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Influence of bromide ions on the synthesis of anomeric thiocyanates

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Dedicated to Professor Marek Chmielewski on the occasion of his 70th birthday

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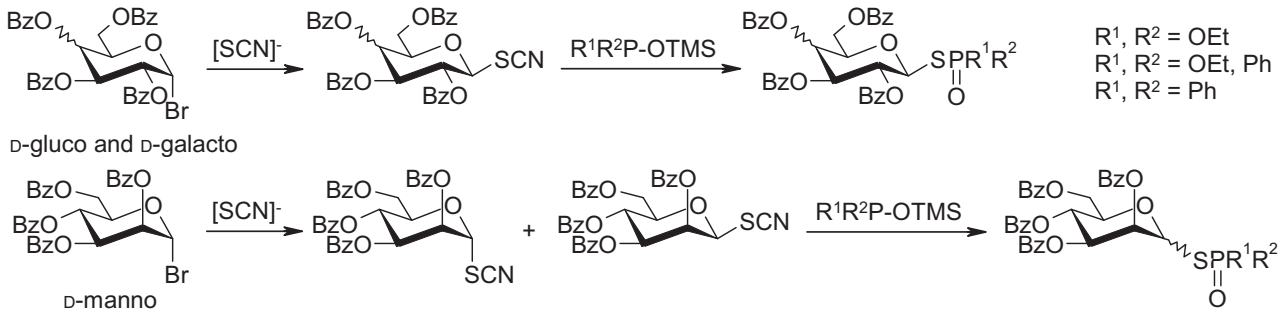
ABSTRACT

The synthesis of anomeric thiocyanates with the α- and β-configuration is described. Reactions performed under standard conditions afforded the 1,2-*trans* derivatives as the main products, whereas in the presence of the quaternary ammonium salts, the 1,2-*cis*-thiocyanates were formed preferentially. The strong influence of the bromide ions on the distribution of the products is discussed.

1. Introduction

As part of an ongoing project directed towards the application of *S*-glycosyl thiophosphates, thiophosphonates and thiophosphinates as new glycosyl donors we have recently reported their preparation from anomeric thiocyanates (Scheme 1);[1,2] the latter are readily available by treatment of the corresponding glycosyl bromides with potassium thiocyanate in acetone, or with potassium thiocyanate in the presence of 18-crown-6[3,4] or 1-butyl-3-methylimidazolium chloride ([bmim]Cl).[2] However, this procedure affords only 1,2-*trans* D-gluco- and D-galactopyranosyl thiocyanates, hence, the 1,2-*trans*-thiophosphorus donors may be conveniently obtained on a preparative scale. From D-mannopyranosyl bromide, 1,2-*trans* anomeric thiocyanate was isolated as prevailing product.[1] Such strong preference may be considered as a result of an S_N2 nucleophilic substitution supported by the neighbouring-group effects involving the 2-*O*-benzoyl group.

The lack of 1,2-*cis* isomers significantly restricted the investigation of the potential usefulness of thiophosphorus donors in the synthesis of oligosaccharides. Currently, there are no preparative methods for the synthesis of the 1,2-*cis* anomeric thiocyanates, although few derivatives were isolated incidentally by



Scheme 1.

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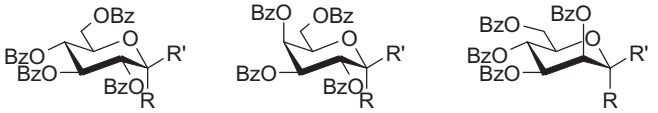
Kochetkov,[3,5] Somsak,[6] and by us.[2] Therefore, an effective preparation procedure to open the access to 1,2-*cis* isomers is needed.

In spite of the fact that anomeric thiocyanates are stable below 0 °C in the solid state (and may be stored for months without decomposition), they easily undergo isomerisation to the corresponding glycosyl isothiocyanates in solutions, especially at slightly elevated temperatures. For example, in a THF solution of β-D-gluco thiocyanate (**4**) approximately 5% of the corresponding isothiocyanate is present after 24 h at room temperature, 10% at 40 °C, whereas almost complete isomerisation occurs at 60 °C. Isomerisation of the anomeric −SCN group at elevated temperatures clearly shows that effective preparation of the glycosyl thiocyanates is only possible in a very narrow temperature window, which restricts possible modification of the reaction conditions. Considering the short reaction time and the relatively low temperature involved, careful control of the reactions progress is crucial for the successful preparation of the glycosyl thiocyanates (Fig. 1).



1: R = Br, R' = H
2: R = SCN, R' = H
3: R = NCS, R' = H
4: R = H, R' = SCN
5: R = H, R' = NCS

6: R = Br, R' = H
7: R = SCN, R' = H
8: R = NCS, R' = H
9: R = H, R' = SCN
10: R = H, R' = NCS

11: R = Br, R' = H
12: R = SCN, R' = H
13: R = NCS, R' = H
14: R = H, R' = SCN

Fig. 1. Structure of studied compounds.

2. Results and discussion

Herein, we report on modifications of the synthetic procedure, which allows either the 1,2-*trans*- or the 1,2-*cis*-glycosyl thiocyanates to be prepared preferentially. The stability of the products under the reaction conditions, the detailed composition of the reaction mixtures, the influence of bromide ions on the distribution of the products and a plausible mechanism of the reaction in the presence of bromide ions are discussed.

To find out optimal reaction conditions for the synthesis of glycosyl thiocyanates with a 1,2-*trans* or 1,2-*cis* configuration, we initially investigated the effects of solvent by using tetrahydrofuran, acetone and acetonitrile. Reactions, performed at 20 °C and 40 °C were monitored by HPLC, and were quenched when the yield of thiocyanates began to decrease; the results are shown in Table 1. Below 10 °C neither formation of the products nor decomposition of the starting materials was observed.

As expected, under the classical reaction conditions (reaction of glycosyl bromides with potassium or ammonium thiocyanates), the 1,2-*trans* products (**4**, **9** and **12**) strongly predominated. No significant differences between the yields of the 1,2-*trans* products were observed in the above solvents. However, in all cases small amounts of the 1,2-*cis*-thiocyanates (**2**, **7** and **14**) were detected in the reaction mixtures. Consumption of glycosyl bromides depended on the configuration of the starting material, and was highest in the case of galactosyl bromide **6**.[7] At 40 °C consumption of the starting material was higher, but at the cost of increased amounts of isomeric isothiocyanates. Chemical yields of the 1,2-*trans* products were usually very close to those obtained at 20 °C. By comparison, the yield of 1,2-*cis*-thiocyanates was slightly higher at elevated temperatures. In some cases, small amounts of the 1,2-*cis*-isothiocyanates, not characterised before, were also detected (Table 1).

Because the solubility of potassium thiocyanate in organic solvents is low and the solubility of ammonium thiocyanate is limited, we tried to use quaternary ammonium isothiocyanates {1-(2-hydroxyethyl)-3-methylimidazolium isothiocyanates—[hydemim]NCS; 1-(2-ethoxyethyl)-3-methylimidazolium isothiocyanates—[eoemim]NCS; 2-hydroxyethyl-tributylammonium isothiocyanates—[hetba]NCS[8]} as new donors of thiocyanate ions (Fig. 2) separately, or in the presence of ammonium thiocyanate in tetrahydrofuran, acetone and dichloromethane solutions. The results are presented in Table 2. Reactions of glycosyl bromides with tetraalkylammonium isothiocyanates usually provided the 1,2-*trans*-glycosyl thiocyanates as the main products, however, the amounts of the 1,2-*cis*-thiocyanates were significantly higher than in the previous reaction system. Also, the 1,2-*cis*-isothiocyanates were formed in higher yields.

Finally, we tested the application of ammonium thiocyanate in the presence of tetrabutylammonium salts {1-butyl-3-methylimidazolium chloride and bromide—[bmim]Cl and [bmim]Br; 1-(2-ethoxyethyl)-3-methylimidazolium chloride—[eoemim]Cl;[9] Bu_4NBr; Bu_4NI; and 2-hydroxyethyl-tributylammonium bromide—[hetba]Br[8]} as catalysts in tetrahydrofuran, acetone and dichloromethane solutions (Fig. 2). In these cases corresponding tetrabutylammonium isothiocyanates were formed in situ, and the

Table 1
Product distribution in the reaction of glycosyl bromides with ammonium and potassium thiocyanate[a]

Glycosyl bromide	Y−SCN	Solvent	Temp (°C)	Time (h)	Recovered glycosyl bromide (%)	1,2-*trans*-Thiocyanate/yield (%)	1,2-*cis*-Thiocyanate/yield (%)	1,2-*trans*-Isothiocyanate/yield (%)	1,2-*cis*-Isothiocyanate/yield (%)
1	NH_4SCN	THF	20	19	43	**4**/43	**2**/5	**5**/9	—
1	NH_4SCN	THF	40	5	24	**4**/52	**2**/9	**5**/15	—
1	NH_4SCN	Acetone	20	19	21	**4**/55	**2**/6	**5**/18	—
1	NH_4SCN	Acetone	40	5	13	**4**/55	**2**/9	**5**/23	—
1	NH_4SCN	CH_3CN	40	3	13	**4**/56	**2**/5	**5**/26	—
1	KSCN	Acetone	20	24	3	**4**/55	**2**/15	**5**/24	**3**/3
1	KSCN	CH_3CN	40	3	9	**4**/60	**2**/7	**5**/22	**3**/2
6	NH_4SCN	THF	20	6	12	**9**/66	**7**/10	**10**/12	—
6	NH_4SCN	Acetone	20	5	10	**9**/69	**7**/6	**10**/15	
6	NH_4SCN	Acetone	40	2	3	**9**/61	**7**/11	**10**/22	**8**/3
6	NH_4SCN	CH_3CN	20	5	7	**9**/71	**7**/4	**10**/18	—
6	KSCN	Acetone	40	1	3	**9**/64	**7**/12	**10**/17	**8**/4
6	KSCN	CH_3CN	20	4	3	**9**/72	**7**/7	**10**/16	**8**/2
11	NH_4SCN	THF	20	18	28	**12**/40	**14**/7	**13**/25	—
11	NH_4SCN	THF	40	9	20	**12**/43	**14**/10	**13**/27	—
11	NH_4SCN	Acetone	40	4	21	**12**/36	**14**/5	**13**/30	—
11	NH_4SCN	CH_3CN	40	2	18	**12**/46	**14**/2	**13**/34	—
11	KSCN	Acetone	20	10	26	**12**/30	**14**/10	**13**/29	—
11	KSCN	Acetone	40	4	20	**12**/33	**14**/13	**13**/34	—
11	KSCN	CH_3CN	40	2	18	**12**/39	**14**/4	**13**/34	—

[a] Composition of the reaction mixture was determined by HPLC (RP-18 column, eluent: acetonitrile/water, 80:20).