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Note

Acetylation of carbohydrates using ferric chloride in acetic anhydride*

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Ferric chloride dissolves in organic and inorganic solvents that are capable of donating electrons[1]. We have reported[2] its use as a Lewis-acid catalyst in the preparation of *O*-isopropylidene derivatives of carbohydrates. We now report on acetylation using acetic anhydride–ferric chloride.

Acetic anhydride ionises to only a small extent[3], but the addition of Lewis acids generates ion pairs[4] and acylium ions (Ac^+) responsible for acetylation[5]. Various types of carbohydrate have been acetylated with the Ac_2O–$FeCl_3$ system. The reaction is exothermic, fast, and produces mainly the α-acetates. If the reaction is prolonged, acetolysis of glycosides can occur. The time of reaction and yield of product are dependent on the proportion of ferric chloride used (Table I).

By employing the Ac_2O–$FeCl_3$ reagent, α-acetates of monosaccharides, disaccharides, and other carbohydrates have been prepared in good yield (Table II).

TABLE I

EFFECT OF CONCENTRATION OF FERRIC CHLORIDE ON REACTION EFFICIENCY[a]

	$FeCl_3$ (mg)	*Time[b] (min)*	*Yield (%)*
D-Glucose	80	7	83[c]
	40	15	79[c]
	4	60	72[c]
	0.4	16 h	64[c]
myo-Inositol	80	10	96
	0.4	45	91

[a]Carbohydrate (1 g) and acetic anhydride (6 ml) at 28–32°. [b]Time for complete dissolution of of carbohydrate. [c]Yield of α-D-glucose penta-acetate.

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TABLE II

ACETYLATION OF CARBOHYDRATES WITH ACETIC ANHYDRIDE–FERRIC CHLORIDE

	Reaction time (min)[a]	*Acetate*[b]		
		Yield (%)	*M.p. (degrees)*	$[\alpha]_D$ *(chloroform) (degrees)*
D-Xylose	10	95	Syrup[c]	+46
L-Arabinose	15	94	Syrup	+44
D-Glucose	7	83	110–111	+104
D-Galactose	15	78	92–94	+105
D-Mannose	15	75	Syrup	+49
D-Glucitol	10	96	99	+10
D-Mannitol	30	95	123–124	+27
myo-Inositol	10	96	211–212	—
Cellobiose	30	78	223–224	+37
Lactose	60 (20)	70	151–152	+54
Maltose	20 (20)	72	124–125	+123
Sucrose	60 (20)	65	83–85	+53
Melibiose	15 (25)	70	170–171	+112
Methyl α-D-glucopyranoside	10	95	100–101	+130
	36 h	80	111–112[d]	+102
Methyl α-D-galactopyranoside	10	85	85–86	+133
	38 h	70	92–93[d]	+107

[a]Carried out at room temperature (28–32°) unless stated otherwise in parentheses. [b]M.p. and $[\alpha]_D$ values corresponded to literature data[10–12]. [c]Tetra-*O*-acetyl-β-D-xylopyranose (m.p. 128°, $[\alpha]_D$ −32°) crystallized out on keeping below 0°. [d]Penta-acetate of the parent sugar.

TABLE III

ACETYLATION OF D-XYLOSE USING ACID CATALYSTS

Catalyst	*Sugar addition*		*Stirring after addition*		*Yield (%)*[a,b]				
	Temp. (degrees)	*Time (min)*	*Temp. (degrees)*	*Time (min)*	α-p	β-p	α-f	β-f	*Acyclic*
$ZnCl_2$	10	30	28–32 100	40–60 60	56.5	15.2	7.4	7.1	13.7
$HClO_4$	10	30	28–32	40–60	65.4	14.3	2.3	2.1	16.0
$FeCl_3$	0–5	40	0	3 days	68.3	10.4	4.0	3.7	13.6
$FeCl_3$	10	30	28–32	40–60	61.4	15.5	4.9	4.7	13.5
$FeCl_3$	Not controlled	5	50	40–60	59.0	14.7	5.1	4.6	16.7
$FeCl_3$	Not controlled	5	70	4 days	36.8	12.0	3.5	5.6	42.1

[a]Based on the area of peaks in g.l.c. [b]Key: *p*, pyranose; *f*, furanose.

For disaccharides, especially sucrose, maltose, and lactose, the heat of reaction caused partial acetolysis, thereby affecting the yield, and the reactions were therefore performed at ~20°. The αβ-ratio (determined by g.l.c.) for the syrupy product obtained from D-mannose was 95:5. A similar product mixture was obtained by using zinc chloride as catalyst.

D-Xylose gave a syrupy mixture of five products, as shown by g.l.c., which were identified as tetra-*O*-acetyl-α- (*T* 5.1 min, 61.4%) and tetra-*O*-acetyl-β-D-xylopyranose (*T* 6.7 min, 15.5%), hexa-*O*-acetyl-*aldehydo*-D-xylose aldehydrol (*T* 20.4 min, 13.5%), and tetra-*O*-acetyl-α- (*T* 8.3 min, 4.9%) and tetra-*O*-acetyl-β-D-xylofuranose (*T* 9.3 min, 4.7%). The β-pyranose tetra-acetate crystallized from the mixture, but isolation of the α anomer required chromatography on silica gel.

Treatment of the syrupy, xylose reaction-product with Ac_2O–$FeCl_3$ gave mainly hexa-*O*-acetyl-*aldehydo*-D-xylose aldehydrol[6,7] (60–70% after purification by column chromatography). Treatment of D-xylose using BF_3-etherate in acetic anhydride produces[8] the acyclic hexa-acetate in one step. However, with Ac_2O–$FeCl_3$, complete conversion into the hexa-acetate could not be achieved in one step, even when the reaction was performed at 70° for 4 days (Table III).

The results of acetylation of D-xylose in the presence of $FeCl_3$ and other acidic catalysts, under various conditions, are shown in Table III. Acetolysis occurred to a small but significant extent in each reaction, with the formation of acyclic product. For maximum conversion into the aldehydrol hexa-acetate, more than one step is required, since the acetic acid generated inhibits the acetolysis process[9].

G.l.c. analysis of the L-arabinose reaction-product revealed tetra-*O*-acetyl-β- (*T* 5.8 min, 60.2%) and tetra-*O*-acetyl-α-L-arabinopyranose (*T* 8.8 min, 19.2%), hexa-*O*-acetyl-*aldehydo*-L-arabinose aldehydrol (*T* 15.2 min, 17.0%), and a minor, unidentified component (*T* 7.6 min, 3.6%).

Methyl glycosides were quickly acetylated with Ac_2O–$FeCl_3$, but acetolysis of the aglycon occurred if the reaction was prolonged. Thus, after reaction for 7–15 min at room temperature, methyl α-D-gluco- and -galacto-pyranoside gave the corresponding tetra-acetates, but the penta-acetates of the corresponding sugars were obtained after 36–40 h. At 60°, the penta-acetates are obtained within 3 h.

EXPERIMENTAL

General. — Melting points are corrected. Solutions were concentrated at <45° under diminished pressure. Optical rotations were measured with a Hilger polarimeter. I.r. spectra (KBr pellets) were recorded with a Perkin–Elmer R180 spectrometer. G.l.c. was performed on a Perkin–Elmer 3920B gas chromatograph equipped with a flame-ionisation detector and a glass column (6 ft. × 0.125 in. o.d.) packed with 3% of ECNSS-M on Gas Chrom Q. Retention times (*T*) are given as absolute retention-times in minutes, calculated from the solvent peak. T.l.c. was performed on Silica Gel G with benzene–methanol (96:4) and detection by charring with sulphuric acid.

Anhydrous ferric chloride (BDH) was reagent grade, and acetic anhydride was distilled before use.

General procedure for acetylation. — To a solution of anhydrous ferric chloride (80 mg) in acetic anhydride (6 ml) was added, portionwise, the dry sugar (1 g) with stirring, and the stirring was usually continued until dissolution was complete. The dark solution was poured with stirring into ice–water (100–150 ml). If a solid separated, it was collected, washed with water, and recrystallised from ethanol. When no solid separated, the aqueous solution was extracted with chloroform (3 × 20 ml), and the extract was washed with 10% aqueous sodium hydrogencarbonate until free of acid, and finally with water, dried (Na_2SO_4), and concentrated to a syrup. The results are given in Table II. Complete conversion into fully acetylated derivatives was shown by the absence of hydroxyl absorption in the i.r. spectrum.

Dissolution of cellobiose and *myo*-inositol did not occur, but acetylation proceeded.

Hexa-O-*acetyl*-aldehydo-D-*xylose aldehydrol.* — The syrup (2.04 g) obtained by the reaction of xylose (1 g) with Ac_2O–$FeCl_3$ was reacetylated three times with the same reagent for 4 h at 60°. After each acetylation, the product was isolated by the usual procedure. The final, syrupy product (1.8 g) was eluted from a column (56 cm × 1.5 cm i.d.) of silicic acid with benzene–ethanol (200:1, 400 ml), to remove impurities, and then with benzene–ethanol (100:1), to yield the title compound as a pale-yellow syrup (1.68 g), $[\alpha]_D$ +6° (*c* 0.9, chloroform).

N.m.r. data (60 MHz, $CDCl_3$): τ 3.15 (d, $J_{1,2}$ 4.8 Hz, H-1), 4.4–4.9 (m, H-2,3,4), 5.43–6.24 (2 q, 5.62, $J_{4,5}$ 4, and 6.1, $J_{4,5'}$ 5.6, $J_{5,5'}$ 12.1 Hz, H-5,5′) and 7.87, 7.93 (18 H, 6 Ac).

Anal. Calc. for $C_{17}H_{24}O_{12}$: C, 48.57; H, 5.71. Found: C, 48.13; H, 5.60.

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