

SYNTHESIS OF ULOSES BY THE OXIDATION WITH  
DIMETHYL SULFOXIDE-TRIFLUOROACETIC ANHYDRIDE

Juji YOSHIMURA, Ken-ichi SATO, and Hironobu HASHIMOTO  
Laboratory of Chemistry for Natural Products, Faculty of Science,  
Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152

Application of dimethyl sulfoxide-trifluoroacetic anhydride  
for the oxidation of an isolated hydroxyl group of partially  
protected carbohydrates gave uloses in good yields, and for that of  
2,3-dihydroxyl groups of D-glucosides followed by the reaction with  
carbonyl reagents gave easily 2,3-diulose derivatives.

Although the number of reports on the oxidation method is still increasing,  
1-4) dimethyl sulfoxide( $\text{Me}_2\text{SO}$ ) oxidation<sup>5)</sup> and its variations<sup>6,7)</sup> have been widely  
used for the preparation of uloses: valuable intermediates in synthetic carbohy-  
drate chemistry.<sup>8,9)</sup> However, these methods are often accompanied with epimeriza-  
tion, elimination and the formation of by-products such as methylthiomethyl ether  
and others. Recently, Huang et al. reported that oxidation with  $\text{Me}_2\text{SO}$ -trifluoro-  
acetic anhydride(TFAA) reagent is generally useful, operationally simple and highly  
effective for the conversion of sterically hindered alcohols to carbonyls.<sup>10)</sup> This  
communication describes the application of this reagent for the oxidation of an  
isolated hydroxyl group or 2,3-dihydroxyl groups of carbohydrates.

The experiments have been carried out as follows: To a solution of dry  $\text{Me}_2\text{SO}$   
(2 mmol) in distilled dry  $\text{CH}_2\text{Cl}_2$  (2 ml) cooled below  $-65^\circ\text{C}$  with a dry ice-acetone  
bath was added dropwise TFAA (1.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.5 ml) with stirring in ca. 10  
min, and after 10 min, a solution of a partially protected sugar derivative (1 mmol)  
in  $\text{CH}_2\text{Cl}_2$  (2-3 ml) was subsequently added. The mixture was stirred below  $-65^\circ\text{C}$  for  
30 min, followed by addition of triethylamine (TEA, 0.4 ml) dropwise. The rate of  
addition of TFAA, sugar derivative and TEA was controlled to keep the temperature  
below  $-65^\circ\text{C}$ . The cooling bath was then removed and the reaction mixture was

Table 1. Oxidation of an isolated hydroxyl group of carbohydrates

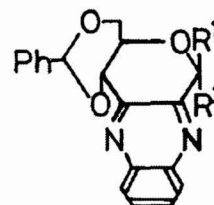
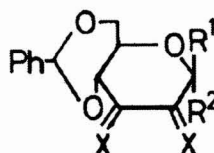
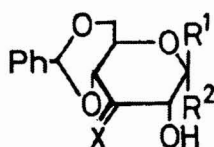
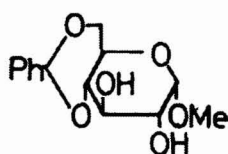
| Products | Me <sub>2</sub> SO-TFAA<br>Yield, % | Me <sub>2</sub> SO-Ac <sub>2</sub> O (or others) |   | CrO <sub>3</sub> -pyridine<br>or RuO <sub>4</sub><br>Yield, %                 |
|----------|-------------------------------------|--|---|---|
|          |                                     | Conditions<br>Time, h<br>(temp, °C)              | Yield, %<br>(methylthiomethyl<br>ether, %)  |   |
| (1)      | 84.8                                | 18   | 62 (20-30)<br>0-70 (DCC) <sup>a</sup><br>45-65 (P <sub>2</sub> O <sub>5</sub> ) <sup>b</sup>                  | 6 (CrO <sub>3</sub> ) <sup>c</sup><br>75-95 (RuO <sub>4</sub> ) <sup>d</sup>  |
| (2)      | 97.0                                | 18<br>18 (25-30)                                 | 52 (2.6)<br>88 (DCC, H <sub>3</sub> PO <sub>4</sub> ) <sup>e</sup>  |   |
| (3)      | 98.2                                | 18<br>18 (25-30)                                 | 47.5 (21.0)<br>90 (DCC, H <sub>3</sub> PO <sub>4</sub> ) <sup>e</sup>   |   |
| (4)      | 87.1                                | 18<br>18   | 46.5 (25.0)<br>90 (DCC, H <sub>3</sub> PO <sub>4</sub> ) <sup>e</sup>   |   |
| (5)      | 86.7                                | 18 (25-30)<br>1.5-2 (65-70)                      | 80 (DCC, H <sub>3</sub> PO <sub>4</sub> ) <sup>e</sup><br>85-92 (P <sub>2</sub> O <sub>5</sub> ) <sup>b</sup> |   |
| (6)      | 89.0                                | 18<br>60   | 70-90 (~19)<br>90 <sup>f</sup>  | 53 (CrO <sub>3</sub> ) <sup>f</sup><br>35 (RuO <sub>4</sub> ) <sup>d</sup>    |
| (7)      | 98.5                                | 72   | 85 (small quantity)   | 78 (RuO <sub>4</sub> ) <sup>e</sup>   |
| (8)      | 93.5                                | 72   | 52 (small quantity)   |   |
| (9)      | 86.7                                | 3-5 (60)   | 81 (P <sub>2</sub> O <sub>5</sub> ) <sup>h</sup>  | 34 (CrO <sub>3</sub> ) <sup>g</sup><br>80-90 (RuO <sub>4</sub> ) <sup>d</sup> |

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allowed to warm up to room temperature, washed with  $\text{H}_2\text{O}$  (5 ml) and the water layer was extracted with  $\text{CH}_2\text{Cl}_2$ . Usual work-up of the combined organic solutions gave an ulose, and the yield was estimated by densitometer and NMR analysis. As shown in Table 1,  $\text{Me}_2\text{SO}$ -TFAA method was widely applicable, and gave better results than hitherto known reagents at lower temperature in a shorter period. No epimerization occurred in the preparation of (8) [mp 113-116°C,  $[\alpha]_D +69.8^\circ$  (c 1.0,  $\text{CHCl}_3$ )], though only 3-epimer of 8 was obtained in 23% yield by the oxidation with  $\text{CrO}_3$ -pyridine.<sup>11)</sup>

On the other hand, it has been known that the direct oxidation of glycosides having vicinal hydroxyl groups with  $\text{CrO}_3$ -pyridine gave a mixture of monouloses in very low yields.<sup>12)</sup> Recently, it was reported that the oxidation of methyl 4,6-O-benzylidene- $\alpha$ -D-glucopyranoside (10) with  $\text{Me}_2\text{SO}$ - $\text{P}_2\text{O}_5$ <sup>13)</sup> or  $\text{Me}_2\text{SO}$ - $\text{Ac}_2\text{O}$ <sup>14)</sup> gave the corresponding mono-3-ulose (11a)<sup>15)</sup> or its 2-O-acetate in 11% and 24% yields, respectively, but not the corresponding 2,3-diulose (12a).

In our experiments, oxidation of 10 with  $\text{Me}_2\text{SO}$ -TFAA and the subsequent reaction of the crude product with phenylhydrazine and 1,2-diaminobenzene gave the bis(phenylhydrazone) (12b)<sup>15)</sup> and the quinoxaline derivative (13a)<sup>16)</sup> of 12a<sup>17)</sup> in 25% and 30% yields, respectively. Similar reactions of the  $\beta$ -anomer of 10 gave also the corresponding (12c) [mp 173-177°C,  $[\alpha]_D +286^\circ$  (c 1.2,  $\text{CHCl}_3$ ), NMR( $\delta$ ): 12.51 and 10.03 (2xNH), 7.64-6.71 (m, 3xPh), 5.77 (=CHPh), 5.30 ( $\text{H}_4$ ;  $J_{4,5}=9.0$ ), 5.25 ( $\text{H}_1$ : s), 4.46 ( $\text{H}_{6e}$ ; q,  $J_{6e,5}=4.0$ ), 3.85 ( $\text{H}_{6a}$ ; t,  $J_{6a,5}=10.0$ ), 3.47 (OMe)] and (13b) [mp 186-188°C,  $[\alpha]_D -158^\circ$  (c 0.74,  $\text{CHCl}_3$ ), NMR: 8.3-7.3 (2xPh), 5.90 (CHPh), 5.86 ( $\text{H}_1$ ; s), 5.26 ( $\text{H}_4$ ; d,  $J_{4,5}=8.0$ ,  $J_{4,6e}=2.0$ ), 4.66-4.42 ( $\text{H}_{6e}$ ; m), 4.12 ( $\text{H}_{6a}$ ; t,  $J_{6a,6e}=J_{6a,5}=9.5$ ), ca. 4.10 ( $\text{H}_5$ ; m), 3.68 (OMe)] in 20% and 25% yields, respectively. In order to disclose the intermediates for the formation of



- |      |   |   |                               |
|------|---|---|-------------------------------|
| (10) | (11a) $\text{R}^1=\text{H}$ , $\text{R}^2=\text{OMe}$ , $\text{X}=\text{O}$     | (12a) $\text{X}=\text{O}$ , $\text{R}^1=\text{H}$ , $\text{R}^2=\text{OMe}$     | (13a) $\text{R}^1=\text{H}$   |
|      | (11b) $\text{R}^1=\text{OMe}$ , $\text{R}^2=\text{H}$ , $\text{X}=\text{O}$     | (12b) $\text{X}=\text{NNHPh}$ , $\text{R}^1=\text{H}$ , $\text{R}^2=\text{OMe}$ | $\text{R}^2=\text{OMe}$       |
|      | (11c) $\text{R}^1=\text{H}$ , $\text{R}^2=\text{OMe}$ , $\text{X}=\text{NNHPh}$ | (12c) $\text{X}=\text{NNHPh}$ , $\text{R}^1=\text{OMe}$ , $\text{R}^2=\text{H}$ | (13b) $\text{R}^1=\text{OMe}$ |
|      | (11d) $\text{R}^1=\text{OMe}$ , $\text{R}^2=\text{H}$ , $\text{X}=\text{NNHPh}$ |   |                               |

these diulose derivatives, the crude oxidation-products which showed three main spots on tlc were separated by a silicagel column chromatography to give the 3-monouloses (11a<sup>13,15</sup>) and 11b) [11b; mp 195-198°C,  $[\alpha]_D -52^\circ$  (c 0.7, acetone)] in 20% and 15% yields, respectively, which were further characterized as the phenylhydrazones (11c<sup>15</sup>) and 11d) [11d; mp 173-175°C,  $[\alpha]_D + 5^\circ$  (c 0.4, CHCl<sub>3</sub>), NMR( $\delta$ ): 4.57 (H<sub>4</sub>; d, J<sub>4,5</sub> = 9.0), 4.30 (H<sub>1</sub>; d, J<sub>1,2</sub> = 7.0). 3.77 (H<sub>2</sub>; d)]. Condensation of pure 11a and 11b with 1,2-diaminobenzene gave quantitatively 13a and 13b respectively, but only 11c and 11d, instead of 12b and 12c, could be obtained in the reaction with phenylhydrazine under various conditions. The former result indicates that the Amadori-type rearrangement occurs in the intermediary step, and that the formation of 13a and 13b does not always imply the presence of 2,3-diuloses in the reaction mixture. While, the latter fact does not exclude the presence of 2,3-diuloses in the crude oxidation-products, because a similar failure of the formation of 12b from 11c was also reported.<sup>16)</sup>

Therefore, factors to control the reproducible formation of 12b and 12c in our experiments will remain ambiguous.

Analytical values of all compounds described here were satisfactory.

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