Ortho lithiation of *N,N*-dimethylbenzenesulfonamide by *n*-butyllithium. Condensation with electrophilic compounds[1]

HAMAO WATANABE, RICHARD A. SCHWARZ, AND CHARLES R. HAUSER
Department of Chemistry, Duke University, Durham, North Carolina

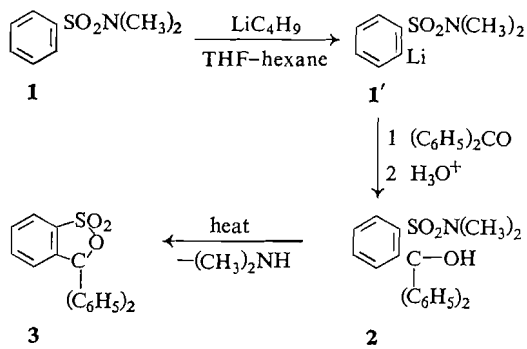
AND

J. LEWIS AND D. W. SLOCUM
Department of Chemistry, Southern Illinois University, Carbondale, Illinois

Received October 30, 1968

N,N-Dimethylbenzenesulfonamide was converted by *n*-butyllithium to the *ortho*-lithiosulfonamide, which was condensed with benzophenone, benzonitrile, phenylisocyanate, and carbon dioxide to form a carbinol, an imine, an amide, and an acid, respectively. The carbinol was cyclized thermally to give a sultone. The imine was converted to the corresponding ketone, oxime, and phenylhydrazone. The oxime underwent a Beckmann rearrangement to afford the same amide that was obtained in the reaction of the *ortho*-lithiosulfonamide with phenylisocyanate.

Canadian Journal of Chemistry, 47, 1543 (1969)



SCHEME 1

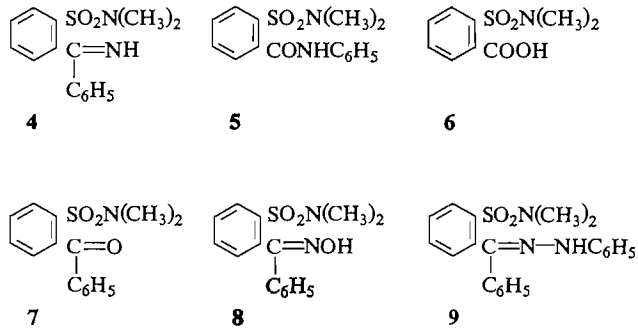
Although the carbonyl group of *N,N*-dimethylbenzamide is attacked by *n*-butyllithium leading to formation of valerophenone (1), the sulfonyl group of *N,N*-dimethylbenzenesulfonamide (**1**) should be less susceptible to attack by this reagent so that ring lithiation of **1** to form *ortho*-lithiosulfonamide **1′** appeared feasible. This was verified in the present investigation by condensation with electrophilic compounds in tetrahydrofuran (THF)–hexane to give *ortho* derivatives. Thus, **1′** underwent an addition reaction with benzophenone to afford carbinol-sulfonamide **2**, which underwent thermal cyclodeamination to produce sultone **3** (Scheme 1).

Similarly, lithiosulfonamide **1′** underwent addition reactions with benzonitrile, phenyl isocyanate, and carbon dioxide to form imine-sulfonamide **4**, carboxamide-sulfonamide **5**, and acid-sulfonamide **6**, respectively. The imine **4** was hydrolyzed to form ketone **7**, and condensed with hydroxylamine and phenylhydrazine to give oxime **8** and phenylhydrazone **9**, respectively; incidentally, the ketone **7** failed to afford oxime **8** or phenylhydrazone **9** under similar conditions.

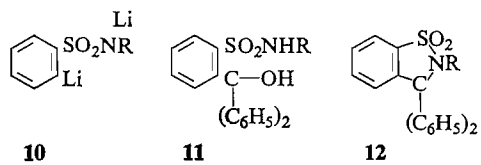
The yields of these products were good to excellent (57–93%), except that for sultone **3**. Their structures were supported by analyses and/or absorption spectra (see Experimental).

Although the yield of sultone **3** was only 30%, this is better than that (18%) obtained previously by the action of hot sulfuric acid on carbinol-sulfonamide **11** (R = C_6H_5), which was prepared by condensation of dilithiosulfonamide **10** with benzophenone (2). The more characteristic reaction of carbinol-sulfonamides of type **11** involves

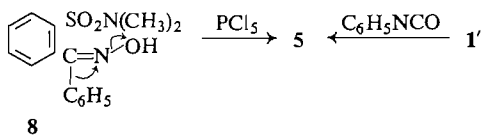
[1]Supported by the Army Research Office (Durham, North Carolina).



cyclodehydration to form sultams of type **12** (2); this reaction has generally been effected by treatment of **11** with cold sulfuric acid, followed by water (2). Similar treatment of carbinol-sulfonamide **2** has now resulted only in recovery of **2**.



Oxime-sulfonamide **8** underwent a Beckmann rearrangement with phosphorus pentachloride to form amide-sulfonamide **5**, which was shown to be identical with that obtained from lithiosulfonamide **1′** and phenylisocyanate, (Scheme 2).



SCHEME 2

Although this result would ordinarily be considered to establish the indicated configuration of the oxime in which phenyl and hydroxyl are *trans* (see Scheme 2), there appears to be a possibility that the other isomer of the oxime might have given the same result by isomerization prior to rearrangement. This might have occurred because of the expected reluctance of the aryl group in oxime **8**, which has the strongly electron attracting sulfonyl substituent, to undergo migration. An attempt to test this possibility by isolation and rearrangement of the other isomer of the oxime, however, was unsuccessful.

An attempt to extend the present method of lithiation and condensation to *N,N*-diphenylbenzenesulfonamide was unsuccessful. Incidently, this sulfonamide was obtained in excellent yield (92%) when benzenesulfonyl chloride and diphenylamine were treated with pyridine (3), but not when this chloride and amine were treated with aqueous alkali or with excess amine in ether according to other earlier methods (4).

Experimental[2]

Ortho-Lithiation of N,N-Dimethylbenzenesulfonamide (1)

A solution of 0.025 mole of *N,N*-dimethylbenzenesulfonamide (**1**, m.p. 47–48°; lit (4, 5) 47–48°) in 50 ml of tetrahydrofuran (THF)[3] in a dry flask under nitrogen was cooled to 0°, and 20 ml (0.030 mole) of a solution of 1.59 *M n*-butyllithium in hexane[4] was added during 5–6 min. After stirring for 30 min at 0°, the brown suspension was considered to contain 0.025 mole of monolithiosulfonamide **1′**. The suspension was employed at 0° as described below.

Condensation of Lithiosulfonamide 1′ with Benzophenone to Form Carbinol-sulfonamide 2

To a stirred, cold suspension of 0.025 mole of lithiosulfonamide **1′** was added under nitrogen, during 4 min, a solution of 5.47 g (0.030 mole) of benzophenone in 30 ml of THF,[3] and the stirring was continued for 30 min at 0°. To the resulting clear, dark-brown solution (cooled in an ice bath) was added, with stirring, 20 ml of water followed by 30 ml of 5% hydrochloric acid. The two layers were separated. After saturation with sodium chloride, the

[2]Melting points are uncorrected. Elemental analyses were performed by Janssen Pharmaceutica, Beerse, Belgium, and by M-H-W Laboratories, Garden City, Michigan, and by Alfred Bernhardt, West Germany. Infrared spectra (KBr method) were produced on Perkin–Elmer Infracord Model 137 and 237 spectrophotometers. Nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer and signals are reported in p.p.m. downfield from an internal tetramethylsilane standard.

[3]Freshly distilled from lithium aluminium hydride.

[4]Foote Mineral Company, Route 100, Exton, Pennsylvania.

aqueous layer was extracted three times with ether, and the extracts were combined with the organic layer. After washing twice with a saturated solution (30 ml) of sodium chloride and drying ($MgSO_4$), the solvent was removed under reduced pressure on the steam bath. The crystalline residue was stirred with a little methanol, and the mixture was filtered. The solid was washed with a little methanol, and dried in air to give 7.46 g (82%) of α,α-diphenyl-*o*-(*N*,*N*-dimethylsulfamyl) benzyl alcohol (**2**), m.p. 162–164° and 164–165° (fine crystals) after recrystallization from acetone–methanol; i.r. 3380 (OH), 1303 and 1140 cm^{-1} (SO_2); n.m.r. ($CDCl_3$) 8.15–6.78 (m, 14.1, aromatic), 6.78 (s, 1.0, OH), and 2.57 p.p.m. (s, 6.0, N-CH_3).

Anal. Calcd. for $C_{21}H_{21}NSO_3$: C, 68.64; H, 5.76; N, 3.81; S, 8.73. Found: C, 68.29; H, 5.76; N, 3.88; S, 8.62.

Cyclization of Carbinol-sulfonamide 2

Cyclization of 1.0 g of **2** was effected by heating it under a slow stream of nitrogen in a Wood's metal bath at 185–195° for 6 h. After cooling, the molten mass was dissolved in a little hot methanol, and the solution was allowed to stand overnight. The resulting crystals were collected, and recrystallized from methanol to afford 0.26 g (30%) of 3,3-diphenyl-2,1-benzoxathiole-1,1-dioxide (**3**) (fine leaflets), m.p. 162–164°, undepressed on admixture with an authentic sample (2) of **3** (m.m.p. 163–165°); the i.r. spectra of the two samples were identical.

When the cyclization of **2** was effected at 205–215° in the presence of 20 mg of benzoyl peroxide, sultone **3**, m.p. 162–164°, was obtained in 10% yield.

Condensation of Lithiosulfonamide 1′ with Benzonitrile to Form Imine-sulfonamide 4

This reaction was effected as described above for benzophenone to give a brown-red suspension which was cooled in an ice bath and stirred with 20 ml of water followed by 30 ml of 10% hydrochloric acid. The resulting two layers were separated. The acidic, aqueous layer, which was combined with acidic extracts of the organic layer, was made basic with potassium carbonate powder. After standing in a current of air under a hood for several hours, the crystalline solid was collected, washed with water, and dried in air to give 5.69 g (79%) of *o*-(*N*,*N*-dimethylsulfamyl)benzophenone imine (**4**), m.p. 153–156° and 155.5–156.5° (as prismatic crystals) after recrystallization from methanol; i.r. 3255 (NH), 1600 (C=N), 1345 and/or 1335 (SO_2), and 1155 cm^{-1} (SO_2); n.m.r. ($CDCl_3$) 8.22–7.17 (m, 9.1, aromatic and NH), and 2.57 p.p.m. (s, 6.0, N—CH_3).

Anal. Calcd. for $C_{15}H_{16}N_2SO_2$: C, 62.47; H, 5.60; N, 9.72. Found: C, 62.69; H, 5.20; N, 9.47.

Hydrolysis of imine-sulfonamide **4** (1.0 g) was effected by refluxing it with 40 ml of 5% sulfuric acid for 1 h. After cooling, the mixture was filtered. The solid was washed with water, and dried to give 0.85 g (85%) of *o*-(*N*,*N*-dimethylsulfamyl)benzophenone (**7**), m.p. 146–147.5°. Recrystallization from methanol afforded 0.76 g (76%) of **7** (fine crystals), m.p. 147–148°; i.r. 1660 (CO), 1330 and 1155 cm^{-1} (SO_2); n.m.r. ($CDCl_3$) 8.08–7.22 (m, 9.1, aromatic), and 2.72 p.p.m. (s, 6.0, N-CH_3).

Anal. Calcd. for $C_{15}H_{15}NSO_3$: C, 62.26; H, 5.23; N, 4.84. Found: C, 62.11; H, 5.19; N, 4.74.

Oximation of imine-sulfonamide **4** (2.50 g) was effected by refluxing it with 1.21 g of hydroxylamine hydrochloride and 3.54 g of sodium acetate (hydrate) in 80 ml of 70% (by weight) aqueous ethanol for 24 h. After cooling, the solution was allowed to stand overnight in a current of air under a hood. The resulting prismatic crystals were collected and recrystallized from methanol to give 2.55 g (97%) of *o*-(*N*,*N*-dimethylsulfamyl)benzophenone oxime (**8**) (large prismatic cluster), m.p. 156–158°. Another recrystallization from methanol gave 2.25 g (85%) of **8**, m.p. 158–160° and 156.5–158.5° i.r. 3420 (broad) and 3250 (broad, OH), 1630 (very weak, C=N), 1320 and 1150 cm^{-1} (SO_2); n.m.r. (acetone-d_6) 10.38 (s, 0.8, OH), 8.17–6.95 (m, 9.4, aromatic), and 2.63 p.p.m. (s, 6.0, N-CH_3).

Anal. Calcd. for $C_{15}H_{16}N_2SO_3$: C, 59.19; H, 5.30; N, 9.20. Found: C, 59.05; H, 5.19; N, 9.14.

Condensation of imine-sulfonamide **4** (2.0 g) with phenylhydrazine (2.25 g) was effected in 100 ml of 50% acetic acid by refluxing the solution for 24 h. After standing overnight at room temperature, the resulting prismatic yellow crystals were collected to give 1.65 g (63%) of *o*-(*N*,*N*-dimethylsulfamyl)benzophenone phenylhydrazone (**9**), m.p. 167–168.5° and 168.5–169° after recrystallization from acetone–methanol; i.r. 3280 (NH), 1580 (C=N), 1315 and 1105 cm^{-1} (SO_2); n.m.r. ($CDCl_3$) 8.45–8.07 (m, 0.9, NH), 7.85–6.60 (m, 14.8, aromatic), and 2.42 p.p.m. (s, 6.0, N-CH_3).

Anal. Calcd. for $C_{21}H_{21}N_3SO_2$: C, 66.46; H, 5.58; N, 11.07. Found: C, 66.54; H, 5.88; N, 10.99.

Condensation of Lithiosulfonamide 1′ with Phenylisocyanate to Form Sulfobenzanilide 5

This reaction was effected as described above for benzophenone to give a dark-brown, clear solution, which was cooled in an ice bath and stirred with 20 ml of water followed by 25 ml of 5% hydrochloric acid. The mixture, which consisted of two layers and suspended solid, was partly evaporated in a current of air under a hood. The mixture was filtered. The solid was washed with water, a little ether, and then dried in air to give 4.35 g (57%) of carboxamide-sulfonamide **5** (fine crystals), m.p. 202–204° and 204.5–205.5° after recrystallization from acetone–methanol; i.r. 3280 and 3258 (NH), 1650 (CO), 1340 and 1160 cm^{-1} (SO_2).

Anal. Calcd. for $C_{15}H_{16}N_2SO_3$: C, 59.19; H, 5.30; N, 9.20. Found: C, 59.49; H, 5.34; N, 9.09.

The two layers of the filtrate (see above) were separated, and the organic layer was worked up to give 1.26 g of fine crystals, m.p. 175–195°, which seemed to consist partly of **5**.

Carbonation of Lithiosulfonamide 1′ to Form Carboxysulfonamide 6

Method A

A solution of **1′** was prepared by slowly adding 47 ml (0.0752 mole) of 1.6 *M* *n*-butyllithium in hexane[4] to a stirred solution of 11.71 g (0.0632 mole) of **1** in 250 ml of dry ether under argon at room temperature. Stirring was continued for 1 h and then carbon dioxide (from a CO_2 generator) was bubbled through the reaction mixture for 30 min. A saturated solution of sodium carbonate was added, the aqueous and ether–hexane layers were separated, and the aqueous layer was made acidic with dilute hydrochloric acid. The cloudy acidic solution was extracted with ether. The ethereal extract was dried ($MgSO_4$)

and the solvent was removed under reduced pressure to give a yellowish oil which crystallized overnight to yield 8.60 g (63%) of *o*-(*N*,*N*-dimethylsulfamyl)benzoic acid (**6**), m.p. 98–102°; i.r. (Nujol mull) 2630 and 2540 (OH) (6), 1710 (C=O), 1370 (SO_2), 1300 (C—O or OH) (6), 1165 and 1155 (SO_2), 735 cm^{-1} (ortho disubstitution); n.m.r. ($CDCl_3$) 11.28 (s, 1.0, CO_2H), 7.70 (m, 4.0, aromatic), and 2.85 p.p.m. (s, 5.8, N-CH_3).

Anal. Calcd. for $C_9H_{11}NSO_4$: C, 47.15; H, 4.83; O, 27.92; N, 6.11; S, 13.99. Found: C, 47.14; H, 4.81; O, 28.05; N, 5.89; S, 13.94.

Method B

A solution of 0.05 mole of **1′** in 200 ml of THF[3] was prepared under nitrogen from 9.16 g (0.05 mole) of **1** and 35 ml (0.055 mole) of 1.59 *M* *n*-butyllithium in hexane.[4] After 1 h, the solution of **1′** was poured onto 500 g of dry ice in a 1 l Erlenmeyer flask which had been swept with dry nitrogen. After the excess dry ice had evaporated, 200 ml of water and 100 ml of ether were added. The layers were separated. The organic phase was extracted twice with saturated sodium bicarbonate solution and the extracts were combined with the aqueous layer. After washing with ether, the aqueous solution was acidified with 3 *N* hydrochloric acid. The resulting acidic solution was extracted with ether and the extracts were combined. After washing with saturated sodium chloride solution, the ethereal solution was dried ($MgSO_4$). The solvent was removed under reduced pressure on the steam bath to yield 8.59 g (75%) of **6** as a pale-yellow oil which crystallized slowly (48 h) to give light-yellow needles, m.p. 96–98° and 97–101° when the sample was placed in the bath at 94° and the temperature then raised.

*Beckmann Rearrangement of Oxime-sulfonamide **8** to Form Sulfobenzanilide **5***

A solution of 1.00 g of oxime **8** in 30 ml of THF[3] and 20 ml of anhydrous ether was cooled to 0° in an ice bath, and 1.00 g of phosphorus pentachloride was added. The mixture was magnetically stirred for 3 h at 0°, and then poured onto 30 g of ice. After making basic with sodium carbonate powder, the mixture was partly evaporated in a current of air under a hood (overnight). The white crystalline solid was collected, washed with water, and dried to give 0.77 g (77%) of carboxamide-sulfonamide **5** (fine bulky crystals), m.p. 203–205°, undepressed on admixture with the authentic sample of **5** prepared as described above (m.m.p. 204–205°), and the i.r. spectra of the two samples were identical.

*Attempt to Prepare Second Isomer of Oxime-sulfonamide **8***

A boiling solution of 0.70 g of oxime **8** in 70 ml of anhydrous ether was saturated with anhydrous hydrogen chloride gas (15 min) to form a white precipitate. After refluxing for 10 min, the mixture was poured onto excess of saturated sodium becarbonate solution in an ice bath. The resulting, basic mixture was partly evaporated in a current of air under a hood (overnight). The solid was collected, washed with water, and dried in air to give 0.67 g of recovered oxime **8**, m.p. and m.m.p. 156–158°; the i.r. spectrum was identical with that of the starting oxime.

Also, a solution of 0.8 g of oxime **8** in 8 ml of concentrated sulfuric acid at 0° was allowed to stand for 1 h, and then poured onto 50 g of ice. The resulting white precipitate was collected, washed with water, and dried in air to give 0.75 g of recovered oxime **8**, m.p. and m.m.p. 157.5–159.5°; the i.r. spectra of the two samples were identical.

Beckmann rearrangement of these samples of oxime **8** (recovered after treatment with the acids) with phosphorus pentachloride in THF–ether under the conditions described above afforded, on work-up, carboxamide-sulfonamide **5** in 73–74% yield.

1. W. H. PUTERBAUGH and C. R. HAUSER. J. Org. Chem. **29**, 853 (1964).
2. H. WATANABE, R. L. GAY, and C. R. HAUSER. J. Org. Chem. **33**, 900 (1968).
3. L. ALMASI and N. SERBAN. Acad. Rep. Poulare Romine, Filiala Cluj, Studii Cercetari Chem. **7**, 141 (1956); Chem. Abstr. **52**, 12871 h (1958).
4. A. GINZBERG. Chem. Ber. **36**, 2706 (1903).
5. L. W. JONES and H. F. WHALEN. J. Am. Chem. Soc. **47**, 1348 (1925).
6. L. J. BELLAMY. The infrared spectra of complex molecules. 2nd ed. John Wiley and Sons, Inc., New York. 1962. p. 162.