Synthesis of *N*-Methoxybenzisothiazole Derivatives

Louis A. Levy

National Institute of Environmental Health Sciences,
National Institutes of Health, Public Health Service and Department of Health, Education and Welfare
Research Triangle Park, North Carolina 27709

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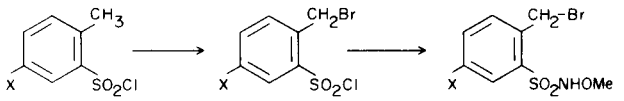
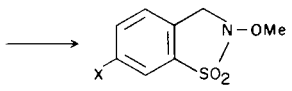
We have been investigating synthetic routes to benzisothiazolines as part of a general program to study the chemistry of saccharin, a derivative of this heterocyclic nucleus, and its possible metabolites. Of special interest is the preparation of *N*-oxygenated derivatives of this heterocyclic system. Toward this goal we have synthesized the cyclic sulfonhydroxamic derivatives IVa and IVb. Although aliphatic sulfonhydroxamic acids are well known (1) the cyclic analogs do not seem to have been described. Our approach (as illustrated below) to the synthesis of these compounds involved formation of the heterocyclic ring, as the last step, from an appropriately *ortho* substituted benzenesulfonhydroxamic acid.



Ia, X = H
b, X = Cl

IIa, X = H
b, X = Cl

IIIa, X = H
b, X = Cl



IVa, X = H
b, X = Cl

The starting toluenesulfonylchloride was available commercially as a mixture of *ortho* and *para* isomers which could be separated efficiently by distillation. The chloro substituted derivative was obtained by chlorosulfonation of *p*-chlorotoluene. This reaction produced the expected mixture of isomers with the chlorosulfonyl group *ortho* and *meta* to the methyl group. As in the case with the mixture of toluenesulfonyl chlorides this mixture was also separated by careful distillation. In each case the isomer ratios were easily determined by comparison of the peak heights of the methyl signals in their nmr spectrum. In the mixtures containing Ia and Ib the isomers containing the *ortho* methyl and chlorosulfonyl groups exhibited the methyl proton resonances at lower field than the methyl proton resonance of the isomers containing the non-adjacent methyl and chlorosulfonyl groups. This is no doubt due to the deshielding effect of the *ortho* chlorosulfonyl group.

Conversion of the methyl group to the desired benzylic bromide was carried out with *N*-bromosuccinimide. Introduction of the oxygenated nitrogen function was effected by reaction of methoxyamine with the more reactive acid halide. The usual method of preparing sulfonhydroxamic acids is to conduct the reaction in aqueous solution (2). However, since the benzylic bromide was potentially sensitive to solvolysis under these conditions it was decided to carry out the reaction in a non-nucleophillic solvent. Conversion to the *O*-methylsulfonhydroxamic acid was effected smoothly in dimethylformamide solution. The correctness of the assigned structure is evidenced by the absorption due to the N-H function in the infrared spectra and the presence of peaks attributable to the benzylic and *O*-methyl protons in the nuclear magnetic resonance spectra. The final step of forming the carbon-nitrogen bond to create the isothiazoline system was carried out with triethylamine in dimethylformamide solution. That the formation of the benzisothiazole ring has occured is confirmed by the absence of any absorption in the infrared spectrum due to the N-H function and a satisfactory elemental analysis.

EXPERIMENTAL (3)

o-Toluenesulfonyl Chloride (Ia).

A commercial mixture (K & K) of *ortho* and *para* isomers (2:1) was carefully distilled using a 36″ spinning band column. *o*-Toluenesulfonyl chloride was obtained as the lower boiling fraction. b.p. 85° (2 mm), in 96% purity.

2-Methyl-5-chlorobenzenesulfonyl Chloride (Ib).

One hundred g. of *p*-chlorotoluene was added dropwise, with stirring, to 300 ml. of chlorosulfonic acid over a period of 1.5 hours. After the addition was complete, stirring was continued for another 1.5 hours. The clear red solution was poured carefully onto cracked ice and extracted three times with chloroform. The combined chloroform extracts were washed twice with sodium

bicarbonate, once with water, then dried and filtered. Removal of the chloroform yielded 210 g. of product as a mixture of isomers. Distillation through a 36" spinning band column yielded 97 g. of 2-methyl-5-chlorobenzenesulfonyl chloride, b.p. 116°/3.4 mm.

2-Bromomethylbenzenesulfonyl Chloride (IIa).

To a solution of 19.0 g. (0.1 mole) of *o*-toluenesulfonyl chloride in 100 ml. of carbon tetrachloride, 17.8 g. (0.1 mole) of *N*-bromosuccinimide was added. The resulting mixture was refluxed for two hours or until all the *N*-bromosuccinimide had been converted to succinimide. The mixture was then cooled, filtered and the solvent removed at reduced pressure. The yield of clear, light yellow oil was 25.7 g. The nmr spectrum indicated the crude product to be a mixture of product and starting material. However, allowing the mixture to stand at room temperature or chilling it in the refrigerator caused the product to crystallize from the mixture. Filtration of this material and washing it with petroleum ether yielded 12.7 g. of white crystals, m.p. 48-55°; nmr (dueteriochloroform); δ 4.98 (S, 2, $ArCH_2Br$), 7.37-8.38 (M, 4, aromatic protons).

2-Bromomethyl-5-chlorobenzenesulfonyl Chloride (IIb).

A solution of 61.0 g. of 2-methyl-5-chlorobenzensulfonyl chloride in 275 ml. of carbon tetrachloride was treated with 52.0 g. of *N*-bromosuccinimide. The reaction proceeded as in the above example and the workup proceeded similarly. The resulting mixture of product and starting material was cooled to -15° which resulted in the precipitation of 30.3 g. of white, slightly oily crystals, m.p. 38-45°; nmr (deuteriochloroform): δ 4.94 (S, 2, $ArCH_2$-Br), 7.37-8.32 (M, 3, aromatic protons).

α-Bromo-*N*-methoxy-*o*-toluenesulfonamide (IIIa).

Addition of 2.02 g. of triethylamine to an ice cooled solution of 0.90 g. of methoxyamine hydrochloride in 50 ml. of dimethylformamide resulted in an immediate precipitate of triethylamine hydrochloride. To this stirred mixture was added 2.78 g. of IIa. The reaction was then removed from the ice bath and allowed to stand overnight. It was then poured into 200 ml. of water and extracted three times with ether. The combined extracts were dried, filtered and the solvent removed to yield 1.8 g. of clear oil which crystallized on standing, m.p. 58-66°; nmr (deuteriochloroform): δ 3.78 (S, 3, $-OCH_3$), 5.10 (S, 2, $ArCH_2Br$), 7.31-8.37 (M, 4, aromatic protons). ir: ν max 3230(s), 2950(m), 1340(s), 1165(s).

2-Bromomethyl-5-chloro-*N*-methoxybenzensulfonamide (IIIb).

In a manner similar to the above sample, 9.10 g. of IIb was added to a solution of 4.20 g. of methoxyamine hydrochloride in 65 ml. of dimethylformamide and 6.5 g. of triethylamine. After stirring overnight, the reaction mixture was worked up as above to yield 6.0 g. of light yellow oil; nmr (deuteriochloroform): δ 3.80 (S, 3, $-OCH_3$), 5.00 (S, 2, $ArCH_2Br$), 7.15-8.11 (M, 3, aromatic protons).

2-Methoxybenzisothiazoline 1,1-Dioxide (IVa).

To a solution of 2.3 g. of IIIa in 20 ml. of dimethylformamide, 1.5 g. of triethylamine was added. Within a few minutes a precipitate of triethylamine hydrobromide appeared. The reaction mixture was stirred for a total of 14 hours. The amine salt was filtered, the resulting dimethylformamide solution poured into 75 ml. of water and extracted three times with ether. The combined extracts were dried, filtered and the ether evaporated to yield 910 mg. of light yellow oil which crystallized on standing. Nmr (deuteriochloroform): ir δ 3.90 (S, 3, $-OCH_3$), 4.60 (S, 2, $ArCH_2N$), 7.22-7.91 (M, 4, aromatic proton); ir: ν max 2940(m), 1350(s), 1170(s). An analytical sample was prepared by sublimation at 0.1 mm, m.p. 68-72°.

Anal. Calcd. for $C_8H_9NO_3S$: C, 48.24; H, 4.55; S, 16.07. Found: C, 48.15; H, 4.46; S, 15.98.

2-Methoxy-6-chlorobenzisothiazoline 1,1-Dioxide (IVb).

A solution of 3.1 g. of triethylamine and 5.9 g. of IIIb in 30 ml. of dimethylformamide were allowed to stir overnight. The precipitated amine salt was filtered off and the resulting solution poured into 200 ml. of water. Following the usual workup and evaporation of the solvent there was obtained 3.6 g. of white solid, m.p. 100-109°; nmr (deuteriochloroform): δ 3.91 (3, s, $-OCH_3$), 4.58 (2, s, $ArCH_2N$), 7.30-7.95 (3, m, aromatic protons); ir: ν max, 2940(w), 1350(s), 1170(s).

A sample for analysis was prepared by recrystallization from carbon tetrachloride, m.p. 110-112°.

Anal. Calcd. for $C_8H_8ClNO_3S$: C, 41.12; H, 3.45; S, 13.72. Found: C, 41.37; H, 3.60; S, 13.64.

REFERENCES

(1) O. Piloti, *Ber.*, 29, 1559 (1896).

(2) M. Fujimoto and Makiko Sakai, *Chem. Pharm. Bull. Japan*, 13, 248 (1965).

(3) Melting points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Infrared spectra were determined in potassium bromide on a Perkin-Elmer Model 621 spectrophotometer. Nmr spectra were determined by means of a Varian Associates T-60 instrument with an internal standard of tetramethylsilane.