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Regioselective Monoacetylation of Methyl Pyranosides of Pentoses and 6-Deoxyhexoses by Acetic Anhydride in the Presence of $MoCl_5$

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Regioselective Monoacetylation of Methyl Pyranosides of Pentoses and 6-Deoxyhexoses by Acetic Anhydride in the Presence of $MoCl_5$

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Abstract: Convenient regioselective syntheses of 3-acetates of methyl pyranosides of α-L-rhamnose, α- and β-L-arabinose, α-D-fucose, α-D-lyxose, and β-D-ribose with good yields have been attained using $MoCl_5$ as catalyst. Methyl β-L-rhamnopyranoside under this conditions gave 2-acetate.

Keywords: Methyl glycopyranosides, regioselective acetylation, transition metals

Partially acetylated carbohydrates have been useful as reference compounds in the analysis of certain natural products containing carbohydrates and are used as versatile intermediates in other synthesis.

Earlier studies on partial acylation of carbohydrates[1] were not always successful from the preparative point of view because of small differences in reactivity of hydroxyl groups. Therefore, regioselective acylation and acetylation, in particular, of carbohydrates is a difficult challenge for chemists. In the past few years, enzymatic[2] and chemical approaches[3–8] for regioselective acetylation of monosaccharides have been developed. Transition metals,[3] some amines,[4] and molecule sieves[5] were used as

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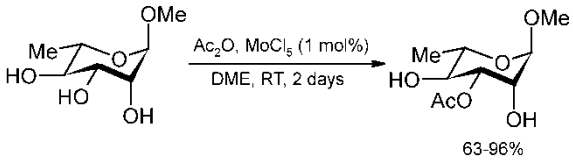


Scheme 1.

catalysts; tin organic compounds,[6] copper,[7,8] and mercury[7] chelats were also used.

Sugars are known to form complexes with transition metals,[9] and the cyclic complexes are more thermodynamically preferable than acyclic ones. In a previous work[10] we have shown that the results of methylation of methyl glycopyranosides by diazomethane in the presence transition-metal chlorides may be interpreted as a consequence of intermediate cyclic bidentate complexes with the participation of two vicinal hydroxyl groups of glycopyranosides and transition-metal atom.

In this article we report the catalytic influence of transition-metal salts on regioselectivity of acetylation of methyl pyranosides of pentose and 6-deoxy hexoses. Our preliminary experiments demonstrated high efficiency of $MoCl_5$ as catalyst under regioselective acetylation of methyl glycosides (Scheme 1).

Table 1 shows that using 1,2-dimethoxyethane (DME) as solvent results in the greatest selectivity at replacement OH-3 in methyl α-L-rhamnopyranoside. The results of acetylation of methyl glycopyranosides by acetic anhydride in DME are given in Table 2. Data of the acetylation of methyl glycosides in basic conditions are given for comparison.

As can be seen from Table 2, use of cerium(III) and yttrium(III) chloride as well as copper(II) and mercuric(II) trifluoroacetates practically does not give 4-acetate in acetylation of methyl α-L-rhamnopyranoside. Probably these transition-metal atoms form intermediate bidentate complexes with

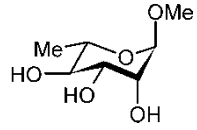
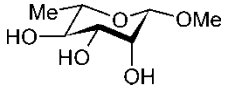
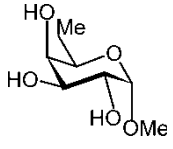
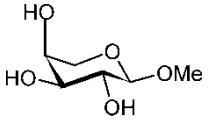
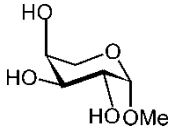
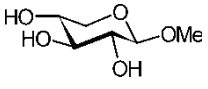
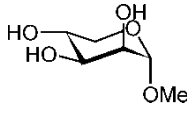
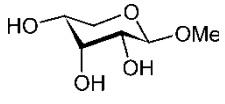
Table 1. Acetylation of methyl α-L-rhamnopyranoside by acetic anhydride in the presence $MoCl_5$[a]

		Acetates (%)[b]			
Solvent	Glycoside (%)	2-Ac	3-Ac	4-Ac	Di + tri-Ac
DME	9	4	81		6
1,4-Dioxane	72	4	24		
CH_3CN	22	10	44	16	8
EtOAc	48	5	43	4	

[a]Reaction conditions: methyl α-L-rhamnopyranoside (0.5 mmol), solvent (3 ml), Ac_2O (1.5 ml), $MoCl_5$ ($5 \cdot 10^{-3}$ mmol); 24 h.

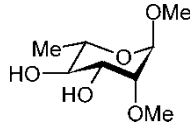
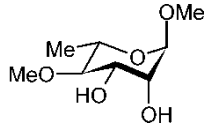
[b]Determined by ^1H NMR analysis of monoacetate fractions.

Table 2. Regioselective acetylation of methyl glycopyranosides by acetic anhydride in DME in the presence of transition-metal salts[a]

			Acetates %[b]			
No.	Methyl pyranoside	Catalyst	2-Ac	3-Ac	4-Ac	Di + Tri-Ac
1		$CeCl_3$	36	42		22
2		YCl_3	46	35	1	18
3		$Cu(CF_3COO)_2$	44	45		11
4		$Hg(CF_3COO)_2$	9	83		8
5		$MoCl_5$[c]		91 (87)		9
6		Pyr[d]	8	22	14	14
7		$MoCl_5$[c]	81 (78)			19
8		Pyr	14	13	20	15
9		$MoCl_5$[c]		94 (91)		6
10		Pyr	17	26	1	12
11		$MoCl_5$[c]		67 (63)	4	29
12		Pyr	20	15	12	18
13		$MoCl_5$[c]		77 (75)	2	21
14		Pyr	13	17	16	17
15		$MoCl_5$[e]	29	1	21	49
16		Pyr	13	16	14	12
17		$MoCl_5$[c]	9	70 (66)		21
18		Pyr	12	18	18	17
19		$MoCl_5$[f]	2	98 (96)		
20		Pyr	13	23	11	20

(*continued*)

Table 2. Continued

No.	Methyl pyranoside	Catalyst	Acetates %[b]			
			2-Ac	3-Ac	4-Ac	Di + Tri-Ac
21		$MoCl_5$[c]		11	31	
22		$MoCl_5$[c]	8	46		

[a]Reaction conditions: methyl glycopyranoside (1 mmol), DME (6 ml), Ac_2O (3 ml), catalyst (0.2 mmol), 48 h.

[b]Determined by ^1H NMR analysis of monoacetate fractions, isolated yields in brackets.

[c]$MoCl_5$—0.01 mmol, 48 h.

[d]Reaction conditions: methyl glycopyranoside (0.5 mmol), pyridine (0.5 ml), Ac_2O (1 mmol), rt, 24 h.

[e]$MoCl_5$—0.05 mmol, 48 h.

[f]$MoCl_5$—0.001 mmol, 24 h.

cis-vicinal hydroxyl groups of methyl α-L-rhamnopyranoside; with subsequent acetylation involved in complexation the hydroxyl groups.

Using $MoCl_5$ as catalyst leads to regioselective synthesis of 3-acetate of methyl α-L-rhamnopyranoside—91% from total mixture and 100% from fraction mono-substituted esters. Under the same conditions methyl β-L-rhamnopyranoside forms 2-acetate with a high yield (81%) that perhaps is a result of the anomeric effect. The acetylation of methyl pyranosides of α- and β-L-arabinose, α-D-fucose, and α-D-lyxose led to 3-acetate as the main product in the monoacetates fraction. It is interesting that methyl β-D-xylopyranoside, which has no cis-vicinal hydroxyl groups, does not form 3-acetate.

The acetylation of methyl 2-*O*-methyl-α-L-rhamnopyranoside in the presence of $MoCl_5$ proceeded slower than parent methyl α-L-rhamnopyranoside and gives a mixture of 3- and 4-acetates with a preponderance of the latter. This indicates a possibility of such complexation between methyl α-L-rhamnopyranoside and $MoCl_5$. On the acetylation of 4-methyl ether of rhamno-pyranoside, 3-acetate predominated in the reaction mixture, but the lower reaction rate and the presence of 2-acetate in mixture support the possibility of the formation of an intermediate tridentate complex between rhamnopyranoside and $MoCl_5$ with participation of three hydroxyl groups. The almost

quantitative yield of 3-acetate (96%) under acetylation of methyl β-D-ribopyranoside is probably due to the participation of three neighboring hydroxyl groups in complexation with the molybdenum atom.

This article suggests the simple and effective method of C-3-*O*-acetylation of methyl pyranosides of pentoses and 6-deoxyhexoses. The progress of this methodology and study of this reaction mechanism will be continued further.

EXPERIMENTAL

Melting points were determined on a Boethius micro-hot-stage apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer model 141. Chloroform was used as a solvent. ^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer. $CDCl_3$ was used as a solvent. Chemical shifts (δ) are reported in ppm related to Me_4Si. TLC was performed on silica gel L (5–40 μm; Chemapol) with 95 : 5 $CHCl_3$–MeOH solvent and detection by charring with sulfuric acid. Column chromatography was performed on silica gel (100–160 μm; Chemapol).

General Procedure for the Monoacetylation of Methyl Glycosides

The solution of methyl glycoside (1 mmol), $MoCl_5$ (0.01 mmol); for methyl β-D-ribopyranoside, 0.001 mmol), and Ac_2O (3 ml, 32 mmol) in DME (6 ml) was allowed to stir at room temperature for 48 h and was monitored by TLC. Cold water (3 ml) was added. After 1 h, the mixture was concentrated to a syrup under reduced pressure at room temperature. The product was isolated by flash chromatography on a column of silica gel using $CHCl_3$–EtOH, 50 : 1.

Data

Methyl 3-O-acetyl-α-L-rhamnopyranoside. Yield 191 mg (87%). R_f 0.42, mp 44–46°C (from EtOAc–hexane), $[\alpha]_D^{20}$ −88.2° (c 0.7, $CHCl_3$). ^{1}H NMR δ: 5.02 (dd, 1H, $J_{2,3} = 3.2$ Hz, $J_{3,4} = 9.4$ Hz, H-3), 4.67 (d, 1H, $J_{1,2} = 1.9$ Hz, H-1), 4.02 (m, 1H, H-5), 3.65 (m, 2H, H-2, H-4), 3.40 (s, 3H, OCH_3), 2.17 (s, 3H, Ac), 1.36 (d, 3H $J_{5,6} = 6.3$ Hz, CH_3). Anal. calcd. for $C_9H_{16}O_6$: C, 49.09; H, 7.32. Found: C, 48.96; H, 7.16.

Methyl 2-O-acetyl-β-L-rhamnopyranoside. Yield 172 mg, (78%). R_f 0.44, mp 134–135°C (from EtOAc–hexane), $[\alpha]_D^{20}$ +57.3° (c 0.5, $CHCl_3$). ^{1}H NMR δ: 5.36 (dd, 1H, $J_{1,2} = 1.1$ Hz, $J_{2,3} = 3.5$ Hz, H-2), 4.47 (d, 1H, H-1), 3.69 (dd, 1H, $J_{3,4} = 9.0$ Hz, H-3), 3.52 (s, 3H, OCH_3), 3.46 (t, 1H, $J_{4,5} = 9.0$ Hz,

H-4), 3.37 (m, 1H, H-5), 2.18 (s, 3H, Ac), 1.41 (d, 3H, $J_{5,6} = 6.1$ Hz, CH_3). Anal. calcd. for $C_9H_{16}O_6$: C, 49.09; H, 7.32. Found: C, 48.84; H, 7.40.

Methyl 3-O-acetyl-α-L-arabinopyranoside. Yield 130 mg, (63%). R_f 0.39, mp 130–131°C (from EtOAc–hexane), $[\alpha]_D^{20}$ +44.3° (c 0.6, $CHCl_3$). ^{1}H NMR δ: 4.86 (dd, 1H, $J_{2,3} = 9.8$ Hz, $J_{3,4} = 3.2$ Hz, H-3), 4.19 (d, 1H, $J_{1,2} = 7.3$ Hz, H-1), 4.06 (m, 1H, H-4), 4.02 (dd, 1H, $J_{4,5a} = 2.5$ Hz, $J_{5a,5b} = 12.8$ Hz, H-5_a), 3.82 (m, 1H, H-2), 3.62 (dd, 1H, $J_{4,5b} = 1.4$ Hz, H-5_b), 3.57 (s, 3H, OCH_3), 2.18 (s, 3H, Ac). Anal. calcd. for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.49; H, 6.77.

*Methyl 3-O-acetyl-β-L-*arabinopyranoside. Yield 154 mg, (75%). R_f 0.49, mp 126–127°C (from EtOAc–hexane), $[\alpha]_D^{20}$ +231.4° (c 0.6, $CHCl_3$). ^{1}H NMR δ: 5.10 (dd, 1H, $J_{2,3} = 10.0$ Hz, $J_{3,4} = 3.2$ Hz, H-3), 4.83 (d, 1H, $J_{1,2} = 3.9$ Hz, H-1), 4.08–3.92 (m, 2H, H-2, H-4), 3.85 (dd, 1H, $J_{4,5a} = 1.4$ Hz, $J_{5a,5b} = 12.5$ Hz, H-5_a), 3.70 (dd, 1H, $J_{4,5b} = 2.2$ Hz, H-5_b), 3.46 (s, 3H, OCH_3), 2.18 (s, 3H, Ac). Anal. calcd. for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.42; H, 6.94.

Methyl 3-O-acetyl-α-D-lyxopyranoside. Yield 136 mg (66%). R_f 0.38, syrup, $[\alpha]_D^{20}$ +74.6° (c 0.4, $CHCl_3$). ^{1}H NMR δ: 5.05 (dd, 1H, $J_{2,3} = 3.2$ Hz, $J_{3,4} = 8.8$ Hz, H-3), 4.65 (d, 1H, $J_{1,2} = 2.7$ Hz, H-1), 4.10–3.90 (m, 2H, H-2, H-4), 3.82 (dd, 1H, $J_{4,5a} = 5.3$, $J_{5a,5b} = 11.3$ Hz, H-5_a), 3.58 (dd, 1H, $J_{4,5b} = 9.3$ Hz, H-5_b), 3.43 (s, 3H, OCH_3), 2.18 (s, 3H, Ac). Anal. calcd. for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.44; H, 6.89.

Methyl 3-O-acetyl-α-D-fucopyranoside. Yield 200 mg (91%). R_f0.52, mp 117.5–118.5°C (from EtOAc–hexane), $[\alpha]_D^{20}$ +239.8° (c 0.4, $CHCl_3$). ^{1}H NMR δ: 5.07 (dd, 1H, $J_{2,3} = 10.3$ Hz, $J_{3,4} = 3.1$ Hz, H-3), 4.79 (d, 1H, $J_{1,2} = 4.0$ Hz, H-1), 4.02 (m, 1H, H-5), 3.94 (dd, 1H, H-2), 3.85 (m, 1H, H-4), 3.44 (s, 3H, OCH_3), 2.17 (s, 3H, Ac), 1.29 (d, 3H, $J_{5.6} = 6.7$ Hz, CH_3). Anal. calcd. for $C_9H_{16}O_6$: C, 49.09; H, 7.32. Found: C, 48.90; H, 7.20.

Methyl 3-O-acetyl-β-D-ribopyranoside. Yield 198 mg (96%). R_f 0.58, mp 111–112°C (from EtOAc–hexane), $[\alpha]_D^{20}$ −158.1° (c 0.4, $CHCl_3$). ^{1}H NMR δ: 5.01 (t, 1H, $J_{2,3} = J_{3,4} = 3.2$ Hz, H-3), 4.78 (d, 1H, $J_{1,2} = 2.0$ Hz, H-1), 4.03 (m, 1H, H-4), 3.93 (dd, 1H, $J_{4,5a} = 1.7$, $J_{5a,5b} = 12.4$ Hz, H-5_a), 3.89 (m, 1H, H-2), 3.81 (dd, 1H, $J_{4,5b} = 2.3$ Hz, H-5_b), 3.42 (s, 3H, OCH_3), 2.19 (s, 3H, Ac). Anal. calcd. for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.72; H, 6.96.

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