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Chloral / DCC – Reagent for Stereospecific Rearrangements and New Protecting Group Techniques in Carbohydrate Chemistry[1)]

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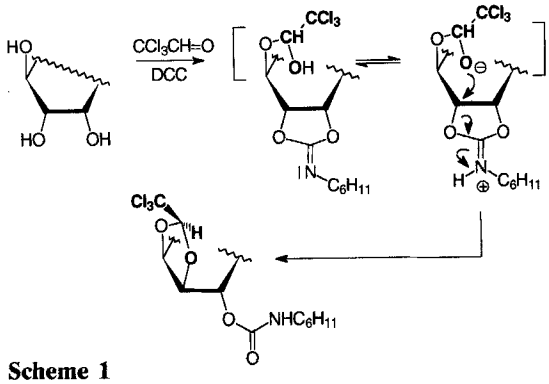
In 1992, a two component system (hexafluoroacetone (HFA) and dicyclohexylcarbodiimide (DCC)) for an one-pot preparation of cyclic, acid-stable acetals from *vicinal* polyols under non-acidic reaction conditions was described [1]. The application of this reagent to selected pyranosides led to the knowledge that the acetalization takes a non-classic pathway including an intramolecular S_N2-step which leads to an epimer of the starting sugar [2]. Subsequently, we exchanged HFA for chloral which likewise is a adequate carbonylactive compound, however, much cheaper and better to handle. Moreover, a chloral acetal, if introduced as protecting group, can easily be converted into the corresponding ethylidene acetal by treatment with Raney-Ni [3] or tributylstannane [4], so that an usual deprotection could follow.

Recently, we started a thorough investigation of the reagent system chloral/DCC in order to characterize its synthetic potential for stereospecific rearrangements of carbohydrates [5–7]. Thus, unprotected methyl pyranosides, phenylthio pyranosides or 1,6-anhydro sugars were converted by the reagent in dichloroethane as solvent (reflux, 4–5 hs). In this way, the following transformations were realized by inversion at the C-atom 3:

D-Arabinose	→	*D-Lyxose* [7]
D-Lyxose	→	*D-Arabinose* [6]
L-Arabinose	→	*L-Lyxose* [6]
D-Mannose	→	*D-Altrose* [5]
D-Galactose	→	*D-Gulose* [6]
L-Rhamnose	→	*6-Deoxy-L-altrose* [5]
L-Fucose	→	*6-Deoxy-L-gulose* [7]

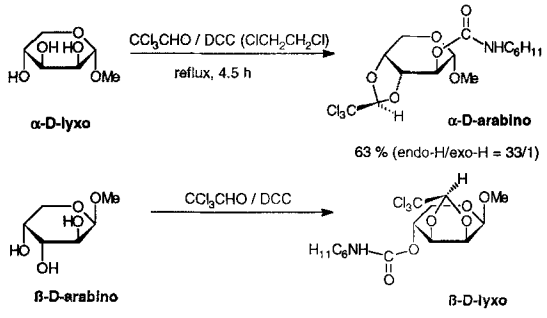
The key step of the reactions is the in situ formation of a cyclic iminocarbonic ester (or an isourea) intermediate [6] (see also ref. [8]), which is intramolecularly attacked by a deprotonated neighbour hemiacetal moiety in a S_N2-type reaction as shown in the Scheme 1.

A transformation is always achievable when the pyranoside (or another cyclic vicinaltriol) has 2,3-*cis*-/3,4-*trans*- or 2,3-*trans*-/3,4-*cis*-arrangement of the OH groups. In this case, the configuration of the chiral central C atom can be inverted like indicated in the Schemes.



Scheme 1

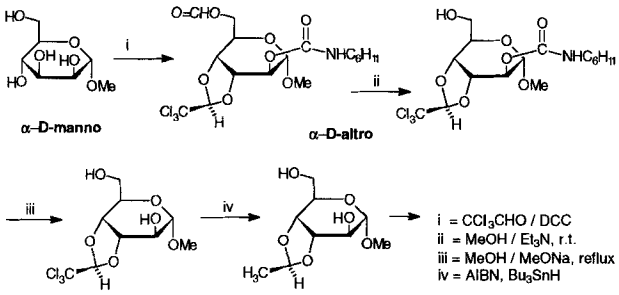
More recently, the reaction also was successfully applied for the transformation of selected monosaccharide moieties in oligosaccharides [9].



Scheme 2

A further favorable aspect using the chloral/DCC reagent in carbohydrate chemistry results from the simultaneous introduction of an acid-stable cyclic acetal protecting group as well as an additional carbamoyl group being strongly neighbouring group active. Scheme 2 and 3 show such a complete reaction for the transformation of methyl α-D-lyxopyranoside, methyl β-D-arabinopyranoside, and methyl α-D-mannopyranoside, respectively. In the case of hexopyranoses, additionally, O-formylation occurs in 6-position (haloform reaction) [5, 6], i.e. three different protecting groups (acetal, carbamoyl, formyl) are simultaneously and regioselectively introduced into the sugar molecule by an one-pot operation. As the Scheme 3 shows, these protecting groups may be cleaved stepwise:

[1)] 14. Mitt. der Reihe „Das Reagenz: 13. Mitt. vgl. J. Prakt. Chem. **337** (1995) ...: Brederecks Reagenz: t-Butyl-aminalester (t-Butoxy-N,N,N′,N′-tetramethyl-methandiamin)



Scheme 3

The cleavage of a formyl group should be carried out by methanol/triethylamine, because this reagent does not cause any intramolecular migration of the carbamoyl group as it was previously observed with methanol/sodium methoxide at a D-gulose derivative [6].

The acetalization produces a further chiral center at which the *endo*-H diastereomer always strongly predominates or is exclusively formed. Generally, cyclic acetals are important protecting groups in the chemistry of carbohydrates [10]. The chloral/DCC reagent allows to add this group by acid stable cyclic acetals.

General Procedure:

6 mmol of the pyranoside [11], 15 mmol of DCC, 21 mmol of chloral and 1,2-dichloroethane (10 ml) were refluxed for 4.5 h, whereby the sugar dissolve successively. Then the solution was cooled to room temp. and filtered to remove the precipitated N,N′-dicyclohexylurea. The filtrate was shaken for 10 min with 0.1 N aqueous HCl in order to destroy excess DCC. Finally, the organic phase was washed with a saturated aqueous $NaHCO_3$ solution and water, dried over $MgSO_4$, and concentrated in a rotary evaporator. The residue was purified by column chromatography (Silica gel 60 /63–200 μm; eluent: toluene / ethyl acetate 2–6 : 1).

We can conclude that chloral/DCC is a new versatile reagent for stereospecific epimerisations at the C-atom 3 of various monosaccharides and pyranoside moieties in oligosaccharides, respectively. Thus, rare natural or non-natural sugars are easily available. This has many implications in carbohydrate chemistry and it should be also applicable for rearrangements of inosites or other suitable arranged chiral polyols. On the other hand, the reagent allows simultaneously and regioselectively the introduction of three useful protecting groups (acid-stable cyclic acetal, carbamoyl, and formyl group) in an one-pot reaction under relatively mild conditions. Both components of the reagent are commercially available.

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[11] Unprotected Alkyl-, Aryl-, Alkylthio- or Arylthio D- or L-manno-, -galacto-, arabino-, lyxopyranosides as well as their 6-deoxy derivatives

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