Selective *p*-Toluenesulfonylation of *myo*-Inositol Derivatives

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Attempt to know the reactivities, toward sulfonylation, of the hydroxyl groups in *myo*-inositol was carried out using partially sulfonylated derivatives of *myo*-inositol. The present studies indicated that the order of reactivity of the hydroxyl groups is 1-OH and 3-OH>4-OH and 6-OH>5-OH>2-OH. From a preparative standpoint, 1,3-di-*O*-*p*-toluenesulfonyl-*myo*-inositol was readily obtained in 59% yield from 1-*O*-*p*-toluenesulfonyl-*myo*-inositol by a selective sulfonylation.

In order to know the reactivities toward sulfonylation of the hydroxyl groups in *myo*-inositol, attempts of a selective sulfonylation of *myo*-inositol derivatives were made. Little information is as yet available on the relative reactivities, toward sulfonylation, of the hydroxyl groups of cyclitols.[1] Because of its insolubility in pyridine, direct esterification of *myo*-inositol could not be conducted, and then five partially sulfonylated *myo*-inositol derivatives (1-, 1,3-, 1,4-, 1,4,5- and 1,4,6-)[2,3] were used for the present studies.

First of all, a selective *p*-toluenesulfonylation of 1-*O*-*p*-toluenesulfonyl-*myo*-inositol (**1**)[2] was attempted. Theoretically, twenty four positional isomers of *p*-toluenesulfonyl derivatives of *myo*-inositol can be obtained from **1**. However, if 2-*O*-*p*-toluenesulfonyl derivatives are excluded in view of the unreactivity of the axial hydroxyl group on C-2,[4] thirteen isomers (diesters 4, triesters 5, tetraesters 3 and pentaester 1) would be expected to be obtainable. When **1** was treated with 4 molar equiv. of *p*-toluenesulfonyl chloride (TsCl) in dry pyridine at 30°C and the progress of the reaction was followed by thin layer chromatography (tlc) using silica gel, after 4 days, at least eight components were detected in the reaction mixture. Six of the products formed could be identified by a direct comparison of *Rf* values on tlc with authentic samples. These were found to be the 1,3- (**2**), 1,3,4- (**3**), 1,3,5- (**4**), 1,3,4,5- (**5**), 1,3,4,6- (**6**) and 1,3,4,5,6-isomers (**7**) (Fig. 1).

Treatment of **1** with 1, 1.2 and 1.5 molar equiv. of TsCl in dry pyridine at 0—30°C for 6—10 days, and subsequent acetylation with acetic anhydride gave 2,4,5,6-tetra-*O*-acetyl-1,3-di-*O*-*p*-toluenesulfonyl-*myo*-inositol (**2a**) in 50, 59, and 49% yield, respectively, in a pure crystalline state by one recrystallization of the crude product from chloroform and ethanol. Accordingly, the hydroxyl group on C-3 is the most reactive among five hydroxyl groups in **1**. This result was in accordance with the fact that, in the case of 1,2-*O*-cyclohexylidene-*myo*-inositol, the C-3 hydroxyl group which is adjacent to *cis*-arranged cyclohexylidene oxygen atom is the most reactive.[3] The high reactivity at C-3 may be explained by hydrogen bonding between the C-2 and C-3 hydroxyl groups in the transition state of esterification.[1]

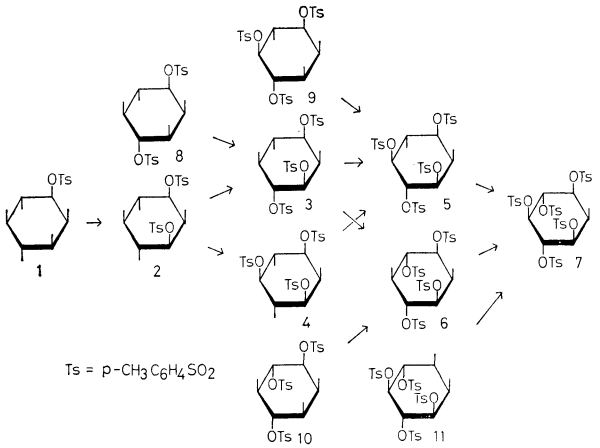

Fig. 1. Course of a selective *p*-toluenesulfonylation of *myo*-inositol[a]

a) All the compounds described in this paper are racemic. In the formulas, the vertical lines represent hydroxyl groups; the hydrogen atoms on the ring carbons are not shown.

When a sulfonylation of **1** was carried out using more than 2 molar equiv. of TsCl, a considerable amount of the tetraesters were formed. On treatment with 3, 4 and 5 molar equiv. of TsCl, **1** gave 1,3,4,6-tetra-*O*-*p*-toluenesulfonyl-*myo*-inositol (**6**) in 9, 34, and 28% yield, respectively, which was characterized by converting it into the known diacetate (**6a**).[4]

Then a selective sulfonylation of 1,3- and 1,4-di-*O*-*p*-toluenesulfonyl-*myo*-inositol (**2** and **8**)[3] was attempted. Monitoring by tlc the progress of the reaction of **2** with 2 and 4 molar equiv. of TsCl, almost the same chromatograms as those observed in the case of **1** under the similar sulfonylation condition were obtained, which indicated that the sulfonylation reaction of **1** proceeded through **2**. On the other hand, from **8**, the 1,3,4,5- and 1,3,4,6-isomers were detected to be formed, then, in view of the high reactivity of C-3 hydroxyl group, the tetraesters should be yielded from the 1,3,4-triester apparently. Therefore, the relative yields of the two tetraesters may accord with the reactivity of C-5 and C-6 hydroxyl groups. According to visual observation of a relative intensity of the 1,3,4,5- and 1,3,4,6-tetraesters on a tlc plate, hydroxyl group on C-6 seemed to be about two times more reactive than that on C-5. This fact might be explained by a steric and electronic effects exerted by an axial hydroxyl group on C-2 in a transition state of esterification.

1) D. H. Ball and F. W. Parrish, *Advan. Carbohyd. Chem.*, **23**, 233 (1968); **24**, 139 (1969).
2) S. J. Angyal, V. Bendor, and J. H. Curtin, *J. Chem. Soc. (C)*, **1966**, 798.
3) T. Suami, S. Ogawa, T. Tanaka, and T. Otake, This Bulletin, **44**, 835 (1971).
4) T. Suami, S. Ogawa, and S. Oki, *ibid.*, **44**, 2820 (1971).

In 4 molar esterification of **2** and **8**, when **8** was completely consumed to be converted into the tetraesters *via* the 1,3,4-triester, the 1,3,4- and 1,3,5-triesters, as well as **2**, were still remaining in the reaction mixture. This indicated that the reactivities of the hydroxyl groups on C-4, 5 or 6 were lower than that on C-3. Furthermore, in the case of **2**, when two triesters almost disappeared on a tlc, the relative intensities of the two spots due to two tetraesters were nearly the same as that observed in **8**. Therefore, in **2**, the hydroxyl group on C-5 was shown to be less reactive than that on C-4 (or 6), even if a theoretical treatment were taken into account. Because the 1,3,4,5-tetraester should be formed from the 1,3,5-triester solely, so that if the latter was yielded from **2** more than half of the 1,3,4-isomer, the yield of the 1,3,4,5-isomer should overwhelmed that of the 1,3,4,6-isomer. This was also understood by an influence of the axial hydroxyl group on C-2.

From the reaction of the 1,4,5- (**9**) and 1,4,6-triesters (**10**) with 4 molar equiv. of TsCl, after 24 hr at 30°C, the 1,3,4,5- and 1,3,4,6-tetraesters were obtained, respectively, in good yield, but even after 10 days, only a trace amount of the 1,3,4,5,6-pentaester was detected in the reaction mixture. On the other hand, from the reaction of the 1,4,5,6-tetraester (**11**) with 4 molar equiv. of TsCl, the 1,3,4,5,6-isomer was obtained comparatively in good yield.[4] Consequently, introduction of *p*-toluenesulfonyloxy group into a vicinal position of hydroxyl group was found to make the remaining free hydroxyl group quite unreactive.[5]

Summarizing the results described above, the reaction sequences of *p*-toluenesulfonylation of *myo*-inositol were shown in Fig. 1. The order of reactivity of six hydroxyl groups in *myo*-inositol could be deduced to be 1-OH and 3-OH>4-OH and 6-OH>5-OH>2-OH. In the case of 1,2-*O*-cyclohexylidene-*myo*-inositol,[3] considering from the relative yield of the isomers, the order of reactivity of its four hydroxyl groups is 3-OH>6-OH>4-OH>5-OH, which seems to be in good accordance with the present result.

Along with the present studies, preferential benzoylation of *myo*-inositol is now underway in our laboratory.

Experimental

Melting points were determined on a Mitamura Riken micro hot stage and are uncorrected. Infrared (IR) spectra were taken in KBr disks. Tlc was done with silica gel (Wakogel B-10, Wako Pure Chemical Industries Ltd.) using toluene-methyl ethyl ketone (4:1, 3:1, 2:1 or 1:1) or benzene-ethyl acetate (7:2, 3:1 or 1:1) as the solvent system. The compounds were detected by exposing the plates to iodine vapor or heating at 100°C after spraying 30% sulfuric acid. Identification of the compounds was accomplished mainly by mixed tlc and comparison of *Rf* value on a tlc. All solutions were concentrated by a rotary evaporator at 40—50°C under reduced pressure.

p-*Toluenesulfonylation of* 1-O-p-*toluenesulfonyl*-myo-*inositol (1).* a) 1 molar sulfonylation: To a solution of **1** (0.2 g) in dry pyridine (2 m*l*) was added TsCl (0.12 g) in one portion under ice cooling. The reaction mixture was kept at 30°C for 10 days, and then acetic anhydride (1 m*l*) was added and heated over boiling water bath for 3 hr. The mixture was poured onto ice and water and the resulting precipitates were collected by filtration. The crude product (0.42 g) was recrystallized from chloroform and ethanol to give colorless needles (0.20 g, 50%) of tetra-*O*-acetyl-1,3-di-*O*-*p*-toluenesulfonyl-*myo*-inositol (**2a**), mp 209—212°C. This compound was identified with an authentic sample[2] by mixed melting point and IR spectra.

b) 1.2 molar sulfonylation: To a solution of **1** (0.20 g) in dry pyridine (2 m*l*) was added TsCl (87 mg) at 0°C and the solution was kept at the same temperature for 24 hr. Then another portion of TsCl (47 mg) was added and the reaction mixture was allowed to stand at 0°C for 2 days. The product was acetylated and processed as described in (a) to afford crystals (0.23 g, 59%) of **2a**, mp 212—213°C.

c) 1.5 molar sulfonylation: Compound **1** (0.21 g) was sulfonylated with TsCl (0.18 g) at 30°C for 10 days and processed as described in (a) to afford crystals (0.20 g, 49%) of **2a**, mp 212—214°C.

d) 2 molar sulfonylation: Compound **1** (0.51 g) was treated with TsCl (0.59 g) in dry pyridine (5 m*l*) at 30°C for 3 days. Then the product was acetylated and processed as described in (a) to give crystals (0.30 g, 30%) of **2a**, mp 213—215°C.

e) 3 molar sulfonylation: Compound **1** (0.50 g) was treated with TsCl (0.88 g) at 30°C for 5 days. The crude product (1.2 g) was fractionated by crystallization from chloroform and ethanol: 0.11 g (the 1,3,4,6-isomer), mp 260—265°C; 0.41 g (the 1,3,4- and 1,3,4,6-isomers); 0.25 g (the 1,3,4-, 1,3,5- and 1,3,4,5-isomers).

f) 4 molar sulfonylation: Compound **1** (0.50 g) was treated with TsCl (1.2 g) in dry pyridine (5 m*l*) at 30°C for 6 days. Then the reaction mixture was poured onto ice and water, and the resulting white precipitates were collected. Recrystallization of the crude product from chloroform and ethanol gave colorless plates (0.40 g, 34%) of 1,3,4,6-tetra-*O*-*p*-toluenesulfonyl-*myo*-inositol (**6**), mp 267—269°C. From the mother liquor, the mixture of the tri- and tetraesters (0.17 g) was isolated.

g) 5 molar sulfonylation: Compound **1** (0.50 g) was treated with TsCl (1.5 g) in dry pyridine (5 m*l*) at 0—5°C for 24 hr, and then at 30°C for 24 hr. After heating at 80°C for 5 hr, the reaction mixture was poured onto ice and water to give white powder (1.1 g), which was fractionated by crystallization from chloroform and ethanol to afford colorless plates (0.33 g, 28%) of **6**, mp 265—268°C.

1,3,4-Tri-O-p-*toluenesulfonyl*-myo-*inositol (3).* A mixture of 5,6-di-*O*-acetyl-1,3,4-tri-*O*-*p*-toluenesulfonyl-*myo*-inositol[4] (0.20 g), conc. hydrochloric acid (2 m*l*) and ethanol (10 m*l*) was refluxed for 3 hr. After cooling, the resulting oily product was collected by decantation and induced to crystallization by addition of chloroform. The crystals were triturated with ethanol and collected by filtration: colorless needles (0.14 g, 80%) of **3**, mp 229—230°C. Recrystallization from ethanol gave an analytical sample, mp 230—230.5°C.

Found: C, 50.02; H, 4.64; S, 15.09%. Calcd for $C_{27}H_{30}O_{12}S_3$: C, 50.45; H, 4.71; S, 14.96%.

1,3,5-Tri-O-p-*toluenesulfonyl*-myo-*inositol (4).* A mixture of 2,4,6-tri-*O*-acetyl-1,3,5-tri-*O*-*p*-toluenesulfonyl-*myo*-inositol[4] (40 mg), conc. hydrochloric acid (10 m*l*) and ethanol (10 m*l*) was refluxed for 10 hr. After cooling, the resulting crystals were collected by filtration: colorless prisms of **4**, mp 259—263°C. IR spectrum did not show any absorption at ester carbonyl region. Tlc showed a single spot in several solvent systems and the *Rf* value was shown to be identical with that of one of the components observed in the

5) R. W. Jeanloz, A. M. C. Rapin, and S. Hakomori, *J. Org. Chem.*, **26**, 3939 (1961).

sulfonylation mixture of both **1** and **2**.

p-*Toluenesulfonylation of the 1,3- and 1,4-Diesters.* A 30 mg portion of the diester was dissolved in dry pyridine (0.3 m*l*) and TsCl (52 mg, 4 molar equiv.) was added, and the reaction mixture was allowed to stand at 30°C. The course of the reaction was monitored by tlc (solvent system: benzene-ethyl acetate=7:2 and 1:1). The chromatograms (the 1,3-diester) were found to be almost identical with those of the reaction mixture of **1** and 4 molar equiv. of TsCl in pyridine prepared under the same condition. The component, which corresponds to the 1,3,5-triester, was not observed in the sulfonylation mixture of the 1,4-diester. After 5 days, when all the 1,4-diester had been consumed to be converted into the tri- and tetraesters, the 1,3-diester was still remaining unchanged partly in the reaction mixture. The relative intensities of the tetraesters (the 1,3,4,5- and 1,3,4,6-isomers) derived from the 1,4-diester was approximately in the ratio of 1:2.

1,3,4,5-Tetra-O-p-*toluenesulfonyl*-myo-*inositol (5).* a) To a solution of 1,4,5-tri-*O-p*-toluenesulfonyl-*myo*-inositol (**9**)[3] (30 mg) in dry pyridine (0.3 m*l*) was added TsCl (38 mg, 4.3 molar equiv.) and the mixture was kept at 30°C for 21 hr. Then the solution was poured onto ice and water and the precipitates (40 mg) were collected by filtration. The crude crystals were recrystallized from methyl ethyl ketone and ethanol to give colorless needles (22 mg, 58%) of **5**, mp 253—256°C (after sintering at 246°C).

Found: C, 51.46; H, 4.61; S, 15.86%. Calcd for $C_{34}H_{36}O_{14}S_4$: C, 51.24; H, 4.56; S, 16.09%.

b) A mixture of 6-*O*-acetyl-1,3,4,5-tetra-*O-p*-toluenesulfonyl-*myo*-inositol[4] (34 mg), conc. hydrochloric acid (10 m*l*) and ethanol (10 m*l*) was refluxed for 10 hr. After cooling, the resulting crystals were collected and recrystallized from ethanol: colorless prisms of **5**, mp 247—249°C. This compound was identified with the sample obtained from **9** by comparing with IR spectra.

1,3,4,6-Tetra-O-p-*toluenesulfonyl*-myo-*inositol (6).* a) To a solution of 1,4,6-tri-*O-p*-toluenesulfonyl-*myo*-inositol (**10**)[3] (0.21 g) in dry pyridine (2 m*l*) was added TsCl (0.24 g, 3.9 molar equiv.) and the mixture was kept at 30°C for 22 hr, Then the solution was poured onto ice and water and the resulting crystals were recrystallized from 2-methoxyethanol to give colorless needles (0.25 g, 95%) of **6**, mp 269.5—270.5°C.

Found: C, 51.21; H, 4.35; S, 16.13%. Calcd for $C_{34}H_{36}O_{14}S_4$: C, 51.24; H, 4.56; S, 16.09%.

b) To a solution of 1,4-di-*O-p*-toluenesulfonyl-*myo*-inositol (**8**)[3] (0.15 g) in dry pyridine (1.5 m*l*) was added TsCl (0.29 g, 4.9 molar equiv.) and the mixture was kept at 30°C for 7 days. The reaction mixture was poured onto ice and water and the crude crystals were recrystallized two times from chloroform and ethanol to give pure crystals (0.14 g, 56%) of **6**, mp 270—272°C. This compound was identified with the sample obtained from **10** by comparing with IR spectra and mixed tlc.

2,5-Di-O-*acetyl-1,3,4,6-tetra*-O-p-*toluenesulfonyl*-myo-*inositol (6a).* Compound **6** (0.4 g) was acetylated with acetic anhydride (5 m*l*) and pyridine (5 m*l*) at room temperature overnight. The reaction mixture was poured into water and the resulting crystals were recrystallized from chloroform and ethanol to afford colorless crystals (0.39 g, 88%) of **6a**, mp 207—209°C. This compound was identified with the authentic sample by comparing with IR spectra and mixed melting point.[4]

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