Unexpected photoinduced electron transfer reactions of two glucose thiobenzoates †

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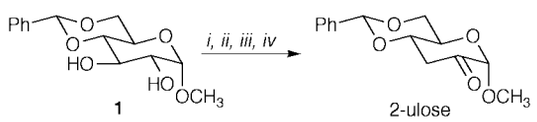
Irradiation of the 2-*O* and 3-*O* thiobenzoate derivatives (**2**, **3**) of methyl 4,6-benzylidene-α-D-glucopyranoside in CH_2Cl_2 with NEt_3 gives solvent incorporation and cyclization to **4a**,**b** and **5a**,**b** by an electron-transfer mechanism.

Introduction

In connection with our interest in functionalizing β-cyclodextrin, we sought an efficient method for converting a *trans*-vicinal diol to a ketone without using protecting groups. Recently, we reported such a transformation on methyl 4,6-*O*-benzylidene-α-D-glucopyranose (**1**),[1] which is a model for cyclodextrin (Scheme 1).



Scheme 1 Formation of a 2-ulose by selenoxide elimination. *i*) NaH, tosylimidazole, *ii*) $PhSe^-$, *iii*) H_2O_2, *iv*) reflux.

The synthetic route consists of an epoxide ring-opening with phenyl selenide, oxidation, and thermal selenoxide elimination to produce the ulose derivative after keto–enol tautomerism. We were unable to apply this methodology to β-cyclodextrin, so we sought another route. We report the application of thiobenzoyl photochemistry towards the preparation of the ulose derivatives of **1** and describe the unusual photochemical behavior of the glucose thiobenzoates in CH_2Cl_2 with NEt_3.

Barton and co-workers have studied the synthetic applications of thiobenzoate photochemistry.[2–7] The elimination of thiobenzoic acid to form an alkene by photochemically induced γ-hydrogen abstraction was demonstrated for a number of systems. With cholesterol the hydrogen abstraction was found to be stereo- and regioselective for the axial allylic hydrogen (Scheme 2).[2] Likewise, photolysis of *O*-(2-ethoxyethyl)thiobenzoate gave ethyl vinyl ether in 46% yield in less than one hour.[4]

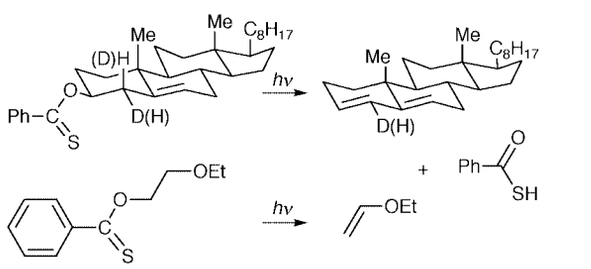
While the elimination occurs with compounds possessing a π-bond or heteroatom at the γ-carbon, it fails with saturated hydrocarbons. The success of the reaction depends on the strength of the γ-C–H bond. For example, the quantum yields for the disappearance of $Ph(C{=}S)OCH_2CH_2R$ are 0.46, 0.12 and 0.01 when R is *p*-$MeOC_6H_4$, EtO and Me, respectively. The corresponding bond γ-C–H bond energies are 81, 91 and 96 kcal mol^{-1}. Thus, an γ-alkoxy group only weakly activates the reaction.[7]

Thiobenzoates **2** and **3** possess both γ-alkoxy and γ-hydroxy groups. We wondered whether these compounds would undergo photochemical elimination, and if so, whether the elimination would be regioselective. Abstraction at the γ-hydroxy C–H would produce the desired ulose derivatives.

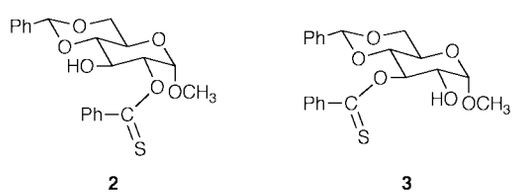
† ^{1}H NMR spectra of **2**, **3**, **4a**,**b** and **5a**,**b** are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p2/b0/b000455n/

Table 1 Half-lives for the photolysis of **2** and **3**

Compd.	Solvent	NEt_3	$t_{\frac{1}{2}}$/min
2	CH_2Cl_2	yes	<7
2	CH_2Cl_2	no	1250
2	PhH	yes	65
2	PhH	no	550
3	CH_2Cl_2	yes	<7
3	PhH	yes	50



Scheme 2 Photolysis of *O*-cholesteryl thiobenzoate and *O*-(2-ethoxyethyl)thiobenzoate.



Results and discussion

The photochemical consumption of reactant exhibits profound dependence on the reaction conditions. The half-lives for the photochemical reactions were estimated by the loss of **2** or **3** within the first hour through HPLC analysis (Table 1).

Irradiation of **2** and **3** in CH_2Cl_2 in the presence of NEt_3 results in nearly quantitative product formation within 15 min. Each thiobenzoate gives two main products that are assigned as **4a**,**b** and **5a**,**b**, respectively. We have been unable to separate the diastereomers by recrystallization or chromatography, and such manipulation results only in product degradation.

These structure assignments follow from several pieces of evidence. ^{1}H NMR of each product mixture reveals two singlets around 6 ppm and two diastereotopic CH_2 groups in addition to all of the protons present in **2** or **3**. The proportion of each

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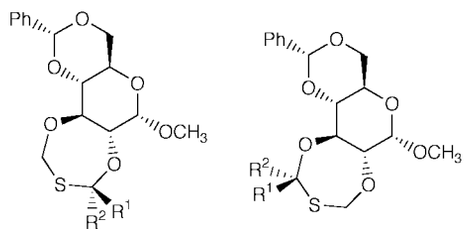
Table 2 Selected ^{1}H NMR chemical shift data for **4a**,**b** and **5a**,**b**

	Mol%	SC*H*Ph	CH_2	CH_2	C*H*OMe	OCH_3
4a	0.56	6.03	5.31	4.66	4.35	3.21
4b	0.44	6.07	5.09	4.63	4.94	3.47
5a	0.72	6.35	5.05	4.54	4.74	3.40
5b	0.28	6.30	5.05	4.63	4.84	3.47



4a, R^1 = H, R^2 = Ph
4b, R^1 = Ph, R^2 = H

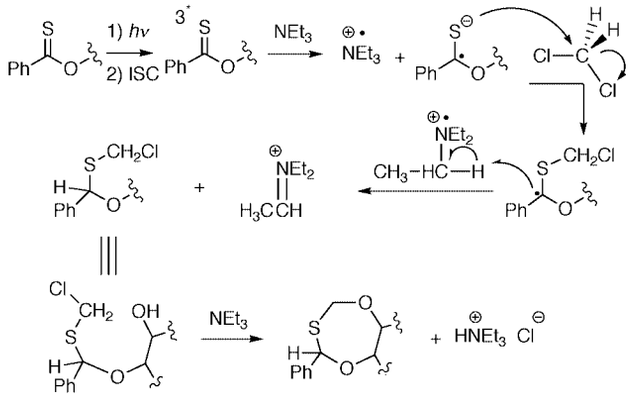
5a, R^1 = Ph, R^2 = H
5b, R^1 = H, R^2 = Ph

diastereomer and chemical shifts are given in Table 2. The downfield chemical shifts of these protons are consistent with the monothioacetal structures.

The existence of the extra ring structure is supported by the large chemical shift differences for the diastereotopic methylene protons. Also, in **4a** the nearby phenyl ring gives rise to dramatic upfield shifts of the anomeric C–H and methoxy group, whereas these effects are absent in **4b**. The diastereomer assignments are based on NOESY cross-peaks between the SC*H*Ph and the C2–H or C3–H. Finally, ESI-MS shows the expected M + H peak at m/z = 417 for both sets of products.

Several NMR experiments with deuterium-labeled solvents and reagents were conducted to further elucidate the reaction. Irradiation in CD_2Cl_2 gives complete loss of the signals assigned to the diastereotopic CH_2 groups. Irradiation using [$^2H_{15}$]NEt_3 leads to partial loss of the thiobenzylic resonances (65 and 66% loss for **2** and **3**, respectively). Finally, with **2**- and **3**-D (exchanged using MeOD) in CH_2Cl_2 using NEt_3, irradiation also leads to partial loss of the thiobenzylic resonances (27% and 31% loss for **2** and **3**, respectively).

The formation of these products can be formulated by a mechanism that involves a photoinduced electron-transfer step (Scheme 3). Irradiation of the thiobenzoate gives rise to the



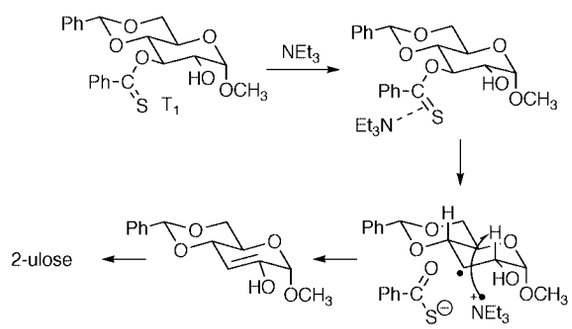
Scheme 3 Mechanism for formation of **4** and **5**.

excited triplet state through intersystem crossing. The excited triplet-state abstracts an electron from NEt_3. The resulting radical anion abstracts a hydrogen atom from the triethylamine radical cation. The thiolate anion reacts with the solvent by nucleophilic substitution to generate a chloromethyl sulfide. In the presence of NEt_3, the chain cyclizes at the adjacent hydroxy group. Presumably, this cyclization is efficient because four of the seven atoms involved are already part of a rigid ring structure. While this mechanism is consistent with most of the deuterium labeling results, it does not account for the slight deuterium incorporation at the thiobenzylic position with the deuterium labeled thiobenzoates.

The electron-transfer mechanism is supported by several observations. Most revealing is that the reaction occurs only with added NEt_3. Cyclic voltammetry studies on **2** and **3** give reduction potentials of −1.56 and −1.57 V in CH_3CN, respectively, *vs.* Ag/Ag^+. Application of the Weller equation[8] shows that the proposed electron-transfer reaction is exothermic by 0.24 eV (a value of 2.75 eV was used for $E_T^{0\text{-}0}$).

When the irradiations are conducted in benzene with NEt_3, the thiobenzoates are consumed slowly. The major product from **3** is the desired 2-ulose, but the yield is poor (~25%), and the ulose is difficult to separate from the product mixture. In contrast, irradiation of **2** gives no trace of the 3-ulose.

The mechanism for the formation of 2-ulose is less clear. It certainly does not occur by γ-H abstraction/elimination since the reaction requires NEt_3. The formation of a triplet exciplex with NEt_3 is exothermic by 0.02 eV.[8] A small fraction of the exciplexes may decompose into contact ion pairs (Scheme 4).



Scheme 4 Formation of 2-ulose from **3**.

Since the radical anion cannot react with the solvent, it may cleave at the adjacent C–O bond to make the thiobenzoate ion and a radical centered at C3. The NEt_3 radical cation could abstract the C2–H giving first the enol and then the 2-ulose by tautomerization. The cleavage of the C–O bond by an adjacent radical center is a known process that is driven by the formation of thiobenzoate carbonyl group. Treatment of **2** and **3** with Bu_4SnH results in deoxygenation by a radical-induced cleavage.[9] Other thiocarbonyl-substituted glucose derivatives undergo photochemically-induced deoxygenation.[10]

The failure of photoexcited **2** and **3** to undergo γ-H abstraction is likely due to constraints imposed by the fused ring systems. The added activation energy counteracts the weakly activating effects of the γ-alkoxy or γ-hydroxy groups.

Experimental

Compounds **2** and **3** were prepared using modified literature methods.[9] *N*,*N*-Dimethyl(chlorophenylmethylene)ammonium chloride was made by treating *N*,*N*-dimethylbenzamide with oxalyl chloride instead of phosgene.[11] The iminium salt was reacted with **1** in the presence of pyridine, and then H_2S was bubbled through the reaction to generate the thiocarbonyl group. Using a CH_2Cl_2 solution of **1** gave a **2**:**3** ratio of 63:37 (65% after chromatography and recrystallization), whereas adding THF solution of **1** (literature approach) gave a **2**:**3** ratio of 24:76 (52%). Irradiation of **2** and **3** was carried out in CH_2Cl_2 or benzene with or without added NEt_3. The latter is a scavenger for thiobenzoic acid.[2] Solutions (1 g/300 mL, some with 1 mL NEt_3) were degassed with Ar. For the NMR tube experiments the typical amounts were 8 mg/2.5 mL with 20 μL NEt_3. Photolysis was conducted using a 450 W Hanovia lamp with a uranium glass filter sleeve. The immersion well was attached to an Ar-filled balloon and was suspended in an ice–water bath.

The reaction progress was monitored by HPLC. A 53 × 7 mm Alltech Rocket column packed with 5 μm silica gel was eluted with a hexane–THF–MeOH gradient at 2.5 mL min^{-1}. Analytes were detected with a photodiode array. Dibromoanthracene was used as an internal standard. ESI-MS was performed by Macromolecular Resources. Cyclic voltammetry of **2** and **3** was performed using a BAS CV-50W Electrochemical Analyzer in 0.1 M Bu_4NPF_6.

Acknowledgements

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