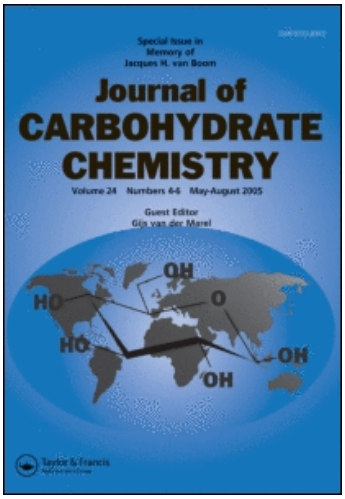

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Clay Catalyzed Acetonation: A Simple Method for the Preparation of Isopropylidene Carbohydrates

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CLAY CATALYZED ACETONATION: A SIMPLE METHOD FOR THE PREPARATION OF ISOPROPYLIDENE CARBOHYDRATES

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ABSTRACT

This paper reports a simple method for the preparation of isopropylidene carbohydrates using clay as a catalyst. Treatment of various monosaccharides and/or ribonucleosides with acetone in the presence of clay such as a montmorillonite K 10 (K 10) under mild reaction conditions gave isopropylidene carbohydrates (**1-7**) in good yields.

INTRODUCTION

Protection or deprotection of hydroxyl groups is one of the most important procedures in the field of carbohydrate chemistry. The acetonation reaction is widely used for protecting hydroxyl groups of carbohydrates and the isopropylidene derivatives are also useful intermediates in the synthesis of various carbohydrate compounds. Classical acetonations of carbohydrates have been achieved with acetone

and several mineral acids, such as sulfuric acid, hydrochloric acid, or phosphoric acid, in the presence or absence of copper (II) sulfate or zinc chloride.[1] Recently, He and coworkers reported that a modified method for acetonation of saccharides was achieved with acetone in the presence of *p*-toluenesulfonic acid and molecular sieves (4Å).[2] 2,2-Dimethoxypropane is also known to be a useful acetonating reagent for the preparation of a variety of isopropylidene carbohydrate derivatives.[3]

Recently, clay minerals have become available for organic syntheses as heterogeneous acid catalysts. For example, various types of montmorillonite clay have been used.[4] The experimental procedure using clay is simple with regard to treatment and removal of the catalyst because of the nonhygroscopic and insoluble property of clay minerals.

We report here a facile method for the acetonation of carbohydrates with acetone in the presence of montmorillonite K 10 (K 10) clay as a catalyst.

RESULTS AND DISCUSSION

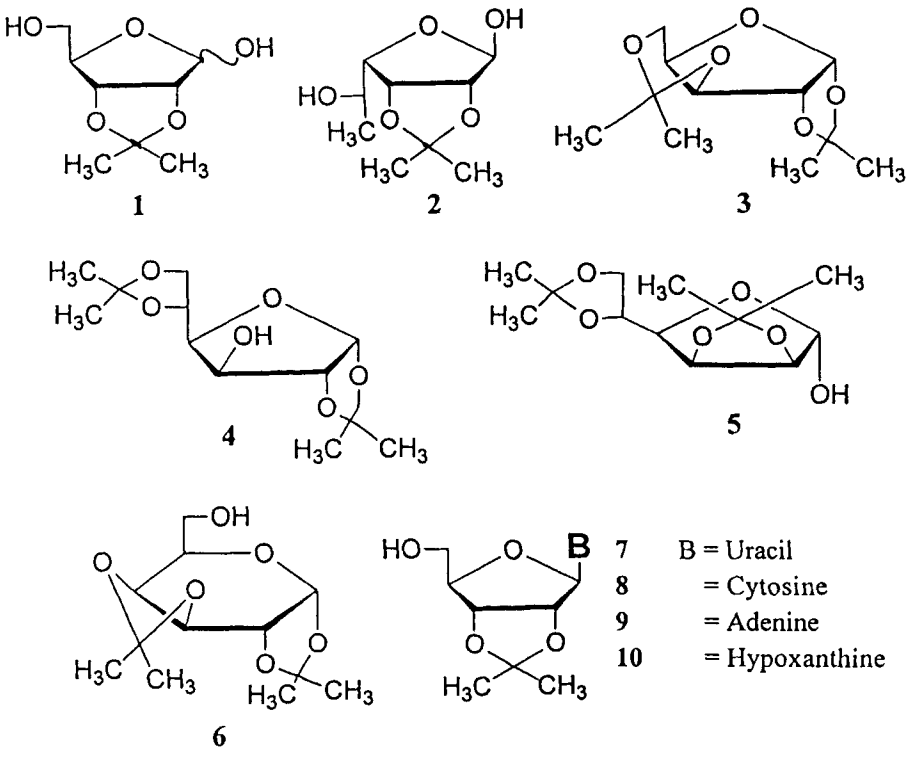
Acetonation of six different monosaccharides with acetone in the presence of K 10 clay as a catalyst gave the corresponding isopropylidene derivatives (**1-6**). Acetonation of four ribonucleosides gave satisfactory product (**7**) from uridine only. The major products were purified by column chromatography on silica gel (**1-6**) or treatment with charcoal (**7**). The reaction conditions and the yields of purified major products are described in the Table.

Treatment of D-ribose and L-rhamnose monohydrate with acetone in the presence of 300 mg of K 10 clay per mmol of substrate at ambient temperature for 7 or 10 h afforded 2,3-*O*-isopropylidene-D-ribofuranose (**1**) and 2,3-*O*-isopropylidene-β-L-rhamnofuranose (**2**) in excellent yields (92 and 95 %, respectively). Similarly, acetonations of D-xylose, D-glucose, D-mannose, and D-galactose, with acetone and K 10 clay gave the di-*O*-isopropylidene derivatives (**3-6**) in good yields (Table). The use of

Table Clay Catalyzed Acetonation of Carbohydrates[a]

Run	Substrate	K 10 mg/mmol	Temp. °C	Time h	Product (Yield %)[b,c,d]	
1	D-Ribose	300	r t	7	**1** (92)	[d](78)[12]
2	L-Rhamnose	300	r t	10	**2** (95)	[d](71)[7]
3		300	r t	72	**3** (<10)[c]	
4		300	50	24	**3** (53)	
5	D-Xylose	600	r t	96	**3** (38)	[d](59-62)[13]
6		600	50	26	**3** (63)	
7		600	50	48	**3** (64)	
8		900	50	29	**3** (61)	
9		300	r t	36	**4** (<10)[c]	
10		300	50	24	**4** (50)	
11	D-Glucose	600	r t	53	**4** (30)	[d](43-46)[14]
12		600	50	24	**4** (67)	[d](91)[9,10]
13		600	50	48	**4** (80)	
14		600	50	72	**4** (82)	
15		600	50	24	**5** (64)	
16	D-Mannose	600	50	48	**5** (84)	[d](92)[10]
17		600	50	72	**5** (88)	
18	D-Galactose	600	50	48	**6** (49)	[d](66)[15]
19		600	50	72	**6** (51)	[d](80)[11]
20	Uridine	300	r t	48	**7** (83)	
21		300	50	8	**7** (97)	
22	Cytidine	300	r t	48	**8** (0)[c]	
23		600	50	48	**8** (trace)[c]	
24	Adenosine	600	50	48	**9** (trace)[c]	
25	Inosine	600	50	48	**10** (<10)[c]	

a. Acetonation reactions were carried out with 500 mg of starting carbohydrate and 15 mL of acetone.
b. Yield of isolated and chromatographically homogeneous major products.
c. Starting carbohydrate was mainly unchanged (by TLC analysis), products were not isolated and characterized.
d. Yield obtained with mineral acid catalyzed methods.



300 mg of K 10 clay per mmol of starting sugars (D-xylose or D-glucose) at ambient temperature resulted in low yields of **3** and **4** (runs 3 and 9). However, increased quantities of K 10 clay (600 mg/mmol), a longer reaction time, and/or elevation of the reaction temperature increased the yields (compare runs 3-4, 3-5, 5-7, 9-10, 9-11, 11-12, and 15-16). The use of an even greater amount of K 10 clay (900 mg/mmol) or a longer reaction time, had little influence on the yields (compare runs 6-8, 13-14, 16-17, and 18-19).

Several methods for the acetonation of the sugar moiety of ribonucleosides also have been reported.[5] K 10 clay catalyzed acetonation of typical pyrimidine or purine ribonucleosides such as uridine, cytidine, adenosine, and inosine was attempted with acetone under several reaction conditions (Table). It was found that the acetonation of uridine with acetone could be effected in the presence of 300 mg of K 10 clay per mmol of uridine at ambient temperature or 50 °C and resulted in the formation of 2',3'-*O*-

isopropylideneuridine (**7**) in high yields (83 and 97 %, Table). Treatment of cytidine with acetone in the presence of 300 mg of K 10 clay per mmol of cytidine at ambient temperature for 48 h did not give the isopropylidene product 2',3'-*O*-isopropylidene-cytidine (**8**) (run 22), and the use of a greater amount of K 10 clay and elevated reaction temperature resulted in only a trace yield of **8** (run 23). Acetonation of adenosine and inosine with K 10 clay also resulted in low yields of the corresponding 2',3'-*O*-isopropylidene ribonucleosides (**9**, **10**, runs 24 and 25). Uridine is so weakly basic that 300 mg of K 10 clay per mmol of uridine can provide sufficient hydrogen ions for the reaction, whereas other nucleosides are appreciably basic, and may require a greater amount of catalyst, or a more active acetonation reagent than acetone. Further investigation on various transformation reactions of organic compounds using clay as a catalyst are being continued in our laboratories.

EXPERIMENTAL

General Methods. Melting or mixed melting points with some commercially available authentic samples were determined on a hot plate stage apparatus and are uncorrected. Proton NMR spectra were recorded with a Jeol JNM GX-400 spectrometer at 400 MHz with solution in $CDCl_3$, unless otherwise noted, with Me_4Si as an internal standard. High-resolution mass spectra were determined by a Jeol HX-100 spectrometer. Elemental analyses were performed by the Analytical Center of Dainippon Pharmaceutical Co., Ltd. UV spectra were obtained in MeOH with a Hitachi U-3000 spectrophotometer. Specific rotations were determined with a Jasco DIP-140 polarimeter. TLC was performed on silica gel (Merck kieselgel 60) F-254 sheets and compounds were detected by spraying TLC plates with a concd H_2SO_4/ MeOH mixture or by visualization under 254 nm light. Merck kieselgel 60 (230-400 mesh) was used for column chromatography. Montmorillonite K 10 clay (K 10, Aldrich) was dried over P_2O_5 in high vacuum at 110 °C for 24 h before use. Acetone was dried with $CaSO_4$, then refluxed with and distilled from $KMnO_4$ before use.

Acetonation of Carbohydrates. A mixture of 500 mg of carbohydrate, K 10 clay, and dry acetone (15 mL) was stirred for several hours with exclusion of moisture under several reaction conditions (see Table). The mixture was filtered through a Celite pad and washed with acetone. The combined filtrate and washings were concentrated. Purification and characterization of the major product from the resulting yellow-colored residues are described as follows: yields of chromatographically homogeneous major products are shown in the Table; minor or trace byproducts and unreacted starting compounds were not isolated or characterized in this work.

2,3,-*O*-Isopropylidene-D-ribofuranose (1). The crude residue was purified by column chromatography (55 g, 2.2 x 37 cm, eluted with $CHCl_3$/MeOH, 50:1) to give homogeneous **1**. An analytical sample was prepared by treatment with charcoal in acetone at ambient temperature. Syrup; $[\alpha]_D^{20}$ -25.9° (*c* 1.1, $CHCl_3$) {lit.[2] $[\alpha]_D^{25}$ -27.5° ($CHCl_3$); lit.[3b] $[\alpha]_D$ -19° (H_2O), -42° (acetone)}. ^1H NMR δ 5.41 (d, J = 5.9 Hz, 1 H, H-1), 5.25 (d, J = 6.2 Hz, 1 H, 1-OH), 4.82 (d, J = 5.5 Hz, 1 H, H-3), 4.58 (d, J = 5.9 Hz, 1 H, H-2), 4.40 (t, J = 2.6 Hz, 1 H, H-4), 3.97 (brm, 1 H, 5-OH), 3.72 (m, 2 H, H-5,5'), 1.49, 1.33 (2s, 3 H x 2, CMe_2). HRMS (FAB, pos.) Calcd for $C_8H_{15}O_5$ (MH^+): *m/z* 191.0920. Found: 191.0893.

2,3-*O*-Isopropylidene-β-L-rhamnofuranose (2). Column chromatography (75 g, 2.2 x 47 cm, eluted with C_6H_6/acetone 4:1) gave homogeneous **2** as a syrup. An analytical sample was crystallized from EtOAc/pet. Et_2O. Needles; mp 87.5-88.5 °C {lit.[2] 88-89 °C; lit.[6] 92-93 °C}. $[\alpha]_D^{20}$ +18.2° (*c* 1.0, H_2O) {lit.[2] $[\alpha]_D^{25}$ +17.8° (H_2O); lit.[7] $[\alpha]_D^{25}$ +17° (H_2O)}. ^1H NMR δ 5.42 (d, J = 2.6 Hz, 1 H, H-1), 4.89 (dd, J = 4.0, 5.9 Hz, 1 H, H-3), 4.62 (d, J = 5.9 Hz, 1 H, H-2), 4.03-4.11 (m, q-like, J = 6.4 Hz, 1 H, H-5). 3.95 (dd, J = 3.7, 7.3 Hz, 1 H, H-4), 3.16 (d, J = 2.9 Hz, 1 H, 1-OH), 2.69 (d, J = 5.9 Hz, 1 H, 5-OH), 1.48, 1.34 (2s, 3 H x 2, CMe_2), 1.34 (d, J = 6.2 Hz, 3 H, Me). HRMS (FAB, pos.) Calcd for $C_9H_{17}O_5$ (MH^+): *m/z* 205.1076. Found: 205.1105.

1,2:3,5-Di-*O*-Isopropylidene-α-D-xylofuranose (3). Column chromatography (75 g, 2.2 x 47 cm, eluted with C_6H_6 200 mL, then C_6H_6/acetone 50:1) gave homogeneous **3**. An analytical sample was prepared by treatment with charcoal in C_6H_6 at ambient temperature. Syrup; $[\alpha]_D^{20}$ +18.9° (*c* 0.91, acetone) {lit.[8] $[\alpha]_D^{25}$ +19.5° (acetone); lit.[3c] $[\alpha]_D^{20}$ +13.0° (H_2O)}. ^1H NMR δ 6.01 (d, J = 3.7 Hz, 1 H, H-1), 4.52 (d, J = 3.7 Hz, 1 H, H-2), 4.29 (d, J = 2.2 Hz, 1 H, H-3), 4.02- 4.13 (m, J = 2.2 Hz, 3 H, H-4,5,5'), 1.50, 1.39, 1.33 (4s, 3 H x 4, $2CMe_2$). HRMS (FAB, pos.) Calcd for $C_{11}H_{19}O_5$ (MH^+): *m/z* 231.1233. Found: 231.1254.

1,2:5,6-Di-*O*-Isopropylidene-α-D-glucofuranose (4). Column chromatography (75 g, 2.2 x 47 cm, eluted with C_6H_6/acetone 20:1, 200 mL, then 10:1) gave homogeneous **4** as a solid. An analytical sample was crystallized from hexane. Needles; mp (mixed) 109-111 °C {lit.[9] 105-109 °C; lit.[10] 110 °C}. $[\alpha]_D^{20}$ -18.9° (*c* 0.78, H_2O) {lit.[10] $[\alpha]_D^{20}$ -18.5° (H_2O)}. ^1H NMR δ 5.94 (d, J = 3.8 Hz, 1 H, H-1), 4.53 (d, J = 3.4 Hz, 1 H, H-2), 4.32-4.37 (m, 2 H, H-3,5), 4.17 (dd, J = 6.3, 8.7 Hz, 1 H, H-6 or 6'), 4.07 (dd, J = 2.9, 7.7 Hz, 1 H, H-4), 3.99 (dd, J = 5.3, 8.7 Hz, 1 H, H-6' or 6), 2.59 (d, J = 3.8 Hz, 1 H, 3-OH), 1.50, 1.45, 1.37, 1.32 (4s, 3 H x 4, $2CMe_2$). HRMS (FAB, pos.) Calcd for $C_{12}H_{21}O_6$ (MH^+): *m/z* 261.1338. Found: 261.1353.

2,3:5,6-Di-*O*-Isopropylidene-α-D-mannofuranose (5). Dry packed column chromatography (90 g, 2.2 x 47 cm, eluted with C_6H_6/acetone 10:1) gave homogeneous **5** as a solid. An analytical sample was crystallized from hexane. Needles; mp (mixed) 124-126 °C {lit.[2, 10] 122-123 °C}. $[\alpha]_D^{20}$ +8.0° (*c* 1.0, $CHCl_3$) {lit.[10] $[\alpha]_D^{16}$ +16° (EtOH)}. ^1H NMR δ 5.38 (d, J = 2.7 Hz, 1 H, H-1), 4.81 (dd, J = 3.7, 5.7 Hz, 1 H, H-3), 4.62 (d, J = 6.0 Hz, 1 H, H-2), 3.38-4.41 (m, J = 7.1 Hz, 1 H, H-5), 4.19 (dd, J = 3.7, 7.0 Hz, 1 H, H-4), 4.03-4.11 (m, 2 H, H-6,6'), 3.02 (s, 1 H, 1-OH), 1.47, 1.46, 1.38, 1.33 (4s, 3 H x 4, $2CMe_2$). HRMS Calcd for $C_{12}H_{20}O_6$ (M^+): *m/z* 260.1260. Found: 260.1242.

1,2:3,4-Di-*O*-Isopropylidene-α-D-galactopyranose (6). Dry packed column chromatography (90 g, 2.2 x 47 cm, eluted with C_6H_6/acetone 10:1) gave homogeneous **6**. An analytical sample was prepared by treatment with charcoal in C_6H_6 at ambient temperature. Syrup; $[\alpha]_D^{20}$ -67.9° (*c* 1.1, $CHCl_3$) {lit.[2] $[\alpha]_D^{25}$ -60.9° ($CHCl_3$); lit.[11] $[\alpha]_D^{20}$ -59° ($CHCl_3$)}. ^1H NMR δ 5.57 (d, J = 5.1 Hz, 1 H, H-1), 4.62 (dd, J = 2.6, 8.1 Hz, 1 H, H-3), 4.34 (dd, J = 2.6, 5.1 Hz, 1 H, H-2), 4.28 (dd, J = 1.5, 8.1 Hz, 1 H, H-4), 3.84-3.90 (m, 2 H, H-5,6 or 6'), 3.72-3.78 (m, 1 H, H-6' or 6), 2.28 (brs, 1 H, 6-OH), 1.54, 1.46, 1.34 (3s, 3 H, 3 H, and 6 H, $2CMe_2$). HRMS (FAB, pos.) Calcd for $C_{12}H_{21}O_6$ (MH^+): *m/z* 261.1338. Found: 261.1368.

2',3'-*O*-Isopropylideneuridine (7). The crude residue was treated with charcoal in hot EtOAc to give chromatographically homogeneous **7** as a foam. An analytical sample was crystallized from acetone/hexane. Needles; mp 161-162 °C {lit.[5a] 163-164 °C; lit.[5b] 165-166 °C}. ^1H NMR (DMSO-*d6*) δ 11.30 (s, 1 H, NH), 7.72 (d, J = 8.3 Hz, 1 H, H-6), 5.76 (d, J = 2.9 Hz, 1 H, H-1'), 5.57 (d, J = 7.8 Hz, 1 H, H-5), 5.02 (t, J = 5.1 Hz, 1 H, 5'-OH), 4.83 (dd, J = 2.9, 6.3 Hz, 1 H, H-2'), 4.68 (dd, J = 3.9, 6.4 Hz, 1 H, H-3'), 4.00 (q, J = 4.4, 8.3 Hz, 1 H, H-4'), 3.46-3.55 (m, 2 H, H-5',5''), 1.42, 1.22 (2s, 3 H x 2, CMe_2). UV (MeOH) λ max 260 nm (ε 10400), λ min 228 nm (ε 2200). HRMS Calcd for $C_{12}H_{16}N_2O_6$ (M^+): *m/z* 284.1008. Found: 284.1009.

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