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Synthesis of Phenyl 1-Thioglycopyranosiduronic Acids using a Sonicated Jones Oxidation

Nigel M. Allanson*, Dashan Liu, Feng Chi, Rakesh K. Jain , Anna Chen, Manuka Ghosh, Liwu Hong and Michael J. Sofia

Transcell Technologies Inc, 8 Cedar Brook Drive, Cranbury, NJ 08512, USA

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Abstract: Jones reagent selectively oxidizes the primary hydroxyl of 1-thiophenyl glycosides in preference to oxidation at sulfur to give phenyl 1-thioglycopyranosiduronic acids in moderate to excellent yields.

Glycopyranosiduronic acid building blocks are found in a variety of important biological substances such as heparin and the antibiotic moenomycin.[1] A key step in their synthesis from glycosides is the oxidation of the primary 6-hydroxyl group to a carboxylic acid. In a project to synthesize moenomycin derivatives by solid phase chemistry, we required a general method for the conversion of partially protected thioglycosides to their corresponding 1-thiouronic acids by selective oxidation of a primary hydroxyl group in the presence of both secondary hydroxyl groups and a thioether linkage. Two methods are known for the conversion of partially protected glycosides to glycopyranosiduronic acids, namely, PtO_2 and molecular oxygen[2] and also TEMPO and sodium hypochlorite.[3] The first of these is reported to be inhibited by the presence of thioacetals,[2] the second in our hands, was found to oxidize the thiogycosidic linkages to a mixture of sulfoxides and sulfones in preference to the oxidation of the primary hydroxyl groups.

The use of Jones reagent (CrO_3 in aqueous acetone)[4] to convert glycosides to glycopyranosiduronic acids,[5,6] or PDC to give the corresponding esters[7] is also well precedented, but these methods had not previously been used on substrates containing unprotected secondary hydroxyl groups, or with thioglycosides . We report that Jones reagent is the reagent of choice for the synthesis of partially or fully protected phenyl thioglycopyranosiduronic acids from thioglycosides. Furthermore we show that by sonicating the reaction, moderate to excellent yields of these products can be rapidly achieved using standard reaction conditions with this inexpensive oxidant.

Using 4-(methylthio)benzyl alcohol as a model substrate (Table 1), we determined that Jones reagent preferentially oxidizes its primary hydroxyl to a carboxylic acid in the presence of a thioether (entry 1). Thus a 73% yield of 4-(methylthio)benzoic acid was obtained together with 13% of the corresponding sulfoxides and 14% of the sulfone, by adding Jones reagent dropwise to a solution of the substrate in acetone at RT until a transient brown color persisted in solution (3 min). Addition of excess oxidant resulted in a 96% yield of 4-(methylsulfonyl)benzoic acid after 2 hr (entry 2).

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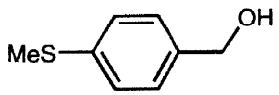
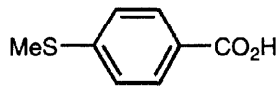
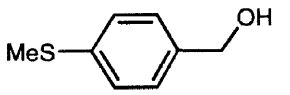
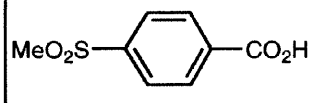
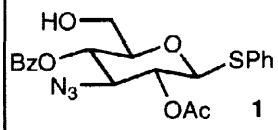
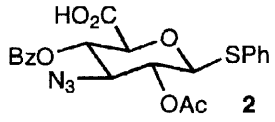
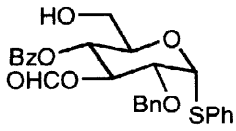
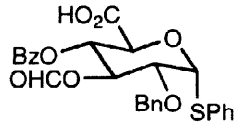
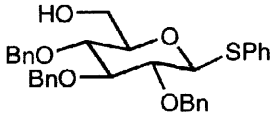
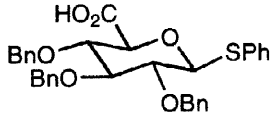
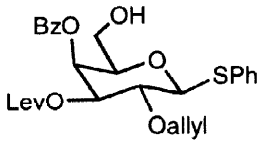
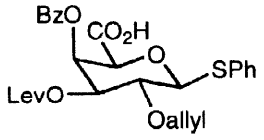
Table 1: Preparation of Phenyl 1-thioglycopyranosiduronic acids using a sonicated Jones oxidation

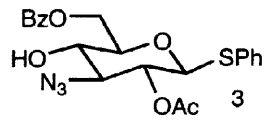
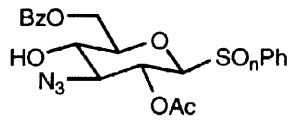
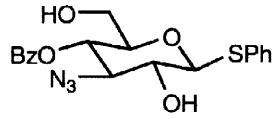
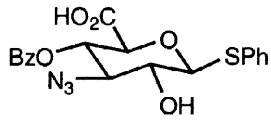
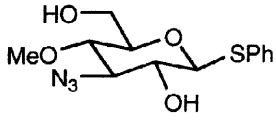
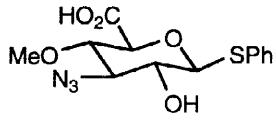
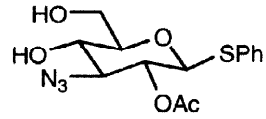
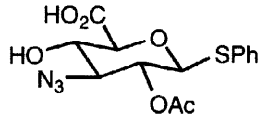
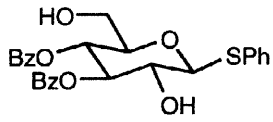
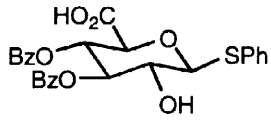
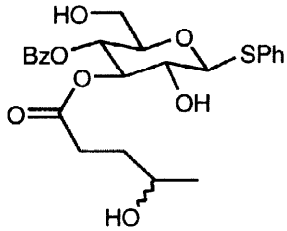
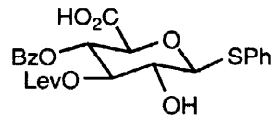
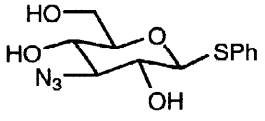
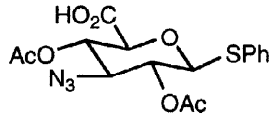
ENTRY	STARTING MATERIAL	MAJOR PRODUCT[9]	CONDITIONS	YIELD
1			1.4 eq, 3min (unsonicated)	72% sulfide 14%sulfoxide 14% sulfone
2			2.6 eq, 2 hr (unsonicated)	96%
3			2.6 eq, 1.5 hr	85-100%
4			2.6 eq, 1.5 hr	100%
5			2.6 eq, 1.5 hr	63%
6			2.6 eq, 1.5 hr	55%

Conditions used are as described in the text. The number of moles of CrO_3 and the reaction time are indicated

On thioglycoside substrates, the oxidation is slower and more selective for the primary alcohol groups. The reaction of **1** with 3 equivalents of CrO_3 in aqueous acetone was incomplete after 3 hr at RT. Although the Jones oxidation of alkyl glycosides has previously been reported using a large excess of oxidant (typically 5-fold),[6] or by heating at 55 ^{0}C,[7] neither set of conditions was compatible with the other oxidizable functionalities in our substrates. We found that the reaction could be driven to completion in about 2 hr by sonication, giving an excellent yield of glucopyranosiduronic acid **2** (entry 3). The increase in reaction rate is probably due to the heating effect of the sonicator bath since a similar yield was obtained by heating of **1** at 35 ^{0}C for 2.5 hr. Nevertheless, sonication was shown to give more consistent results than heating when trials were performed on a small range of substrates using standard amounts of oxidant and a fixed reaction time, and consequently, we have reported the results from the sonicated experiments in this paper.

Entries 3-6 indicate that good to excellent yields of 1-thiouronic acids were obtained when the primary 6-hydroxyl group was the only unprotected hydroxyl group in the thioglycoside substrate. As expected, allyl and benzyl ether protecting groups were stable to the acidic oxidation conditions, as were the potentially sensitive formate (entry 4), acetate and benzoate groups. In entries 4 and 6, the benzoate protecting group at O-4 did not migrate to O-6 during Jones Oxidation[8] as has been reported for acetyl protection of this hydroxyl group.

Table 2: Jones oxidation of thioglycoside substrates containing secondary hydroxyl groups

ENTRY	STARTING MATERIAL	MAJOR PRODUCT[9]	CONDITIONS	YIELD
7			2.6 eq, 1.5 hr	n= 0 85% n=1,2 15%
8			3.9 eq, 5 hr 25 ^{0}C	65%
9			2.4 eq, 1.75 hr 25 ^{0}C	66%
10			2.6 eq, 1.5 hr	50%
11			2.7 eq, 1.5 hr	43%
12			2.8 eq, 1 hr	28%
13			2.6 eq, 1.5 hr acetylated on work up	25%

Conditions used are as described in the text. The number of moles of CrO_3 per mole of substrate and the reaction time are indicated

The Jones oxidation of substrates containing one or more unprotected secondary hydroxyl groups is shown in Table 2. Surprisingly, no oxidation of the 4-hydroxyl of substrate **3** to a ketone was observed after sonicating with excess Jones oxidant for 1.5 hr (entry 7), although approximately 15% of a mixture of sulfoxides and sulfone was obtained in addition to recovered starting material. Substrates containing two hydroxyl groups (entries 8-11), were oxidized in moderate to good yields to partially protected 1-thiouronic acids. The thioglycoside linkage was more susceptible to oxidation in these cases, resulting in increased amounts of sulfoxide-uronic acid by-products. Nevertheless, direct oxidation compared favorably with alternative multistep protection/deprotection sequences for obtaining these products. Relatively poor yields were obtained by Jones oxidation of triols (entries 12 and 13). However, the selectivity of oxidation in the former case was notable, since only one of the two secondary hydroxyls (in addition to the primary hydroxyl group) was oxidized by the reagent. Acetylation ($HClO_4$, Ac_2O) of the crude reaction mixture from entry 13 was used to aid the recovery of the product.

A typical oxidation procedure is as follows:

Phenyl 2-O-acetyl-3-azido-4-O-benzoyl-3-deoxy-1-thio-β-D-glucopyranoside **1** (4.0 g, 9.0 mmol) was dissolved in acetone (60 mL) and treated with (20.2 mL, 23.5 mmol) of Jones reagent (prepared from 7 g of CrO_3, 6 mL of H_2SO_4 and 50 mL of water). The reaction mixture was sonicated in a 60 W sonicator bath for 1.5 hr at 35 ^{0}C until the reaction was complete as judged by TLC. The reaction mixture was quenched with isopropanol (10 mL) and the clear supernatants decanted and evaporated to give the crude product. Flash chromatography of the crude product on silica, eluant 5-15% methanol-dichloromethane gave phenyl 2-O-acetyl-3-azido-4-O-benzoyl-3-deoxy-1-thio-β-D-glucopyranosiduronic acid **2** (3.67 g, 8.0 mmol, 89%) as a white solid. mp 170-172 ^{0}C. ^{1}Hnmr (300MHz, $CDCl_3$) : δ 2.21 (3H,s, OAc); 3.97 (1H,t, J = 9.8 Hz, H-3); 4.21 (1H, d, J = 9.8 Hz, H-5); 4.85 (1H, d, J = 10.1 Hz, H-1); 5.01 (1H, t, J = 10.0 Hz, H-2); 5.36 (1H, t, J = 9.8 Hz, H-4); 7.33-8.03 (10H, m, Ar-H). FAB MS: *m/e* 480 [M+Na] and 502 [M+2Na-H].

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9. All new compounds had satisfactory ^{1}H nmr and mass spectra.