.^[12–15]

The xanthate methylsilyl ether precursors **6–10** were synthesized in high yield from the corresponding alcohols **1–5** using a one-pot procedure involving silylation with (bromomethyl)chlorodimethylsilane and displacement of the chlorine atom by potassium *O*-ethylxanthate (Table 1).

Table 1: Formation of *O*-ethylxanthyl-*S*-methyl-dimethylsilyl ethers and the regioselective de-*O*-benzylation reaction on D-glucopyranosyle substrates.



Entry	Starting substrate	Xanthate ^[a]	Yield [%] ^[b]	DLP ^[c] (equiv)	Prod.	Yield [%] ^[b]
1	1 : R ¹ = R ² = Bn;		92	1.2	11	62
2	X = β-OMe	6	92	1.5	11	74
3			92	2	11	85
4	2 : R ¹ = R ² = Bn;	7	87	2	12	81
5	X = α-OMe	8	94	2	13	84 ^[d]
6	3 : R ¹ , R ² = CHPh;	9	98	2	14	76 ^[d]
7	X = β-OMe	10	99	2	15	80 ^[d]
	X = β-SPh					

[a] General reaction conditions: (bromomethyl)chlorodimethylsilane (1.5 equiv), Et₃N (2 equiv), CH₂Cl₂, 0°C; evaporation of solvent under argon flow; KS(CS)OEt (2 equiv), acetone. [b] Yield after silica gel chromatography. [c] General reaction conditions: DLP, ClCH₂CH₂Cl, reflux, 2 h; H₂O/AcOH (1:1), RT then 1 M TBAF solution in THF (2 equiv) at RT. [d] The acidic step was replaced by a wash of the organic phase with an acidic (HCl) aqueous phase prior to the TBAF treatment.

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Initially, when a solution of the xanthate **6** and dilauroyl peroxide (DLP, 1.2 equiv)^[16] in refluxing 1,2-dichloroethane was heated at reflux under argon and treated successively with acid and TBAF,^[17] regioselective de-*O*-benzylation at C3 cleanly occurred, thus affording the 1,2-diol **11**^[18] in 62 % yield (entry 1, Table 1). Increasing the amount of the promoter to 2 equivalents ensured a complete conversion of the starting xanthate (entries 2 and 3). This transformation, resulting from an apparent unexpected 1,7-HAT, was not the result of a more favorable pathway including two successive 1,5-HATs through the relay of the *syn*-axial anomeric hydrogen atom. This was readily seen by transformation of the α -anomer **2** (*anti*-equatorial anomeric hydrogen) under the optimized reaction conditions to the diol **12** with a similar efficiency (entry 4). Interestingly, benzyldene acetal (as in **8**) and alkyne (as in **9**) functionalities are compatible under these radical conditions (entries 5 and 6). In contrast to many debenzoylation procedures, our methodology also applies to sulfide-containing compounds, as with the thiophenyl glycoside **10**, thus affording the product **15** in 80 % yield (entry 7).

This procedure was then extended to other representative benzylation monosaccharides (Table 2). Treatment of the xanthates **16** and **18** provided vicinal benzyl ether cleavage at O3 to give the diols **17** and **19**, respectively (entries 1 and 2). These results indicated that a 1,7-HAT is largely favored over a 1,8-HAT process which would provide debenzoylation at O6 in both substrates. However, when the 1,8-HAT is the only possible choice as in the xanthate **26**, debenzoylation occurs to provide the diol **27** (entry 6), although with much less efficiency under the general reaction conditions (40 % yield). The methodology operates with 1,2-*trans*-oriented alkoxy groups (*D*-gluco examples) as well as with a 1,2-*cis* orientation found in the *D*-galacto and *D*-manno substrates **18** and **20** to afford, respectively, **19** (61 % yield) and **21** (86 % yield; entries 2 and 3). Interestingly, the azido functionality in the xanthate **22** was unaffected under these radical conditions (entry 4), a moderate yield obtained for the diol **23** (40 %) resulted from the hydrolysis of the acid-sensitive 1,6-anhydro group during workup. Finally, regioselective debenzoylation at O2 occurred by treatment of both the anomeric xanthates **24** (α/β ratio of 1:5), thus providing the product **25** in 58 % yield (or 63 % from the corresponding hemi-acetal of **24**; entry 5). Again, 1,7-HAT was favored over other 1,*n*-HAT options.

The sequence of transformations was studied in detail for the xanthate **6**. Careful chromatographic as well as mass spectrometry analysis of the reaction indicated the formation, in sequence, of the two intermediates **D** ($MS = 757 [M+Na]^+$) and **E** ($MS = 469 [M+Na]^+$), both converted into the diol **11** after suitable workup. We believe that the sequence of reactions proceeded as shown in Scheme 1. The silylmethyl radical **A** produced by thermal decomposition of the initiator probably adds quickly to the xanthate **6** to provide the stabilized radical **F** which can only regenerate the starting xanthate and the same radical **A**. This very powerful way of increasing the effective lifetime of a radical, identified and reported on many occasions by Zard and co-workers,^[9] makes it possible to obtain a 1,7-HAT giving the benzylic radical **B**. With no other external trap than dilauroyl peroxide, **B**

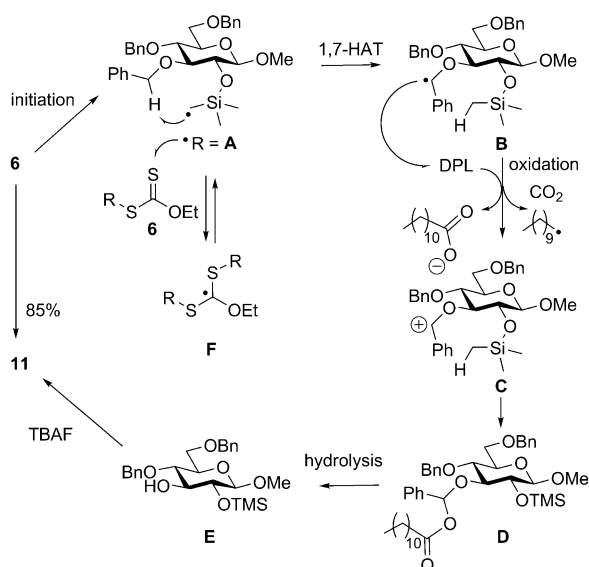
Table 2: Regioselective radical mono-de-*O*-benzylation of benzylation xanthyl methylsilyl ethers.^[a]

Entry	Substrate	Product	Yield [%] ^[b]
1			75
2			61
3			86
4			47 ^[c]
5			58 (63 ^[d])
6			40 ^[e]

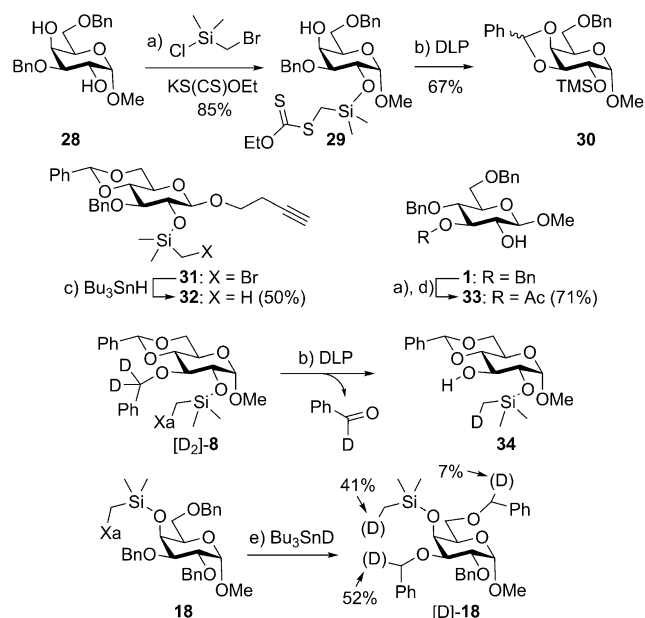
[a] General reaction conditions: DLP (2 equiv), $ClCH_2CH_2Cl$, reflux, 2 h; $H_2O/AcOH$ (1:1), RT then 1 M TBAF solution in THF (2 equiv) at RT. [b] Yield after silica gel chromatography. [c] 2-Azido-2-deoxy-D-glucose resulting from 1,6-anhydro hydrolytic ring opening of the product diol **23** was also formed (20–30 % estimated yield) and separated in the aqueous phase. [d] Yield of isolated product obtained over two steps from the corresponding hemiacetal of **24**. [e] Hydrolysis of unreacted substrate **26** also occurred in about 30 % yield. Xa = $S(CS)OEt$.

obviously undergoes an oxidation to the stabilized benzylic cation **C**, which is quenched in the form of the acyl acetal **D**. In situ acetal cleavage to **E** and desilylation then provided the debenzoylated product **11**. The electron transfer from **B** to DLP, thus providing the benzylic cation **C**, was readily demonstrated by an intramolecular nucleophilic trapping of the cationic intermediate using the xanthate **29**, equipped with a *cis* hydroxy group, which is accessible in one step from diol **28**^[19] (Scheme 2). Trapping of the benzylic cation resulted in the formation of the benzyldene acetal **30**.

Moreover, the conclusive advantage of this xanthate chemistry over the more conventional bromomethylsilyl ether chemistry is readily seen with the bromomethyl dimethyl ether **31** (analogous to the xanthate **9**; Table 1) which only provided the reduction product **32** by a standard tin hydride treatment (slow addition of Bu_3SnH). These results also suggested that a slight change in the workup procedure can provide a new way to perform an overall regioselective exchange of a protecting group from the



Scheme 1. Probable sequence leading to the mono-de-O-benzoylation product.

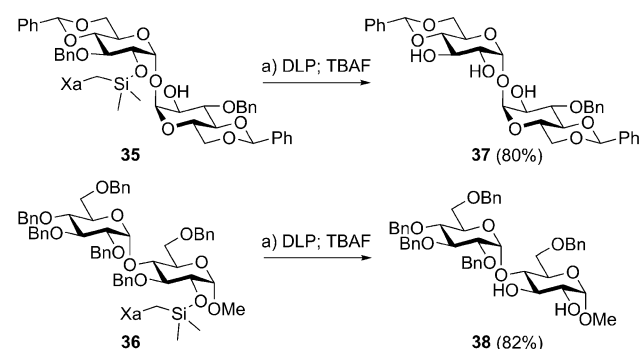


Scheme 2. Reagents and conditions: a) (bromomethyl)chlorodimethylsilane (1.2 equiv), Et₃N (2 equiv), CH₂Cl₂, 0°C; KS(CS)OEt (2 equiv), acetone, RT. b) DLP (2 equiv), ClCH₂CH₂Cl, reflux; c) Bu₃SnH (slow addition up to 1.1 equiv), AIBN (0.1 equiv), benzene, 80°C. 50% with 50% recovered starting material. d) DLP (2 equiv), ClCH₂CH₂Cl, reflux, 2 h then stirred under ambient atmosphere overnight at RT; Ac₂O, py, RT; Dowex-50W(H⁺); 71% overall from **1**. e) Bu₃SnD (1.3 equiv, slow addition), AIBN (0.2 equiv), benzene, 80°C. Percentages shown for [D]-**18** indicate the relative percentage of the D incorporation at a given position. AIBN = α,α' -azobisisobutyronitrile, Xa = S(CS)OEt.

alcohol **1** (Scheme 2). Hence, xanthate formation, DLP treatment and acetal hydrolysis, acetylation and desilylation provided the acetate **33** in an overall yield of 71%. The 1,7-HAT was directly evidenced by treating [D₂]-**8** under reaction conditions to preserve the silyl ether (DLP, 1.2 equiv, reflux, 2 h), and thus provided the deuterated silyl ether **34** as the

only detectable deuterated carbohydrate derivative.^[20] To detect any other minor competing hydrogen atom transfers, an examination of the deuteration sites through treatment of the xanthate **18** under reductive conditions with tributyltin deuteride was finally studied (Scheme 2 and the Supporting Information). This study indicated direct reduction (41%), 1,7-deuterium atom transfer (DAT, 52%), and minor 1,8-DAT (7%). This last 1,8-translocation was not identified under the oxidative debenzoylation conditions for **18**.

Our methodology was briefly extended to the more functionalized disaccharide derivatives trehalose **35** and maltose **36** (Scheme 3).^[21] The procedure provided the expected compounds **37** and **38**, respectively in 80–82% yield. The benzyl group next to the xanthate was cleaved in both cases, thus illustrating the general applicability of this approach.



Scheme 3. Regioselective mono-de-O-benzoylation of disaccharides **35** and **36**. a) DLP (2 equiv), ClCH₂CH₂Cl, reflux, 2 h then wash of the organic phase with an acidic (HCl) phase; 1 M TBAF solution in THF (2 equiv) at RT. THF = tetrahydrofuran. Xa = S(CS)OEt.

In conclusion, we have developed a new and efficient selective method for the deprotection of benzyl ethers next to hydroxy groups. The transformation is initiated by an unprecedented xanthate-mediated 1,7-hydrogen atom transfer of a benzylic hydrogen atom to a *O*-silylmethylene radical which terminates with an ionic mechanism. It tolerates the presence of a variety of functional groups and the extension of this approach to other substrates is currently in progress in our laboratory. Also, it is expected that the synthetic use of the *O*-silylmethylene radical^[7] in the synthesis of complex molecules will be broadened by this xanthate approach.

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- [21] See the Supporting Information for the preparation of these xanthates.