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Sulfoximines. 2. New Method for the Preparation of *N*-Arylsulfoximines

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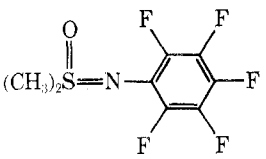
A new method for the preparation of *N*-aryl-*S,S*-dimethylsulfoximines (**8a–l**) is reported. The method involves formation of a complex (**6**) between Me_2SO and *tert*-butyl hypochlorite at low temperatures (−60 °C), followed by reaction of the complex with arylamines to give *N*-aryl-*S,S*-dimethylazasulfoxonium chlorides (**7a–l**). Upon treatment of the salts with base, the corresponding *N*-aryl-*S,S*-dimethylsulfoximines (**8a–l**) are obtained (25–70%-yields). Limitations of the reaction and possible mechanistic pathways are discussed.

At the start of this investigation (1974), a survey of the literature[1,2] showed that no general method existed for the synthesis of *N*-arylsulfoximines, $R_2S(=O)$–N–aryl, and only several *N*-arylsulfoximines were known.

Banks and co-workers[3] prepared *S,S*-dimethyl-*N*-perfluorophenylsulfoximine (**1**) and *S,S*-dimethyl-*N*-tetrafluoropyridylsulfoximine (**2**) by decomposition of the corresponding



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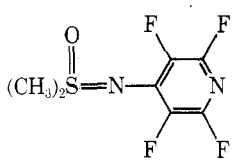
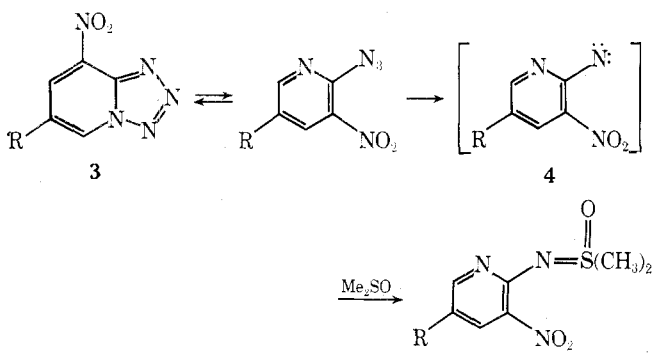


2

azides in dimethyl sulfoxide solution. A nitrene intermediate was proposed. However, the chemistry of perfluoroarylnitrenes is vastly different from the chemistry of other arylnitrenes.[3,4] Therefore, this method would appear to be inapplicable to the preparation of other (nonfluorinated) *N*-arylsulfoximines.

Pollack et al.[5] prepared sulfoximines **5a** and **5b** in extremely low yields from the corresponding tetrazolo[1,5-*a*]pyridines **3a** and **3b.** The reaction was reported to proceed via the nitrene **4** which reacts with dimethyl sulfoxide to give the sulfoximines. Sulfoximine **5a** was prepared in only 4% yield, and **5b** was merely identified in situ by NMR but not isolated.



3 4 5

a, R = H
b, R = NO_2

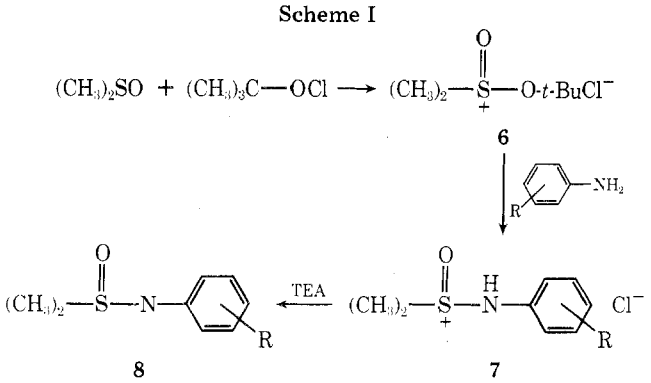
After our investigation was well under way, Claus and coworkers[6] reported the preparation of *N*-arylsulfoximines in good yields by the oxidation of the corresponding iminosulfuranes (sulfilimines) with aqueous potassium permanganate–dioxane. This procedure is an improvement over the original potassium permanganate oxidation of iminosulfuranes reported by Bentley and Whitehead,[7] although it requires that the oxidation be conducted in quite dilute solution. These investigators also reported the preparation of two *N*-arylsulfoximines from Me_2SO, *t*-BuOCl, and aniline or *p*-chloroaniline, respectively, but with lower yields and purity.

Since no convenient general method existed for the preparation of *N*-arylsulfoximines using readily available "off-the-shelf" reactants, and in view of our interest in organic sulfur–nitrogen compounds, we have been investigating new methods for the preparation of these interesting compounds. This paper describes the preparation of a series of previously unreported (see ref 6) *N*-aryl-*S,S*-dimethylsulfoximines (**8a–l**) by a new procedure using readily available reactants (Me_2SO, *t*-BuOCl, arylamines). We also describe experimental results which suggest possible reaction pathways.

Results

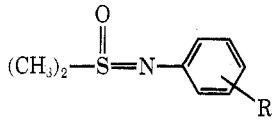
Scheme I shows the method of preparation of *N*-arylsulfoximines (**8a–l**). The initial step involves formation of a complex between Me_2SO and *tert*-butyl hypochlorite at low temperatures (−60 °C). This complex, which has pseudohalogen characteristics, i.e., it oxidizes I^- to I_2, is represented as a salt (**6**). Other structures are possible, however, and will be discussed later. Reaction of this complex with arylamines

Scheme I



6 8 7

Table I. Sulfoximines from Arylamines



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Compd	R	Yield, %	Mp, °C	Reaction solvent
8a	*p*-NO_2	0		CH_2Cl_2, CH_3OH
8b	*p*-CN	27	108–109[b]	CH_2Cl_2
8c	*p*-F	60	93–94.5	CH_2Cl_2
8d	*p*-Cl	68, 65	59.5–60.5[b]	CH_2Cl_2, CH_3OH
8e	*p*-Br	45	77–79[b]	CH_2Cl_2
8f	*p*-I	57	90.5–91.5	CH_2Cl_2
8g	*o*-F	40	78.5	CH_2Cl_2
8h	*o*-Cl	0		CH_2Cl_2
8i	*p*-CH_3	45	76–77[b]	CH_2Cl_2
8j	*p*-OCH_3	*a*		CH_2Cl_2
8k	H	54	73–74.5[b]	CH_2Cl_2
8l	*o*-Br	0		CH_2Cl_2

[a] Sulfoximine identified by NMR but not isolated. [b] Also reported in ref 6.

yields azasulfoxonium chlorides (**7**) which, upon treatment with base, yield the corresponding *N*-aryl-*S*,*S*-dimethylsulfoximines (**8**).

Triethylamine (TEA) is the preferred base; aqueous sodium hydroxide (10%) requires higher temperatures and gives more by-products. Best results are obtained with a slight excess of complex (≈15% excess) and reaction times of 3–5 h. In most cases, the crude products consist largely (>90%) of sulfoximine and unreacted arylamine. Attempts to increase the yield of sulfoximines by increasing the reaction time significantly lead only to formation of more azobenzenes, a minor by-product in the ordinary procedure. Increasing the reaction temperature above −30 °C causes decomposition of the complex.

Methylene chloride is the solvent of choice. For compounds not soluble in methylene chloride, methanol may be used. The complex (**6**), however, must be prepared in methylene chloride prior to addition of methanol because reaction of Me_2SO with *tert*-butyl hypochlorite in the presence of methanol even at −60 °C gives a quantitative yield of dimethyl sulfone. These results will be discussed later when we consider reaction pathways.

Table I summarizes the results. As Table I shows, sulfoximines are obtained in 27–68% yields from arylamines containing electron-donating or electron-releasing substituents. The reaction fails with certain arylamines. For example, *p*-nitroaniline is recovered unchanged; its failure to react is probably a consequence of the low nucleophilicity of the amino group. *p*-Anisidine reacts with the complex to form sulfoximine as evidenced by an NMR absorption at about δ 3 ppm characteristic of sulfoximines. However, the reaction mixture is very dark and attempts to isolate a product, even at low temperatures, yield only a black oily solid containing no sulfoximine (NMR). The sulfoximine is presumably being formed but is too unstable to survive during the workup procedure. Its instability is probably due to the presence of the electron-donating methoxy group which is increasing the electron density on an already electron-rich nitrogen. (Aryliminosulfuranes that contain electron-donating groups on the *N*-aryl substituent are also quite unstable.) Attempts to isolate this sulfoximine as its azasulfoxonium chloride or picrate were equally unsuccessful.

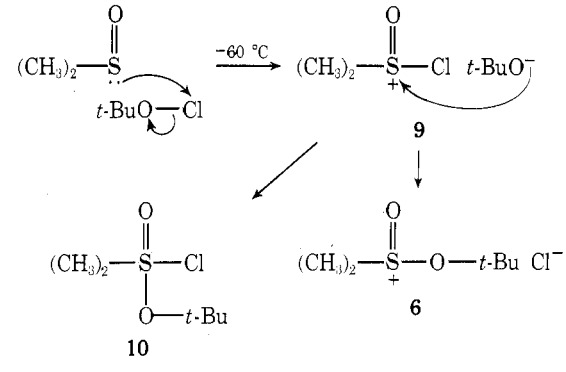
Compounds with large ortho substituents, e.g., **8h** and **8l**, could also not be obtained. This is a result of steric hindrance in the initial arylamines which are required to perform a nucleophilic displacement reaction. Thus, *o*-chloroaniline and *o*-bromoaniline fail to react but *o*-fluoroaniline does, and *p*-chloroaniline gives good results.

Discussion

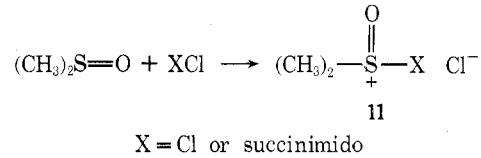
These results show that the method has general application, with some exceptions, for the synthesis of previously unreported *N*-aryl-*S*,*S*-dimethylsulfoximines. Despite some limitations, this method gives rapid access to these compounds from readily available starting materials (Me_2SO, *t*-BuOCl, and the arylamine) and it is also a "one-pot" procedure.

Mechanistic Considerations. The detailed mechanism for this reaction is not yet known. Information is available, however, which supports the idea that an intermediate such as **6** is formed (Scheme II). When Me_2SO reacts with *tert*-butyl hypochlorite (a pseudohalogen) at −60 °C, intermediate **9** is probably the initial species formed. Attack of *tert*-butoxide ion on **9** would then lead either to **6** (an ion pair) or **10** (a neutral tetracoordinate sulfur compound). At this point we cannot distinguish between the two.

Scheme II



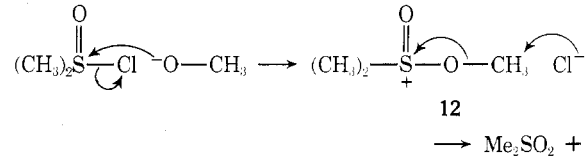
The formation of an ion pair, such as **6**, has precedent in the literature.[8,9] Corey and Kim[8] reported the reaction of Me_2SO with chlorine and also with *N*-chlorosuccinimide at low temperatures to form a complex for which they suggested structure **11**. However, other structures were not ruled out.



11

X = Cl or succinimido

Addition of Me_2SO to a cold (−60 °C) solution of *tert*-butyl hypochlorite in methanol yields dimethyl sulfone quantitatively. The addition of methanol to a cold (−60 °C) solution of *tert*-butyl hypochlorite and Me_2SO in methylene chloride, after complex formation has been completed, yields no dimethyl sulfone, however. These results support the supposition that **9** is formed followed by rapid and irreversible formation of **6** or **10**. If, however, methanol is present during addition of *tert*-butyl hypochlorite, the strongly basic *tert*-butoxide ion (**9**) would react with methanol to give *tert*-butyl alcohol and methoxide ion, the weaker base. Methoxide ion could then attack sulfur to produce **12**, which is able to eliminate methyl chloride and form dimethyl sulfone.

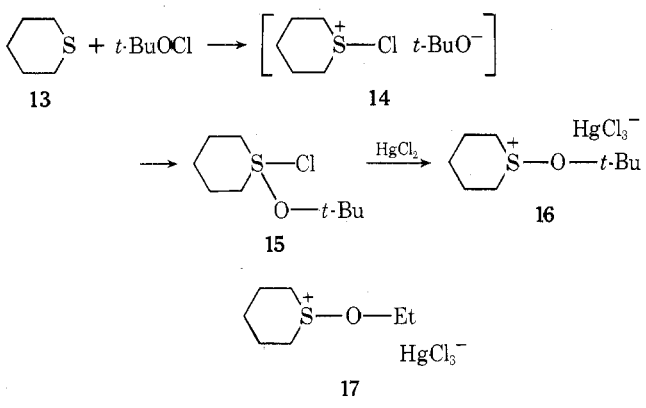


12

$\longrightarrow Me_2SO_2 + CH_3Cl$

Support for our conclusion is based on earlier studies of Johnson and Rigau,[9] who isolated and identified **16** from the reaction of mercuric chloride with intermediate **15** which, in

turn, had been formed from *tert*-butyl hypochlorite and thiane (**13**). Ion pair **14** was suggested as the initial product of the reaction because if ethanol was present initially, **17** was



isolated. When ethanol was added to a solution already containing *preformed* **15**, then **16** rather than **17** was isolated. This indicated that **15** was formed rapidly and irreversibly, so long as the ion pair **14** was not intercepted by ethanol. This earlier work supports the intermediacy of **9** followed by rapid and irreversible formation of **6** or **10**.

Experimental Section

Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian XL-100 spectrometer using Me_4Si as internal standard. Infrared spectra were recorded on a Unicam SP-1000 or a Perkin-Elmer Model 137 spectrophotometer. Elemental analyses were performed by Micro-Analysis, Wilmington, Del. All solvents and chemicals were the purest grade available. *tert*-Butyl hypochlorite was the best commercial grade; it was analyzed for positive halogen content just before use. It was stored in a refrigerator.

***S,S*-Dimethyl-*N*-arylsulfoximines. General Procedure.** To a solution of *tert*-butyl hypochlorite (17.4 mmol) in dry methylene chloride (45 ml, distilled from P_2O_5) at −60 °C, a solution of Me_2SO (56.6 mmol, distilled from CaH_2) in dry methylene chloride (20 ml) was added slowly. The mixture was stirred at this temperature for 1 h followed by slow addition of a solution of arylamine (15.0 mmol) in dry methylene chloride (or methanol) (20 ml). The temperature was allowed to rise to −40 to −50 °C and the reaction mixture was stirred for 3–5 h at that temperature. Triethylamine (TEA, 5 ml) in methylene chloride (10 ml) was added slowly and the solution was allowed to come to room temperature. The reaction mixture was washed with water to remove Me_2SO, *tert*-butyl alcohol, TEA, and TEA hydrochloride, dried over sodium sulfate, and concentrated. TLC of the reaction mixture (silica gel, ether) usually showed the presence of sulfoximine (R_f ~0.13), unreacted arylamine (R_f ~0.51) and occasionally "azobenzene" (R_f ~0.63 or higher). Column chromatography on silica gel cleanly separated the components. Elution with hexane and hexane–ether mixtures yielded the azobenzene and arylamine. Further elution with methylene chloride and methylene chloride–methanol gave the sulfoximine. Table I summarizes the results.

***S,S*-Dimethyl-*N*-(*p*-cyanophenyl)sulfoximine (8b).** Recrystallization from methylene chloride–ether gave a light tan solid: 0.80 g (27%); mp 108–109 °C; NMR ($CDCl_3$) δ 3.16 (6 H, s), 7.04 (2 H, d, J = 9 Hz), 7.44 (2 H, d, J = 9 Hz); ir (KBr) 2210 (CN), 1295 (NSO), 1200 (NSO), 1039 cm^{-1} (NSO). Anal. Calcd: C, 55.65; H, 5.19; N, 14.42; S, 16.51. Found: C, 55.55; H, 5.14; N, 14.26; S, 16.46.

***S,S*-Dimethyl-*N*-(*p*-fluorophenyl)sulfoximine (8c).** Recrystallization from hexane–ether gave a white solid: 1.25 g (60%); mp 93–94.5 °C; NMR ($CDCl_3$) δ 3.05 (6 H, s), 6.74–7.12 (4 H, m); ir (KBr) 1275, 1178, and 1052 cm^{-1} (NSO). Anal. Calcd: C, 51.32; H, 5.38; N, 7.48. Found: C, 51.29; H, 5.34; N, 7.39.

***S,S*-Dimethyl-*N*-(*p*-chlorophenyl)sulfoximine (8d).** Recrystallization from ether–petroleum ether gave a white, crystalline solid: 2.08 g (68%); mp 59.5–60.5 °C; NMR ($CDCl_3$) δ 3.06 (6 H, s), 6.97 (2 H, d, J = 9 Hz), 7.16 (2 H, d, J = 9 Hz); ir (KBr) 1270, 1184, and 1043 cm^{-1} (NSO). Anal. Calcd: C, 47.17; H, 4.95; N, 6.88; S, 15.74. Found: C, 46.92; H, 5.06; N, 6.83; S, 15.62.

***S,S*-Dimethyl-*N*-(*p*-bromophenyl)sulfoximine (8e).** Recrystallization from ether gave a white, crystalline solid: 1.68 g (45%); mp 77–79 °C; NMR ($CDCl_3$) δ 3.04 (6 H, s), 6.88 (2 H, d, J = 9 Hz), 7.26 (2 H, d, J = 9 Hz); ir (KBr) 1285, 1182, and 1050 cm^{-1} (NSO). Anal. Calcd: C, 38.72; H, 4.06; N, 5.64; S, 12.92; Br, 32.20. Found: C, 39.50; H, 4.08; N, 5.66; S, 13.08; Br, 32.13.

***S,S*-Dimethyl-*N*-(*p*-iodophenyl)sulfoximine (8f).** Recrystallization from ether gave 2.53 g (56%): mp 90.5–91.5 °C; NMR ($CDCl_3$) δ 3.04 (6 H, s), 6.79 (2 H, d, J = 8 Hz), 7.46 (2 H, d, J = 8 Hz); ir (KBr) 1281, 1165, and 1041 cm^{-1} (NSO). Anal. Calcd.: C, 32.56; H, 3.42; N, 4.75; S, 10.86. Found: C, 32.66; H, 3.32; N, 4.78; S, 10.91.

***S,S*-Dimethyl-*N*-(*o*-fluorophenyl)sulfoximine (8g).** Recrystallization from ether gave 0.68 g (40%): mp 78.5 °C; NMR ($CDCl_3$) δ 3.10 (6 H, s), 6.84–7.38 (4 H, m); ir (KBr) 1290, 1195, and 1042 cm^{-1} (NSO). Anal. Calcd: C, 51.32; H, 5.38; N, 7.48. Found: C, 51.54; H, 5.38; N, 7.42.

***S,S*-Dimethyl-*N*-(*p*-tolyl)sulfoximine (8i).** Recrystallization from ether–petroleum ether gave 1.28 g (45%): mp 76–77 °C; NMR ($CDCl_3$) δ 3.07 (6 H, s), 7.00 (4 H, m), 2.28 (3 H, s); ir (KBr) 1270, 1180, and 1050 cm^{-1} (NSO). Anal. Calcd: C, 58.98; H, 7.15; N, 7.64; S, 17.52. Found: C, 59.25; H, 7.11; N, 7.59; S, 17.33.

***S,S*-Dimethyl-*N*-phenylsulfoximine (8k).** Recrystallization from ether gave a white solid: 1.37 g (54%); mp 73–74.5 °C; NMR ($CDCl_3$) δ 2.99 (6 H, s), 6.80–7.32 (5 H, m). Anal. Calcd: C, 56.77; H, 6.55; N, 8.28; S, 18.95. Found: C, 56.71; H, 6.53; N, 8.13; S, 18.98.

Acknowledgment. We thank the National Cancer Institute of the U.S. Public Health Service (CA-07803, 12227, and 05280) and the Samuel S. Fels Fund for partial support.

Registry No.—**8b,** 56158-12-4; **8c,** 58873-25-9; **8d,** 56157-98-3; **8e,** 56158-10-2; **8f,** 58873-26-0; **8g,** 58873-27-1; **8i,** 56157-99-4; **8j,** 58873-28-2; **8k,** 56157-97-2; *p*-cyanoaniline, 873-74-5; *p*-fluoroaniline, 371-40-4; *p*-chloroaniline, 106-47-8; *p*-bromoaniline, 106-40-1; *p*-iodoaniline, 540-37-4; *o*-fluoroaniline, 348-54-9; *p*-methylaniline, 106-49-0; *p*-methoxyaniline, 104-94-9; aniline, 62-53-3; *tert*-butyl hypochlorite, 507-40-4; Me_2SO, 67-68-5.

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