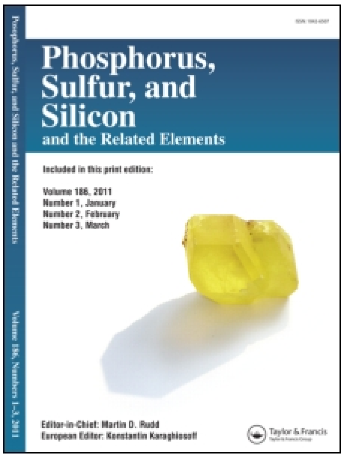

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SULFOXIMINES

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To cite this Article Huang, Shui Lung and Swern, Daniel(1976) 'SULFOXIMINES', Phosphorus, Sulfur, and Silicon and the Related Elements, 1: 2, 309 — 314
To link to this Article: DOI: 10.1080/03086647608073340
URL: http://dx.doi.org/10.1080/03086647608073340

Phosphorus and Sulfur
1976, Vol. 1, pp. 309-314

SULFOXIMINES

by

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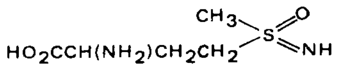
CONTENTS

I. Introduction

This review of sulfoximines is not intended to be an in-depth, detailed review but rather an overview of a relatively new class of reactive, interesting compounds. Topics selected for discussion reflect both the authors' interests as well as the importance of the subjects.

The first sulfoximine was isolated and characterized in 1950, when Bentley, McDermott, Pace, Whitehead, and Moran[1a] showed that the sulfoximine, 1, derived



1

from methionine is the compound responsible for the toxicity of wheat flour treated with nitrogen trichloride. Subsequently, Bentley, McDermott and Whitehead[1b] prepared 1 by reaction of methionine sulfoxide with hydrazoic acid in sulfuric acid-chloroform medium under the conditions of the Schmidt reaction. Other sulfoxides were similarly treated and also yielded sulfoximines. Thus, sulfoximines are relatively new additions to the many classes of sulfur compounds known to organic chemists.

Sulfoximines are isoelectronic with sulfones but, unlike the latter, many of their physical and chemical properties remain unreported.[2-7] A recent review focuses on and emphasizes the use of sulfoximines and their derivatives as reagents for organic synthesis.[8a]

II. Structure and Physical Properties

Spectral studies of sulfoximines[9-12] reveal that they are similar to the corresponding sulfones and not to the sulfoxides. There is a marked difference in behavior, however, between sulfoximines and the corresponding sulfones in that sulfoximines are often readily soluble in protic solvents, such as water and alcohols. This difference in solubility may be a consequence of special solvation about the sulfoximino group, a result that has been verified by nmr spectroscopy.[12]

Sulfoximines have strong ir absorption bands around 3200 and 1220 cm^{-1}, assigned to the N–H and N–S stretching frequencies, respectively. The N–S band appears at a considerably higher wave number than the corresponding absorption of N-sulfonylsulfilimines whose N–S band is considered to be semipolar. Hence the N–S bond in sulfoximines must have considerable double bond character.[12] An X-ray crystallographic study of methionine sulfoximine (1) supports this suggestion.[13]

The uv spectra of sulfoximines and sulfones are quite similar. As reported by Barash,[9] conjugative interaction occurs by p_π-d_π overlap between phenyl and sulfoximino groups. Sulfoximines can be protonated in acid solutions to provide a discrete positive charge on the sulfur atom, thus enhancing the p_π-d_π resonance interaction. The site of attachment of the proton in aminophenylsulfoximines is believed to be the sulfoximine nitrogen.

The pK_a values of various sulfoximines have been measured.[12a] The relatively large positive pK_a values (*i.e.*, basic) are in marked contrast to those of the corresponding sulfones. When the pK_a values of sulfoximines are plotted against Hammett sigma values, good straight lines are obtained.

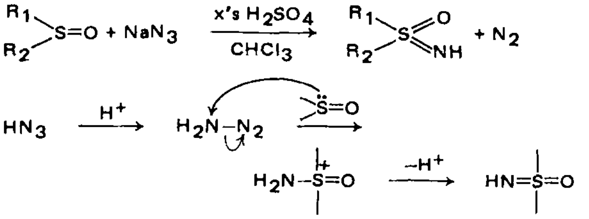
Mass spectral studies of sulfoximines have also been reported.[12]

III. Preparative Methods

Various methods have been reported but none are generally applicable for all types of sulfoximines.

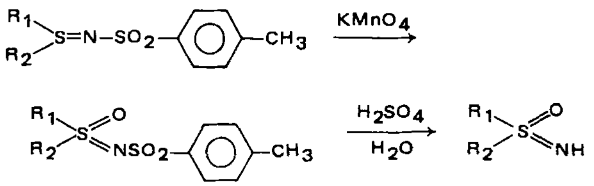
A. Reaction of Sulfoxides with Hydrazoic Acid (Sodium Azide-Sulfuric Acid)

The reaction of sulfoxides with hydrazoic acid, generated *in situ* from sodium azide and excess sulfuric acid (analogous to the Schmidt reaction) in chloroform medium, was first developed by Bentley, Whitehead, and coworkers,[1,2,4] and broadened in scope by Misani, Fair, and Reiner.[3] As Johnson has noted,[8] however, the reaction is exceedingly good only if both carbon substituents of the sulfoxide are either primarily alkyl (or aryl); otherwise heterolysis of carbon-sulfur bonds occurs in the highly acidic and polar medium. The mechanism given below has been suggested by Johnson and Janiga.[14] That hydrazoic acid must first be protonated is supported by the fact that excess sulfuric acid is required; no reaction takes place when only one equivalent is used. Many sulfoximines substituted on nitrogen have been prepared by alkylation or acylation of the unsubstituted compound, as discussed under Reactions (IV below).

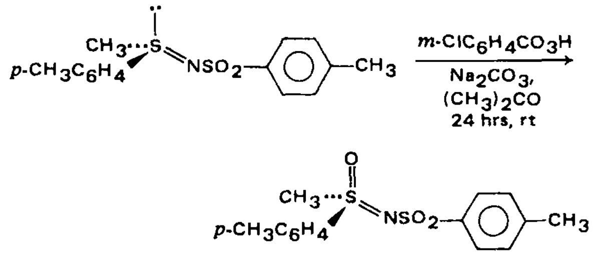


B. Oxidation of Iminosulfuranes

This method was first reported by Bentley and Whitehead[2] who used neutral or alkaline potassium permangenate to oxidize S,S-dialkyl-N-*p*-toluenesulfonyliminosulfuranes to the corresponding sulfonylsulfoximines, followed by strong acid hydrolysis to obtain the unsubstituted sulfoximines. Oxidation routes to sulfonyl sulfoximines are reported to have serious limitations due to the low nucleophilicity of the sulfur atom substituted by the strongly electron-withdrawing N-tosyl group.[15]



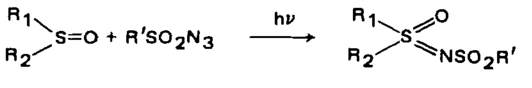
In one instance, *m*-chloroperoxybenzoic acid has been used to oxidize an optically active S,S-dimethyl-N-*p*-toluenesulfonyliminosulfurane to the corresponding sulfonylsulfoximine in fair yield.[16-19]



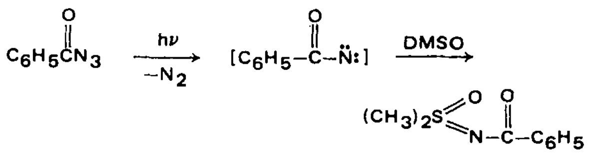
Stoss and Satzinger[20a] have prepared tricyclic sulfoximines in 42–86% yields from cyclic iminosulfuranes by oxidation with sodium periodate. Recently[20b] they prepared diphenyl sulfoximine by oxidation of diphenylsulfilimine monohydrate with sodium periodate, potassium permanganate or lead tetraacetate in acetic acid, pyridine or chloroform, respectively.

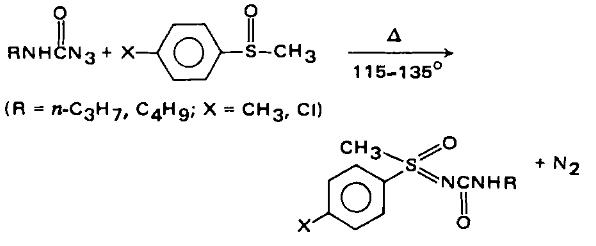
C. Reaction of Sulfoxides with Azides

This method appears to be the most general, although it has received only modest study and as originally reported yields were usually only fair to low. Horner and Christmann[21] photolyzed sulfonyl azides in various sulfoxides and obtained 13-32% yields of N-sulfonylsulfoximines. The low yields were attributed to the photochemical instability of the products. Similar results were obtained on thermolysis of the azide in the sulfoxide in the dark.



Photolysis of benzoyl azide in dimethyl sulfoxide gives S,S-dimethyl-N-benzoylsulfoximine in 28% yield. A nitrene intermediate was suggested. Carbamoyl azides were also reported to undergo similar reactions on heating to 115-135° with sulfoxides;[22] yields of sulfoximines were low (8-12%).





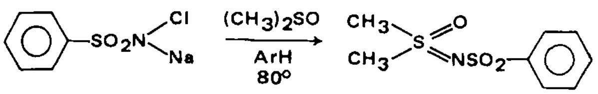
(R = n-C_3H_7, C_4H_9; X = CH_3, Cl)

(8-12%)

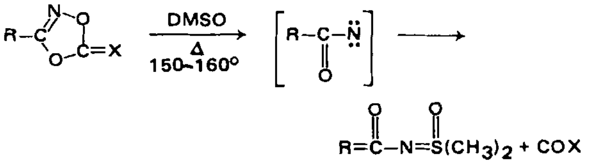
In an improved procedure, Kwart and Khan[23] prepared S,S-dimethyl-N-benzesulfonylsulfoximine in 97% yield from approximately equimolar quantities of benzenesulfonyl azide and dimethyl sulfoxide in refluxing methanol in the presence of freshly reduced copper. Johnson and co-workers[15] report that this is the method of choice for reaction of toluenesulfonyl azide with a variety of sulfoxides; yields of N-tosylsulfoximines are from 52-94%, a considerable improvement over the earlier procedure.[21]

D. Other Preparations of Sulfoximines from Dimethyl Sulfoxide

When chloramine-T is heated at 80° for three hours with dimethyl sulfoxide in the presence of copper powder, the sulfoximine is obtained in 80% yield.[24] This reaction appears to be limited to dimethyl sulfoxide.[15]

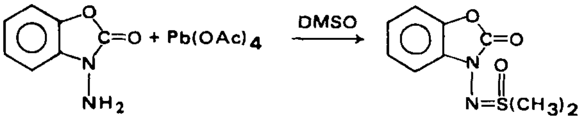


Δ^2-1,4,2-Dioxazolin-5-ones (or thiones) yield sulfoximines (30-90%) when heated to 150-160° in dimethyl sulfoxide,[25] presumably via nitrene intermediates.

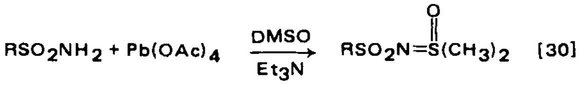


(R = C_6H_5, m- and p-$CH_3OC_6H_4$, p-$O_2NC_6H_4$, $C_6H_5CH{=}CH$; X = O, S).

Other preparations of sulfoximines that may also involve nitrene intermediates include the oxidation of N-aminolactams or N-aminophthalimide with lead tetraacetate usually in a solution of dimethyl sulfoxide but also in other sulfoxides,[26-29] the oxidation of sulfonamides with lead tetraacetate in dimethyl sulfoxide,[30] and the thermolysis of an aminimide in dimethyl sulfoxide.[31]

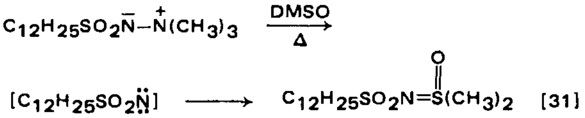


[26-29]



$$RSO_2NH_2 + Pb(OAc)_4 \xrightarrow[Et_3N]{DMSO} RSO_2N{=}\overset{O}{\overset{\|}{S}}(CH_3)_2 \quad [30]$$

(R = C_2H_5, p-$CH_3C_6H_4$)

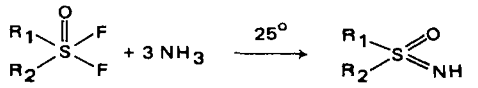


$$C_{12}H_{25}SO_2\bar{N}{-}\overset{+}{N}(CH_3)_3 \xrightarrow[\Delta]{DMSO}$$

$$[C_{12}H_{25}SO_2\ddot{N}] \longrightarrow C_{12}H_{25}SO_2N{=}\overset{O}{\overset{\|}{S}}(CH_3)_2 \quad [31]$$

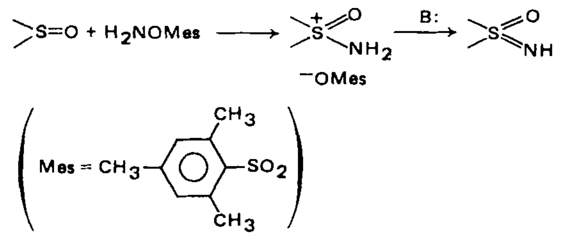
E. Miscellaneous

Reaction of ammonia with perfluoroalkyl substituted sulfur oxyfluorides is a direct route to the preparation of fluorinated sulfoximines.[32]



(R_1 = R_2 = CF_3 or C_2F_5; R_1 = CF_3; R_2 = C_2F_5)

Reaction of O-mesitylenesulfonylhydroxylamine with acyclic or cyclic sulfoxides at room temperature followed by reaction with base gives good yields of sulfoximines.[20a,33]



IV. Reactions of Sulfoximines

As Johnson has so aptly pointed out,[8] sulfoximines are especially versatile: they contain acidic hydrogens on carbon and nitrogen, they are basic and nucleophilic at nitrogen, and they are potentially chiral at sulfur. Yet with few exceptions,[8] the literature on the chemical reactions of sulfoximines is rather sparse.

A. *Stability*

The resistance of sulfoximines to hydrolysis prompted Whitehead and Bentley[4] to suggest that the N–S bond is stronger than that in iminosulfuranes. Infrared evidence already mentioned shows that the N–S bond has considerable double bond character.[12] Misani, Fair and Reiner[3] reported that sulfoximines are relatively stable compounds and are decomposed only when heated to high temperatures or by prolonged hydrolysis in concentrated acid or base at reflux. Mass spectral fragmentation studies of sulfoximines have been reported by Oae and co-workers.[12a]

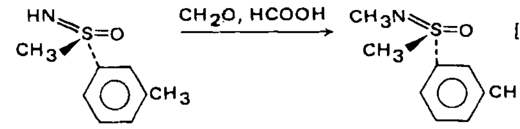
B. *Nitrous Acid Reaction*

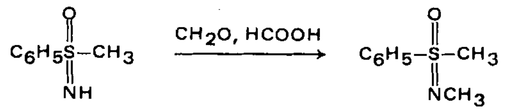
Misani, Fair and Reiner[3] reported that sulfoximines react with nitrous acid more slowly than aromatic amines do at 0°. Whitehead and Bentley[4] reported that treatment of dimethyl sulfoximine with nitrous acid at 74–80° gives dimethyl sulfone. Cram and coworkers[18, 19] succeeded in oxidizing optically active tolyl methyl sulfoximine with nitrous acid at 25° to form 99% optically pure tolyl methyl sulfoxide.

Whitehead and Bentley's result[4] has very recently been reported to be incorrect by Stephani and Meister.[34] These latter investigators showed tht N-unsubstituted sulfoximines yield amino acid sulfoxides on treatment with stoichiometric quantities of nitrous acid at 0° for 30 minutes.

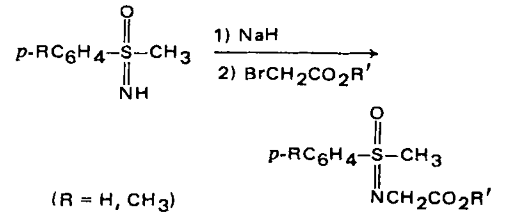
C. *Alkylation at Imino Nitrogen*

A few characteristic reactions are listed:

1.  [18]

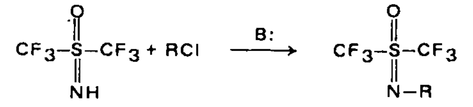
 [8]

$$\mathrm{C_6H_5}\overset{O}{\underset{NH}{\overset{\|}{\underset{\|}{S}}}}\mathrm{-CH_3} \xrightarrow{\mathrm{CH_2O,\ HCOOH}} \mathrm{C_6H_5-}\overset{O}{\underset{NCH_3}{\overset{\|}{\underset{\|}{S}}}}\mathrm{-CH_3}$$

2.  [35]

$$p\text{-}\mathrm{RC_6H_4-}\overset{O}{\underset{NH}{\overset{\|}{\underset{\|}{S}}}}\mathrm{-CH_3} \xrightarrow[\text{2) BrCH}_2\text{CO}_2\text{R}']{\text{1) NaH}} p\text{-}\mathrm{RC_6H_4-}\overset{O}{\underset{NCH_2CO_2R'}{\overset{\|}{\underset{\|}{S}}}}\mathrm{-CH_3}$$

(R = H, CH_3)

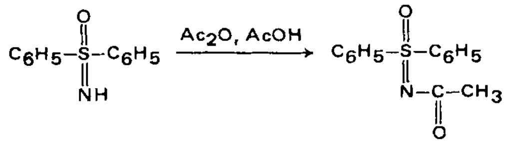
3.  [32]

$$\mathrm{CF_3-}\overset{O}{\underset{NH}{\overset{\|}{\underset{\|}{S}}}}\mathrm{-CF_3} + \mathrm{RCl} \xrightarrow{\mathrm{B:}} \mathrm{CF_3-}\overset{O}{\underset{N-R}{\overset{\|}{\underset{\|}{S}}}}\mathrm{-CF_3}$$

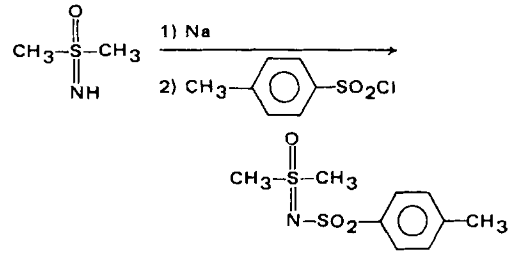
(R = CF_3S, CN, $(CH_3)_3Si$)

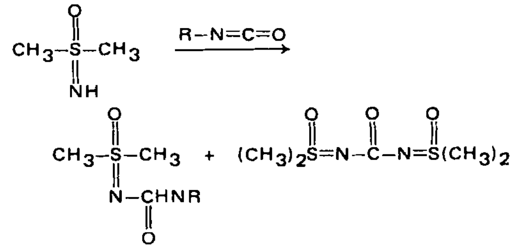
D. *Acylation at Imino Nitrogen*

A few characteristic reactions are listed:

1.  [3]

$$\mathrm{C_6H_5-}\overset{O}{\underset{NH}{\overset{\|}{\underset{\|}{S}}}}\mathrm{-C_6H_5} \xrightarrow{\mathrm{Ac_2O,\ AcOH}} \mathrm{C_6H_5-}\overset{O}{\underset{N-C(=O)-CH_3}{\overset{\|}{\underset{\|}{S}}}}\mathrm{-C_6H_5}$$

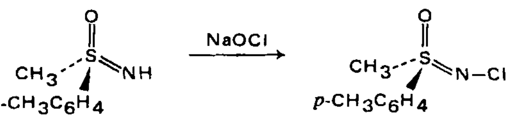
2.  [4]

3.  [6]

$$\mathrm{CH_3-}\overset{O}{\underset{NH}{\overset{\|}{\underset{\|}{S}}}}\mathrm{-CH_3} \xrightarrow{\mathrm{R-N=C=O}} \mathrm{CH_3-}\overset{O}{\underset{N-C(=O)NHR}{\overset{\|}{\underset{\|}{S}}}}\mathrm{-CH_3} + \mathrm{(CH_3)_2}\overset{O}{\overset{\|}{S}}\mathrm{=N-}\overset{O}{\overset{\|}{C}}\mathrm{-N=}\overset{O}{\overset{\|}{S}}\mathrm{(CH_3)_2}$$

Orthoformates,[36] phosgene[36] and carbonyldiimidazole[37] have also been used in acylation and cyclization reactions.

E. *Chlorination*

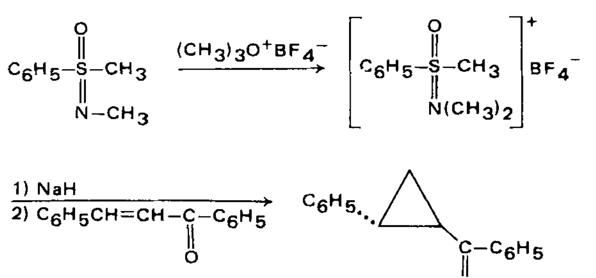
 [17]

The stability of sulfoximines, coupled with their ready conversion to N-metallo and N-chloro products, has prompted Cram and co-workers[17] to suggest that these derivatives can be used to prepare a large variety of compounds by electrophilic or nucleophilic substitution on nitrogen.

F. *Reactions of Acidic Hydrogen α to Sulfur*

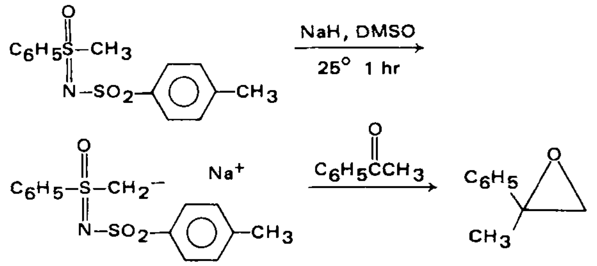
Ylids[37,38] and carbanions[15,39] can be easily prepared; they are powerful nucleophilic alkylidene transfer agents[8a,b14,15] useful in the synthesis of oxiranes, aziridines and cyclopropanes. All of these products can be obtained in chiral form by using chiral sulfoximines. The chirality of sulfoximines has been extensively studied.[40–43]

1. Ylids



Ylids with wide structural variety derived from sulfoximines should be available and may indeed be superior to ylids from trialkyloxosulfonium compounds.[27,32]

2. Anions



Reaction of the sulfoximine shown, as well as analogous compounds, with either sodium hydride or butyl lithium yields sulfonimidoyl-stabilized carbanions which act as nucleophilic alkylidene transfer agents upon reaction with substrates containing electrophilic double bonds. Ketones, as illustrated above, yield oxiranes, imines yield aziridines and α,β-unsaturated ketones yield cyclopropanes. Cycloalkylidene group transfer yields spiro compounds. These anions also add to oxiranes, carbodiimides and nitriles. A chiral sulfoximine yielded a cyclopropane 49% optically pure on reaction of its anion with benzalacetophenone; reaction with acetophenone yielded an active oxirane and reaction with benzalaniline yielded an active aziridine.

G. *Miscellaneous*

The first two heterocyclic systems based on the sulfoximine function were prepared by Stoss and Satzinger[44] and Johnson *et al.*[45] These contained five-membered rings. By intramolecular ring closure of phenylmethylsulfoximine, a sulfoximine also containing the β-lactam ring has been prepared.[35] Other preparations of cyclic sulfoximines can be found in references 46 and 47.

Cyanogen bromide reacts with diphenylsulfoximine and its N-diethylaminoethyl derivative to introduce the N-cyano function in place of H and $CH_2CH_2N(C_2H_5)_2$ respectively.[48]

Aluminium amalgam reduction of sulfoximines to sulfenamides is an interesting new reaction which proceeds with retention of configuration at chiral sulfur.[8]

H. *Conclusion*

Sulfoximines are an interesting, useful and versatile class of organic compounds. Approximately 400 examples are known; space limitations prevent their tabulation. The reader is referred to selected references 1-4, 6, 8b, 12, 14-17, 19, 21, 29, 32, 35, 40, 46, 49-59 for preparative details, isolation, purification and proof of structure of sulfoximines, as well as chemical reactions.

I. *Acknowledgement*

The authors thank the Samuel S. Fels Fund and the National Cancer Institute (CA-07803 and 07174) for financial support.

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