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HYDRAZINEDITHIOCARBONATE (HDTC) AS A NEW REAGENT FOR THE IMPROVED REMOVAL OF CHLOROACETYL AND BROMOACETYL PROTECTIVE GROUPS.

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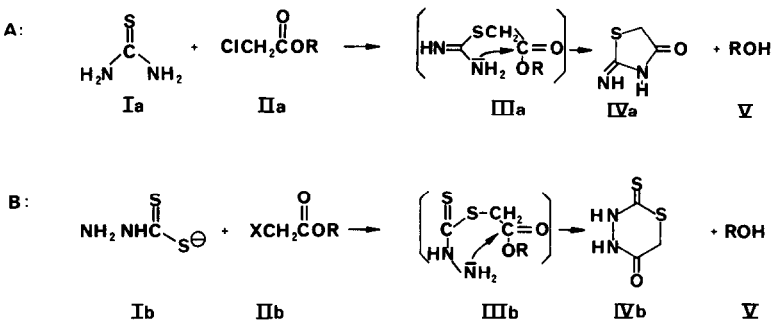
Abstract : The use of hydrazinedithiocarbonate (HDTC) for the removal of chloroacetyl and bromoacetyl groups is described. The advantage of this reagent is the selective deprotection under mild conditions, which was demonstrated on carbohydrate derivatives.

The availability of convenient temporary and persistent protective groups as well as the improvement of existing removal procedures are of fundamental importance in carbohydrate chemistry. It is essential for these groups to be sufficiently stable to withstand the conditions necessary for halogenation of the anomeric centre and of subsequent coupling reactions. Furthermore it is a prerequisite for temporary protective groups that they can be removed under mild conditions that do not affect persistent groups such as benzyl ethers and acetyl esters. Temporary protective groups which have been shown to fulfil these demands are allyl[1], 2,2,2-trichloroethyloxycarbonyl[2], trichloroacetyl[3], levulinoyl[4], and chloroacetyl[5] groups. Unfortunately, several disadvantages are associated with the use of these protective groups. Allyl ethers for instance, usually must be removed in two distinctive steps[1] and form a complex with Hg^{2+} during coupling reactions[6]. The trichloroacetyl group is highly labile to base[3] and decreases the reactivity of the carbohydrate in coupling reactions[7]. The levulinoyl group may be unstable during coupling reactions performed in the presence of $Hg(CN)_2$[2b].

The chloroacetyl ester could be a very convenient protective group, because it can cope with many of the reaction conditions usually employed in carbohydrate chemistry. Unfortunately up to now this protective group must be removed under relatively strenuous conditions which give rise to side reactions (see yield in Table, entry 1).

In this communication we wish to present an improved method for the removal of chloroacetyl groups and to present bromoacetyl as a new protective group. The most widely accepted method of removing the chloroacetyl group is thiourea treatment under slightly basic conditions at elevated temperature (see Table, entry 1). The two-step mechanism underlying this procedure is depicted in Scheme 1A. The chlorine of chloroacetyl ester II**a** first is substituted by the sulphur of thiourea (I**a**) in an S_N2 reaction to give intermediate III**a**. The next step consists of an intramolecular reaction in which the NH_2-group of intermediate III**a** displaces the alcohol ROH (V) forming the cyclic amide IV**a**.



SCHEME 1

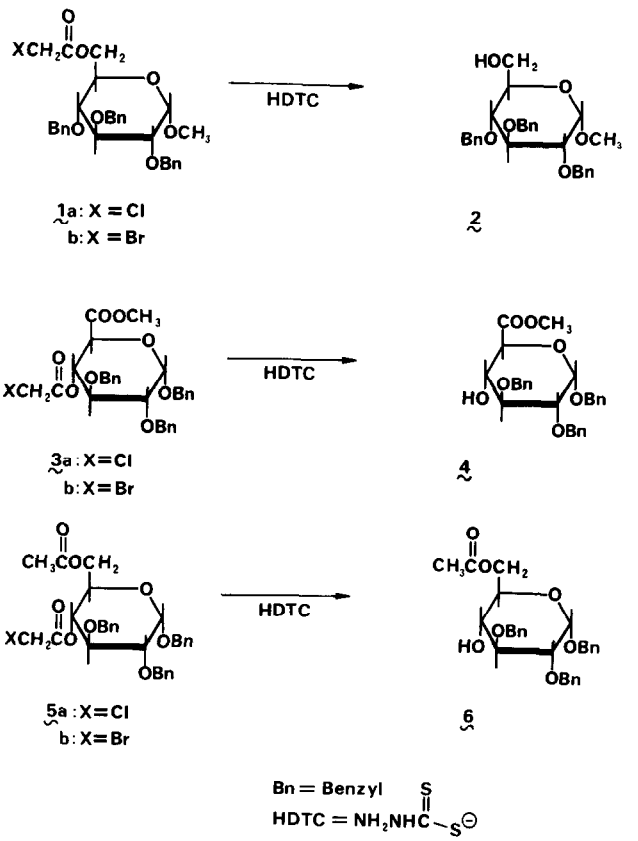
In order to facilitate deblocking we can i) replace the chlorine atom by a better leaving group, ii) improve the nucleophilicity of the sulphur atom, iii) facilitate the intramolecular displacement by enhancing the nucleophilicity of the nitrogen atom.

The possibility mentioned under i) was realized by introduction of the bromoacetyl group. For instance, it was established that the bromoacetyl group of 1b (Scheme 2) could already be cleaved with thiourea at room temperature (see Table, entry 2) to give 2 in 90% yield. This result shows that the sluggish removal of a chloroacetyl group can be circumvented by taking advantage of a bromoacetyl protective group. However, at this moment little is known about the properties of the bromoacetyl group in carbohydrate chemistry.

Apart from the introduction of a bromoacetyl group, we also had the intention of developing a highly effective reagent for cleavage of the chloroacetyl protective group by applying the possibilities mentioned under ii) and iii). Hydrazinedithiocarbonate (HDTC , Ib)[8] meets these requirements in that it has nucleophilic sulphur and nitrogen atoms. Model studies with HDTC on compounds 1a, 3a, and 5a revealed a smooth cleavage of the chloroacetyl group at room temperature.

In a typical experiment HDTC was prepared in situ[8] (2 ml of standard solution, 0.75 mmole) and added to derivative 1a (0.25 mmole), which was dissolved in a mixture of lutidine (1.8 ml) and acetic acid (0.6 ml). TLC analysis revealed a complete deblocking within 10-20 min. at room temperature without the formation of side products. Work-up and purification by column chromatography afforded 2 in 96% yield (see Table, entry 3).

SCHEME 2



entry	compound	reagent	product	temp.	time (min.)	yield (%)
1	IIa	thiourea	V	80-100 °C	30-120	40-80[5)]
2	1b	thiourea	2	r.t.	120	90
3	1a	HDTC	2	r.t.	10	96
4	1b	HDTC	2	r.t.	2	98
5	3a	HDTC	4	r.t.	20	88
6	3b	HDTC	4	r.t.	2	95
7	5a	HDTC	6	r.t.	15	96
8	5b	HDTC	6	r.t.	2	99

It was found that under the same conditions a bromoacetyl group was cleaved within two minutes at room temperature (see Table, entry 4).

Finally, it was established that chloroacetyl and bromoacetyl protective groups could be selectively deblocked without affecting other ester functions. Thus, treatment of 3a, b and 5a, b with HDTC under the conditions described, gave compounds 4 and 6 respectively in high yield (see Table, entries 5-8).

In conclusion, the preliminary studies presented here show that a) the bromoacetyl group can be cleaved much more easier than the chloroacetyl group, b) HDTC is an easily accessible reagent, which cleaves chloroacetyl and bromoacetyl protective groups under mild conditions[9], c) other protective groups are not affected by HDTC treatment.

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8. A stock solution of HDTC was prepared by dropwise adding of CS_2 (0.7 ml, 15 mmole) in dioxane (6 ml) to a cooled solution (0°C) of hydrazine hydrate (0.73 ml, 15 mmole) in ethanol/water (30 ml, 2:1, v/v) in the presence of diisopropylethylamine (2.61 ml, 15 mmole). See also T. Curtius and R. Heidenreich, Ber., 27, 58 (1894) (cf. Beilstein, Bd. 3, S. 221).
9. HDTC presumably also cleaves N-chloroacetyl groups.

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