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Note

Acyl chloride/DABCO-promoted acetal migration of 1,2:4,5-di-*O*-isopropylidene-D-fructopyranose

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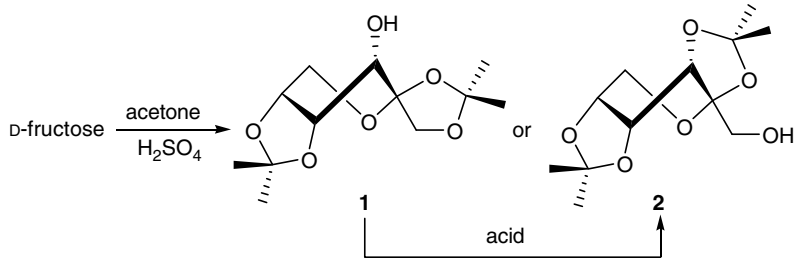
Abstract—An unprecedented acetal migration was observed when 1,2:4,5-di-*O*-isopropylidene-D-fructose was treated with various acyl chlorides and 1,4-diaza-bicyclo[2.2.2]octane (DABCO). 2,3:4,5-Di-*O*-isopropylidene-D-fructose derivatives were isolated as the only product in high to quantitative yields. The acylium cations generated in situ were speculated as the electrophilic species to initiate the migration process.

Keywords: Acetal migration; Acetylation; Acylium cations; Fructose; DABCO

More than 110 years ago Emil Fisher first described the formation of acetals from D-fructose and acetone.[1] Since then, the *O*-isopropylidene group has been extensively used in organic synthesis, especially in the field of carbohydrate chemistry. Acetal migration is a well-documented phenomenon, among which di-*O*-isopropylidene sugars are found to form thermodynamically favored isomers under acidic conditions (proton acids or Lewis acids).[2] Herein, we report that a novel acetal migration occurred when 1,2:4,5-di-*O*-isopropylidene-D-fructose was treated with an acyl chloride in the presence of DABCO.

Two kinds of diacetonide D-fructosides (**1** and **2**, Scheme 1) can be formed when D-fructose is treated with concentrated H_2SO_4 in dry acetone. The ratios of **1** and **2** depend on the amount of H_2SO_4 used in the reaction mixture. If a small amount of H_2SO_4 is used, compound **1** is the major product,[3] whereas a large amount of H_2SO_4 leads predominately to compound **2**.[4] Furthermore, **1** is readily converted into the more stable product



Scheme 1. Formation of 1,2:4,5-di-*O*-isopropylidene-D-fructose and 2,3:4,5-di-*O*-isopropylidene-D-fructose.

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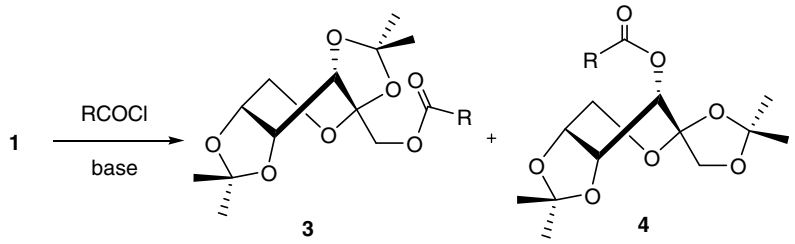


Scheme 2. Various acyl chloride/base combinations that promoted acetal migration.

2 after the treatment with H_2SO_4 in acetone.[5] To the best of our knowledge, no reagents other than strong acid can accomplish this type of migration.

Compound **4a**, where the sugar is used as a chiral auxiliary, has been used as a dienophile in an asymmetric Diels–Alder reaction.[6] In our synthesis of **4a**, after we changed the base from pyridine to DABCO in CH_3CN, to our astonishment, compound **3a** was found as the only product in quantitative yield, and the 'normal' acetylated product was not observed at all (Scheme 2).

When either acryloyl chloride or DABCO was used independently (Table 1, entries 1 and 2), the starting material **1** remained intact. These results excluded the possibility of the migration caused by DABCO or by a trace of HCl. Furthermore, no migration product was formed when compound **3a** was treated with acryloyl chloride and DABCO, indicating that the migration took place before the acylation.

Various acyl chloride and base combinations were subsequently tried (Scheme 2 and Table 1) to investigate the efficacy and scope of this reaction. When cinnamoyl chloride, chloroacetyl chloride, and benzoyl chloride were used under similar conditions, acetal migration products **3b**, **3c**, and **3d** were isolated as the only products in excellent yields, respectively, though the last one was produced in a sluggish manner (Table 1, entries 5, 7 and 9). In contrast, when pyridine was used instead of DABCO, no migration product was observed.

Compounds **3a**–**d** and **4a**,**b**,**d** can be unambiguously characterized by ^{1}H NMR spectroscopy. Both compounds **3** and **4** adopt a skew boat conformation because of the two five-membered rings that are cis-fused onto the central pyranose ring. However, the coupling constant between H-3 and H-4 is ~2.4 Hz; and ~5 Hz, respectively. Another criterion is the relative chemical shifts of H-1 and H-6,6a: HO-1 was acylated in compounds **3**, and its H-1 signal was found at lower field than that of H-6,6a. HO-3 was acylated in compounds **4**, and the signal of H-1 was closer to that of H-6,6a.

A proposed mechanism for this unique transformation is shown in Scheme 3. An acylium cation, the electrophilic species, that is generated in the presence of acyl chloride and DABCO in CH_3CN, reacts with the most reactive oxygen, O-1, to give the migration product via a ring-opening and ring-closing procedure (path A) or in a concerted manner (path B). The free hydroxyl group, which is reluctant to react with the highly reactive oxocarbonium ion, may be sterically hindered from the bulky 1,2-acetal.

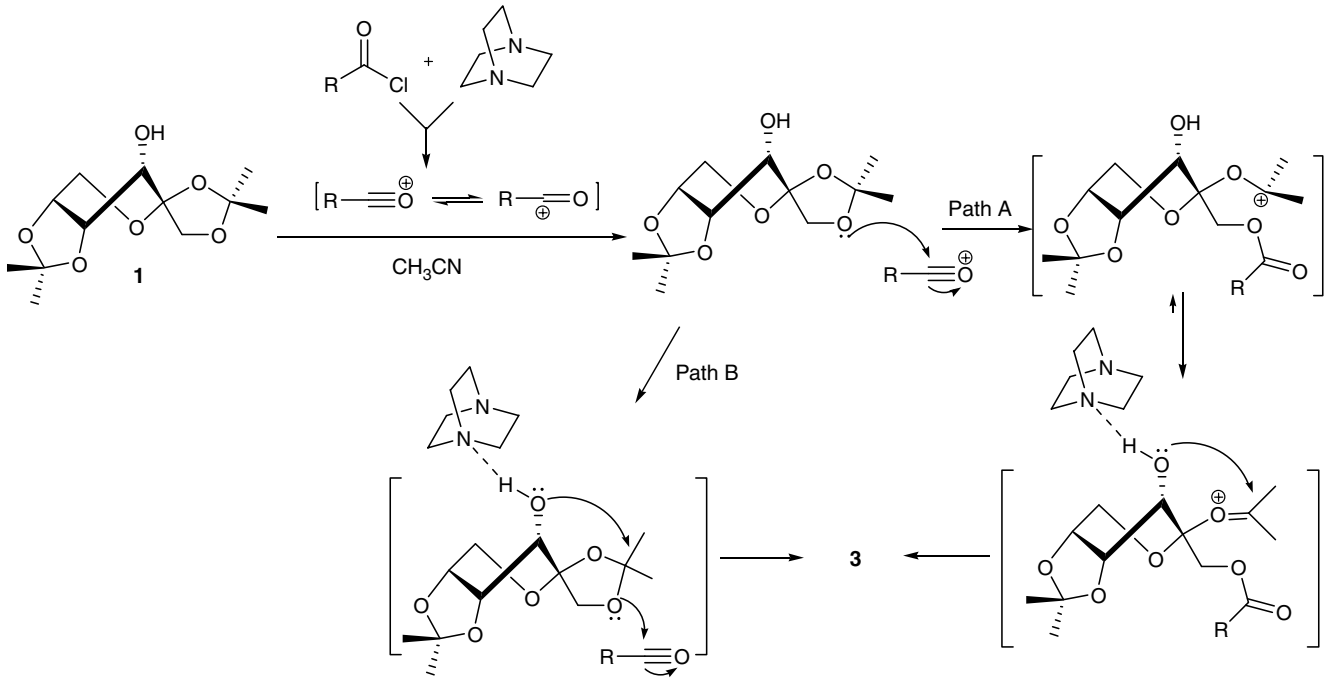
1. Experimental

1.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on a Jeol-300 instrument using TMS as internal standard. Mass spectra were measured on an IBI-MDS Sciexciex Q-Star mass spectrometer. Optical rotations were measured at 25 °C using an Optical Activity AA-10R automatic polarimeter. TLC was performed on self-made glass plates coated with Silica Gel GF254 (Hai Yang Chemical Factory, Qingdao, Shandong, PR China). Column chromatography was performed on Silica Gel H60

Table 1. Various acyl chloride/base combinations that promoted acetal migration

Entry	RCOCl	Base	Product **3**/**4**	Yield (%)
1	CH_2=CHCOCl	No	—	0
2	No	DABCO	—	0
3	CH_2=CHCOCl	DABCO	**3a**/**4a**, 100/0	Quantitative
4	CH_2=CHCOCl	Pyridine	**3a**/**4a**, 0/100	Quantitative
5	$ClCH_2COCl$	DABCO	**3b**/**4b**, 100/0	Quantitative
6	$ClCH_2COCl$	Pyridine	**3b**/**4b**, 0/100	Quantitative
7	*trans*-PhCH=CHCOCl	DABCO	**3c**/**4c**, 100/0	91
8	PhCOCl	DABCO	**3d**/**4d**, 100/0	81
9	PhCOCl	Pyridine	**3d**/**4d**, 0/100	83



Scheme 3. Proposed mechanism for acetal migration.

(Hai Yang Chemical Factory, Qingdao, Shandong, PR China). Melting points were measured on an X4 melting point apparatus, and the thermometer was uncorrected. Solvents were purified by standard procedures. Yields are given in Table 1.

1.2. General procedure for the acetal migration

To a solution of compound **1** (260 mg, 1.0 mmol) and DABCO (183 mg, 1.5 mmol) in anhyd CH_3CN (3 mL), was added acyl chloride (1.5 mmol, for PhCOCl, 2.5 mmol was used) dropwise. The resulting mixture was stirred at room temperature (monitored by TLC, 2–24 h). After quenching with MeOH, the mixture was evaporated and purified on a silica-gel column. The data for compounds **4a**, **3a**, **4b**, and **4d**, were consistent with those of Refs. 6–9, respectively.

1.3. 1-*O*-Chloroacetyl-2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (3b)

$[\alpha]_D$ −22.4 (*c* 1.07, $CHCl_3$). ^1H NMR δ 4.62 (dd, 1H, *J* 7.8 Hz, 2.7 H-4), 4.65 (d, 1H, *J* 11.7 Hz, H-1a), 4.32 (d, 1H, *J* 2.4 Hz, H-3), 4.25 (d, 1H, *J* 7.2 Hz, H-5), 4.14 (d, 1H, *J* 11.7 Hz, H-1b), 4.13 (s, 2H, $-CH_2Cl$), 3.91 (dd, 1H, *J* 12.9, 1.8 Hz, H-6a), 3.78 (d, 1H, 12.9 Hz, H-6b), 1.55, 1.49, 1.42, 1.35 (4s, $4 \times 3H$, $4CH_3$). ^{13}C NMR δ 109.1, 108.9, 70.6, 70.5, 69.9, 66.6, 61.3, 40.7, 26.4, 25.8, 25.1, 24.0. ESI TOF MS *m*/*z* found 337.1 $[M+H]^+$, 354.1 $[M+NH_4]^+$. Anal. Calcd for $C_{14}H_{21}ClO_7$ (336.1): C, 49.93; H, 6.29. Found: C, 49.86; H, 6.40.

1.4. 1-*O*-Cinnamoyl-2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (3c)

$[\alpha]_D$ −26.2 (*c* 1.22, $CHCl_3$). ^1H NMR δ 7.75 (d, 1H, *J* 16.2 Hz), 7.50–7.53 (m, 2H, Ph), 7.38–7.40 (m, 3H, Ph), 6.47 (d, 1H, *J* 16.2 Hz), 4.63 (d, 1H, *J* 2.4, 7.8 Hz, H-4), 4.57 (dd, 1H, *J* 11.7 Hz, H-1a), 4.40 (d, 1H, *J* 2.4 Hz, H-3), 4.26 (d, 1H, *J* 8.4 Hz, H-5), 4.20 (d, 1H, *J* 11.7 Hz, H-1b), 3.94 (dd, 1H, *J* 12.9, 1.8 Hz, 6a), 3.80 (d, 1H, *J* 12.9 Hz, H-6b), 1.56, 1.50, 1.44, 1.35 (4s, $4 \times 3H$, $4CH_3$). ^{13}C NMR δ 166.2, 145.5, 134.2, 130.4, 128.9, 128.1, 117.5, 109.1, 108.7, 70.8, 70.6, 70.1, 65.3, 61.3, 40.7, 26.5, 25.9, 25.3, 24.0. ESI TOF MS *m*/*z* 390.2, found 391.1 $[M+H]^+$, 408.1 $[M+NH_4]^+$. Anal. Calcd for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71. Found: C, 64.44; H, 6.82.

1.5. 1-*O*-Benzoyl-2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose (3d)

Mp 80–82 °C (82 °C, Ref. 10). ^1H NMR δ 8.06–8.09 (m, 2H, Ph), 7.54–7.60 (m, 1H, Ph), 7.41–7.47 (m, 4H, Ph), 4.69 (d, 1H, *J* 12.0 Hz, H-1a), 4.65 (dd, 1H, *J* 2.4, 7.8 Hz, H-4), 4.48 (d, 1H, *J* 2.4 Hz, H-3), 4.33 (d, 1H, *J* 12.0 Hz, H-1b), 4.27 (d, 1H, *J* 7.8 Hz, H-5), 3.96 (d, 1H, *J* 12.9 Hz, H-6a), 3.81 (d, 1H, 12.9 Hz, H-6b), 1.55, 1.47, 1.38, 1.35 (4s, $4 \times 3H$, $4CH_3$).

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References

1. Calinaud, P.; Gelas, J. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1996; pp 3–33.
2. Clode, D. M. *Chem. Rev.* **1979**, *79*, 491–513.
3. Banks, M. R.; Cadogan, J. I. G.; Gosney, I.; Gould, R. O.; Hodgson, P. K. G.; McDougall, D. *Tetrahedron* **1998**, *54*, 9765–9784.
4. Beksan, E.; Schieberle, P.; Robert, F.; Blank, I.; Fay, L. B.; Schlichtherle-Cerny, H.; Hofmann, T. *J. Agric. Food Chem.* **2003**, *51*, 5428–5436.
5. Ohle, H. *Ber. Dtsch. Chem. Ges.* **1924**, *57B*, 1566–1576.
6. Enholm, E. J.; Jiang, S. *J. Org. Chem.* **2000**, *65*, 4756–4758.
7. Kossmehl, G.; Volkheimer, J. *Liebigs Ann. Chem.* **1989**, 1127–1130.
8. Chittenden, G. J. F.; Regeling, H. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 44–47.
9. Tian, H.; She, X.; Shi, Y. *Org. Lett.* **2001**, *3*, 715–718.
10. Montgomery, T. N. *J. Am. Chem. Soc.* **1934**, *56*, 419–423.