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A Novel "One-Pot" Synthesis of Thiosugar-Derived *S*-Xanthates

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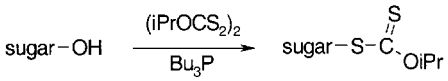
ABSTRACT



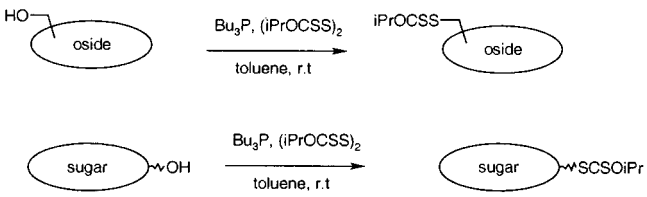
The preparation of sugar-derived *S*-xanthates continues to attract significant attention owing to their importance as osidic radical precursors or anomeric activators. Herein we report a simple and original protocol to introduce regiospecifically the *S*-xanthate group on primary and anomeric positions of sugars.

The introduction of a thio function onto a carbon in chiral molecules is a very important chemical modification, particularly in the field of carbohydrate chemistry.[1] In our goal to study and develop some thiochemistry in the carbohydrate field, we were interested in the xanthate (*O*,*S*-dithiocarbonate) ester group. This particular function has played an important part as a very versatile tool in organic thiochemistry: easy deprotection to thiols,[2] glycosidations,[3] Chugaev thermolytic elimination,[4] aminolysis[5] and radical chemistry[6] (stannane reduction,[7] *C*-glycoside synthesis[8]).

An efficient procedure for the direct conversion of a hydroxyl group into a thioether function is the Hata protocol which makes use of the dismutation of a disulfide by tri-*n*-butylphosphine. The former procedure[9] was first introduced for the preparation of thionucleosides and has now been widely applied to different kinds of substrates.[10]

We herein report a simple "one-pot" procedure[11] to obtain a *S*-xanthate function from a hydroxyl group using the Hata protocol (Scheme 1).

Scheme 1



The results are shown in Table 1 and Table 2 with a sample of representative carbohydrate substrates.[12] As can be seen, the Hata procedure using $(^{i}PrOCSS)_2$ leads to reasonable yields with primary hydroxyl groups. The reaction is fairly compatible with a variety of protective groups such

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(11) **Typical Procedure for the One-Pot Synthesis of *S*-Xanthate Derivatives**. 2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranose (0.5 g, 1.92 mmol) was dissolved in toluene (20 mL) in the presence of molecular sieves (4 Å). Tri-*n*-butylphosphine (1.05 mL, 4.21 mmol) and *O*,*O*-diisopropyl dithiocarbonate disulfide (1.04 g, 3.84 mmol) were then added. After 5 h of stirring at room temperature, the mixture was concentrated in vacuo and purified by flash chromatography (petroleum ether/ethyl acetate 9/1) to furnish *O*-isopropyl *S*-(2,3:4,5-di-*O*-isopropylidene-α-D-mannofuranosyl) dithiocarbonate as a syrup (0.617 g, 87%).

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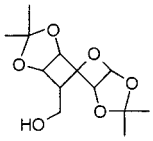
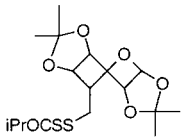
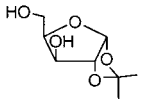
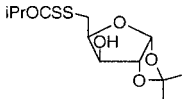
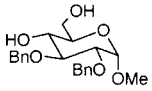
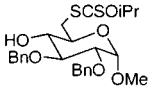
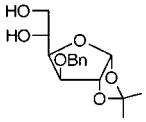
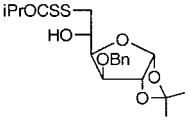
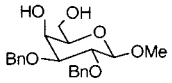
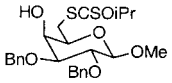
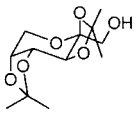
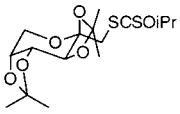
Table 1. Regiospecific Synthesis of *S*-Xanthates Derived from Sugars on a Primary Position

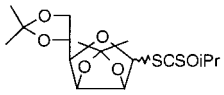
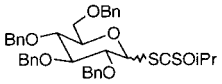
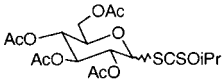
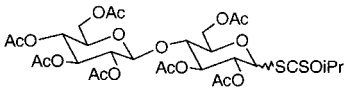
entry	starting material	*S*-xanthate derivative	yield (%)
1			80
2			77
3			86
4			82
5			83
6			27[a]

[a]: starting material was recovered.

as ether, acetal, and ester. The reaction was performed on diverse carbohydrate structures, including furan and pyran rings with different conformations. Moreover, a complete selectivity for the primary hydroxyl site could be observed on diol substrates possessing a secondary hydroxyl function (entries 2−5). This results is important when compared to the Mitsunobu reaction which is well known to affect both positions.[13] The reaction also seemed to be quite sensible to steric hindrance as can be seen on the low yield obtained when the neopentylic site of D-fructopyranose is involved (entry 6).

(12) All compounds were fully characterized by ^{1}H and ^{13}C NMR, MS, $[\alpha]_D$, and melting point. Selected compounds: *O*-Isopropyl *S*-(1,2:3,4-di-*O*-isopropylidene- α-D-galactopyranos-6-yl) dithiocarbonate: ^{1}H NMR (250 MHz, $CDCl_3$) 1.29, 1.31, 1.42 and 1.48 (4s, 12 H, ^{i}Prd), 1.33 (d, 6H, J = 6.2 Hz, ^{i}Pr), 4.15 (m, 1H, H5), 4.25 (dd, 1H, J = 7.8 Hz, J = 1.9 Hz, H4), 4.29 (dd, 1H, J = 5.0 Hz, J = 2.6 Hz, H2), 4.41 (dd, 1H, J = 11.3 Hz, J = 7.0 Hz, H6b), 4.60 (m, 2H, H6a and H3), 5.37 (m, 1H, CH ^{i}Pr), 5.50 (d, 1H, H1); ^{13}C NMR (62.89 MHz) 21.6 (CH_3 ^{i}Pr), 23.5, 23.9, 24.9, 25.0 (4 CH_3), 65.9 (C5), 70.8, 71.0 and 71.3 (C2, C3 and C4), 71.2 (C6), 78.0 (CH ^{i}Pr), 96.6 (C1), 107.8 and 108.6 (C ^{i}Pr), 193.6 (CS). *O*-Isopropyl *S*-(2,3:4,5-di-*O*-isopropylidene-α-D-mannofuranos-1-yl) dithiocarbonate: ^{1}H NMR (250 MHz, $CDCl_3$) 1.31, 1.33, 1.41 and 1.46 (4s, 12 H, ^{i}Prd), 1.34 (d, 6H, J = 6.2 Hz, ^{i}Pr), 3.98−4.09 (m, 3H, H6a, H6b and H4), 4.38 (m, 1H, H5), 4.81 (m, 2H, H2 and H3), 5.40 (m, 1H, CH ^{i}Pr), 6.42 (s, 1H, H1); ^{13}C NMR (62.89 MHz) 21.5 (CH_3 ^{i}Pr), 25.0, 25.5, 26.3, 27.4 (4 CH_3), 67.2 (C6), 73.1 (C5), 78.2 (CH ^{i}Pr), 79.4 and 85.4 (C2 and C3), 83.2 (C4), 107.6 (C1), 109.8 and 113.7 (C ^{i}Pr), 192.6 (CS).

Table 2. Synthesis of Anomeric *S*-Xanthates

entry	*S*-glycosyl xanthate	yield (%)	ratio α/β[a]
1		87	100/0
2		82	80/2
3		87	57/43
4		86	13/87

[a]: determined by ^{1}H NMR.

The Hata procedure has attracted more attention to introduce a sulfur function on the anomeric carbon of carbohydrates as hetero-aryl and aryl thioglycosides.[14] Glycosyl xanthates and thioglycosides are well known as glycosyl donors in carbohydrate chemistry. Therefore, we examined the direct conversion of the anomeric hydroxyl into *O*-alkyl *S*-glycosyl dithiocarbonates. Some synthetic methods have already been developed to synthesize *S*-xanthates,[15] but new direct approaches on anomeric carbon have never been developed. The preliminary results summarized in Table 2 do not provide a complete picture but clearly reveal the efficiency of the method. In all the cases explored, high yields were obtained. The unexpected retention of configuration, observed in entry 1, seemed to indicate an SN1 mechanism in that case.

In conclusion, we have developed a simple and efficient protocol for the synthesis of *S*-xanthate derivatives from sugars on the hemiacetalic function or on an primary hydroxyl site.

Acknowledgment. The authors thank Dr. S. Zard and F. Chéry for fruitful discussions. Prof. P. Rollin dedicates this paper to Prof. P. Sinaÿ (Ecole Normal Supérieure, Paris) who taught him modern chemistry.

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