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Dimethyl Sulfoxide Oxidation of Inositol Derivatives

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Abstract

Dimethyl sultoxide oxidation was applied to inositol derivatives. 1, 3, 4, 5, 6-Pentaacetyl-epi-inositol was oxidized to epi-inosose-2 pentaacetate with dimethyl sulfoxide and phosphorus pentoxide, but aromatized to 1, 2, 3, 5-tetraacetoxy benzene when a mixture of dimethyl sulfoxide and acetic anhydride was used.

Dimethyl sulfoxide has been used as an oxidizing agent since 1957. Kornblum et al. 1 reported first about dimethyl sulfoxide oxidation. They found that some of the bromides, for example phenacyl bromide, could be oxidized to carbonyl compounds by dissolving the halide in dimethyl sulfoxide. Recently, a precise review about dimethyl sulfoxide oxidation appeared 2 and it covers literatures until May 1966. After that time, various kinds of compounds, such as α- and β-naphthol 3, 4-3β-sterols 4, were oxidized also by dimethyl sulfoxide. F. W. Sweat and W. W. Epstein 5 oxidized tritium labeled cholestanol to investigate oxidation mechanism. This oxidation is considered to be valuable since it requires rather mild conditions and gives high yields in most cases.

Many discussions were made about dimethyl sulfoxide (DMSO) oxidation mechanism, and most of the DMSO oxidations are considered to involve a dimethylalkoxysulfonium salt intermediate which subsequently reacts with a base to give the carbonyl product and dimethyl sulfide (DMS). There are two routes by which a substrate may be converted into the dimethylalkoxysulfonium salt intermediate, and the route is determined by the structure of the substrate. These two routes are illustrated in general fashion below.

Pathway A

\[(\text{CH}_3)_2\text{S}=\text{O} + \text{E} \rightarrow (\text{CH}_3)_2\text{S}^\ominus -\text{O} - \text{E}' + \text{R-CH-R}\]

Pathway B

\[(\text{CH}_3)_2\text{S}^\ominus -\text{O} - \text{CH} \rightarrow \text{CH}_3\text{S}^\ominus -\text{CH}_3 + \text{C}=\text{O} + \text{R}\]

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The first pathway involves reaction of DMSO with an intermediate “activating” electrophilic species, E (or E’; for example, E is CH$_3$CO-O-COCH$_3$ and E’ is –COCH$_3$), which is subsequently displaced by the substrate to be oxidized, usually an alcohol, to form dimethylalkoxysulfonium salt intermediate. The second pathway involves a leaving group X (X=Cl, Br, I or sulfonate) being displaced by DMSO acting as a nucleophile and resulting directly in the dimethylalkoxysulfonium salt.

The method of oxidation to use a solution of dicyclohexylcarbodiimide (DCC) in DMSO with phosphoric acid or pyridinium trifluoroacetate present as a proton source which results in reaction condition near neutrality is generally referred to as the “Pfitzner-Moffatt” technique$^{6,7,8}$. The extremely mild conditions and high yields give this method great potential in carbohydrate chemistry to oxidize most free hydroxyl groups to the corresponding carbonyl compound. But some sugar derivatives, such as I, II, and III, were reported to remain resistant to oxidation by DMSO and DCC mixture perhaps because of the too much steric requirement of the oxidation intermediate$^{9}$. The mixture of DMSO and acetic anhydride is also used to oxidize primary and secondary alcohols to corresponding carbonyl compounds$^{10,11}$. This oxidation gives lower yields when applied to many unhindered primary and secondary alcohols compared with the Pfitzner-Moffatt technique. Formation of acetates$^{5,10}$ as well as increased amount of methylthiomethyl ether as a side product are also distinct disadvantages. In hindered system, however, this method appears to be superior to the DMSO-DCC method. More hindered axial alcohol groups of steroids are oxidized in higher yields than the corresponding equatorial epimers contrary to the Pfitzner-Moffatt technique$^{10}$. Phosphorus pentoxide and DMSO have been used to oxidize carbohydrate$^{12}$. There are not so many literatures about this method, but this oxidation method, like DMSO-AC$_2$O, will probably be capable of oxidizing some carbohydrates which remain inert to the Pfitzner-Moffatt technique. Phosphorus pentoxide (P$_2$O$_5$), which is an anhydride, probably acts as an E group to activate the DMSO resulting in oxidation via pathway A.

Halides$^{13,14,15}$ and tosylates$^{16,17,18}$ are also oxidized easily by DMSO, and the oxidation of these compounds is considered to proceed via pathway B.
On the other hand, oxidation of the secondary hydroxyl group of inositol to carbonyl group is important problem as it gives valuable intermediates in synthesizing aminocyclitols and other compounds. Catalytic oxidation\(^\text{[19]}\) and biological method of using *Acetobacter suboxydans*\(^\text{[20]}\) have been employed to oxidize inositol derivatives. These methods are very stereospecific; only the axial hydroxyls are attacked, and in the case of catalytic oxidation, moreover, only one axial hydroxyl group is oxidized to form monoketone, even if other axial hydroxyls are present\(^\text{[21]}\). Nitric acid is used to oxidize myo-inositol to *epi*-inosose-2\(^\text{[22]}\). This oxidation is done under a very drastic condition and cannot be applied to produce other inososes.

The author applied DMSO oxidation to inositol derivatives. 1, 3, 4, 5, 6-Pentaacetyl-*epi*-inositol (IV) has only one free hydroxyl group in an axial position, and it was found that this hydroxyl group could be changed to a carbonyl group by DMSO under very mild condition. That is, IV, which was prepared from myo-inositol by the method of Posternak\(^\text{[23]}\), was settled at room temperature in a mixture of DMSO and phosphorus pentoxide. An excess amount of DMSO was evaporated under reduced pressure and the residue was extracted with chloroform. *epi*-Inosose-2 pentaacetate was obtained from the chloroform layer in a yield of 66.5%. The yield decreased to 53.8% when the mixture was kept for ten days.

The mixture of DMSO and acetic anhydride was used also to oxidized IV. Heated at 70°C for five hours, IV changed into 1, 2, 3, 5-tetraacetoxy benzene (88.4%) perhaps as a result of aromatization occurred soon after the oxidation\(^\text{[24]}\). It was identified by comparing IR spectrum and mixed melting point determination with an authentic sample, which was synthesized from *epi*-inosose-2 pentaacetate and sodium acetate by the method of Posternak\(^\text{[22]}\). *epi*-Inosose-2 pentaacetate also changed into 1, 2, 3, 5-tetraacetoxy benzene when heated for four hours at 70°C in the mixture of DMSO and acetic anhydride (the yield was 84.2%).

Under the conditions (a) the mixture of IV, DMSO and phosphorus pentoxide was heated several hours or (b) the reaction mixture of IV, DMSO and acetic anhydride at 70°C was extracted directly with chloroform, unstable intermediate was obtained as fine needles. Stanacev et al.\(^\text{[25]}\) found that *epi*-inosose-2 pentaacetate decomposed to 2, 4, 5, 6-tetraacetoxy-cyclohexen-2-one-1. The melting point and the result of analysis of the isolated needles were coincident with reported data, but the IR spectrum was not superimposable. The attempt to synthesize this compound from *epi*-inosose-2 pentaacetate by the method of Stanacev et al. failed. T. Posternak and J. Deshusses\(^\text{[26]}\) investigated precisely about this intermediate, but the author did not make further investigation about this compound.

1, 4, 5, 6-Tetraacetyl-myo-inositol\(^\text{[27]}\) was oxidized by DMSO-acetic anhydride or DMSO-phosphorus pentoxide mixture under various conditions, but in most cases, starting material was recovered. The mother liquor reduced Fehling’s solution,
but the attempts to get some kinds of derivatives of oxidized material, for example phenyl hydrazone or oxime, unsucceeded.

**Experimental**

DMSO was distilled under reduced pressure from calcium hydride and stored over Linde molecular sieves, Type 4A. Melting points were determined in soft glass capillaries and are uncorrected.

1. **DMSO-phosphorus pentoxide oxidation at room temperature**

   One millimole (390 mg) of 1, 3, 4, 5, 6-pentaacetyl-epi-inositol was added to a mixture of dimethyl sulfoxide (3 ml) and phosphorus pentoxide (357 mg) and kept for seven days at room temperature. The excess DMSO was distilled off under reduced pressure and the residue was diluted with water and extracted several times with chloroform. The chloroform layer was washed with water until pH 5, dried over anhydrous sodium sulfate, and concentrated. Syrupy residue, dissolved in ethanol and kept in the refrigerator overnight, gave colorless crystals (250 mg, 66.5% d. Th.). Recrystallized twice from ethanol, it showed mp. 102.5–103.5°C and was identical with epi-inosose-2-pentaacetate in IR spectrum and mixed melting point determination.

   Anal. Calcd. for C_{49}H_{52}O_{5}: C 49.48%, H 5.19%
   Found: C 49.73%, H 5.64%

2. **DMSO-acetic anhydride oxidation at elevated temperature**

   a) 1, 3, 4, 5, 6-Pentaacetyl-epi-inositol (780 mg, 2 mmole) was dissolved in a mixture of DMSO (6 ml) and acetic anhydride (4 ml) and heated at 70°C for 5 hours. Reaction mixture was kept at room temperature one night, the excess DMSO and acetic anhydride were evaporated under reduced pressure, and the residue was dried in a desiccator. Addition of ethanol to the residue gave colorless crystals (539 mg) melting at 108–108.5°C (recrystallized once from ethanol). This product showed melting point depression when mixed with epi-inosose-2 pentaacetate or 1, 3, 4, 5, 6-pentaacetyl-epi-inositol, and was identified to be 1, 2, 3, 5-tetraacetoxy-benzene by IR spectrum and mixed melting point determination with the authentic sample which was synthesized from epi-inosose-2-pentaacetate by the method of Posternak. The yield of the crude product was 88.4% d. Th.

   Anal. Calcd. for C_{49}H_{52}O_{5}: C 54.19%, H 4.55%
   Found: C 53.83, 54.00%, H 4.62, 4.58%

   b) 1, 3, 4, 5, 6-Pentaacetyl-epi-inositol (390 mg) was oxidized under the same condition as a). The reaction mixture was not evaporated but extracted directly with
chloroform. The chloroform layer was concentrated and 221 mg of solid was obtained. It showed mp. 117–118.5°C after recrystallization several times from ethanol.

Analytical data:

Calcd. for C_{14}H_{16}O_9: C 51.22%, H 4.91%
Found: C 51.89%, H 5.04%

This compound was considered to be 2, 4, 5, 6-tetraacetoxy-cyclohexen-2-one-1 reported by Stanacev et al. from the melting point and the result of analysis, but the IR spectrum was not identical with reported one.

3. DMSO-phosphorus pentoxide oxidation at elevated temperature

1, 3, 4, 5, 6-Pentaacetyl-epi-inositol (390 mg, 1 mmole) was added to the mixture of DMSO (3 ml) and phosphorus pentoxide (337 mg). The mixture was heated at 100°C for three hours. epi-Inosose-2 pentaacetate was not obtained from the reaction mixture, but the compound which was given in 2b) was isolated in 13% yield.

4. Reaction of epi-inosose-2 pentaacetate with DMSO and acetic anhydride

Into a mixture of DMSO (3 ml) and acetic anhydride (2 ml), epi-inosose-2 pentaacetate (388 mg, 1 mmole) was added and heated for four hours at 70°C. The reaction mixture was evaporated under reduced pressure and the residue was crystallized from ethanol. Colorless crystals (261 mg) melting at 101–105.5°C were obtained. The melting point raised to 104.5–106°C after three recrystallizations from ethanol, and this compound was identified to be 1, 4, 5, 6-tetraacetoxy benzene by mixed melting point determination and IR spectrum. The yield of the crude product was 84.2% d. Th.

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