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Greatly Accelerated Condensation of D-Mannose Diacetonide with Aqueous Formaldehyde (Formalin)

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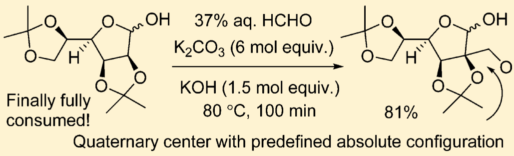
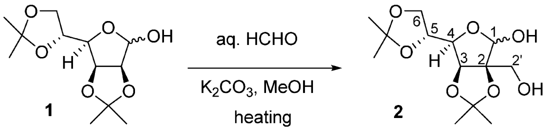
S *Supporting Information*

ABSTRACT: Condensation of D-mannose diacetate with aqueous formaldehyde, a long known quaternary center-generating transformation, was reinvestigated to solve the hidden problem of incomplete conversion, a lasting challenge since 1979 despite many previous efforts. The mysterious cause for the retarded transformation was found to be generation of formic acid by a Cannizzaro reaction. By using additional amounts of base, the reaction time was shortened from 48 h to 100 min and the product was readily isolated in 81% yield.



Condensation of D-mannose diacetate **1** (Scheme 1) with aqueous formaldehyde (formalin) in the presence of K_2CO_3 to afford the aldol **2** was first reported by Ho[1] in 1979 as an extension of his pioneering work[2] on gaining access to starting materials for branched sugars. As all reactants and reagents involved are inexpensive and readily available while the carbon chain branching at the C-2 offers many possibilities for further elaborations into various branched sugars and analogues, not to mention the utilities of the resulting quaternary center of predefined absolute configuration in total synthesis, this transformation along with its applications to other furanoses has received considerable[3,4] attention in the synthetic community.

Scheme 1



1 **2**

We became aware of this condensation when the need for **2** arose in our synthesis[5a] of furospongin-1. From our hands-on experience, we soon noticed that Ho's original procedure contained some problems not reflected in the report: The starting material **1** could never be fully consumed, and the crude product mixture always contained large amounts of unidentified side products with a strong smell of formalin. Because of the presence of unreacted **1** and large amounts of side products, chromatographic separation had to use a longer/wider column and much more eluent for sample application and elution, and repeated chromatography was required.

In many cases, incomplete conversion of the starting material is not really a problem because using larger amounts of the other reactant/reagent or a longer time would eventually lead to complete reaction. However, conversion of **1** into **2** seemed to be an exception. From the modified[3a−c] procedures developed for this particular transformation since 1979, it can be seen that the use of larger amounts of formaldehyde or longer reaction times all led to increased formation of polymeric side products while the starting **1** was still not fully consumed. As implicitly mentioned in the previous[3a] work, and also in our own experience, the more polymer that is present in the crude product, the more difficult the chromatographic purification of **2** becomes. To find out the mysterious cause for the strange phenomenon, we did the work described below.

After careful examination of all reported procedures for the conversion of **1** into **2**, we realized that the solution to the problem must exist outside the parameters examined by the previous investigators. We began with a side product **6**. This species was always present in the reaction system no matter what sets of the documented conditions were employed, but somehow was never[6] mentioned in the previous studies on this particular transformation. With the aid of NMR and other spectroscopic means, diol **6** was characterized (Scheme 2). Judging from the reaction conditions, **6** can only be formed from a Cannizzaro reaction with formaldehyde. We reasoned that, with the formation of **6**, formic acid[7] must also be generated. This was apparently overlooked in the previous investigations, prompting us to consider whether it could be the fundamental cause for the resistance of **1** to full conversion.

Superficially, K_2CO_3 was only a catalyst, which first deprotonated the transient aldehyde **3** to initiate the subsequent addition to formaldehyde and then protonated the resulting aldol anion to afford **4** and eventually **2**. This perhaps was why in all previous procedures the added K_2CO_3 was never significantly larger than stoichiometric amounts.

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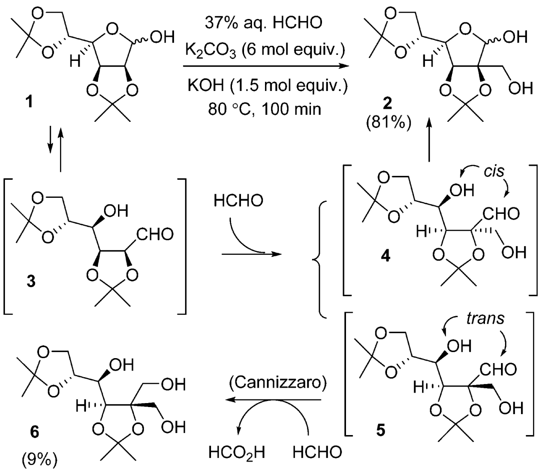
Scheme 2



However, generation of formic acid introduced additional acid and hence unavoidably reduced the basicity of the reaction system. By closely monitoring the condensation, we indeed observed that the basicity (measured to be ca. pH 12 in the beginning) of the reaction mixture went down to only ca. pH 8−9 after 4−5 h. The reaction rate also dropped significantly with the decrease of the basicity.[8] All these findings suggested that use of more K_2CO_3 might help to maintain the initial high reaction rate and lead to full conversion of the starting **1** in much shorter time.

Indeed, when we utilized 2 mol equiv of K_2CO_3, the previous sluggish reaction was substantially facilitated, although traces of **1** still remained by 20 h (Table 1, entry 1). In the presence of 4 mol equiv of K_2CO_3, the added **1** was fully consumed by 5 h (Table 1, entry 2). When the amount of K_2CO_3 was increased to 6 mol equiv (partially insoluble in the beginning, but fully dissolved later), the reaction was complete within 4 h (Table 1, entry 3, ca. pH 10 in the end).

Table 1. Representative Results of Conversion of 1 into 2[a]

entry	K_2CO_3[b]	KOH[b,c]	time	yield (%)[d]
1[e]	2	0	20 h	85[f]
2[e]	4	0	5 h	82[g]
3	6	0	4 h	83
4[h]	0	6	2.5 h	82
5	6	1.5	100 min	81

[a] Performed in MeOH (1.25 mL/mmol of **1**) in the presence of 12 mol equiv (with respect to **1**) of 37% aq. formaldehyde with eventual formal concentration for **1** being ca. 0.8 M. [b] Molar equiv (with respect to **1**). [c] Added in three portions, 0.5 mol equiv each at 15, 30, and 45 min, respectively. [d] Along with ca. 10% of **6** unless otherwise stated. [e] 20 mol equiv of formaldehyde was used. [f] Along with 6% of **6**. [g] Along with 8% of **6**. [h] A dark-red/brown color developed soon.

The use of 6 mol equiv of KOH (without any K_2CO_3) as the base led to an even faster reaction. The starting **1** was fully consumed by 2.5 h, affording **2** in 82% yield (Table 1, entry 4). However, in this case, a dark-red brown color developed quickly and could not be removed from the **2** even after repeated chromatography. The color always appeared under the strongly basic conditions (ca. pH 13) even if the aqueous formaldehyde was not present.

The above results suggested that the basicity of this reaction should be controlled within pH 10−12, the range of a phosphate buffer. Therefore, we also briefly examined the use of Na_2HPO_4 instead of K_2CO_3. Similar acceleration was also observed under such conditions, with **2** obtained in slightly lower yields (74−76%) within 2.5−4 h, but not as satisfactory as with the K_2CO_3/KOH system. Therefore, the conditions of entry 5 (ca. pH 12 at the end of reaction) was eventually chosen for preparative runs.

It should be noted that the newly developed conditions not only tremendously shortened the reaction time but also (more importantly in a sense) greatly simplified the isolation/purification process: In the absence of any **1** (less polar than **2**) and larger amounts of polymers, chromatographic separation became much easier (using a smaller column and lesser amounts of silica gel/eluent) than ever before. The previous unavoidable repeated chromatography was no longer needed.

It is also worth mentioning that the only isolable side product of this reaction (**6**) appeared from the very beginning in parallel to the formation of **2** under any sets of conditions. A reasonable explanation is shown in Scheme 2: Addition of the anion of **3** to formaldehyde may proceed with an approximately 9:1 ratio to afford **4** and **5**, respectively. The main intermediate has the aldehyde and the hydroxyl group cis to each other (with respect to the acetonide ring) and thus may form a hemiacetal quickly. The minor intermediate **5** has the two groups trans to each other (unable to form the hemiacetal), with undergoing the Cannizzaro reaction to provide diol **6** as the only fate under the given conditions. This mechanistic picture also explains why more or less the same **2**/**6** ratios were observed for all runs (independent of the reaction time).

In summary, a long known condensation with great potential in synthesis was reinvestigated in efforts to circumvent its hidden operational difficulties. Through a side product overlooked in previous investigations with the aid of mechanistic knowledge of the base catalyzed condensation of **1** with formaldehyde, the “long-hidden mysterious” cause for the peculiar sluggish condensation was attributed to previously overlooked generation of formic acid via concurrent Cannizzaro reaction(s), which consumed the added K_2CO_3 (supposed to be only a catalyst, not consumed during the reaction), reduced the basicity of the system, and retarded the desired condensation. Introduction of additional amounts of base indeed greatly accelerated the condensation, not only tremendously shortened the reaction time but also (more importantly) made the isolation/separation much easier. The knowledge gained and improvements made in this work should be also useful for condensations of other furanose with aqueous formaldehyde.

■ EXPERIMENTAL SECTION

General Information. Column chromatography was performed on 300−400 mesh silica gel under slightly positive pressure. TLC plates, solvents, and reagents were purchased from commercial suppliers and used as received without any purification.

(3a*S*,6*R*,6a*S*)-6-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-3a-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]-dioxol-4-ol (2) and ((*S*)-5-((*R*)-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)(hydroxy)methyl)-2,2-dimethyl-1,3-dioxolane-4,4-diyl)-dimethanol (6). To a 500 mL two-neck flask equipped with a thermometer and a condenser were placed a magnetic stirring bar, **1** (17.0 g, 65.4 mmol), and MeOH (82 mL). The mixture was stirred for a while. When **1** was fully dissolved, K_2CO_3 (54.2 g, 392.4 mmol) was added. The mixture was stirred at 70 °C (inner temperature, the same below) in an oil bath to give a milky suspension. Commercially available 37% formaldehyde (formalin, 58 mL, 784.8 mmol) was introduced. The mixture was stirred at 80 °C (reflux began) for 15 min

(TLC showed ca. 50% of **1** reacted). A portion of KOH (pellets, 1.8 g, 32.7 mmol) was added. After stirring/refluxing at 80 °C for another 15 min, the second portion of KOH (1.8 g, 32.7 mmol) was added. Stirring/refluxing was continued at 80 °C for 35 min (TLC showed most of **1** already consumed) before the third portion of KOH (1.8 g, 32.7 mmol) was added. The mixture was stirred/refluxed for another 35 min (TLC showed complete disappearance of **1**). The heating bath was removed. The mixture was cooled in an ice−water bath. All solids were filtered off. The filtrate was cooled in an ice−water bath. aq. (10%) H_2SO_4 (20−30 mL) was added carefully until the filtrate became almost neutral. The MeOH in the filtrate was removed by rotary evaporation. The residue was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration. The filtrate was concentrated on a rotary evaporator. The residue was purified by column chromatography (EtOAc) on silica gel (ϕ 7.5 × 25 cm) to give **2** as a ca. 2:1 mixture of two epimers (a colorless oil, less polar than **6**, 15.4 g, 53.0 mmol, 81% from **1**), along with **6** (more polar than **2**, also a colorless oil, 1.7 g, 5.8 mmol, 9% from **1**). The R_f's for **1**, **2**, and **6** were 0.65, 0.34, and 0.01, respectively (with the TLC plates developed using EtOAc).

Data for **2** (2:1 epimers): $[\alpha]_D^{26}$ +1.3 (c 1.2, MeOH) (lit.[1] $[\alpha]_D^{26}$ +11 (c 1.2, MeOH)). (lit.[3c] $[\alpha]_D^{26}$ +9.1 (c 1.2, MeOH) for a 3:2 epimers). ^{1}H NMR (500 MHz, $CDCl_3$, for assignments, cf. ref 3c) δ 5.36 (s, 0.66H), 4.92 (s, 0.34H), 4.66 (d, J = 3.1 Hz, 0.66H), 4.65 (d, J = 3.6 Hz, 0.34H), 4.41 (ddd, J = 4.8, 6.2, 7.3 Hz, 0.66H), 4.37 (ddd, J = 4.4, 6.1, 8.2 Hz, 0.34H), 4.15 (dd, J = 2.9, 7.6 Hz, 0.66H), 4.03−4.13 (m, 2H), 3.98 (d, J = 11.9 Hz, 0.66H), 3.85 (d, J = 12.0 Hz, 0.66H), 3.80 (d, J = 11.7 Hz, 0.35H), 3.77 (d, J = 11.7 Hz, 0.34H), 3.53 (dd, J = 2.9, 8.2 Hz, 0.34H), 1.56, 1.49, 1.46, 1.45, 1.44, 1.42, 1.38, and 1.37 (eight singlets, 12H altogether). ^{13}C NMR (125 MHz, $CDCl_3$, two C-1 epimers) δ 114.0, 113.8, 109.4, 109.2, 103.7, 97.5, 93.6, 89.4, 82.8, 81.9, 80.9, 76.4, 73.1, 72.8, 67.1, 66.6, 63.6, 62.7, 27.3 (2C's), 27.0, 26.9, 26.80, 26.77, 25.12, 25.10.

Data for **6**: $[\alpha]_D^{26}$ −6.9 (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (d, J = 0.7 Hz, 1H), 4.15−4.04 (m, 3H), 3.83 (d, J = 6.4 Hz, 1H), 3.81 (d, J = 11.9 Hz, 1 H), 3.71 (br s, 2H), 3.61 (d, J = 11.9 Hz, 1H), 3.24 (br s, 3H, 3 OH's), 1.49 (s, 3H), 1.42 (s, 6H), 1.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.4, 108.4, 83.1, 77.1, 76.5, 68.9, 66.7, 64.5, 62.5, 28.0, 26.8, 26.6, 25.3. IR (film): 3435, 2985, 2935, 2896, 1462, 1373, 1257, 840, 756 cm^{-1}. ESI-MS: m/z 315.0 $[M + Na]^+$. HRMS (ESI): calcd for $C_{13}H_{25}O_7$ $[M + H]^+$ 293.1595; found 293.1594.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01000.

^{1}H, ^{13}C NMR and IR spectra for **2** and **6** (PDF)

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Notes

The authors declare no competing financial interest.

[§]D.-X.T. was a graduate student registered in Harbin University of Science and Technology while carrying out all experimental work in the Shanghai Institute of Organic Chemistry.

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(6) Fleet et al. reported a Cannizzaro product in a similar condensation of ribo-furanose; see: Best, D.; Jenkinson, S. F.; Saville, A. W.; Alonzi, D. S.; Wormald, M. R.; Butters, T. D.; Norez, C.; Becq, F.; Bleriot, Y.; Adachi, I.; Kato, A.; Fleet, G. W. J. *Tetrahedron Lett.* **2010**, *51*, 4170−4174.

(7) Formic acid should also result from the Cannizzaro reaction between two molecules of formaldehyde. The more formaldehyde was present, the more formic acid would be generated. This explains why addition of very large amounts of formaldehyde did not facilitate the conversion of **1** into **2** so much as expected.

(8) We were not the first to notice this. Fleet and co-workers must have already realized that conversion of **1** into **2** became sluggish after 4−5 h and hence opted to run the reaction for only 5 h (cf. ref 3c above) when substantial amounts of **1** were still unreacted; all other investigators unanimously chose to extend the reaction time to more than 20 h.