[CONTRIBUTION FROM AVERY LABORATORY, THE UNIVERSITY OF NEBRASKA]

THE UTILITY OF THE METHANESULFONYL BLOCKING GROUP. A NEW SYNTHESIS OF *p*-HYDROXYPHENYLACETIC ACID[1]

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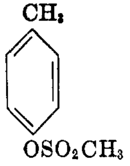
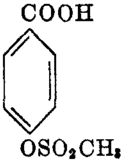
The utility of the methanesulfonyl blocking group in organic syntheses, exclusive of the sugar series, has been very little investigated. The work described in the present paper establishes the remarkable stability of the methanesulfonoxy group under conditions simultaneously strongly acidic and strongly oxidizing. The use of an acid chloride, containing the methanesulfonoxy group, in the Arndt-Eistert reaction is also described.



I



II

Inasmuch as the direct methanesulfonation of *p*-hydroxybenzoic acid in either pyridine or mild aqueous alkali does not lead to the desired esterification product, we have investigated an alternative route from *p*-cresol. *p*-Tolyl methanesulfonate (I) is available in high yield from the reaction of *p*-cresol with methanesulfonyl chloride in pyridine. Schall (1), by the use of either potassium permanganate in acetic acid or potassium dichromate in dilute sulfuric acid, obtained *p*-methanesulfonoxybenzoic acid (II) from I, characterized II with respect to melting point and analysis, but gave neither yields nor experimental details. In our hands, a method employing potassium permanganate in acetic acid gave low yields. A procedure utilizing potassium permanagnate in dilute sulfuric acid also gave rather low yields of *p*-methanesulfonoxybenzoic acid (II). Finally, a new procedure taking advantage of the acid stability of the methanesulfonoxy group (1–3) was developed. The methanesulfonic ester (I) is soluble in 88% sulfuric acid to give a faintly yellow solution, which appeared quite stable. Treatment of the acidic solution with chromium trioxide at temperatures between 80° to 100° has led to yields of II as high as 50%, although yields of the latter magnitude have not been consistently obtained. Even when the reaction temperature was permitted to reach 100–110°, II was isolated in 44% yield. Once the pure acid II was obtained, its conversion by thionyl chloride to the acid chloride III proceeded in 90% yield. Propylene chloride was found to be a superior solvent for the recrystallization of III. The melting point of *p*-methanesulfonoxybenzoyl chloride (III), 77–78°, can be contrasted with the low melting point (27–28°) of anisoyl chloride, probably the most frequently

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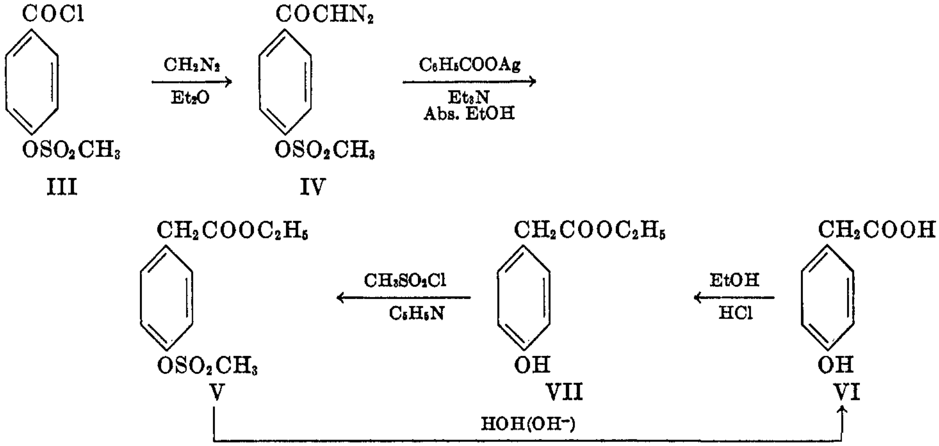
[1] The major portion of the material presented herein is abstracted from the M. S. Thesis of Donald Nixon Thatcher.

employed derivative of the unavailable *p*-hydroxybenzoyl chloride. The reactions employing III as starting material are given in Chart I.

CHART I



Reaction of III with a 200% excess of diazomethane in ethereal solution gave the very pale yellow diazoketone (IV). Attempts to convert IV directly to *p*-methanesulfonoxyphenylacetic acid using the classical conditions of Wolff (4) failed. However, use of the Newman-Beal modification (5) of the Wolff rearrangement, employing ethanol in the homogeneous catalytic medium of silver benzoate in triethylamine, gave the ester V in yields as high as 84%. An independent synthesis of V was effected from an authentic sample of *p*-hydroxyphenylacetic acid *via* methanesulfonation of the known ethyl ester VII. The methanesulfonation of VII proceeded smoothly to give the desired esterification product (V), in contrast to the complex reaction given by free *p*-hydroxybenzoic acid. The hydrolysis of V by boiling 10% sodium hydroxide removed both ethyl and methanesulfonyl blocking groups to give *p*-hydroxyphenylacetic acid (VI). The over-all yield of VI from the acid chloride III was 65%.

Although the methanesulfonoxy group is known to be hydrolyzed by sodium hydroxide (1–3), the stability of this group in other basic media apparently has not been reported. When the acid II, an ideal compound for study because of its complete solubility in all basic media employed, was subjected to the action of 5% sodium bicarbonate, 10% sodium carbonate, and 5% sodium hydroxide for 21 hours at room temperature, II was recovered in 90%, 70%, and 0% yield respectively. *p*-Hydroxybenzoic acid was isolated from the sodium hydroxide mixture in 70% yield, thus completing a synthesis of the phenolic acid from *p*-cresol. In II, the methanesulfonoxy group (in comparison to other blocking groups) appears almost unique in its combined properties of stability toward acid hydrolysis and cleavage by dilute strong base, even at room temperature.

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EXPERIMENTAL

All melting points and boiling points are uncorrected. Microanalyses performed by one of us (DNT) are denoted by (T), those performed by the Clark Microanalytical Laboratory by (Clark).

p-Tolyl methanesulfonate (I).[2] To 54 g. of *p*-cresol (colorless; freshly distilled *in vacuo*) in 200 ml. of reagent pyridine was added, at 0°, 100 g. of methanesulfonyl chloride. After 16 hours the crude ester was isolated by addition of 10 volumes of water containing sufficient hydrochloric acid to neutralize the pyridine. The precipitate was collected, washed well with water and air-dried; yield, 89 g. (93%), m.p. 34–39°. One recrystallization from the minimal quantity of methanol gave 71 g. of ester, m.p. 41–43°, sufficiently pure for oxidation. Repeated crystallization from ethanol gave pure ester, m.p. 43–44° [lit. m.p. (1), 44.5–46°].

p-Methanesulfonoxybenzoic acid (II). Three procedures were studied:

(*A*). *Potassium permanganate in acetic acid.* To 18.6 g. of *p*-tolyl methanesulfonate in 200 ml. of glacial acetic acid was added in small portions a potassium permanganate solution (20 g. in 50 ml. of water). Heating under reflux three hours, dilution to 600 ml. with water, and decolorization with solid sodium bisulfite gave 6.5 g. (30%) of crude acid. Repeated crystallization from ethanol-water gave pure acid, m.p. 223–224° [lit. m.p. (1), 224°].

(*B*). *Potassium permanganate in dilute sulfuric acid.* *p*-Tolyl methanesulfonate (4.7 g.) was suspended in 100 ml. of 10% sulfuric acid. Solid potassium permanganate (5 g.) was added in small portions with vigorous stirring. Heating under reflux for one hour, filtration of the separated product from the hot mixture, and lixiviation with 5% sodium bicarbonate gave upon acidification 1.9 g. (35%) of acid, m.p. 210–216°. The product was not studied further.

(*C*). *Chromium trioxide in 88% sulfuric acid.* *p*-Tolyl methanesulfonate (9.3 g.), m.p. 41–43°, was dissolved completely in 80 ml. of 88% sulfuric acid by vigorous stirring. To the pale yellow mixture was added, dropwise, with vigorous stirring, a solution of 10 g. of chromic acid in 40 ml. of water over a 15 minute interval. The temperature of the mixture rose rapidly to 100°, remained there during most of the chromic acid addition, then slowly rose to 110°. The reaction mixture was poured immediately into 1500 ml. of water and permitted to stand 48 hours. The separated solid was collected, washed well with water and air-dried; yield 9.6 g. (90%, calc'd as acid). The crude product was suspended in 300 ml. of 2.5% sodium bicarbonate, and the mixture was covered with 80 ml. of ethyl acetate with vigorous stirring. The ethyl acetate removed considerable tar and facilitated solution of the acid in the sodium bicarbonate. After phase separation, the ethyl acetate layer was extracted with additional 5% sodium bicarbonate, and the bicarbonate extract was combined with the 2.5% bicarbonate extract previously obtained. The combined bicarbonate extracts were acidified to Congo Red paper with conc'd hydrochloric acid, the mixture cooled in ice, and the separated crude acid was removed by filtration (filtrate F retained), and air-dried; yield, 4.3 g. The filtrate F was extracted exhaustively with ethyl acetate (total volume 1 liter) to give an additional 0.4 g. of acid, total yield 4.7 g. (44%), melting 204–214°. Three recrystallizations from ethanol-water, or from ethyl acetate, gave the pure acid, m.p. 223.5–224° [lit. m.p. (1), 224°]. In a separate run, a 1.17 g. quantity of a somewhat purer crude product, m.p. 214–221°, was obtained, which upon recrystallization from the minimal quantity of ethyl acetate gave 0.90 g. of substantially pure acid, m.p. 222–224°.

Reaction and isolation conditions are critical. Employment of the general conditions outlined above at 50° and 70° gave 14% and 24% yields respectively. Use of 60% of the theoretical quantity of chromium trioxide at 100° gave a 6% yield, and use of conditions maintaining sulfuric acid concentration at 84–88% at a temperature of 60–80° gave only traces of acid.

p-Methanesulfonoxybenzoyl chloride (III). Pure *p*-methanesulfonoxybenzoic acid (5.4 g.)

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[2] This ester also has been prepared, in unstated yield, by the methylation of a salt-like product obtained from the reaction of sulfur dioxide with sodium *p*-cresoxide (1).

was heated under reflux with excess thionyl chloride (Eastman Kodak white label; total volume 30 ml.) until all of the acid dissolved. The clear solution was then heated an additional 30 minutes under reflux, and the excess thionyl chloride was removed by distillation under reduced pressure. The residual solid product obtained was recrystallized three times from propylene chloride to give the acid chloride in beautiful colorless needles, m.p. 77–78°; yield of once recrystallized product, 5.3 g. (90%).

Anal. Calc'd for $C_8H_7ClO_4S$: Cl, 15.1. Found: Cl, 14.5 (Clark).

p-Methanesulfonoxy-ω-diazoacetophenone (IV). *p*-Methanesulfonoxybenzoyl chloride (1 g.) was suspended in 10 ml. of dry ether, and the ethereal solution added to a cold (0°) solution of diazomethane prepared from 5 g. of nitrosomethylurea (*ca.* 200% excess of diazomethane). Immediate evolution of nitrogen commenced. After refrigeration overnight, the separated crystalline diazoketone was collected by filtration (two crops), yield 0.98 g. (96%). Three recrystallizations from propylene chloride-Barnsdall solvent (petroleum naphtha, b.p. 90–95°) gave analytically pure *p*-methanesulfonoxy-ω-diazoacetophenone in very pale yellow plates, m.p. 100.5–101.5°.

Anal. Calc'd for $C_9H_8N_2O_4S$: N, 11.66. Found (T): N, 11.94.

Ethyl p-methanesulfonoxyphenylacetate (V). (*A*). *From ethyl p-hydroxyphenylacetate. p*-Hydroxyphenylacetic acid (5 g.) was esterified with 100 ml. of absolute ethanol and dry hydrogen chloride to give ethyl *p*-hydroxyphenylacetate (VIII), b.p.$_{732}$ 300° [lit. b.p.$_{761}$ (corr., 6), 314°].

Ethyl *p*-hydroxyphenylacetate (2 ml.) was methanesulfonated by dissolving in 10 ml. of reagent pyridine, cooling strongly in ice, and adding 2 ml. of methanesulfonyl chloride. The reaction mixture was refrigerated overnight, and the crude methanesulfonate was isolated by pouring into 10 volumes of water containing enough hydrochloric acid to neutralize the pyridine. Repeated recrystallization from a large volume of boiling water gave colorless glistening plates of ethyl *p*-methanesulfonoxyphenylacetate, m.p. 91.5–92.5°.

Anal. Calc'd for $C_{11}H_{14}O_5S$: C, 50.75; H. 5.42; S, 12.41.
Found (T): C, 50.81; H, 5.43; S (Clark), 12.24.

(*B*). *From rearrangement of p-methanesulfonoxy-ω-diazoacetophenone.* The general conditions of Newman and Beal (5) were employed with 0.5 g. of crude *p*-methanesulfonoxy-ω-diazoacetophenone in 50 ml. of absolute alcohol to give 0.45 g. (84%) of ethyl *p*-methanesulfonoxyphenylacetate, m.p. 91.5–92.5°, no depression upon admixture with the analytical sample prepared by Procedure A.

p-Hydroxyphenylacetic acid (VI). Ethyl *p*-methanesulfonoxyphenylacetate (0.5 g.) was heated under reflux in 25 ml. of 10% sodium hydroxide for two hours. The reaction mixture, after cooling, was just neutralized with 10% hydrochloric acid, and extracted with 20-ml. portions of ether until the aqueous layer gave a negative ferric chloride test. Evaporation of the ether and recrystallization of the residual product from the minimal quantity of boiling water gave 0.24 g. (82%) of *p*-hydroxyphenylacetic acid, m.p. 146.5–147.5° [lit. m.p. (7), 148°], no depression upon admixture with authentic material (repeatedly recrystallized acid, initially obtained from Bios Laboratories).

Hydrolysis studies with p-methanesulfonoxybenzoic acid. Three 0.5-g. quantities of *p*-methanesulfonoxybenzoic acid (II) were dissolved in 100 ml. of 5% sodium bicarbonate, 20 ml. of 10% sodium carbonate, and 15 ml. of 5% sodium hydroxide respectively, and permitted to stand at room temperature for 21 hours. Acidification, with conc'd hydrochloric acid, of the sodium bicarbonate and sodium carbonate solutions gave instant precipitation of II in 0.45 g. and 0.35 g. yield respectively. The recovered II gave a strong positive test for sulfur with lead acetate after sodium fusion, negative ferric chloride test, was almost completely insoluble in boiling water (0.25 g. per 10 ml. of water), and after recrystallization from ethyl acetate gave m.p. 223° [lit. m.p. (1), 224°]. Acidification, with conc'd hydrochloric acid, of the sodium hydroxide solution and strong cooling in ice gave 0.22 g. (70%) of *p*-hydroxybenzoic acid, identified by its complete solubility in boiling water (0.25 g. per 10 ml. of water), negative sulfur test after sodium fusion, positive ferric chloride test, and m.p. and mixture m.p. 215° [lit. m.p. (8), 214–215°].

SUMMARY

A new synthesis of *p*-hydroxyphenylacetic acid from *p*-cresol is described. The stability of *p*-tolyl methanesulfonate (I) in 88% sulfuric acid is recorded, and the remarkable acid stability of the methanesulfonoxy group further demonstrated by the acidic oxidative conversion of I to *p*-methanesulfonoxybenzoic acid (II) at 100°. The preparation of *p*-methanesulfonoxybenzoyl chloride (III) from II is indicated, and the successful application of the Arndt-Eistert reaction to III is described. The stability of the methanesulfonoxy group of II in various alkaline media is discussed.

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REFERENCES

(1) Schall, *J. prakt. Chem.*, **48,** 241 (1893).
(2) Helferich and Papalambrous, *Ann.*, **551,** 235 (1942).
(3) Looker, *J. Org. Chem.*, **17,** 510 (1952).
(4) Wolff, *Ann.*, **394,** 23 (1912).
(5) Newman and Beal, *J. Am. Chem. Soc.*, **72,** 5161 (1950).
(6) Salkowski, *Ber.*, **22,** 2140 (1889).
(7) Salkowski and Salkowski, *Ber.*, **12,** 650 (1879).
(8) Willstätter and Mieg, *Ann.*, **408,** 77 (1915).