

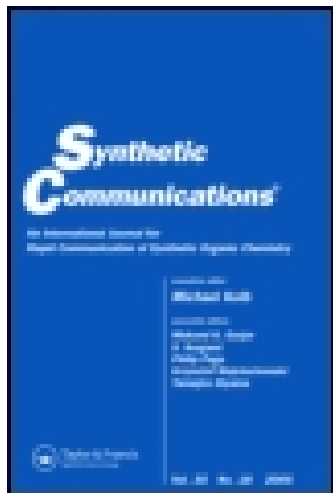
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Formation of (\pm)-1,2-O-Ethylidene-myoinositol During the Reaction Between Triethyl Orthoformate and myo-Inositol in DMSO

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**FORMATION OF (+)-1,2-O-ETHYLIDENE-*myo*-INOSITOL
DURING THE REACTION BETWEEN TRIETHYL
ORTHOFORMATE AND *myo*-INOSITOL IN DMSO**

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ABSTRACT: Besides *myo*-inositol monoorthoformate (**1**), (+)-1,2-O-ethylidene-*myo*-inositol (**2**) was obtained as another product in the reaction between triethyl orthoformate and *myo*-inositol in DMSO catalyzed by acid under N₂

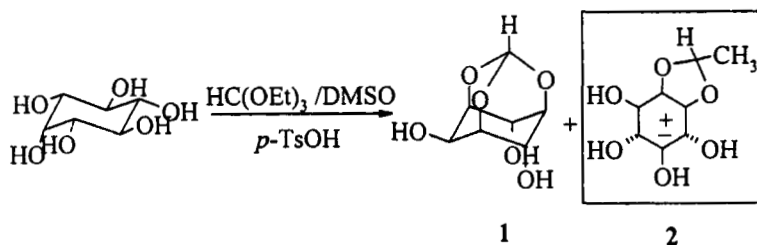
myo-Inositol derivatives, and particularly *myo*-inositol phosphates are now well recognized for their biological properties.¹⁻⁵

As biological receptors usually recognize selectively one of the possible enantiomers, the structure-activity relationships require the synthesis of optically active products. One strategy to obtain optically active inositol derivatives is the resolution of racemates through the formation of diastereomeric derivatives.⁶⁻⁸

myo-Inositol monoorthoformate was selected as the starting point for our research scheme. The synthesis of *myo*-inositol monoorthoformate (**1**) (42% yield) was based on literature.⁹ However, (+)-1,2-O-ethylidene-*myo*-inositol (**2**) was

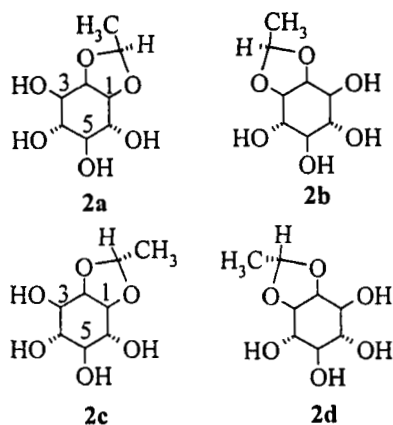
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obtained (33% yield) as another product in the reaction, which was not referred in the literature. (Scheme 1) And the same results were obtained when the reported reaction was strictly repeated three times. If *p*-toluenesulfonic acid instead of by mineral acid, such as phosphoric acid, the same result was also obtained except for the little difference of the products yielding.



Scheme 1

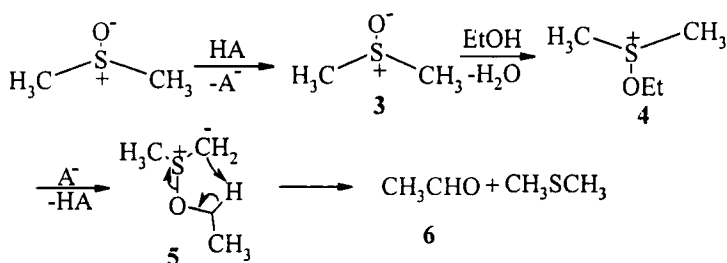
Compound 2 is a new inositol derivative, and will be useful in inositol chemistry. Since the C_2 symmetry of the *myo*-inositol molecule and the chiral carbon of the ethylidene, compound 2 was the mixtures of four isomers which could not be isolated by silica gel column chromatography. But the diastereomers(2a(2b) vs 2c(2d)) could be distinguished by NMR spectral.



It was thought that the ethylidene part of compound **2** was derivatived from the ethoxy group of triethyl orthoformate. Ethanol released when triethyl orthoformate reacted with inositol to form compound **1** was oxidized in DMSO to acetaldehyde **6** which reacted with inositol to produce compound **2**.

As we know, the use of dimethyl sulfoxide as an oxidizing agent began with the discoveries by Kornblum and co-workers.¹⁰ Later, other procedures that were soon developed utilize dimethyl sulfoxide activated by acetic anhydride,¹¹ phosphorus pentoxide,¹² sulfur trioxide/pyridine complex,¹³ chlorine,¹⁴ oxygen,¹⁵ etc. In the DMSO involved oxidation procedures, the activators are very important.

As said above, the reaction was carried out under N₂, no oxygen involved. So the oxidation procedure may be promoted by acid. And the mechanism of oxidation was considered as follows. (Scheme 2)



Scheme 2

Dimethyl sulfoxide obtains a proton from the acid to form oxysulfonium ion **3**. At the same time, the conjugate base (A⁻) of the acid was released. Then the released ethanol from triethyl orthoformate would nucleophilic attack on the positively charged sulfur atom of **3** with back-side displacement of hydroxy that forming water by abstracting a proton to give ethoxysulfonium ion **4**. The former

released conjugate base promoted removal of a proton from the methyl group of **4**, to give the sulfur stabilized ylid **5** which through a cyclic transition state, collapses to give acetaldehyde **6** and dimethyl sulfide through the intramolecular proton abstraction.

More work is in progress to check this mechanism by direct oxidation of varied alcohols in DMSO without oxygen involving catalyzed by *p*-TsOH or mineral acid. Maybe this is a new oxidation procedure, in which the activation of dimethyl sulfoxide is by acid.

EXPERIMENTAL

A solution of *myo*-inositol ($C_6H_{12}O_6 \cdot 2H_2O$) (25g, 116mmol) and triethyl orthoformate (50ml) in 500ml of dimethyl sulfoxide in the presence of *p*-toluenesulfonic acid monohydrate (*p*-TsOH $\cdot H_2O$) (2g) was heated for 24h at 100°C under N_2 . After cooling, 1g of sodium bicarbonate was added, and stirring was continued for 30min. The color of the solution changed from dark brown to purple. The reaction mixture was evaporated to dryness in vacuo, and chromatographed on silica gel column by eluting with ethyl acetate/methanol (100:1-10:1) to give *myo*-inositol monoorthoformate **1** (9.27g, 42% yield) ($R_f=0.78$, ethyl acetate/methanol=4:1(v)) and (\pm)-1,2-O-ethylidene-*myo*-inositol **2** (7.95g, 33% yield) ($R_f=0.28$, ethyl acetate/methanol=4:1(v)); m.p. 120-122°C. MS, m/e(relative intensity) 205(M^+-H , 2.02), 191(M^+-CH_3 , 28.68; Anal. Calcd. for $C_8H_{14}O_6$: C, 46.60, H, 6.80. Found: C, 46.08, H, 7.02.

2a(2b): 1H -NMR(D_2O , 300MHz) δ 1.29(3H, d, $J=5$ Hz), 3.31(1H, t, $J=9.8$ Hz),

3.59(1H, dd, J=10 Hz, 7.8 Hz), 3.65(1H, t, J=9.8 Hz), 3.89(1H, dd, J=9.8 Hz, 4.5 Hz), 4.23(1H, dd, J=7.8 Hz, 4.5 Hz), 4.34(1H, t, J=4.5 Hz), 5.45(1H, q, J=5Hz) ppm; $^{13}\text{C-NMR}$ (D_2O , 100MHz) δ 22.86($\underline{\text{C}}\text{H}_3$), 72.18(C_3), 74.30(C_6), 74.99(C_4), 75.20(C_5), 78.11(C_2), 81.98(C_1), 104.10($\underline{\text{C}}\text{H}$) ppm; the assignment used two dimensional H-C correlation.

2c(2d): $^1\text{H-NMR}$ (D_2O , 300MHz) δ 1.39(3H, d, J=4.9 Hz), 3.31(1H, t, J=9.8 Hz), 3.51(1H, dd, J=9.8 Hz, 7.8 Hz), 3.59(1H, t, J=10 Hz), 3.83(1H, dd, J=9.8 Hz, 4.0 Hz), 4.07(1H, dd, J=7.5 Hz, 5.3 Hz), 4.34(1H, t, J=4.5 Hz), 5.18(1H, q, J=4.9 Hz) ppm; $^{13}\text{C-NMR}$ (D_2O , 100M) δ 23.08($\underline{\text{C}}\text{H}_3$), 72.47(C_3), 74.74(C_4), 75.39(C_5), 78.46(C_6), 80.44(C_1), 81.13(C_2), 105.55($\underline{\text{C}}\text{H}$) ppm; the assignment used two dimensional H-C correlation.

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