PHOTOINDUCED GENERATION OF GLYCOSYL CATIONS FROM THIOGLYCOSIDES≠

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Abstract - Photochemically induced cleavage of thioaryl β-D-glucopyranosides using 1,4-dicyanonaphthalene as an electron-transfer agent, produces glycosyl cations potentially useful in glycosylation reactions.

INTRODUCTION

The chemical synthesis of oligosaccharides has captured considerable attention in recent years, because of their significance in a host of cell-cell interactions.[1] In assembling such molecules, the availability of efficient methods for glycosylation is of paramount importance. In previous studies, it has been demonstrated that glycosyl cations which are intermediates in glycosylation reactions may be generated from phenyl glycosides by electron-transfer induced cleavage.[1,2]

Recently, thioglycosides have been the focus of extensive interest as glycosyl donors in the convergent block synthesis of oligosaccharides.[3] Thioglycosides are stable under a wide variety of conditions required during functional group manipulations thus permitting construction of oligosaccharides with the anomeric center protected as a thioglycoside. At the appropriate stage the thioglycosyl group may be activated in a number of ways[3] and used for the generation of glycosyl cations as intermediates in forming glycosidic bonds.

Several useful methods for activating thioglycosides, which may be transformed into glycosyl donors, have recently appeared.[3] These include their conversion into glycosyl halides,[3-5] which are isolated and subsequently activated by various promoters such as silver or mercuric salts, or conversion, *in situ*, into halides in the presence of an acceptor and an activating agent.[6] Alternatively, and more directly, the thioglycosides may be activated by various thiophilic reagents, such as methyl triflate,[7,8] dimethyl(thiomethyl)sulfonium triflate,[9,10] or methylsulfenium salts.[11] When such strategies are required, it would be highly advantageous if all glycosyl donors in an oligosaccharide synthesis were thioglycosides, i.e. if both the glycosyl acceptors and the donors were thioglycosides. This requires a method for activating the donor in some unique way, which so far is only possible by a two-step procedure involving

≠ In memory of Professor Tetsuji Kametani; ≠ Deceased October 8, 1989

initial conversion of the thioglycoside donor to a glycosyl halide (normally bromide or fluoride) followed by isolation and use as a conventional glycosyl donor. The larger thioglycoside blocks may then be activated for condensation with the succeeding acceptor by various thiophilic reagents.

We projected that the thioglycoside approach could be exploited using the lability of photosensitive aryl thioglycoside donors in conjunction with their alkyl analogs as acceptors. The larger alkyl thioglycoside oligosaccharides thus generated could in turn be activated and transformed into a glycosyl donor by one of the aforementioned agents.

EXPERIMENTAL

Acetonitrile (spectral grade), methanol (spectral grade) and pyridine were purified by fractional distillation after drying over type 4Å molecular sieves; dichloromethane was distilled from P_2O_5; each solvent was collected and stored over type 4Å molecular sieves. Other reagents used were of the highest grade available commercially and used without further purification. 1,4-Dicyanonaphthalene (DCN) was prepared from 1,4-dibromonaphthalene by treatment with cuprous cyanide, in accordance with literature directions.[12]

Analytical tlc was performed on commercially available Chromatogram silica gel sheets (Kodak 13181). Preparative (radial) chromatography was conducted on a model 7924T Chromatotron (Harrison Research) using Merck $PF_{254}60$ silica gel. Solvent mixtures with varying ratios of ethyl acetate and hexane were used as eluants in the chromatographic separations. Melting points were determined on a Thomas-Hoover melting-point (Uni-Melt) apparatus and are uncorrected. Nmr spectra were recorded in $CDCl_3$ solutions (using Me_4Si as an internal standard) with a Varian VXR 200 spectrometer. Gas chromatographic separations were achieved on a Hewlett-Packard 5880 Chromatograph using a 30 m cross-linked and bonded DB-5 capillary column. The flame ionization detector was maintained at 275 °C with an injection port temperature of 250 °C. Samples were dried and equilibrated in pyridine for about an hour and then silylated prior to injection with hexamethyldisilazane and trimethylchlorosilane (2:1). The gc/ms analyses were performed on a Perkin-Elmer Sigma 300 Gas Chromatograph using a 50 m OV-54 capillary column (0.324 I.D.), crosslinked, but not bonded. This unit was coupled to a Finnigan ion trap detector (Model 700); scan range 46-1000 (MW), 1 scan per second, filament/multiplier delay 6 min, 1500 volts, isothermal 200 °C for 60 min. The hplc analyses were performed on a Waters Associates Model 2000 Liquid Chromatograph equipped with a Model 6000 A pump, a Model 440 absorbance detector and a R410 differential refractometer (Waters Associates, Milford, MA). The samples were injected by Waters WISP 710A sample autoprocessor. The chromatograms were displayed on a Linear Model 500 recorder (Linear Instruments Corp., Hackensack, NJ). Data were stored and analyzed by an in-house LAS computer system (Hewlett-Packard 3357). The detector was set at 254 nm on a range of 0.2 AUFS. A Bio Rad Amine 5S column and the absorbance detector were employed for the analysis of the

reaction mixture from the glucoside **1**, using acetonitrile and water (3:1) containing 0.1% tetraethylenepentamine (TEPA) as the mobile phase. The analysis of the reaction mixture from the glucoside **2** was conducted on a Radial Pak 5μ silica cartridge, using a refractive index detector with ethyl acetate and hexane (2:3) as the mobile phase. Separations of the reaction mixtures obtained from **6** and **7** were achieved on a μ Bondpak C18 column with a solvent mixture of acetonitrile and water (19:1) and the uv absorbance detector. All products were identified by co-tlc, -glc and -hplc by comparison with authentic samples, and by reference to a computer gc/ms facility. A Rayonet RPR-100 Chamber Reactor equipped with sixteen 8 W, 350 nm lamps was used for irradiation experiments.

Photoinduced Reactions: Typically, 5-50 ml aliquots of either a 1 or 5 mM solution of the sample dissolved in acetonitrile and methanol (9:1) or acetonitrile containing DCN (0.1 mM) in a Pyrex test tube capped with a rubber serum cap (covered with aluminum foil), was saturated with argon and irradiated. In the experiments where the photolysis was monitored against time, one of the following methods was used. Samples of 1-2 ml were withdrawn at selected times during the irradiation period. Alternatively, several small tubes containing 1-2 ml of the reaction mixture were irradiated and at a given time a single tube was withdrawn for subsequent analysis.

Control Experiments Performed on Thioglycoside **2**: (a) A 5 mM solution of **2** in 5 ml of acetonitrile and methanol (9:1) was irradiated for 32 h as described above in the absence of DCN and the mixture was analyzed by tlc. (b) Two samples of the solvent mixture of acetonitrile and methanol (9:1), each containing DCN only, were separately irradiated first. The compound **2** was then added to the tubes in the dark, immediately and 20 min after irradiation. The reaction mixtures were analysed by tlc after magnetically-stirring each tube for 10 min and 1 h.

Preparation of Glucopyranoside Derivatives: Phenyl 1-thio-β-D-glucopyranoside (**1**),[13] phenyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (**3**),[14] phenyl and methyl 2,3,4,6-tetra-O-benzyl-1-thio-β-D-gucopyranosides (**6** and **7**),[15,16] methyl 2,3,4,6-tetra-O-benzyl-α- and -β-D-glucopyranosides (**14** and **15**)[17,18] and tetra-O-benzyl-α- and -β-D-glucosides (**16** and **17**)[17] were prepared as previously described.

Phenyl 2,3,4,6-tetra-O-methyl-1-thio-β-D-glucopyranoside (**2**) was obtained by methylation[19] of phenyl-1-thio-β-D-glucopyranoside (**1**). NaH (180 mg) was added to a cooled solution of **1** (70 mg) in DMF (6 ml) and stirred at 5 °C. After 1 h, MeI (0.8 ml) was added and stirring was continued at room temperature overnight. The reaction mixture was quenched with dry MeOH and concentrated under reduced pressure. The resulting syrup was dissolved in CH_2Cl_2, washed with water, dried over anhydrous $MgSO_4$ and the volatile solvent was removed. The crude syrup was purified on a Chromatotron (eluant: ethyl acetate and hexane, 35:65) to obtain the pure compound (53mg, 63%); mp 66-68 °C, lit.[20] mp 70.5-72 °C; ^{1}H nmr ($CDCl_3$, 200 MHz) δ 7.57-7.50 (m, 2H, Ar), 7.34-7.20 (m, 3H, Ar), 4.48 (d, $J_{1,2}$ 9.7 Hz, 1H, H-1), 3.65, 3.60, 3.53, 3.39 (4s, 12H, OCH_3), 3.52-3.00 (m, 6H,

H-2,3,4,5,6a,6b). Methyl 2,3,4,6,-tetra-O-methyl-α- and -β-D-glucopyranosides (**12** and **13**)[21,22] were prepared by a similar methylation procedure as described above using NaH (150 mg), methyl α- and β-D-glucopyranosides (**10** and **11**) (50 mg) in DMF (4 ml) and MeI (0.7 ml).

4'-Methoxyphenyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (**4**). To a solution of β-D-glucopyranose pentaacetate (230 mg) in CH_2Cl_2 (3 ml), type 4Å molecular sieves and p-methoxythiophenol (86 μl) were added, and the mixture stirred at 5 °C for 20 min.[14] Anhydrous $FeCl_3$ (100 mg) was then added and the mixture stirred at 5 °C for another 45 min. The mixture was filtered into cold water and the organic layer was seperated, washed with 10% $NaHCO_3$, and dried over anhydrous $MgSO_4$. The crude product (173 mg) was purified by two passes on a Chromatotron using ethyl acetate and hexane (2:3) as the eluant. Finally, recrystallization from EtOH afforded the pure product **4** (52 mg, 19%); mp 89-90 °C, lit.[23] mp 95-97 °C; ^{1}H nmr ($CDCl_3$, 200 MHz) δ 7.45 (d, J 9 Hz, 2H, Ar), 6.85 (d, J 9 Hz, 2H, Ar), 5.25-4.85 (m, 3H, H-3,2,4), 4.55 (d, $J_{1,2}$ 10 Hz, 1H, H-1), 4.20 (d, $J_{6,5}$ 4 Hz, 2H, H-6a,6b), 3.82 (s, 3H, OCH_3), 3.68 (dt, $J_{5,4}$ 10 Hz, $J_{5,6}$ 4 Hz, 1H, H-5), 2.11, 2.08, 2.01, 1.99 (4s, 12H, $OCOCH_3$).

4'-Methylphenyl 2,3,4,6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (**5**) was prepared in a similar manner as described above from β-D-glucopyranose pentaacetate (182 mg) using p-methylthiophenol (71 mg) and type 4Å molecular sieves in CH_2Cl_2 (3 ml) and anhydrous $FeCl_3$ (80 mg). The crude product (126 mg) upon further purification as described, yielded the pure product **5** (47 mg, 22%); mp 114-115°C, lit.[23] mp 113-115°C; ^{1}H nmr ($CDCl_3$, 200 MHz) δ 7.40 (d, J 8 Hz, 2H, Ar), 7.12 (d, 8 Hz, 2H, Ar), 5.26-4.88 (m, 3H, H-3,2,4), 4.63 (d, $J_{1,2}$ 10 Hz, 1H, H-1), 4.20 (m, 2H, H-6a,6b), 3.70 (m, 1H, H-5), 2.35 (s, 3H, CH_3), 2.09, 2.08, 2.02, 1.99 (4s, 12H, $OCOCH_3$).

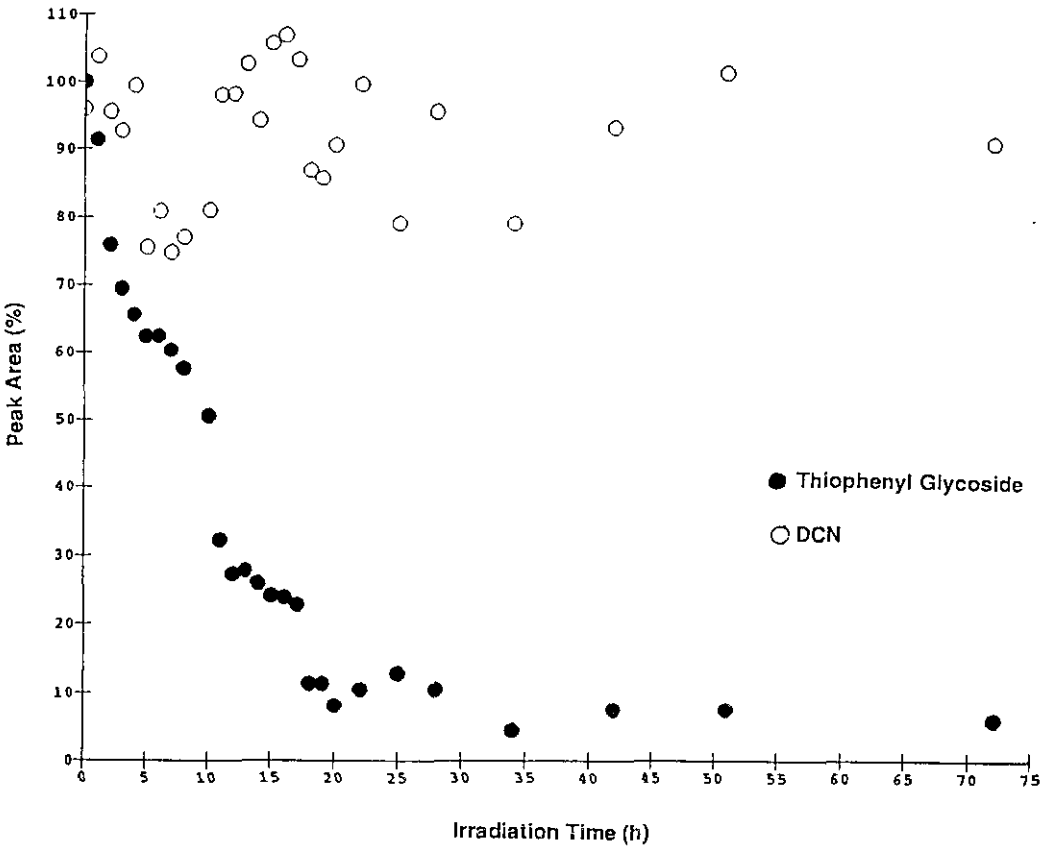
RESULTS AND DISCUSSION

A solution of 1 mM thiophenyl glucoside (**1**)[13] in acetonitrile and methanol (9:1) containing 0.1 mM 1,4-dicyanonaphthalene(DCN) was irradiated at 350 nm for 72 h. Small aliquots were withdrawn from the reaction mixture at regular intervals over the course of the irradiation, and analyzed by hplc for the presence of the glucoside **1** and DCN. The results are presented in Figure 1. The consumption of **1** was rapid during the first 6-9 h and nearly complete after 24 h. The concentration of DCN, however, did not change markedly which affirms its role as a catalyst in the process. The gc analyses indicated the presence of five reaction proudcts which were identified as the methyl glucosides **10** and **11**, D-glucono-1,4-lactone (**22**), D-gluconic acid (**23**) and PhSS(O)Ph by comparison with authentic samples and gc-ms techniques.

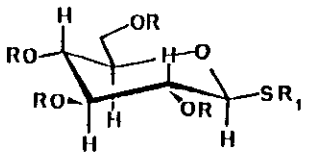
An entirely different product profile was observed when the same experiment was performed in the absence of methanol. The products were established as α- and β-D-glucoses (**8** and **9**) and 1,6-anhydro- β-D-glucose (**21**) by gc, using the authentic samples, and from gc-ms data. The formation of the anhydroglucose **21** requires intramolecular involvement of the free OH group on C-6 of the molecule, at the reaction center. For this reason, in subsequent experiments, the OH groups of the thioglucosides were protected prior to illumination.

The protected glucoside **2** was prepared by methylation of **1** using MeI/NaH/DMF.[19] A solution of **2** and DCN in acetonitrile and methanol (9:1) was irradiated (40 h) at 350 nm. Tlc analysis of the aliquots, withdrawn from the reaction mixture at regular time intervals, established that the conversion of **2** to at least four products was complete within 24 h. Three of the products displayed tlc characteristics identical to those of methyl glycosides **12** and **13** and thiophenol. The formation of **12** and **13** was confirmed by hplc studies using authentic samples. A fourth product has yet to be identified.

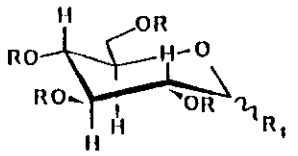
Figure 1 Peak Area *vs* Irradiation Time



In the absence of DCN, the glucoside **2** proved unreactive upon irradiation as demonstrated by periodic sampling and tlc analysis conducted over the course of the illumination. This observation clearly demonstrates that DCN is an essential component in the process. It was also determined that no effect was induced upon addition of **2** to the pre-irradiated mixture of acetonitrile, methanol and DCN. This result eliminates any possibility of the involvement of a stable "photogenerated acid" of a type observed in other reactions.[24]

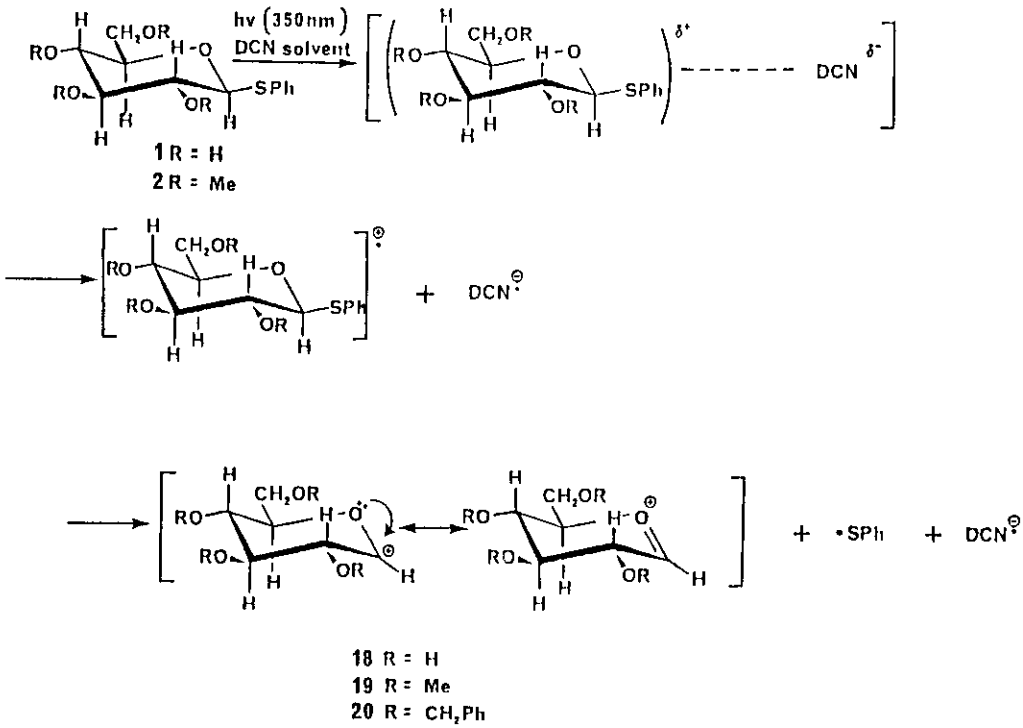


	R	R_1
1	H	Ph
2	Me	Ph
3	Ac	Ph
4	Ac	Ph–Me
5	Ac	Ph–OMe
6	CH_2Ph	Ph
7	CH_2Ph	Me

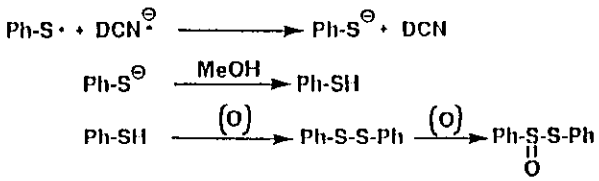


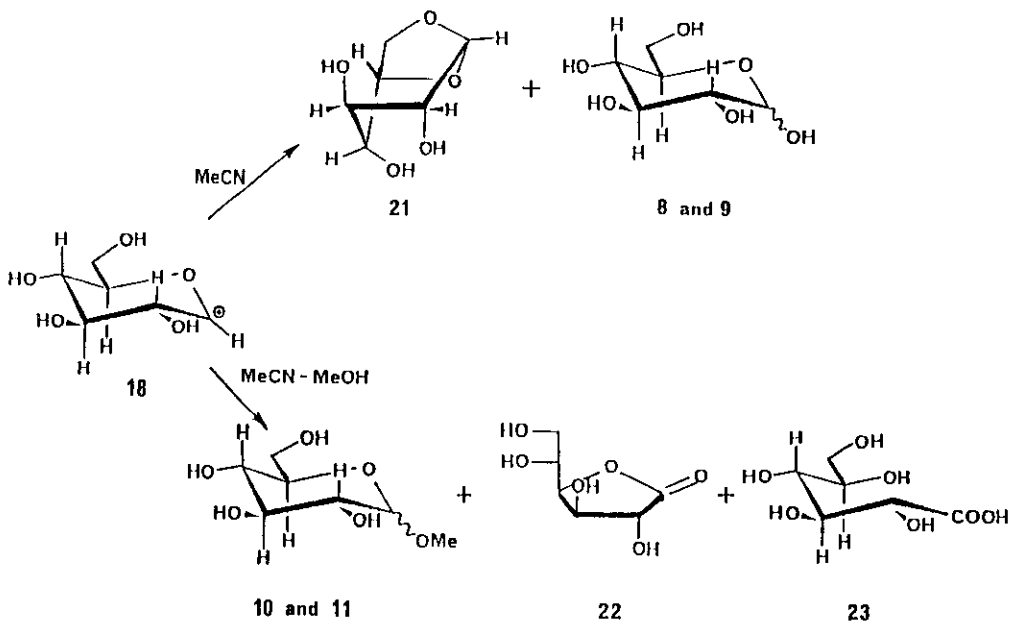
	R	R_1
8	H	α-OH
9	H	β-OH
10	H	α-OMe
11	H	β-OMe
12	Me	α-OMe
13	Me	β-OMe
14	CH_2Ph	α-OMe
15	CH_2Ph	β-OMe
16	CH_2Ph	α-OH
17	CH_2Ph	β-OH

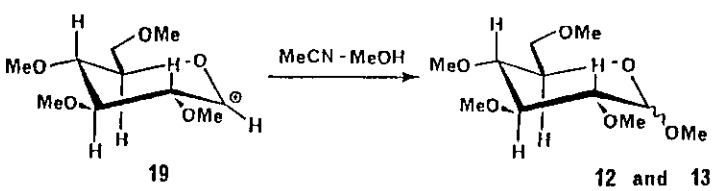
Scheme 1



Scheme 1 (con't)







The photolability of the glucosides **1** and **2** in the presence of DCN may be explained by invoking an electron-transfer mechanism. The electron-transfer sensitizer DCN in its excited singlet state has enhanced electron affinity over that in its ground state. Consequently, upon irradiation, DCN may form encounter complexes[25] through available electrons of the thiophenyl moiety of the thioglucoside (Scheme 1). In a polar solvent such a complex may, among other processes, dissociate with transfer of an electron from the donor to the acceptor components of the complex forming a radical ion pair. The thiophenyl glucoside radical cation may then dissociate in a ground state process to give the thiophenyl radical and the comparatively stable glucopyranosyl cation.

The glucopyranosyl cation **18** (Scheme 1) formed from the glucoside **1** may react with a suitable nucleophilic entity such as water or methanol or intramolecularly with a hydroxy group. The hydroxyl group at the 6-position has the appropriate steric disposition to achieve formation of the 1,6-anhydro derivative **21**. The reaction of the cation **8** with water would give α- and β-D-glucoses (**8** and **9**). In the presence of methanol, the analogous methyl glucosides **10** and **11**, were formed.

Presumably the gluconic acid **23** was formed by hydrolysis of the lactone **22**, however, the production of these oxidation products from **1** is not fully understood. In the early stage of irrdadiation, a considerable amount of the lactone **22** was formed relative to gluconic acid **23**. The relative concentration of **23** then increased with time at the expense of the lactone **22** over the course of the irradiation. The equilibrium between **22** and **23** has been adequately discussed elsewhere.[26]

The glucopyranosyl cationic intermediate **19** resulting from irradiation of the protected glucoside **2**, reacted with methanol to give the methyl glucosides **12** and **13** respectively (Scheme 1). In an extension of the work on protected glucosides, the acetylated derivatives **3**, **4**, and **5** were prepared from glucosepentaacetate and the corresponding thiophenols in the presence of $FeCl_3$.[14] Unfortunately, none of these glucosides displayed photolability upon irradiation (350 nm, 24 h) with DCN in acetonitrile and methanol (9:1).

The benzylated thioglucosides **6** and **7** were irradiated (48 h) with DCN in the absence of methanol. The concentration of each glucoside markedly decreased with concommitant formation of several unidentified products (hplc), and the anticipated glucosides (**16** and **17**) were not detected as products. A similar observation was made when the glucoside **6** was irradiated in the presence of DCN and methanol, and neither **14** nor **15** was produced. In the case of the benzylated glucosides, DCN did not presumably form an encounter complex with the thioaryl or thioalkyl groups, the precursor for the reactive glucopyranosyl cation **20** (Scheme 1). It is proposed that DCN may instead form encounter complexes with the benzyl protecting groups leading to various unidentified products.

ACKNOWLEDGEMENT

We wish to extend our gratitude to Miss Frances Caldwell for her help in perparing this manuscript. Our gratitude is also extended to Dr. David C. Lankin for preparation of the figures and scheme. We also acknowledge and thank Dr. Samuel E. Ellzey, Jr. for technical assistance in obtaining high resolution nmr data.

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Received, 11th September, 1989