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Note

Ferric chloride–molecular sieve-catalyzed formation of a nonreducing disaccharide derivative

Leon M. Lerner
Department of Biochemistry, State University of New York, Health Science Center, Brooklyn, New York 11203 (U.S.A.)

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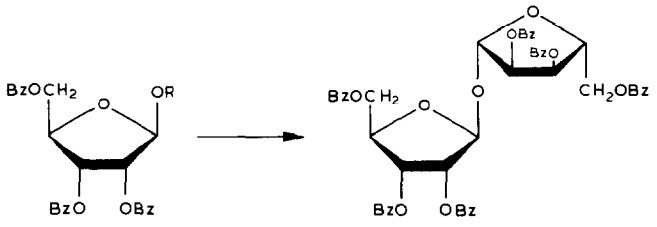
Anhydrous ferric chloride has been used for a number of synthetic reactions in carbohydrate chemistry, such as the acetonation of various monosaccharides[1] and glycosides[2], acetylation[3], acetolysis of benzyl ethers[4], preparation of oxazolines[5], and formation of glycosides[6] and 1-thioalkyl(aryl)glycosides[7]. Recently, a reinvestigation[8] of the synthesis of a nonreducing disaccharide was carried out using boron trifluoride etherate[9]. The goal was to develop a practical method to prepare nonreducing disaccharides from small amounts of sugars without having to use the Koenigs–Knorr reaction[10] or one of its variations. The conversion of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**1**) and 1,2,3,5-tetra-*O*-benzoyl-β-D-ribofuranose (**2**) to β-D-ribofuranosyl β-D-ribofuranoside hexabenzoate (**3**) was used as a model system because of the ready availability of the substrates commercially or by synthesis, and because the product of the dimerization was easy to crystallize fractionally.



1 R = Ac
2 R = Bz

3

Although under optimal conditions the yields of **3** were virtually the same with both boron trifluoride etherate and the ferric chloride reaction reported here, the mechanisms of the reactions appear to be very different, with an absolute requirement for molecular sieves as a cocatalyst when ferric chloride is used.

The reaction of a dichloromethane solution of **1** with ferric chloride in either the absence of molecular sieves or in the presence of Drierite gave many products (t.l.c.), but

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TABLE I

Yields of β-D-ribofuranosyl β-D-ribofuranoside hexabenzoate (3)

Starting compd.[a]	$FeCl_3$ (mmol)	Molecular sieves[b]		Solvent	Time (h)	Yield (%)
		Type	Amount (g)			
1	1.5	3A	1	CH_2Cl_2	24	49
1	0.38	3A	1	CH_2Cl_2	24	48
1	1.5	3A	1	CH_2Cl_2	6	41
1	1.5	3A	1	CH_2Cl_2	72	50
2	1.5	3A	1	CH_2Cl_2	24	50
2	0.38	3A	1	CH_2Cl_2	24	51
1	0.38	4A	1	CH_2Cl_2	24	45
1	0.38	5A	1	CH_2Cl_2	24	45
1	1.5	3A	3	CH_2Cl_2	24	46
1	0.38	3A	1	$ClCH_2CH_2Cl$[c]	1.5	48
2	0.38	3A	1	$ClCH_2CH_2Cl$[c]	1.5	45
1	1.5	3A	1	CH_3NO_2	24	27
1	1.5	3A	1	CH_3CN	24	17

[a] One mmol of **1** or **2** was used. [b] Davison Chemical; the exact amounts varied from 0.9–1.2 g because of the bead form. [c] At 84°.

no **3**. In contrast, in the presence of Davison molecular sieve, type 3A (bead form), disaccharide **3** was obtained in approximately 50% yield (Table I). If the molecular sieve was used alone, **1** was completely recovered. The reaction is generally performed for 24 h, or at least overnight, for it is not yet complete after 6 h, but periods beyond 24 h did not increase the yields. Substitution of **2** for **1** did not affect the yield of **3**. Molecular sieves, types 4A and 5A, could be substituted for type 3A with only slightly lowered yields. However, the powdered form of molecular sieve 3A gave only a 26% yield of **3** when 1.5 equiv. of ferric chloride was used per mmol of **1**; if 0.38 equiv. was used, **1** was recovered. A similar problem arose with pellets of Linde molecular sieve, type 3A, except that a 49% yield of **3** was obtained in the presence of 1.5 equiv. of the Lewis acid. There was no advantage to performing the reaction in hot 1,2-dichloroethane except to shorten the reaction time; however, the smaller amount of ferric chloride had to be used in order to avoid extensive degradation. Increasing the amount of molecular sieve did not change the yield either; however, in all cases the sieve must be dry. When molecular sieve was allowed to equilibrate with water vapor in a sealed chamber prior to running the reaction, the yield of **3** fell to 10%.

Other solvents, some of which dissolve ferric chloride, were used with poor results. Nitromethane and acetonitrile gave 27 and 17% yields of **3**, respectively, whereas no reaction was observed for solutions in pyridine, acetone, and *N,N*-dimethylformamide. Ethyl ether and benzene caused the formation of sticky beads that could not be stirred properly, and afforded many products, but no **3**. When ferric chloride was first dissolved in ethyl acetate and the solution diluted with dichloromethane, so that the final solvent ratio was 4:1 (v/v) dichloromethane–ethyl acetate,

only an 8% yield of **3** was obtained. These experiments demonstrated that it was necessary to use solvents that would not form stable complexes with the Lewis acid.

In another set of experiments, the reaction was performed in the usual way with ferric chloride (1.5 equiv. per mmol of **1**) at room temperature, the molecular sieve was isolated by filtration and immediately used in a second reaction. The yields of **3** in the two reactions were nearly the same, suggesting that the beads were acting catalytically.

Anhydrous ferric chloride is virtually insoluble in both dichloromethane and 1,2-dichloroethane. Dissolution only occurs upon addition of the esterified sugar. This can be interpreted to mean that the Lewis acid is forming an acid–base complex with the ester oxygen atoms, which then renders it soluble in this complex form. When the other solvents containing oxygen or nitrogen were used, the complexes with ferric chloride were apparently too tight to allow interaction with the ester groups of the sugar, most importantly the anomeric ester group. Therefore, it appears that unhindered binding to the oxygen atoms of the substrate is a necessary feature of this reaction. The need for molecular sieves also suggested a role for the oxygen atoms in the aluminosilicate structure of the sieves. These may bind to the ferric chloride–sugar complex in such a way as to create a new catalytic surface due to the advantageous juxtaposition of all of the participants in the reaction. The fact that powdered 3A molecular sieve gave only about half the yield of **3**, as compared to the beads, suggested that the clay used in the manufacture of the beads may also play a catalytic role.

Under optimal conditions, the preparation of **3** from **1** by the present procedure is competitive with the Koenigs–Knorr method previously used[11]. The overall yield is actually somewhat better since there is no need to prepare either the glycosyl halide or the OH-1 derivative from **1**.

EXPERIMENTAL

General methods. — Melting points were determined with a Kofler hot-stage and are corrected. Optical rotations were measured with a Perkin–Elmer Model 141 polarimeter. I.r. spectra were recorded with a Perkin–Elmer Model 21 spectrophotometer. T.l.c. was performed with Silica Gel GF-254, type 60 (E. Merck, Darmstadt), plates and 1,2-dichloroethane, with multiple irrigations (5–10) for best separation. Moist organic solutions were dried over anhydrous $MgSO_4$. Evaporations were carried out under reduced pressure with a rotary evaporator at a bath temperature of 30°. Molecular sieves from Davison Chemical were either purchased from Fisher Scientific or were kindly provided as a gift from the manufacturer. The identity of **3** in every preparation was confirmed by at least one other method in addition to the m.p., such as mixed m.p., optical rotation, t.l.c., or i.r. spectroscopy.

2,3,5-Tri-O-*benzoyl*-β-D-*ribofuranosyl 2,3,5-tri*-O-*benzoyl*-β-D-*ribofuranoside* (**3**). — *Method A.* Anhydrous ferric chloride (243 mg, 1.5 mmol) was weighed directly into a 15-mL round-bottom flask containing a magnetic stirring bar, and immediately covered with dry dichloromethane (7 mL). Molecular sieve 3A (~ 1 g) was added, followed by **1**

(ref. 12; 505 mg, 1 mmol) dissolved in dry dichloromethane (3 mL). The ferric chloride dissolved almost immediately to give an orange solution. After being stirred for 24 h, the brown mixture was filtered through a plug of glass wool directly into a stirred solution of saturated $NaHCO_3$ (30 mL), and the flask and funnel were washed several times with a total of 20 mL of 1,2-dichloroethane. The mixture was stirred vigorously for 30 min, the brown solids were removed by suction filtration on a pad of Celite 545, and the pad was washed thoroughly with solvent. The organic layer was separated, washed with water (50 mL), dried, and concentrated to give a thick, colorless gum (545 mg), which was dissolved in hot ethanol (7–8 mL). The warm solution was seeded[8] with **3**, and after 1–2 days the crystals were isolated by filtration and dried, (266 mg, 59%), m.p. 138–141° with softening from 127–130°. One recrystallization from ethanol gave 220 mg (49%) of **3**, m.p. 143–145° with softening above 130°, $[\alpha]_D^{26}$ +32.2° (*c* 0.45, chloroform); lit.[11] m.p. 144–145°, $[\alpha]_D^{25}$ +32.5° (*c* 0.1, chloroform). These data were the same as those of **3** obtained previously[8], and the i.r. spectra were identical.

Method B. This procedure was the same as in Method A, except that 62 mg (0.38 mmol) of anhydrous $FeCl_3$ was used to give **3** (218 mg, 48%), m.p. 142–144° with softening above 130°.

Method C. This procedure was the same as in Method B except that **2** (ref. 12; 567 mg, 1 mmol) was substituted for **1**. The yield of **3** was 232 mg (51%), m.p. 141–144° with softening above 130°.

Method D. This procedure was the same as in Method B, except that 1,2-dichloroethane was substituted for dichloromethane. The mixture was heated under reflux for 90 min, and then was cooled to room temperature and worked up as described above to give a colorless gum (551 mg). Crystallization from hot ethanol (7–8 mL) gave 216 mg (48%) of **3**, m.p. 143–145° with softening above 130°.

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REFERENCES

1 P. P. Singh, M. M. Gharia, F. Dasgupta, and H. C. Srivastava, *Tetrahedron Lett.*, (1977) 439–440.
2 F. Dasgupta, P. P. Singh, and H. C. Srivastava, *Ind. J. Chem.*, 19B (1980) 1056–1059.
3 F. Dasgupta, P. P. Singh, and H. C. Srivastava, *Carbohydr. Res.*, 80 (1980) 346–349.
4 K. P. R. Kartha, F. Dasgupta, P. P. Singh, and H. C. Srivastava, *J. Carbohydr. Chem.*, 5 (1986) 437–444.
5 K. L. Matta and O. P. Bahl, *Carbohydr. Res.*, 21 (1972) 460–464.
6 M. Kiso and L. Anderson, *Carbohydr. Res.*, 136 (1985) 309–323.
7 F. Dasgupta and P. J. Garegg, *Acta Chem. Scand., Ser. B.*, 43 (1989) 471–475.
8 L. M. Lerner, *Carbohydr. Res.*, 199 (1990) 116–120.
9 J. A. Zderic, *Experientia*, 20 (1964) 48.
10 W. L. Evans, D. D. Reynolds, and E. A. Talley, *Adv. Carbohydr. Chem.*, 6 (1951) 27–81; K. Igarashi, *Adv. Carbohydr. Chem. Biochem.*, 34 (1977) 243–283.
11 E. Rosenberg and S. Zamenhof, *J. Biol. Chem.*, 237 (1962) 1040–1042.
12 R. K. Ness, H. W. Diehl, and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, 76 (1954) 763–767.