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# FREE-RADICAL ADDITION OF 1-THIOSUGARS TO ALKENES A NEW GENERAL APPROACH TO THE SYNTHESIS OF 1-THIOGLYCOSIDES

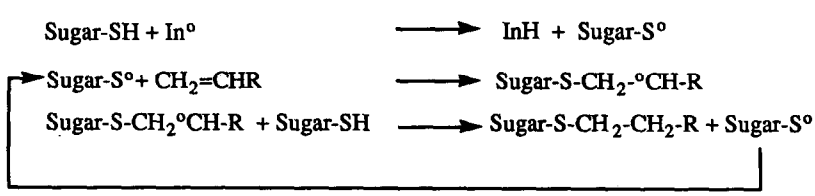
J.M. LACOMBE, N. RAKOTOMANOMANA and A.A. PAVIA*

Faculté des Sciences d'Avignon, Laboratoire de Chimie Bioorganique
33 Rue Louis Pasteur, 84000 Avignon (France)

**Summary :** Addition of peracetylated 1-thiosugars to alkenes in the presence of azobis(isobutyronitrile) (AIBN) as initiator constitutes an efficient route to alkyl 1-thioglycosides as well as to 1-thioglycosides bearing a reactive group on the aglycon.

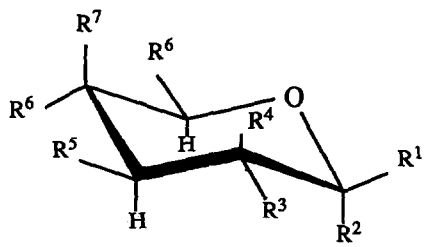
We have recently reported the preparation of macromolecular conjugates suitable for the study of various biological phenomena including affinity-labeling of cell lectins, by telomerization of unsaturated monomers bearing appropriate ligands [1, 2]. Several acryloyl derivatives were synthesized and their polymerization performed in the presence of various thiols including 1-thiosugars as transfer reagents [2]. In our hands, the latter proved suitable reagents for free-radical addition to alkenes.

Although addition of thiols to unsaturated compounds is a quite general reaction, so far, this approach has never been used for the synthesis of 1-thioglycosides. In this paper, we wish to report preliminary results dealing with the facile synthesis of various 1-thioglycosides in which the carbohydrate moiety is either a mono- (glucose, galactose, mannose, xylose etc...) or a disaccharide (cellobiose, maltose etc...). The reaction proceeds according to the following general scheme and leads in all cases to glycosides in fairly good yield (50 to 93%, see table 1).




**In :** Initiator e.g., azobis(isobutyronitrile) (AIBN)
**Sugar-SH :** 1-thiosugar (mono or disaccharide)
**Sugar-$SCH_2CH_2R$** or **Sugar-$SCH_2CHR_2$ :** 1-thioglycoside
**R :** hydrocarbon chain with or without a reactive group.

The method allows the preparation of alkyl 1-thiolycosides e.g. *iso*-butyl and *n*-octyl derivatives as well as alkyl 1-thioglycosides containing at the terminal position of the aglycon an amino, acid, ester, -including active ester- functional group (see below).




**2** $R^1 = SCH_2CH(CH_3)_2$ ; $R^3, R^5, R^6 = OAc$ ; $R^2, R^4, R^7, R^8 = H$ (Xyl)

**3** $R^2 = SCH_2CH(CH_3)_2$ ; $R^4, R^5, R^6 = OAc$ ; $R^8 = CH_2OAc$ ; $R^1, R^3, R^7 = H$ (Man)

**4** $R^1 = SCH_2CH(CH_3)_2$ ; $R^3, R^5, R^7, = OAc$ ; $R^8 = CH_2OAc$ ; $R^2, R^4, R^6 = H$ (Gal)

**5** $R^1 = SCH_2CH(CH_3)_2$ ; $R^3, R^5, R^6 = OAc$ ; $R^8 = CH_2OAc$ ; $R^2, R^4, R^7 = H$ (Glc)

**6** $R^1 = SCH_2CH(CH_3)_2$ ; $R^3, R^5 = OAc$ ; $R^6 = \beta$-D-Glc $(OAc)_4$ ; $R^8 = CH_2OAc$ ; $R^2, R^4, R^7 = H$ (Cell)

**7** $R^1 = S(CH_2)_7CH_3$ ; $R^3, R^5 = OAc$ ; $R^6 = \beta$-D-Glc $(OAc)_4$ ; $R^8 = CH_2OAc$ ; $R^2, R^4, R^7 = H$ (Cell)

**8** $R^1 = S(CH_2)_7CH_3$ ; $R^3, R^5, R^6 = OAc$ ; $R^8 = CH_2OAc$ ; $R^2, R^4, R^7 = H$ (Glc)

**9** $R^1 = S(CH_2)_3CO_2Bzl^*$ ; $R^3, R^5, R^6 = OAc$ ; $R^8 = CH_2OAc$ ; $R^2, R^4, R^7 = H$ (Glc)

**10** $R^1 = S(CH_2)_3CO_2C_6F_5$ ; $R^3, R^5, R^6 = OAc$ ; $R^8 = CH_2OAc$ ; $R^2, R^4, R^7 = H$ (Glc)

**11** $R^1 = S(CH_2)_3CONHNH_2$ ; $R^3, R^5, R^6 = OH$ ; $R^8 = CH_2OAc$ ; $R^2, R^4, R^7 = H$ (Glc)

**12** $R^1 = S(CH_2)_3NHZ^*$ ; $R^3, R^5, R^6 = OAc$ ; $R^8 = CH_2OAc$ ; $R^2, R^4, R^7 = H$ (Glc)

* : $Bzl = CH_2C_6H_5$ ; $Z = COO\text{-}CH_2C_6H_5$

Compounds of this type are of interest in view of their use as carbohydrate ligands for the preparation of various glycoconjugates especially neoglycoproteins [3] and affinity adsorbents [4].

1-Thioglycosides with an aglycon having a terminal carboxyl group can be coupled through a short spacer arm to protein amino groups via acyl azide (formed from ester via hydrazide), N-hydroxysuccinimide or mixed anhydride [5].

Analogues with the aglycon terminated by an amino group are suitable for conjugation to either protein carboxyl groups or to N-hydroxysuccinimide-activated polyacrylamide gel [5] and other materials [4].

In that respect, resistance to glycosylhydrolases together with a better chemical stability to both hydrolysis and β-elimination constitute a significant advantage of S-thioglycosides over O-glycosidic analogues. In addition, the method allows the preparation of carbohydrate-containing non-ionic detergents as for example octyl 1-thioglucoside (**8**), octyl 1-thiocellobioside (**7**) and other similar compounds.

| Compounds[a] | Yield (%) | Optical rotation | M.p (°C) |
|---|---|---|---|
| **2** | 90 | - 70° (c 1, $CHCl_3$) | 73 - 74 |
| **3** | 92 | + 44° (c 0.6, $CHCl_3$) | 69 - 70 |
| **4** | 83 | - 11° (c 1, $CHCl_3$) | oil |
| **5** | 80 | - 31° (c 1, $CHCl_3$) | 98 - 99 |
| **6** | 72 | - 22.5° (c 1, $CHCl_3$) | 190 - 191 |
| **7** | 50 | - 25° (c 1, $CHCl_3$) | 154 - 155 |
| **8** | 93 | - 29° (c 1, $CHCl_3$) | 67 - 68 |
| **9** | 75 | - 17.5° (c 1, $CHCl_3$) | oil |
| **10** | 50 | - 22° (c 1, $CHCl_3$) | oil |
| **11** | 75 | - 14.5° (c 1, $H_2O$) | 142 - 143 |
| **12** | 50 | - 19.5° (c 1, $CHCl_3$) | oil |

**Table 1.** Physical constants for 1-thioglycosides **2-12**

[a] structures and anomeric configurations were assigned by $^1H$- and $^{13}C$-nmr spectroscopy and comparison with authentic sample when already described.

We have selected D-glucopyranose as model hexose. The starting material was 2,3,4,6- tetra-O-acetyl-β-D-1-thioglucopyranose (**1**) obtained by treatment of routinely available 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide with thiourea by a conventional procedure [6,7]. In an illustrative example, a solution of **1** (5g, 13.7 mmol) in acetonitrile(5 mL) was added dropwise to a mixture of 1-octene (55 mL) and azobis(isobutyronitrile) (175 mg) at 80°C and the mixture maintained at this temperature for an additional 15 min after the addition was completed . Distillation of 1-octene under reduced pressure left a solid material which crystallyzed from diethyl ether-hexane to give pure octyl β-D-1-thioglucopyranoside tetra-acetate (6,15 g, 93%). All other compounds reported in table 1 were prepared in a similar manner except for *iso* -butyl derivatives **2-6**. Due to the low boiling point of isobutylene ($CH_2$=CH($CH_3$)$_2$), a mixture of the latter, appropriate peracetylated 1-thioglucose and AIBN in acetonitrile was reacted at 80°C in a sealed vessel for approximatively 2 h then treated as above. 4-(-β-D-Glucopyranosylthio)butanoic acid hydrazide (**11**) was obtained by treatment of compound **9** for two hours with hydrazine in refluxing methanol [8].

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