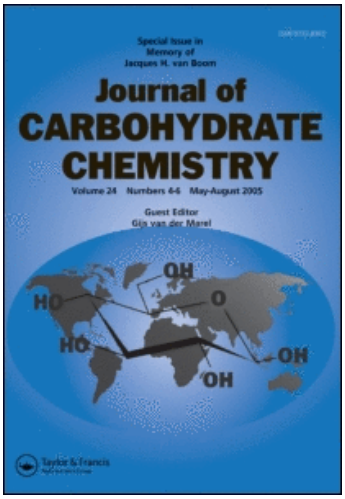

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COMMUNICATION

USE OF AN α-HALOETHER FOR THE ACETONATION OF CARBOHYDRATES.

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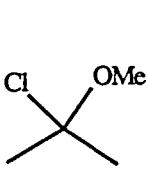
Cyclic acetals are important and commonly used protective groups for polyhydroxy compounds, *e.g.*, carbohydrates. The formation of cyclic acetals has been thoroughly investigated and much is now known about the factors that influence the outcome of these reactions. Several reviews have been written on this subject.[1,2,3]

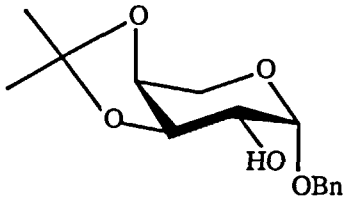
Some carbohydrates give different products depending on whether the acetalation reaction is performed under thermodynamic or kinetic control. Condensing a polyol with acetone using a protic acid as catalyst gives mainly the thermodynamic product. Better total yields and higher ratios of kinetic to thermodynamic product are achieved using 2,2-dimethoxypropane in DMF using a restricted amount of acid catalyst.[4] Alkyl isopropenyl ethers together with an acid catalyst was shown[5] to give acetonation of carbohydrates under kinetic control. Another approach for kinetic formation of cyclic acetals is the use of *gem*-dihalides under basic conditions.[6,7,8]

α-Haloethers have been widely used as reagents for protecting isolated hydroxyls as mixed acetals,[9] *e.g.*, methoxymethyl and benzyloxymethyl derivatives. Since they react readily with hydroxyls and the reaction liberates acid, we reasoned that α-haloethers could also be used for cyclic acetal formation. After the initial displacement of the halide by a hydroxyl group, a proton shift to the alkoxy oxygen and subsequent liberation of the alcohol would give an oxycarbonium ion ready for ring closure. One potential problem with this type of reagent is the increasing acidity of the reaction mixture during the course of the reaction. The acetal initially formed (the kinetic product) may undergo acid catalyzed rearrangement to a more stable thermodynamic product. However, the presence of an acid scavenger should eliminate this problem.

To investigate whether an α-haloether could be used for cyclic acetal formation, benzyl β-L-arabinopyranoside (prepared as previously reported by Ballou[10] in the D-series) was treated with 2-chloro-2-methoxypropane[11] (**1**) in *N,N*-dimethylformamide (DMF) at room temperature. This led to a complete conversion to the 3,4-*O*- isopropylidene derivative (**2**), which, after work-up, was isolated in a yield of 92%.

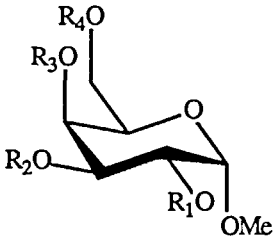


1

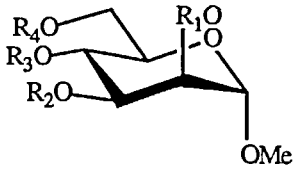


2

Our assumption was that the α-chloro ether should give mostly the kinetic product, and in order to investigate this the methyl α-glycosides of D-galactose and D-mannose were choosen as substrates. Both compounds are able to form two different monoacetal derivatives, the kinetic 4,6-isopropylidene (**5** and **8** respectively), and the thermodynamic 3,4- (**4**) and 2,3-isopropylidene (**7**) derivatives respectively. Various concentrations of reagent were employed and the reactions were allowed to stand for 15 minutes, whereafter they were quenched with anhydrous Na_2CO_3. The products were peracetylated, run through a short silica gel column and the ratios between different products were determined by integration of ^{1}H-NMR signals in the anomeric region.



3 R_1=R_2=R_3=R_4=Ac
4 R_1=R_4=Ac, R_2,R_3=$(CH_3)_2C<$
5 R_1=R_2=Ac, R_3,R_4=$(CH_3)_2C<$



6 R_1=R_2=R_3=R_4=Ac
7 R_1,R_2=$(CH_3)_2C<$, R_3=R_4=Ac
8 R_1=R_2=Ac, R_3,R_4=$(CH_3)_2C<$
9 R_1,R_2=R_3,R_4=$(CH_3)_2C<$

When methyl α-D-galactopyranoside was treated with 3 equivalents of **1** mainly the thermodynamic 3,4-acetal (**4**) was formed. However, we found that addition of powdered 4Å molecular sieves (200 mg/mmol of reagent) as acid scavenger altered the product composition to give mainly the kinetic 4,6-acetal (**5**). Another effect of the molecular sieves was to reduce the rate of the reaction. Increasing the amount of reagent to 4 equivalents increased the rate of the reaction but also gave a lower ratio of kinetic to thermodynamic product. The results are summarized in Table 1.

Methyl α-D-mannopyranoside was treated with different molar ratios of **1** with or, in one case, without the presence of molecular sieves. In all reactions the monoacetal compound preferably formed was the kinetic 4,6-acetal (**8**). In the abscence of molecular sieves the ratio of kinetic to thermodynamic product decreased but was still about 4:1. All reaction mixtures contained unreacted starting material in various amounts which,

Table 1. Product composition in reactions between methyl α-D-galactopyranoside and **1** after acetylation.

1 (Equiv.)	Mol. sieves	**3**	**4** (% yield)	**5**
3	-	0	74	11
3	+	15	11	56
4	+	7	31	52

Table 2. Product composition in reactions between methyl α-D-mannopyranoside and **1** after acetylation.

1 (Equiv.)	Mol. sieves	**6**	**7**	**8**	**9**
			(% yield)		
1	+	57	3	37	-
1	-	30	13	54	-
1.5	+	22	7	65	5
2	+	23	9	62	6
3	+	22	10	45	14
4	+	15	8	43	26

as expected, decreased with increased concentration of **1**. The use of more reagent also gave an increased yield of the 2,3:4,6-diacetal derivative (**9**). The results are summarized in Table 2.

The molecular sieve can play two roles in these reactions, firstly it can act as acid scavenger and secondly it can remove the liberated methanol from the mixture. The first role is probably the more important one and this assumption prompted us to see whether other acid scavengers could be used instead of molecular sieves to achieve similar results on acetalating methyl α-D-galactopyranoside. Both heterogenous (Na_2CO_3 and $Ca(OH)_2/CaO$) and homogenous bases (pyridine, 2,6-di-*tert*-butylpyridine, *N,N,N',N'*-tetramethylurea, *N,N*-diisopropyl ethylamine and 1,8-diazabicyclo-[5,4,0]undec-7-ene) were used, but in all these reactions the rates and yields were lowered, compared to when molecular sieves were used.

To summarize, 2-chloro-2-methoxypropane is an efficient reagent for the formation of cyclic acetals of glycosides. This reagent gives fast and clean conversions and the workup procedure is simple. Despite the thermal instability of the chloro ether, which has to be stored at temperatures below -40 °C, the reactions can be performed at room temperature. When performing the reaction in the presence of 4Å molecular sieves mainly the kinetic product is formed.

EXPERIMENTAL

General procedures. DMF was dried over CaH_2, distilled and stored over 4Å molecular sieves. TLC was performed on Silica Gel F_{254} (Merck) with detection by UV light when applicable or by charring with 8% aqueous sulfuric acid. Column chromatography was performed on Matrex™ Silica Gel 60 (0.035-0.070 mm, Amicon Corp.). Concentrations were performed at 1-2 kPa at <40 °C. Optical rotation was recorded at 22-24 °C using a Perkin-Elmer 241 polarimeter. NMR spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si, δ=0.0) using a JEOL JNM-GSX 270 instrument.

Benzyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside (2). Benzyl β-L-arabinopyranoside[10] (100 mg, 0.42 mmol) was dissolved in DMF (5 mL) and 93 μL (0.84 mmol) 2-chloro-2-methoxypropane[11] was added at room temperature. After two hours the reaction was quenched by addition of triethylamine. The solution was diluted with ether and washed with water, aqueous $NaHCO_3$-solution and water, dried with $MgSO_4$ and concentrated to give the title compound (107 mg, 92%) as a syrup. Crystallisation from ether-light petroluem gave material with mp 54-56 °C and $[\alpha]_D$ +192° (*c* 1, $CHCl_3$). (Litt. mp 55-57 °C, $[\alpha]_D$ -195°, D-form[12]).

Acetalation procedure. The glycosides were dissolved in DMF (2 mL/mmol). In some reactions powdered molecular sieves (200 mg/mmol reagent) were added. The mixtures were stirred for 15 minutes. 2-Chloro-2-methoxypropane was added at room temperature and the reaction mixtures were stirred for 15 minutes. The reactions were then quenched by addition of anhydrous Na_2CO_3. The solid material was filtered off, pyridine-acetic anhydride 2:1 (3 mL/mmol glycoside) was added and the mixture stirred at room temperature. When all the material was acetylated the reaction mixtures were concentrated and partitioned between toluene and water. The aqueous phases were extracted with toluene and the combined organic phases were dried over Mg_2SO_4 and concentrated to syrups. The residues were subjected to short silica gel columns and eluted with appropriate mixtures of toluene and ethyl acetate. All fractions containing carbohydrate derivatives were pooled and concentrated and the product compositions were determined by ^1H NMR. The yields were calculated from the integrals of the anomeric protons (**3** δ 5.00, **4** δ 4.85, **5** δ 5.03, **6** δ 4.72, **7** δ 4.95, **8** δ 4.61 and **9** δ 4.90).

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REFERENCES

1. A. N. de Belder, *Adv. Carbohydr. Chem. Biochem.*, **34**, 179 (1977).
2. D. M. Clode, *Chem. Rev.*, **79**, 491 (1979).
3. J. Gelas, *Adv. Carbohydr. Chem. Biochem.*, **39**, 71 (1981).
4. M. E. Evans, F. W. Parrish, and L. Long, Jr., *Carbohydr. Res.*, **54**, 105 (1977).
5. J. Gelas and D. Horton, *Heterocycles*, **16**, 1587 (1981) and references cited therein.
6. J. S. Brimacombe, A. B. Foster, B. D. Jones, and J. J. Willard, *J. Chem. Soc., C*, 2404 (1967).
7. N. Baggett, J. M. Duxbury, A. B. Foster, and J. M. Webber, *Carbohydr. Res.*, **1**, 22 (1965).
8. P. J. Garegg and C.-G. Swahn, *Acta Chem. Scand.*, **26**, 3895 (1972)
9. T. W. Green, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York (1981), p 16.
10. C. E. Ballou, *J. Am. Chem. Soc*, **79**, 165 (1957).
11. F. Strauss und H.-J. Weber, *Liebigs Ann. Chem*, **498**, 101 (1932).
12. P. J. Garegg, *Acta Chem. Scand.*, **14**, 957 (1960).