Synthesis of β-Disulfones from Sulfonyl Fluorides and Organometallic Compounds

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The reaction of sulfonyl fluorides with Grignard reagents to form β-disulfones has been known for many years; however, the yields were low and the intermediate steps uncertain.[2] This method now has been improved by raising the yields, extending the reaction to an organolithium compound, and clarifying the reaction conditions and steps.

The reaction of *p*-toluenesulfonyl fluoride with ethylmagnesium bromide and with *n*-butyllithium in refluxing ether for 13–15 hours produced 1,1-bis(*p*-toluenesulfonyl)ethane and 1,1-bis(*p*-toluenesulfonyl)-butane in 83% and 66% yields, respectively. The structures of the β-disulfones were verified by mixture melting points and comparison of their infrared spectra with authentic samples. In accordance with these structures, Raney nickel hydrogenolysis[3] of each β-disulfone produced only toluene.

This over-all conversion presumably involved reaction of the organometallic compound with the sulfonyl fluoride to form a monosulfone, followed by α-metallation and reaction with more sulfonyl fluoride to produce the β-disulfone. The intermediacy of the alkyl *p*-tolyl sulfone was supported by the fact that independently prepared monosulfone reacted with the organometallic compound and sulfonyl fluoride to give the β-disulfone. *n*-Butyl *p*-tolyl sulfone was metallated and carbonated to produce an acid; cleavage with lithium in methylamine yielded pentanoic acid, thereby proving that metallation occurred alpha to the sulfone group.[4]

Experimental

1,1-Bis(*p*-toluenesulfonyl)ethane.—A solution of 8.7 g. (0.050 mole) of *p*-toluenesulfonyl fluoride[5] in ether was added dropwise to ethylmagnesium bromide prepared from 10.9 g. (0.10 mole) of ethyl bromide and 3.6 g. (0.15 mole) of magnesium in ether. After refluxing for 13–15 hr., the mixture was hydrolyzed with cold hydrochloric acid and the ether layer separated, washed with water, and dried. Evaporation of ether yielded 7 g. (83%) of product, m.p. 107–109° (from ethanol).[6]

Anal. Calcd. for $C_{16}H_{18}O_4S_2$: C, 56.80; H, 5.32; S, 18.93. Found: C, 56.97; H, 5.43; S, 18.64.

1,1-Bis-(*p*-toluenesulfonyl)butane.—The previous procedure was used with 0.1 mole of *n*-butyllithium (Foote Mineral Co., 15% solution in hexane) and 8.7 g. (0.05 mole) of *p*-toluenesulfonyl fluoride. The yield was 6 g. (66%), m.p. 102–104° (from ethanol).

Anal. Calcd. for $C_{18}H_{22}O_4S_2$: C, 59.01; H, 6.01; S, 17.49. Found: C, 59.29; H, 6.13; S, 17.72.

Metallation and Reactions of *n*-Butyl *p*-Tolyl Sulfone. A. Reaction with *p*-Toluenesulfonyl Fluoride.—*n*-Butyllithium (30 g. of the solution, 0.07 mole) was added to 6.3 g. (0.03 mole) of *n*-butyl *p*-tolyl sulfone[7] in ether. *p*-Toluenesulfonyl fluoride (5.2 g., 0.03 mole) was added and the solution refluxed for 1 hr. The ether solution was washed with water, dried, and the ether evaporated to give 6.6 g. (60%) of white crystals, m.p. 102–104°. A mixture melting point with authentic 1,1-bis(*p*-toluenesulfonyl)-butane showed no depression and the infrared spectra were identical.

B. Carbonation.—*n*-Butyllithium (50 g. of the solution, 0.12 mole) was added to 21.2 g. (0.1 mole) of *n*-butyl *p*-tolyl sulfone in ether. The solution was carbonated with an excess of Dry Ice; the resulting viscous oil was dried in a desiccator under pressure for a month to produce 20 g. (78%) of 2-(*p*-toluenesulfonyl)pentanoic acid, m.p. 75–76°.

Anal. Calcd. for $C_{12}H_{16}O_4S$: C, 56.25; H, 6.25; S, 12.50. Found: C, 56.36; H, 6.45; S, 12.48.

Cleavage of 2-(*p*-Toluenesulfonyl)pentanoic Acid.—The acid (7 g., 0.026 mole) was dissolved in 100 ml. of methylamine; 1.11 g. (0.16 g.-atom) of lithium was placed in the thimble[8] and the reaction allowed to proceed to completion. Methanol (15 ml.) was added and the amine allowed to evaporate. Water was added; the aqueous layer was extracted with ether and then acidified with hydrochloric acid. The resulting mixture of acids was distilled to give 1.2 g. (0.01 mole) of *p*-toluenethiol and 2 g. (0.02 mole) of pentanoic acid, b.p. 183–186° (lit., b.p. 186.4°). Comparison of the vapor phase chromatogram of authentic *n*-pentanoic acid with the above verified its identity.

1,1-Bis(*p*-Toluenesulfonyl)ethane.—Acetaldehyde (6.6 g., 0.15 mole) was added dropwise to a solution of 24.8 g. (0.20 mole) of *p*-toluenethiol in 30 ml. of glacial acetic acid at 0–5°. After being stirred for 25 hr. at room temperature, the mixture was diluted with water, extracted with chloroform, dried, and the chloroform evaporated to yield 21 g. of crude 1,1-bis(*p*-tolylmercapto)ethane. To a solution of 10 g. of crude β-disulfide dissolved in 60 ml. of glacial acetic acid, 30 ml. of 30% hydrogen peroxide was added. Heating for 1 hr. was followed by pouring into water and filtering to obtain 4 g. (0.013 mole, 34% over-all based on thiol) of β-disulfone, which was crystallized from ethanol (m.p. 107°).

1,1-Bis(*p*-Toluenesulfonyl)butane.—A solution of 22.4 g. (0.18 mole) of *p*-toluenethiol, 37 ml. (30 g., 0.42 mole) of *n*-butyraldehyde, and 40 ml. of glacial acetic acid was stirred at 25° under nitrogen for 24 hr. Pouring into ice–water produced two layers which were separated. The organic layer was washed twice with saturated sodium bisulfite, once with 10% sodium hydroxide, once with water, and dried yielding 23.6 g. of crude β-disulfide. To a cold solution of 11.3 g. of this product and 41 ml. of glacial acetic acid, 31 ml. of 30% hydrogen peroxide was added slowly. After the solution had refluxed by itself for 1 hr., it was heated on a steam bath for another hour then poured into ice–water. The liquid was decanted and the solid washed with water to give 3.2 g. (0.0085 mole, 21% over-all) of the β-disulfone, m.p. 101–103°.

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(3) R. Mozingo, D. E. Wolf, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).

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(6) It was reported by E. Fromm, *Ann.*, **394**, 349 (1912), that the melting point was 156°. However, repetition of this literature preparation produced a compound (m.p. 154–155°) which by elemental analysis and n.m.r. proved to be 1,1-bis(*p*-toluenesulfonyl)propane.

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(8) The apparatus is described by W. E. Truce, D. P. Tate, and D. N. Burdge, *ibid.*, **82**, 2872 (1960).

Fluorinated Heterocyclics

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In connection with investigations in these laboratories of biologically important heterocyclic compounds, it was

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