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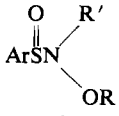
N-Alkoxybenzenesulfinamides. Evidence for an Alkylation Reaction

Sir:

We wish to report on some unusual chemical properties of the *N*-alkoxybenzenesulfinamides (**1**). The nature of their reactions is strongly dependent upon the substituent, R′, on nitrogen. If R′ is hydrogen, a novel N → S alkoxy group migration readily occurs. When R′ is alkyl, a facile fragmentation of the sulfinyl–nitrogen bond occurs. On the other hand, little reaction is evident at elevated temperatures when nitrogen has an acyl substituent.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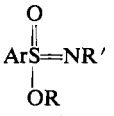
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The N-unsubstituted alkoxysulfinamides (**1**, R′ = H) are particularly noteworthy because they represent a new class of alkylating agents. Our results indicate that the alkylating properties result from rearrangement of **1** (R′ = H) to an *O*-alkylsulfonimidate intermediate **2**, which is structurally analogous to the sulfonate ester alkylating agents.[1]

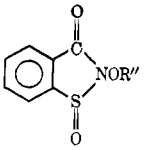
The synthesis of some *N*-alkoxyalkanesulfinamides has been reported by Zinner and Ritter,[2] but very little information concerning their chemical properties was provided. We have synthesized a variety of previously unknown *N*-alkoxybenzenesulfinamides (**1**)[3] from the appropriate sulfinyl chlorides and alkoxyamines in recrystallized yields ranging from 30–70% (Table I).

N-Methoxybenzenesulfinamide (**1a**) was observed to rearrange to *N*-methylbenzenesulfonamide (30%) on standing neat at room temperature for about 2 weeks.[4] A complicated mixture of other products such as benzenesulfonamide, ammonium benzenesulfinate, ammonium benzenesulfonate, phenyl disulfide, and phenyl benzenethiolsulfonate were also obtained. Decomposition of **1a** in an alcohol results in the formation of benzenesulfonamide and alkylation of the alcohol to give an ether. These results suggest that **1a** rearranges to a sulfonimidate ester intermediate (**2a**), which in turn alkylates itself (perhaps intermolecularly) or alkylates the alcohol (Scheme I).

To establish the scope and pursue the mechanism of the alkylation reaction, we investigated the reactions of **1** with different alcohols. *N*-Benzyloxybenzenesulfinamides **1c**, **1e**, and **1g** were completely converted on heating at 50° in dry methanol for 48 hr to benzenesulfonamides, benzyl methyl ether, and benzyl alcohol (Table II). Reaction of **1a** with benzyl alcohol at the same temperature also gave benzyl methyl ether. Reaction of **1c** with water in dioxane at 50° gave benzyl alcohol. But more significantly, reaction of **1c** with 1-butanol gave the alkylated cross-product dibutyl ether.

The mechanism (Scheme II) suggested by these results involves a dissociative rearrangement process from **1** to **2**, whereby the migrating alkoxy group can exchange with the alcohol solvent. The sulfonimidate intermediates (**2** and **2′′**) then alkylate the solvent. A delocalized nitrenium ion[5] intermediate (**3**), which is stabilized by the nonbonded sulfinyl electron pair, is

Table I. *N*-Alkoxybenzenesulfinamides, *p*-$XC_6H_4SN(O)OR$

Compd no.	X	R	R′	% yield	Mp, °C
1a	H	CH_3	H	20–40	48–51
1b	H	$C_6H_5CH_2$	H	45	91–92
1c	CH_3	$C_6H_5CH_2$	H	71	71–72
1d	Cl	CH_3	H	50	117–118
1e	Cl	$C_6H_5CH_2$	H	38	116–117
1f	NO_2	CH_3	H	28	126–127
1g	NO_2	$C_6H_5CH_2$	H	65	137–138
1h	H	CH_3	CH_3	94	Liquid[a]
1i	H	C_2H_5	C_2H_5	97	Liquid[a]
1j	NO_2	CH_3	CH_3	64	62–63
1k	Cl	CH_3	CH_3	50	35–39
4a	R′′ = CH_3			40	122–123
4b	R′′ = $CH_2C_6H_5$			20	110–111

[a] Decomposes on attempted vacuum distillation.

Scheme I

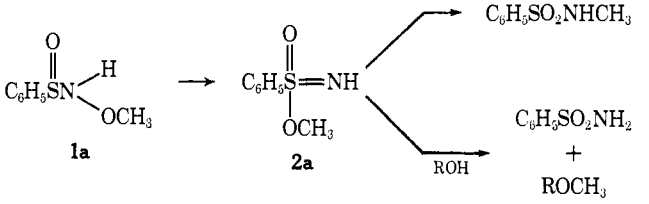


Table II

	X =	% yield[a] CH_3	Cl	NO_2
p-$XC_6H_4SNHOCH_2C_6H_5$ (O) —50°, 48 hr, CH_3OH→	*p*-$XC_6H_4SO_2NH_2$	65	58	39
	$C_6H_5CH_2OCH_3$	20	26	10
	$C_6H_5CH_2OH$	52	42	58

[a] Average of duplicate runs.

(1) (a) G. C. Barrett in "Organic Compounds of Sulfur, Selenium, and Tellurium," Vol. 1; D. H. Reid, Ed., The Chemical Society, Burlington House, London, 1970, pp 95–97; (b) J. A. Montgomery, T. P. Johnston, and Y. F. Shealy in "Medicinal Chemistry," 3rd ed, Part I, A. Burger, Ed., Wiley-Interscience, New York, N. Y., 1970, p 698.

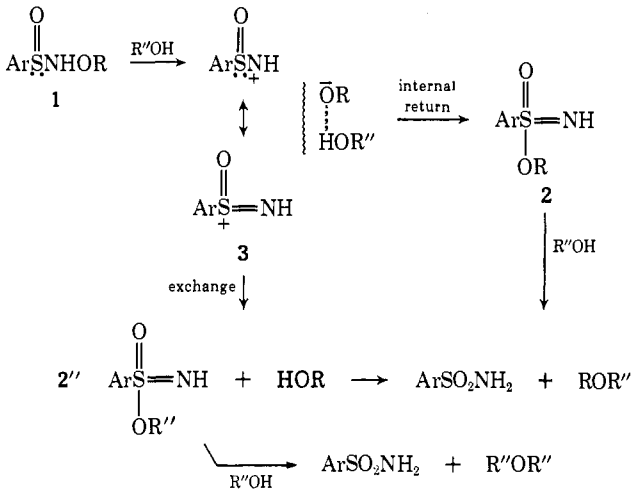
(2) G. Zinner and W. Ritter, *Arch. Pharm. (Weinheim)*, **296**, 681 (1963).

(3) Satisfactory elemental analyses were obtained for all of the compounds or for their sulfonamide oxidation products; ir and nmr spectra were consistent with their proposed structures.

(4) T. J. Maricich, Abstracts, 157th National Meeting of the American Chemical Society, Minneapolis, Minnesota, April 1969, ORGN-122.

(5) For a recent review of nitrenium ion chemistry, see P. G. Gassman, *Accounts Chem. Res.*, **3**, 26 (1970).

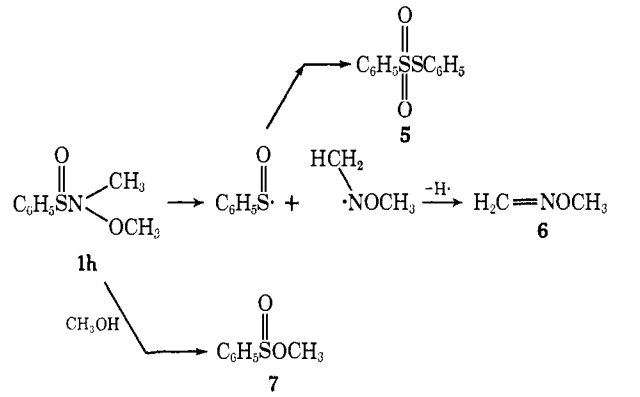
Scheme II



proposed. Failure of the cyclic *N*-acyl derivative **4b** to rearrange after refluxing in *o*-dichlorobenzene for 20 hr supports this proposition, since the nitrenium ion from **4b** would be destabilized by the *N*-acyl group.[6] A reaction does occur between **4b** and methanol, resulting in simple esterification to a ring-opened methyl sulfinate.

The *N*-alkylbenzenesulfinamide **1h** decomposed on heating in toluene at 50° for 48 hr to give primarily phenyl benzenethiolsulfonate (**5**, 50%), some phenyl disulfide, and the volatile *O*-methylformaldoxime (**6**). Compounds **1i**, **1j**, and **1k** decomposed similarly. These products can be explained by homolytic cleavage of the S–N bond followed by coupling of the benzenesulfinyl radicals[7] and loss of a hydrogen atom from the methoxymethylamine radical (Scheme III). The additional stabilization of the amine radical by the *N*-methyl group is apparently sufficient to divert the N → S rearrangement reaction. The *N*-alkyl sulfinamide **1h** is simply esterified to methyl benzenesulfinate (**7**, 35%) on reaction with methanol. Some fragmentation also occurs, but no rearrangement to sulfonamide is observed.

Scheme III



The rearrangement of **1** (R′ = H) to **2** is unprecedented. It is the first reported case or a migration of an alkoxy group (or any other group) from nitrogen to adjacent sulfur. The closest analogy (and a poor one) is the O → S 1,2 alkyl shift of the sulfinate → sulfone rearrangement.[8] The isomerization reaction leading to *N*-methylbenzenesulfonamide and the alkylation of alcohols are typical reactions of alkyl sulfonimidate esters.[9] Our results represent a novel route to the alkyl sulfonimidate intermediates and may provide unusual alkylating properties, especially as potential carcinostatic agents.[1b]

Acknowledgment. This investigation was supported in part by Public Health Service Research Grant No. CA-13201 from the National Cancer Institute.

(6) A referee has noted the possibility that the rearrangement may occur by a base-catalyzed α-elimination mechanism involving a sulfinylnitrene. We observed that small amounts (<5%) of formic acid, triethylamine, or potassium hydroxide added to **1c** in methanol had little effect on the outcome. These results are neither conclusive for nor against the nitrenium ion or nitrene mechanism.

(7) R. M. Topping and N. Kharasch, *J. Org. Chem.*, 27, 4353 (1962).

(8) A. H. Wragg, J. S. McFadyen, and T. S. Stevens, *J. Chem. Soc.*, 3603 (1958); D. Darwish and E. A. Preston, *Tetrahedron Lett.*, 113 (1964).

(9) Alkyl sulfonimidates are known, but are unstable under our reaction conditions: E. S. Levchenko and L. N. Markovskii, *J. Org. Chem. USSR*, 3, 1439 (1967); C. R. Johnson and E. U. Jonsson, *J. Amer. Chem. Soc.*, 92, 3815 (1970).

(10) National Science Foundation Undergraduate Research Participant, 1970.

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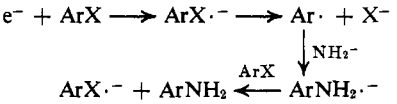
Reaction of 3-Cyclohexenyl Radical with Nucleophiles[1]

Sir:

A number of studies have been reported which point rather clearly to the ability of radicals to unite with nucleophiles to form radical ion intermediates.[2-5] Most such adducts are uniquely structured to impart stability to the radical ion. These include nitroarenes,[2] nitroaliphatics,[3] and, most recently, relatively simply substituted benzenes.[4] The mechanistic rationale which best accommodates all the facts,[2a] and for which the designation SRN1 has been proposed,[4b] is as follows



We now present results of a study of the 3-cyclohexenyl radical which suggest that stability in the radical ion intermediate may not be a requirement and that the coupling of radicals with nucleophiles may be a general reaction. 3-Cyclohexenyl radical was generated from cyclohexene, either by irradiation in the presence of benzophenone and the nucleophile (*tert*-butyl alcohol solvent) or by irradiation of a solution con-

(1) This research was supported by the National Science Foundation.

(2) (a) N. Kornblum, R. E. Michel, and R. C. Kerber, *J. Amer. Chem. Soc.*, 88, 5660, 5662 (1966), and earlier papers cited therein; (b) N. Kornblum, T. M. Davies, G. W. Earl, N. L. Holy, R. C. Kerber, M. T. Musser, and D. H. Snow, *ibid.*, 89, 725 (1967); (c) N. Kornblum, T. M. Davies, G. W. Earl, G. S. Greene, N. L. Holy, R. C. Kerber, J. W. Manthey, M. T. Musser, and D. H. Snow, *ibid.*, 89, 5714 (1967); (d) N. Kornblum and F. W. Stuchal, *ibid.*, 92, 1804 (1970); (e) N. Kornblum, R. T. Swiger, G. W. Earl, H. W. Pinnick, and F. W. Stuchal, *ibid.*, 92, 5513 (1970); (f) M. Barreau and M. Julia, *Tetrahedron Lett.*, 1537 (1973).

(3) G. A. Russell and W. C. Danen, *J. Amer. Chem. Soc.*, 88, 5663 (1966); G. A. Russell, R. K. Norris, and E. J. Panek, *ibid.*, 93. 5839 (1971).

(4) (a) J. F. Bunnett and C. C. Wamser, *ibid.*, 89, 6712 (1967); (b) J. K. Kim and J. F. Bunnett, *ibid.*, 92, 7464 (1970); (c) R. A. Rossi and J. F. Bunnett, *ibid.*, 94, 683 (1972); (d) R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, 37, 3570 (1972).

(5) J. G. Lawless and M. D. Hawley, *J. Electroanal. Chem.*, 21, 365 (1969); D. E. Bartak, W. C. Danen, and M. D. Hawley, *J. Org. Chem.*, 35, 1206 (1970).