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DESULFURIZATION OF GLYCOSYL ISOTHIOCYANATES WITH TRIBUTYLTIN HYDRIDE

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Summary: Desulfurization of glycosyl isothiocyanates with tributyltin hydride in the presence of AIBN led to the formation of 1,5-anhydro-D-alditols via intermediate isocyanides.

Glycosyl isothiocyanates are useful and versatile intermediates for the synthesis of nucleoside analogs[1,2], since the isothiocyanato group can be readily transformed into a variety of other functional groups. One such transformation is reduction of the isothiocyanato function to the isocyanide by triethyl phosphite[3], triethyl phosphine[4] or by triphenyltin hydride[5] as reported for aryl and alkyl isothiocyanates. The synthetic approach which has been reported for synthesis of glucosyl isocyanides[6] proceeds by nucleophilic attack of the ambident cyanide ion on glycosyl halides[6-9] or by the dehydration of corresponding N-glycosyl formamides.[10] However, the glycosyl isocyanides[11] have not yet been prepared by reduction of the corresponding isothiocyanates. This encouraged us to use tributyltin hydride for reduction of the isothiocyanato group similarly to isoselenocyanato as recently reported.[12] However, a recent report in the literature indicates that the isocyanide function could be further reduced to the corresponding deoxy derivative.[13-16] It was found that the yields and the ratio of products of the desulfurization reaction are strongly dependent on time, temperature, and the presence of a free-radical initiator (AIBN/azo-bis-(isobutyronitrile).

Isocyanides 6-10 were obtained in good yields (76-58%) when the reaction was carried out with 1 equivalent of tributyltin hydride in ether solution at room temperature for 2-6 h (Table I) under N_2 atmosphere. Under these conditions, in the case of compounds 2, 3, and 4, the formation of coproducts, i.e. 1,5-anhydro-alditols 12, 13, and 14 in 1-3% yield has been observed. At 40° in ether/benzene solution with a catalytic amount of AIBN for 4-6 h the yields of isocyanides 6-10 was decreased to 30-51% and the formation of 1,5-anhydro-alditols 11-15 was observed in 12-41% yield. The reaction was monitored by TLC (AcOEt/CH_2Cl_2/MeOH, 7:2:1, V/V) and products were separated by flash column chromatography using the same solvent system.

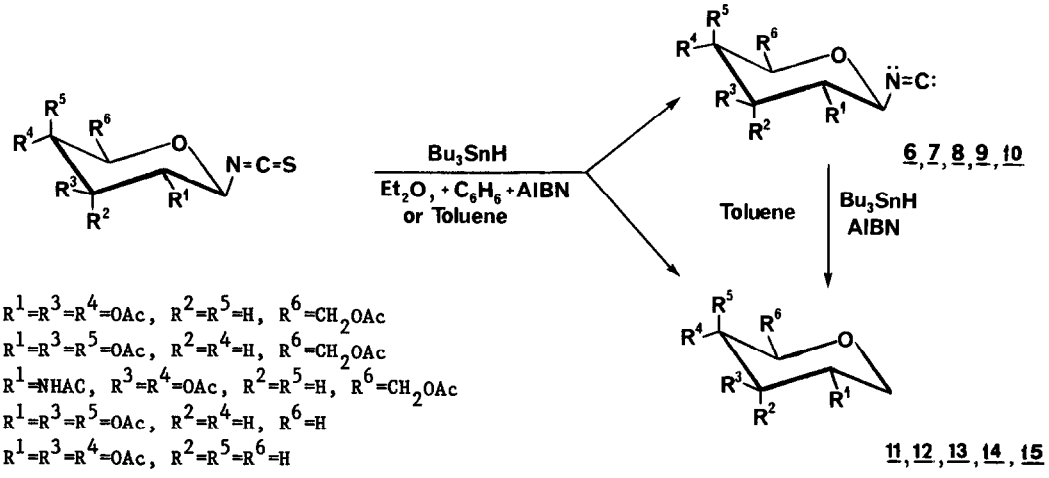
Under forcing conditions - in toluene at reflux temperature for 6-10h and in the presence of a catalytic amount of AIBN (N_2-atmosphere)-reduction of isothiocyanates 1-5 led to the formation of 1,5-anhydro-alditols 11-15 in 82-94% yield. However, trace amounts of intermediate isocyanides 6-10 in 1-2% were also observed, as indicated by TLC.

Table I

Products of reduction of isothiocyanates 1-5 with Bu_3SnH

Starting Material Compound No.	Time (h)	Solvent and radical initiator	Temp. °C	Isocyanides No.	Yield (%)	m.p.°C	$[\alpha]^D_{25}$,	1,5-Anhydro-alditols No.	Yield (%)	m.p.°C	$[\alpha]^D_{25}$,
	6	Et_2O	25°		76				--		
1[a]	6	$Et_2O+C_6H_6$+AIBN	40°	6[f]	51	103-105°	+4°(C 0.2$CHCl_3$)	11[k]	25	72-73°	+42°
	8	Toluene + AIBN	110°		<2				89		(c 1.0 $CHCl_3$)
	4	Et_2O	25°		61				<3		
2[b]	6	$Et_2O+C_6H_6$+AIBN	40°	7[g]	30	164-166°	+32°(C 1.5$CHCl_3$)	12[l]	41	103-105°	+48.1°
	8	Toluene + AIBN	110°		<1				82		(c 1.0 $CHCl_3$)
	4	DME	25°		59				<1		
3[c]	8	DME + AIBN	40°	8[h]	32	syrup	+6°(c 1.0 $CHCl_3$)	13[m]	38	168-169°	0°
	10	Toluene + AIBN	110°		<1				94		
	4	Et_2O	25°		69				<2		
4[d]	6	$Et_2O+C_6H_6$+AIBN	40°	9[i]	28	syrup	+16.9°(c 1.5 $CHCl_3$)	14[n]	36	126-128°	0°
	8	Toluene + AIBN	110°		<2				85		
	2	Et_2O	25°		58				--		
5[e]	4	$Et_2O+C_6H_6$+AIBN	40°	10[j]	70	syrup	+71°(c 1.0 $CHCl_3$)	15[o]	12	58-59°	-74.6°
	6	Toluene + AIBN	110°		<2				82		(c 1.0 $CHCl_3$)

a. Ref 17; b. Ref 17a; c. Ref 18; d. see note 19; e. see note 20; f. Ref 7. m.p. 102-104°, $[\alpha]^D_{25}$ + 4° (c 1.0 $CHCl_3$), g. Ref 7 m.p. 164-165°, $[\alpha]^D_{25}$, + 32° (c 1.5 $CHCl_3$); h. see note 21; i. see note 22; j. see note 23; k. Ref 24, 25, m.p. 71-73° $[\alpha]^D_{25}$ + 42° (c 1.4 $CHCl_3$; 1. Ref 24, 25, m.p. 103-104° $[\alpha]^D_{25}$ +47.9° (c 1.0 $CHCl_3$); m. Ref 26, m.p. 166-168°, $[\alpha]^D_{25}$ 0°; n. Ref 27, m.p. 122-123°, $[\alpha]^D_{25}$ 0°; o. Ref 28, m.p. 58°, $[\alpha]^D_{20}$ - 74.2°, (c 1.0 $CHCl_3$).



1 $R^1=R^3=R^4=OAc$, $R^2=R^5=H$, $R^6=CH_2OAc$
2 $R^1=R^3=R^5=OAc$, $R^2=R^4=H$, $R^6=CH_2OAc$
3 $R^1=NHAC$, $R^3=R^4=OAc$, $R^2=R^5=H$, $R^6=CH_2OAc$
4 $R^1=R^3=R^5=OAc$, $R^2=R^4=H$, $R^6=H$
5 $R^1=R^3=R^4=OAc$, $R^2=R^5=R^6=H$

Reduction of isocyanides 6-10 under the conditions as for isothiocyanates 1-5 produced 1,5-anhydro-alditols 11-15 in near quantitative 89-94% yield. These results clearly indicate that the isocyanide function can be reduced with tributyltin hydride only at elevated temperature and in the presence of radical initiator (AIBN) - (radical character reaction). No anomerization or isomerization to the cyanides, was observed under these conditions.

In contrast the isothiocyanato function easily undergoes desulfurization with tributyltin hydride at room temperature, and without radical initiation by AIBN. The selectivity of this reaction gives good access to preparation of the required anomer of monosaccharide isocyanides which was available only as an anomeric mixture by the previous method.[6-11]

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19. The starting 2,3,4-tri-O-acetyl-β-D-xylopyranose isothiocyanate (4) was prepared according to the recent procedure of M.J. Camarasa, P. Fernandez-Resa, M.T. Garcia-Lopez, F. C. De Las Heras, P.P. Mendez- Castrillon and A. San Felix, Synthesis 509, (1984). M.p. 72-73° (ether/hexane); $[\alpha]_{20}^{D}$-31.2° (c 1.2 $CHCl_3$); ^{1}H-NMR (200 MHz), 1.95, 2.02, 2.06 (S 9H, 3x OAc) 5.9 (t, 1H, $J_{2,3} = J_{3,4} = 4$Hz, H-3), 4.8(d 1H, $J_{1,2} = 9$Hz H-1), 4.5-4.2 (m, 3H H-1,2,4) 4.07(q 1H, $J_{5a,5e} = 12$ Hz, H-5e), 3.4 (q 1 H, H-5a); ^{13}C-NMR (50.3 MHz); 91.7 (C-1), 69.4 (C-2), 70.9 (C-3), 68.2 (C-4), 62.6 (C-5) and 141.3 (N=C=S). Anal. Calc. for $C_{12}H_{15}NO_7S$; C, 45.41;H,4.36; N,4.41; Found: C, 45.02; H, 4.6; N, 4.69.

20. The starting 2,3,4-tri-O-acetyl-β-L-arabinose isothiocyanate (5) was prepared according to the method of K.K. De, G.T. Shiau and R.E. Harmon, J. Carbohydr. Nucleos. Nucleot., 2, 171 (1975); $[\alpha]_{20}^{D}$ - 45.5° (c. 1.0 $CHCl_3$); ^{1}H-NMR (200 MHz); 1.87, 1.93, 2.00 (s 9H, 3x CH_3CO-) 4.1 (q 1H, $J_{5a,5e} = 12$Hz, H-5e, 3.8 q 1H, H-5e), 4.86 (d 1H, $J_{1,2} = 9$ Hz, H-1), 5.16 (q 1H, $J_{2,3}$ 10Hz, $J_{3,4}$ 3.2 Hz, H-3), 5.4 (q 1H, H-2), ^{13}C-NMR (50.3 MHz); 93.8 (C-1), 69.3 (C-2), 69.8 (C-3), 69.8 (C-4), 63.6 (C-5), 141.4 (N=C=S).

21. ^{1}H-NMR (200 MHz); ($CDCl_3$), 1,87, 1.93, 1.96, (s 9H 3x OAc), 2.01 (s 3H NAc), 4.1 - 3.4 broad m (H-2,3,4,5) 4.29 (d, 2H, H-6,6´), 4.67 (d 1H, $J_{1,2} = 12$ Hz H-1), 6.27d (1H, J = 8Hz NH), ^{13}C-NMR (50.3 MHz); 102,3 (C-1), 56.0 (C-2), 74.3 (C-3), 70.6 (C-4), 76.1 (C-5), 61.5 (C-6), 164.1 (N=C), Anal. Calc. for $C_{14}H_{20}N_2O_9$; C, 46.66; H, 5.59; N, 7.77; Found: C, 46.18; H, 5.67; N, 7.31.

22. ^{1}H-NMR (60 MHz); ($CDCl_3$), 1.97, 2.01, 2.09 (s 9H 3xOAc), 5.1 (t 1H H-3), 4.86 (d 1H, $J_{1,2} = 9$Hz H-1), 4.6-4.2 (m 3H H-1,2,4, 4.1 (q 1H H-5), 3.4 (q 1H - H-5). ^{13}C-NMR (50.3 MHz); ($CDCl_3$) 91.7 (C-1), 69.4 (C-2), 70.9 (C-3), 68.3 (C-4), 62.6 (C-5), 164.3 (N=C); Anal. Calc. for $C_{12}H_{15}NO_7$; C, 50.52; H, 5.3; N, 4.91; Found: C, 49.96; H, 5.41; N, 4.58.

23. ^{1}H-NMR (60 MHz); ($CDCl_3$) ; 1.86, 1.91, 2.01 (S, 9H 3xOAc), 4.16 (q H-5), 3.86 (q 1H H-5^1), 4.79 (d 1H $J_{1,2} = 9$ Hz, H-1, 5.0 (q 1H H-3), 5.46 (q 1H H-2). ^{13}C-NMR (50.3 MHz); ($CDCl_3$) 93.7 (C-1), 69.1 (C-2), 69.6 (C-3), 69.6 (C-4) 63.5 (C-5), 164.1 (N=C). Anal. Calc. for $C_{12}H_{15}NO_7$; C, 50.52; H, 5.3; N, 4.91; Found: C, 50.02; H, 5.01; N, 4.69.

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