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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(1) Deceased. August, 1962.
(2) W. Steinkopf, *J. prakt. Chem.*, **142**, 223 (1935).
(3) R. Mozingo, D. E. Wolf, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).
(4) J. Strating, "Organic Sulfur Compounds," Vol. I, N. Kharasch, ed., Pergamon Press, London, 1961, p. 150.
(5) W. Davies and J. H. Dick, *J. Chem. Soc.*, 2104 (1931).
(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.
(7) H. Gilman and N. J. Beaber, *J. Am. Chem. Soc.*, **47**, 1450 (1925).
(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

(1) Abstracted in part from the M. S. thesis of H. M. Mork.

of interest to obtain fluorinated derivatives of thiophenes and thianaphthenes. One of the simplest fluoro heterocyclics, 2-fluorothiophene, has previously been reported as obtainable, in less than 10% yields, by the reaction of thiophene with antimony pentafluoride in nitromethane as a reaction media.[2] However, simple fluorothianaphthalenes such as the 2- or 3-fluoro derivatives have, as yet, to be reported. A convenient laboratory method has now been developed in these laboratories, for the synthesis of 2-fluoro-5-methylthiophene (I), 2-fluorothiophene (II), and 2-fluorothianaphthene (III) by the exothermic reaction of gaseous perchloryl fluoride with the corresponding organolithium heterocyclic compounds in anhydrous ether as a reaction solvent. This simple procedure gives 44, 49, and 70% yields of these fluoro heterocyclics, respectively. Vapor phase chromatography, infrared spectra, nuclear magnetic resonance, and elemental analysis of these products supports the structures of these fluoro compounds.

The application of this fluorination procedure with perchloryl fluoride, in these laboratories, to the lithium derivatives of arene hydrocarbons, such as phenyllithium and 1-naphthylithium, yielded negligible amounts of the corresponding fluoro derivatives.

The difluorination of diethyl malonate, 2,4-pentadione, and ethyl acetoacetate with perchloryl fluoride in strong base media has been reported[3] as well as the fluorination of the sodium salts of nitro compounds in metal methoxide–methanol solutions with perchloryl fluoride[4]. These findings and those reported here give some indication as to the mechanism of this fluorination reaction. With lithium derivatives of thiophene and thianaphthene the electronegativity of the sulfur atom delocalizes the carbon ion charge yielding a stable anionic system, which may react effectively with the slightly polar chlorine–fluorine bond in the perchloryl fluoride, displacing the chlorate ion. Thus, the more stable an anion is the more it should yield a fluorinated product. Evidence for this is found in the reaction of diethyl malonate in excess ethoxide with perchloryl fluoride to give an almost quantitative yield of diethyl α,α-difluoromalonate.[3] Phenyl and 1-naphthylithium–carbon bonds are more covalent with less delocalization of the anionic charge, and apparently these less stable anionic species are unable to activate the chlorine–fluorine bond of perchloryl fluoride in the displacement step. To the limited extent that reaction occurs, less discrimination, in favor of the fluorine, is achieved in the displacement step. Experimental evidence for this was found in this study by the observation that some perchlorylbenzene results from the reaction of phenylithium and perchloryl fluoride.

Experimental

2-Fluoro-5-methylthiophene—An *n*-butyllithium–ether solution, 1.5 moles of alkyl lithium dissolved in 500 ml. of anhydrous ether, was prepared according to the method of Gilman.[5]

A 98.0-g. (1.0 mole) quantity of 2-methylthiophene dissolved in an equal volume of anhydrous ether was added dropwise during 1 hr. to the alkyl lithium ether solution kept at 0–5° by immersion in an ice bath. If a gradual color change from purple to green, indicating the formation of the 5-methyl-2-thienyllithium, did not appear in the reaction mixture, the flask was evacuated to remove butane forcing the metallation equilibrium reaction to completion. The resultant organolithium–ether solution was stirred under nitrogen for an hour at 0–5°. Gaseous perchloryl fluoride was bubbled, at a moderate rate, through this solution at 0°. When the highly exothermic fluorination reaction had increased the reaction temperature to 30°, the addition of fluorination reagent was stopped, the reaction solution was cooled, and further addition of perchloryl fluoride was continued. A constant reaction temperature and the disappearance of an intense blue fluorescence indicated the completion of the reaction. During the period of reaction (2 hr.) the reaction mixture darkened considerably and a white solid precipitated. At the completion of the reaction nitrogen was passed through the mixture for an hour to remove excess perchloryl fluoride. The mixture was then poured into a saturated sodium carbonate solution and the ethereal layer was separated. It was washed with an additional amount of carbonate solution, once with water, and dried over anhydrous magnesium sulfate. The ether was removed and the residue distilled, the fraction boiling from 102–112° at atmospheric pressure being collected (74 g.). Vapor phase chromatography analysis using a 30% silicone column showed the distillate contained 69.1% of 2-fluoro-5-methylthiophene, 9.9% of 2-methylthiophene, and unidentifiable side products, accounting for over-all yield of 51.9 g. (44%) of 2-fluoro-5-methylthiphene. A sample of the major product was isolated for analysis, infrared and n.m.r. spectra by preparative gas chromatography utilizing a 30% silicone on 40-mesh Chromasorb column (108 × 0.75 in.) in a Perkin-Elmer Model 154 vapor fractometer. Infrared analysis by comparison of 2-fluoro-5-methyl and 2-fluorothiophenes gave a C–F peak at 7.6 μ, and n.m.r. gave the correct ratio of methyl to ring hydrogens (3:2) and showed additional splitting from the fluorine atom.

Anal. Calcd. for C_5H_5SF: C, 51.70; H, 4.34; F, 16.36; S, 27.60. Found: C, 51.99; H, 4.58; F, 16.34; S, 27.55. Strong infrared peaks at 3.5, 4.7, 6.5, 6.6, 6.9, 7.6, 8.2, 8.3, 8.4, 9.8, and 11.9 mμ.

2-Fluorothiophene—An 84-g. (1 mole) quantity of thiophene was added to 500 ml. of the butyllithium–ether solution as previously described. Distillation, after perchloryl fluoride addition and the usual product isolation from the reaction mixture, gave 62.5 g. of a colorless liquid boiling in the range 80–90° (760 mm.), which contained 87.4% of 2-fluorothiophene and 12.3% of thiophene, thus giving an over-all yield of 54.6 g., 48.8% of fluorinated product. A sample for analysis and infrared was isolated by preparative gas chromatography in the manner previously described.

Anal. Calcd. for C_4H_3SF: C, 47.04; H, 2.96; F, 18.60. Found: C, 47.23; H, 3.16; F, 18.23. $n^{20}D$ 1.4896.

2-Fluorothianaphthene.—To a solution cooled in an ice bath and containing 0.3 mole of butyllithium in 100 ml. of anhydrous ether was added 26.8 g. (0.2 mole) of thianaphthene dissolved in 50 ml. of ether followed by the addition of gaseous perchloryl fluoride. When the blue fluorescence had subsided, addition of the fluorinating agent was stopped. The reaction slurry was treated with a carbonate solution and washed with water. The ethereal layer was separated, dried, and the ether removed. Distillation of the residue gave a liquid product (21.3 g., 70%) boiling at 93–94° (25 mm.), $n^{27}D$ 1.5910, m.p. 20–20.5°. A sample for analysis, n.m.r. and infrared spectra was isolated by preparative gas chromatography. Nuclear magnetic resonance spectra showed the correct ratio of thiophene to benzene hydrogens (1:4).

Anal. Calcd. for C_8H_5SF: C, 63.16; H, 3.29; S, 21.05; F, 12.50. Found: C, 63.19; H, 3.51; S, 21.20; F, 12.67.

2-Fluoro-3-bromothianaphthene.—A solution of 14.9 g. (0.93 mole) of bromine in 14.0 ml. of anhydrous chloroform was added dropwise, at 25°, during a half-hour to a solution containing 14.3 g. (0.093 mole) of 2-fluorothianaphthene and 14.5 g. (0.17 mole) of anhydrous sodium acetate dissolved in 65 ml. of anhydrous chloroform. The orange-colored reaction solution was stirred an additional hour and 50 ml. of water was added to dissolve the inorganic material. The organic layer was separated, washed successively with 100 ml. of water, 50 ml. of 5% aqueous sodium hydroxide, 100 ml. of water, 100 ml. of a saturated sodium chloride solution, and finally with 100 ml. of water. The organic extract was dried over anhydrous magnesium sulfate, filtered, and the solvent was removed on a steam bath, and the residue was distilled using a 6-in. Vigreux column to obtain 11.0 g. (0.0475 mole, 51.5%) of a pale yellow oil boiling at 76–78° (1 mm.), m.p. 21–21.5°.

(2) R. T. Van Vleck, *J. Am. Chem. Soc.*, **71**, 3286 (1949).

(3) C. E. Inman, R. E. Osterling, and R. E. Tyczkowski, *ibid.*, **80**, 6533 (1958).

(4) H. Schecter and E. B. Roberson, Jr., *J. Org. Chem.*, **25**, 175 (1960).

(5) H. Gilman, *Org. Reactions*, **8**, 285 1954.

Anal. Calcd. for C_8H_4SFBr: C, 41.56; H, 1.73; S, 13.85; F, 8.23; Br, 34.63. Found: C, 41.65; H, 1.86; S, 13.78; F, 8.23, 8.26; Br, 34.27, 34.35.

2-Fluoro-3-thianaphthenecarboxylic Acid—To 1.47 g. (0.023 mole) of *n*-butyllithium dissolved in 3 ml. of anhydrous ether was added, under a nitrogen atmosphere at −70°, a solution of 5.34 g. (0.023 mole) of 3-bromo-2-fluorothianaphthene dissolved in 5.0 ml. of anhydrous ether during 5 min. The reaction mixture was then poured rapidly over a Dry Ice–ether slurry and allowed to warm to room temperature. The ether solution was extracted with 25 ml. of water followed by two 50-ml. portions of a 5% aqueous sodium hydroxide solution. The aqueous extracts were combined, boiled to remove the ether, cooled, and acidified with concentrated hydrochloric acid. The white precipitate which formed on acidification was recovered by filtration and washed with water. It was crystallized three times from a minimum of 95% ethanol to afford 2.5 g. (0.0127 mole; 55%) of fine white needles which had a melting point of 188–188.5°.

Anal. Calcd. for $C_9H_5O_2SF$: C, 55.10; H, 2.55; S, 16.33; F, 9.69. Found: C, 54.94; H, 2.60; S, 16.49; F, 9.48, 9.46.

Perchlorylbenzene—A solution of phenyllithium, 0.1 mole, in 50 ml. of anhydrous ether was prepared according to Gilman's[6] procedure and treated with perchloryl fluoride in the manner already described. Product isolation, by procedures discussed before and vacuum distillation of the crude product gave 1.8 g. (0.011 mole, 11.0%) of perchlorylbenzene, b.p. 78–79° (2 mm.) as identified by infrared spectra.[7]

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(6) H. Gilman, *Org. Reactions*, **8**, 286 1954.

(7) C. E. Inman, R. E. Oesterling, and E. A. Tyczkowski, *J. Am. Chem. Soc.*, **80**, 5286 (1958).

The 6-Deoxytetracyclines.[1] VI. A Photochemical Transformation

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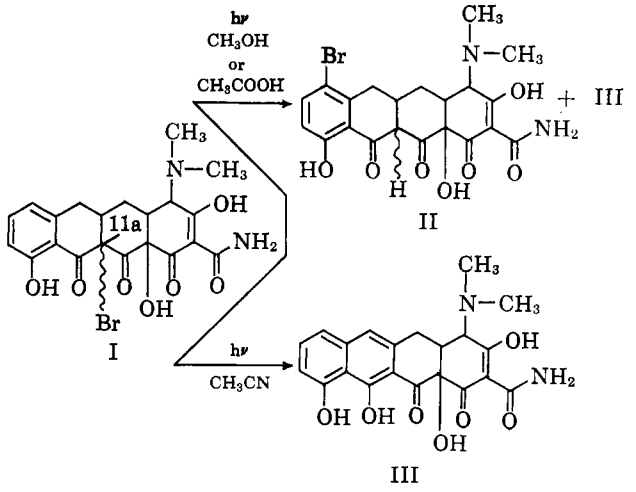
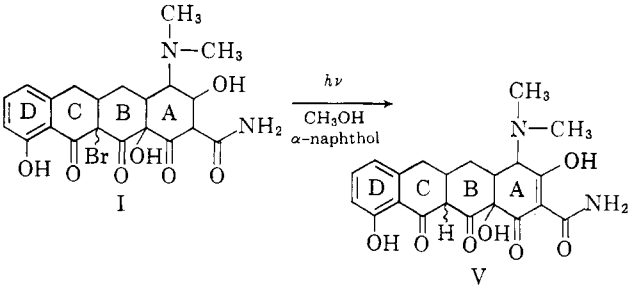
We have found that photolysis of 11a-bromo-6-demethyl-6-deoxytetracycline[2] (I) in either methanol or glacial acetic acid yields primarily 7-bromo-6-demethyl-6-deoxytetracycline[3] (II) and, as a minor component, 6-demethylanhydrotetracycline[4] (III). The remarkable selectivity of this photorearrangement indicated, at first, an intramolecular mechanism. In order to elucidate the reaction path, the bromo compound, I, was irradiated in the presence of α-naphthol. Under these conditions very little (<10%) brominated tetracycline (II) was obtained, the major product being 6-demethyl-6-deoxytetracycline[5] (V). The isolation of V establishes the intermolecular pathway of the reaction, the α-naphthol acting as a scavenger for the bromine atom produced during irradiation.





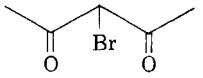
When the photolysis was run in acetonitrile, there was no aromatic bromination only dehydrohalogenation *via* 5a,11a to give 6-demethylanhydrotetracycline[4a,b] (III). Similarly the small amount of anhydro material[4a] (III) obtained from methanol or acetic acid is due to this (competing) dehydrohalogenation *via* 5a,11a.

Whatever the initial excited state(s) of the α-bromodicarbonyl system, there is probably an eventual formation of a substituted hypobromite (CH_3OBr when methanol is the solvent or CH_3COOBr when acetic acid is the solvent) which acts as a selective electrophilic brominating agent[6] to yield the 7-halo product, II. This intermediate hypobromite may result from either nucleophilic attack of the solvent (in the case of methanol or acetic acid) on a photoactivated carbon–halogen bond (Ia) to give the substituted hypobromite, Ib, as shown in Chart I, or from a stepwise process initiated by light-induced elimination of hydrogen bromide which in turn participates in the reaction sequence given in Chart II.

The report[7] that bromine in methanol does participate in an equilibrium with the formation of methyl

(1) For the previous paper in this series, see J. J. Hlavka, H. Krazinski, and J. H. Boothe, *J. Org. Chem.*, **27**, 3674 (1962).

(2) J. J. Hlavka, A. Schneller, H. Krazinski, and J. H. Boothe, *J. Am. Chem. Soc.*, **84**, 1426 (1962).

(3) This photo rearranged product (II) still contains bromine but no longer has the bromo system  as evidenced by the lack of a positive starch iodide test and the absence of the isolated carbonyl (at carbon 12) stretching at 1739 cm.$^{-1}$ in the infrared. In addition this material was compared by infrared, ultraviolet, and paper strip chromatography in four different systems to authentic material.[2] It was identical in all cases.

(4) (a) An authentic sample of this material was prepared by treating [see J. Webb, R. Broschard, D. Cosulich, W. Stein, and C. Wolf, *ibid.*, **79**, 4563 (1957)] 6-demethyltetracycline with concentrated hydrochloric acid. This authentic sample was identical to the photo-product (III) in all respects, *i.e.*, ultraviolet, infrared, and paper strip chromatography in different solvent systems. (b) This type of dehydrohalogenation was reported by D. Kevill and N. Cromwell, *J. Am. Chem. Soc.*, **83**, 3812 (1961). They found that α-halo ketones undergo facile elimination reactions in acetonitrile using a variety of catalysts.

(5) (a) J. R. D. McCormick, E. R. Jensen, P. A. Miller, and A. P. Doerschuk, *ibid.*, **82**, 3381 (1961); (b) C. R. Stephens, *et al.*, *ibid.*, **80**, 5324 (1958).

(6) We have found previously (see ref. 2) that electrophilic halogenation in concentrated sulfuric acid gave exclusively the 7-halo isomer.

(7) R. Meinel, *Ann.*, **510**, 129 (1934); **516**, 237 (1935).