Hydrogen Transfer

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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

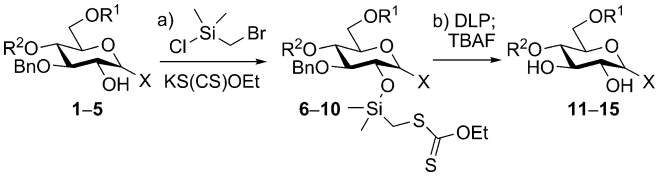
Intramolecular hydrogen atom transfer (HAT) has emerged as a powerful tool in organic synthesis for the functionalization of unreactive C–H bonds.[1] Notably, carbon-centered radicals have been used as intermediate species to trigger the most common 1,5-HAT, thus affording a new alkyl radical, involved 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**: $R^1 = R^2 = Bn$; X = β-OMe	**6**	92	1.2	**11**	62
2			92	1.5	**11**	74
3			92	2	**11**	85
4	**2**: $R^1 = R^2 = Bn$; X = α-OMe	**7**	87	2	**12**	81
5	**3**: $R^1,R^2 = CHPh$; X = α-OMe	**8**	94	2	**13**	84[d]
6	**4**: $R^1,R^2 = CHPh$; X = β-$OCH_2CH_2C{\equiv}CH$	**9**	98	2	**14**	76[d]
7	**5**: $R^1,R^2 = CHPh$; X = β-SPh	**10**	99	2	**15**	80[d]

[a] General reaction conditions: (bromomethyl)chlorodimethylsilane (1.5 equiv), Et_3N (2 equiv), CH_2Cl_2, 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, $ClCH_2CH_2Cl$, reflux, 2 h; H_2O/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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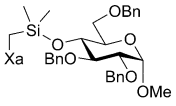
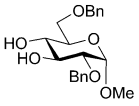
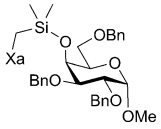
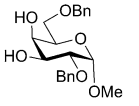
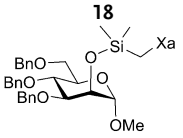
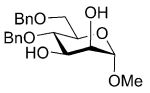
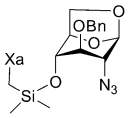
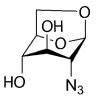
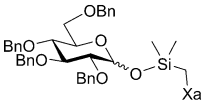
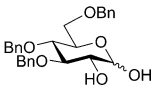
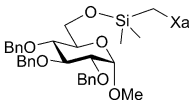
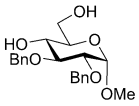
Initially, when a solution of the xanthate **6** and dilauroyl peroxide (DLP, 1.2 equiv)[16] in refluxing 1,2-dichoroethane was heated at reflux under argon and treated successively with acid and TBAF,[17] regioselective de-*O*-benzylation at C3 cleanly occurred, thus affording the 1,2-diol **11**[18] 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, benzylidene acetal (as in **8**) and alkyne (as in **9**) functionalities are compatible under these radical conditions (entries 5 and 6). In contrast to many debenzylation 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 benzylated 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 debenzylation at O6 in both substrates. However, when the 1,8-HAT is the only possible choice as in the xanthate **26**, debenzylation 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 debenzylation 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.

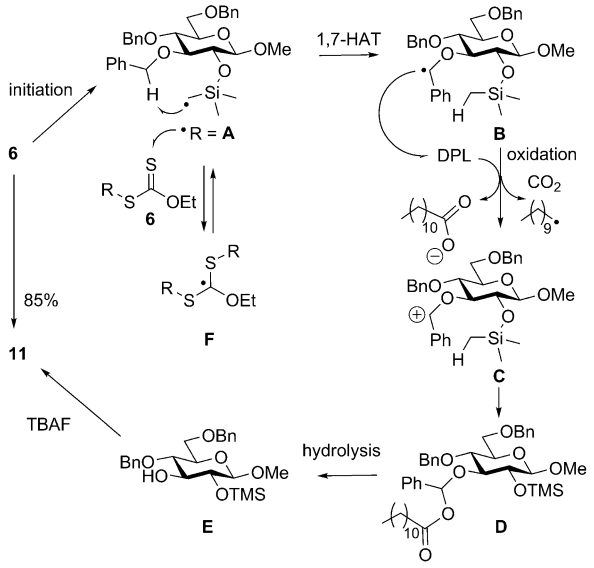
The sequence of transformations was studied in detail for the xanthate **6**. Careful chromatographic as well as mass spectrometry analysis of the reaction indicated the formation, in sequence, of the two intermediates **D** (MS = 757 $[M+Na]^+$) and **E** (MS = 469 $[M+Na]^+$), both converted into the 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** 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 debenzylated 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 benzylidene 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

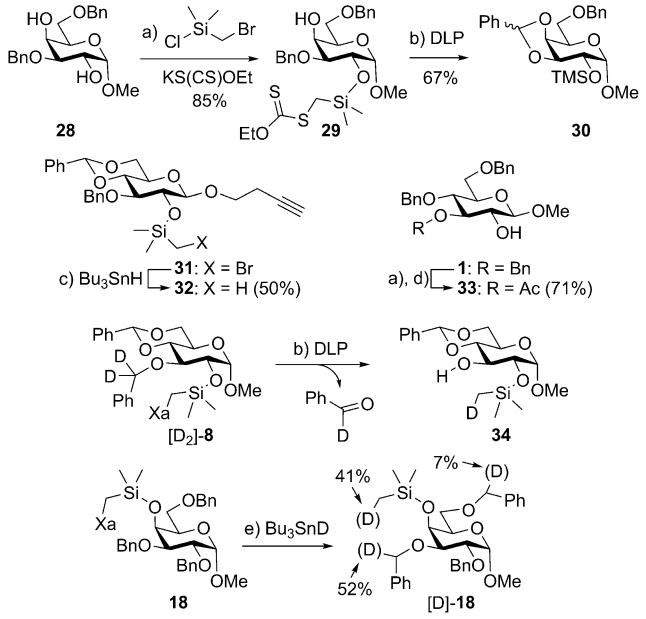
Table 2: Regioselective radical mono-de-*O*-benzylation of benzylated xanthyl methylsilyl ethers.[a]

Entry	Substrate	Product	Yield [%][b]
1	 **16**	 **17**	75
2	 **18**	 **19**	61
3	 **20**	 **21**	86
4	 **22**	 **23**	47[c]
5	 **24**	 **25**	58 (63[d])
6	 **26**	 **27**	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 occured in about 30% yield. Xa = S(CS)OEt.



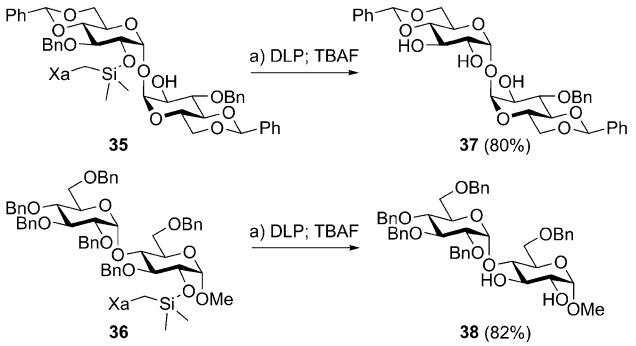
Scheme 1. Probable sequence leading to the mono-de-*O*-benzylation product.



Scheme 2. Reagents and conditions: a) (bromomethyl)chlorodimethylsilane (1.2 equiv), Et_3N (2 equiv), CH_2Cl_2, 0 °C; KS(CS)OEt (2 equiv), acetone, RT. b) DLP (2 equiv), $ClCH_2CH_2Cl$, reflux; c) Bu_3SnH (slow addition up to 1.1 equiv), AIBN (0.1 equiv), benzene, 80 °C. 50% with 50% recovered starting material. d) DLP (2 equiv), $ClCH_2CH_2Cl$, reflux, 2 h then stirred under ambient atmosphere overnight at RT; Ac_2O, py, RT; Dowex-50W(H+); 71% overall from **1**. e) Bu_3SnD (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 [D_2]-**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 debenzylation 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*-benzylation of disaccharides **35** and **36**. a) DLP (2 equiv), $ClCH_2CH_2Cl$, 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*-silylmethyl radical[7] in the synthesis of complex molecules will be broadened by this xanthate approach.

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[16] AIBN and ACCN were inefficient as radical initiators. Only the starting material was recovered under these conditions.
[17] On small-scale experiments, the reaction mixture stirred under ambient atmosphere overnight at room temperature with subsequent TBAF treatment produce the diol **11**.
[18] The regioselectivity of the reaction was determined through chemical correlation after acetylation of both hydroxy groups.
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[20] Analysis of the crude reaction mixture by ^{2}H NMR spectroscopy showed D signals at $\delta = 0.21$ ppm (D-CH_2-Si in **34**, t) and $\delta =$ 10.04 ppm (deuterated benzaldehyde, D-COPh, s, resulting from the hydrolysis of the intermediate acyl acetal analogous to **D** in Scheme 1).
[21] See the Supporting Information for the preparation of these xanthates.

