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A convenient method for the synthesis of cyclic trithiocarbonates on carbohydrate scaffolds

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Abstract—An efficient regio- and stereoselective method for the synthesis of cyclic trithiocarbonates on carbohydrate skeleton is described. A freshly prepared solution of sodium trithiocarbonate reacts with *cis*-oriented epoxytriflate pentoses **7**–**11** to yield the corresponding cyclic trithiocarbonates **12**–**16**. Structures of all new compounds are established through MS, ^{1}H and ^{13}C NMR techniques. © 2002 Published by Elsevier Science Ltd.

The preparation of monosaccharides in which one or more oxygen atoms are replaced by a sulfur atom have received considerable attention, primarily because these compounds provide a route to the synthesis of deoxysugar.[1] Trithiocarbonate derivatives of carbohydrates are versatile intermediates for the synthesis of dithiosugars[2] and dideoxysugars.[3] Only a few methods are available for the synthesis of such carbohydrate derivatives, including the reaction of potassium methyl xanthate on epoxide[4] and episulphides[5] or, in some cases, the use of highly toxic thiophosgene gas.[6]

The reaction of organic halides with sodium trithiocarbonate (Na_2CS_3) has been widely used for the preparation of disubstituted trithiocarbonates.[7] It has been demonstrated that alkyl mono- and dihalides, upon treatment with sodium trithiocarbonate, could easily be converted into corresponding mono- or dimercaptans.[8] Recent efforts toward the preparation of dialkyl trithiocarbonates[9] prompted us to investigate the epoxytriflates **7**–**11** as possible candidate of sugar-based trithiocarbonates.

In the past, we have used the triflates of 2,3-anhydroribopyranoside **7** and **8** as starting materials toward the synthesis of either new and useful chiral building blocks[10] or biologically active natural product.[11] The strategy banks on difference in the reactivity between the *cis*-oriented triflate at C-4, which acts as a powerful leaving group, and the epoxide. This strategy enabled us to control the regioselective nucleophilic displacement of the triflate group to form *trans*-oriented systems which can be modified by further chemical transformations. In this communication, a simple and efficient route for the synthesis of cyclic trithiocarbonates **12**–**16** from the epoxytriflates **7**–**11** is described. The *cis*-oriented epoxytriflates were synthesized from the partially blocked sugars **2**–**6**, respectively, by reaction with triflic anhydride in the presence of pyridine at 0°C (Scheme 1).[12] Formation of the cyclic trithiocarbonates involved the addition of a red colored aqueous solution of Na_2CS_3[13] to a stirred solution of epoxytriflate.[14] The nucleophilic displacement of triflyl group at C-4 by sulfur was followed by the simultaneous intramolecular ring opening of the epoxide to afford the required trithiocarbonates in the yields given in Table 1.

Structures of all products were established through MS, elemental analysis, ^{1}H and ^{13}C NMR spectroscopy.[15] Conformations adopted by pyranoside rings in the product **12** and **13** were determined by vicinal coupling

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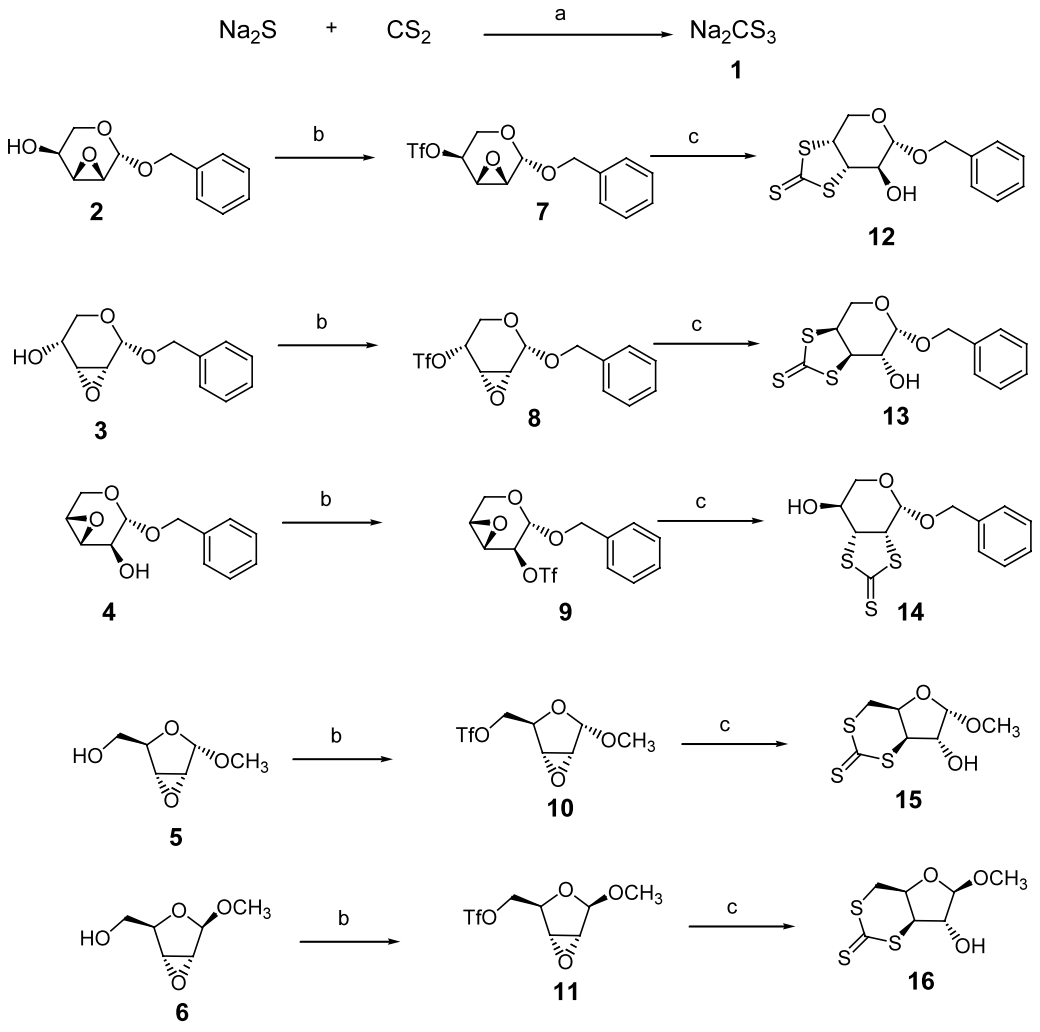


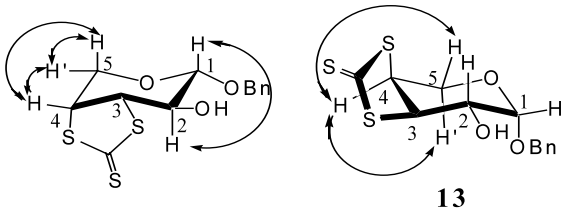
Scheme 1. Synthesis of sugar-based trithiocarbonates. *Reagents and conditions*: (a) Aliquat 336®, H_2O, 40°C, 90 min; (b) pyridine, Tf_2O, CH_2Cl_2, 0°C; (c) **1**, ethanol, H_2O, rt, 0.5 h.

constants and chemical shifts of their ^{1}H NMR spectra (Fig. 1). 5-H and 5′-H were recognized easily from their large geminal coupling constant (~13 Hz) at $\delta = 4.30$ and 3.87 ppm, respectively, in **12**, and at $\delta = 4.15$ and 3.88 ppm, respectively in **13**. A symmetrical ddd pattern appeared for 4-H of **12** with $J_{4,5} = 3.05$, $J_{4,5'} = 3.05$ and $J_{3,4} = 4.27$ Hz. This indicated a quasi equatorial–quasi equatorial relationship between 4-H and 5′-H and quasi equatorial–axial relationship between 4-H and 5-H; the conformation of the pyranoside ring in **12** is, therefore, predominately $^1C_4$. This was further supported by the large axial–axial coupling constant for 1-H and 2-H ($J_{1,2} = 6.41$ Hz). On the other hand in **13**, 4-H appeared as a multiplet at $\delta = 4.81$ ppm buried under the signal of the benzylidene proton. Although, the direct calculation of the coupling constants was not possible in this case, the coupling interaction of 4-H with 5-H and 5′-H ware calculated from dd patterns observed for the latter protons, revealing a 1.83 Hz value for $J_{4,5}$ and a 3.06 Hz value for $J_{4,5'}$. From these assignments, we assumed a quasi equatorial position for 4-H; hence, the pyranoside ring in **13** occurs predominately in $^4C_1$ conformation (Fig. 1).

Epoxyfuranosides **5** and **6**[16] were triflated by the standard method[12] and treated with Na_2CS_3. The yields of the trithiocarbonates **15** and **16** were, however, very low due to the reasons unknown to us. The reaction was sluggish and many unknown side products are also formed. The reason for the low yield may be due to low reactivity of furanoside epoxide or instability of the six-membered trithiocarbonate unit. Further investigations in this context are under observations in our laboratory.

Table 1. Synthesis of trithiocarbonates on sugar scaffold

Entry	Epoxy triflate	Trithio-carbonate	Time (min)	Yield (%)
1	**7**	**12**	10	95
2	**8**	**13**	10	90
3	**9**	**14**	25	75
4	**10**	**14**	60	30
5	**11**	**15**	65	25



12 **13**

$^1C_4$-Conformation
$J_{5,5'} = 13.4$ Hz
$J_{4,5} = 3.05$ Hz
$J_{4,5'} = 3.05$ Hz
$J_{1,2} = 6.41$ Hz

$^4C_1$-Conformation
$J_{5,5'} = 13.4$ Hz
$J_{4,5} = 1.8$ Hz
$J_{4,5'} = 3.05$ Hz

Figure 1. Preferred conformations of the pyranoside rings in **12** and **13** as determined from coupling interactions in ^{1}H NMR spectroscopy.

In conclusion, an easy and efficient method for the synthesis of cyclic trithiocarbonates on a carbohydrate scaffold has been discovered, which may lead to further chemical modifications to prepare dithio- and/or dideoxysugars.

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14. *General method for the preparation of trithiocarbonates*: To a stirred solution of freshly prepared Na_2CS_3 ($\sim$2 mmol) in water (5 ml) was added a solution of epoxytriflate (1 mmol) in ethanol (1 ml) at room temperature. The red color of Na_2CS_3 disappeared with the formation of yellow colored precipitate. After the time indicated in the Table 1, the precipitate was washed with water and recrystallized with ethylacetate.
15. *Data for* ***12***: yellow crystals; mp 131–133°C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.36–7.38 (m, 5H, Ph), 4.95 (d, $J=11.9$ Hz, 1H, OC*H*HPh), 4.76 (ddd, $J=4.27$, 3.05 Hz, 1H, H-4), 4.62 (d, $J=11.9$ Hz, 1H, OCH*H*Ph), 4.46 (d, $J=6.41$ Hz, 1H, H-1), 4.30 (dd, $J=3.05$, 13.42 Hz, 1H, H-5), 4.07 (m, 2H, H-3, H-2), 3.87 (dd, $J=3.35$, 13.42 Hz, 1H, H-5′); ^{13}C NMR (63 MHz, $CDCl_3$): δ 58.7, 61.4 (C-3, C-4), 61.6 (C-5), 69.9 (C-2), 70.8 (*C*H_2Ph), 102 (C-1), 128.1, 128.3, 128.7 (Ph), 162.1 (C=S); FAB-MS: $m/z=314.1$ (M^+).
Data for ***13***: yellow crystals; mp 162.3°C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.34–7.42 (m, 5H, Ph), 5.07 (brs, 1H, H-1), 4.81 (m, 2H, H-4, OC*H*HPh), 4.61 (d, $J=11.6$ Hz, 1H, OCH*H*Ph), 4.17 (m, 3H, H-5, H-3, H-2), 3.88 (dd, $J=1.83$, 13.42 Hz, 1H, H-5′); ^{13}C NMR (63 MHz, $CDCl_3$): δ 56.8 (C-5), 60.1, 60.4 (C-3, C-4), 68.3 (C-2), 70.4 (*C*H_2Ph), 97.05 (C-1), 128.3, 128.5, 128.8 (Ph); FAB-MS: $m/z=314.1$ (M^+).
Data for ***15***: yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.23 (s, 1H, H-1), 4.29 (t, $J=7.3$ Hz, 1H, H-4), 3.66 (m, 2H), 3.52 (2H), 3.35 (s, 3H, OCH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 28.3 (C-6), 55.6 (OCH_3), 56.8 (C-3), 74.1, 75.7 (C-2, C-4), 104.3 (C-1); FAB-MS: $m/z=238.1$ (M^+)
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