The Reaction of the Bromo- and Fluoronaphthalenes with Butyl Mercaptide in Dimethyl Sulfoxide[1]

JERALD S. BRADSHAW,* J. ALLAN SOUTH, AND RICHARD H. HALES[2]

Chemistry Department, Brigham Young University, Provo, Utah 84601

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1-Fluoro- and 1-bromonaphthalenes reacted with *n*-butyl mercaptide in DMSO to give *n*-butyl 1-naphthyl sulfide in good yields. 2-Fluoro- and 2-bromonaphthalenes reacted in a similar manner to yield *n*-butyl 2-naphthyl sulfide. *tert*-Butyl mercaptide reacted with the fluoro- and bromonaphthalenes to give the corresponding *tert*-butyl naphthyl sulfides. These reactions proved to be direct aromatic nucleophilic substitution reactions.

In a continuation of our interest in the base-catalyzed reactions of the halonaphthalenes,[3,4] we have treated the bromo- and fluoronaphthalenes with *n*-butyl and *tert*-butyl mercaptides in dimethyl sulfoxide (DMSO). The products of these reactions were the corresponding alkyl naphthyl sulfides.

Although there is much knowledge concerning the reactions of thiophenoxide and thiocyanate with aromatic halogen compounds[5-7] very little work has been done with the alkyl mercaptides. Miller has reported that methyl mercaptide is a much stronger nucleophile in aromatic nucleophilic substitution than thiophenoxide.[8,9] Caubere and coworkers have studied the reactions of ethyl mercaptide with bromo- and fluorobenzene in hexamethylphosphotriamide (HMPT).[10,11]

Results and Discussion

A mixture of the halonaphthalene, butanethiol, sodium methoxide, and DMSO was heated at reflux for 1 hr. Sodium methoxide was used as the base since the thiol is a much stronger acid than methanol.[12] Thus the solution would contain methanol and sodium butyl mercaptide. The completed mixture was added to water. The neutral fraction was separated and the products were analyzed by vapor phase chromatography (vpc).

The products proved to be the appropriate alkyl naphthyl sulfide and the dibutyl disulfide. For example, *n*-butyl 2-naphthyl sulfide was obtained in the reaction using *n*-butyl mercaptide and 2-bromo- or 2-fluoronaphthalene. No methyl naphthyl ether was observed in any of these reactions. Also no evidence of the 1,2-dehydronaphthalene intermediate, previously observed,[3,4] was detected. This was shown by the fact that no 2-napththyl sulfide was isolated from 1-bromo- or 1-fluoronaphthalene.

These results are very different from those previously observed for the reaction of bromonaphthalene with potassium *tert*-butoxide.[3,4] Both 1- and 2-bromonaphthalene (as well as the chloro- and iodonaphthalenes) gave a mixture of *tert*-butyl 1-naphthyl ether and *tert*-butyl 2-naphthyl ether with a product ratio of 0.36.[3,4] Fluoronaphthalene, on the other hand, gave only direct nucleophilic substitution products.[3] Direct nucleophilic substitution was observed in this latter case presumably because the electron-withdrawing fluorine atom facilitates attack by the nucleophile. This in effect makes fluoride ion a superior leaving group in aromatic nucleophilic substitutions. Indeed, the rate for nucleophilic substitution of various para-substituted halobenzenes is hundreds of times faster with fluorobenzene than bromobenzene.[13] This two orders of magnitude enhancement of the rate for nucleophilic substitution is enough to change the dehydronaphthalene mechanism to direct nucleophilic substitution in the case of the oxide bases.[3]

In the present work, only direct nucleophilic substitution was observed even in the case of bromonaphthalene. The alkyl mercaptides are very powerful nucleophiles. Miller has shown that thiomethoxide is 87 times more reactive to 1-fluoro-2,4-dinitrobenzene than methoxide in methanol solvent.[8] This type of enhancement in nucleophilicity may even be greater in DMSO. Bartoli and Todesco show a rate enhancement of over 100 for the reaction of *p*-nitrobromobenzene with phenoxide and thiophenoxide in DMSO.[7] Thus we would expect *tert*-butyl mercaptide to be about two orders of magnitude more reactive than *tert*-butoxide toward aromatic nucleophilic substitution. This enhancement toward nucleophilic substitution again would tip the scales from the dehydronaphthalene mechanism to direct nucleophilic substitution in the case of bromonaphthalene.

One other factor probably greatly affects this reaction. The alkoxides are very powerful bases in DMSO. *tert*-Butyl alcohol has a pK in DMSO of 29.2.[14] A comparable number for an alkyl mercaptan is not known. However, the pK probably would be below the alcohols. The use of a base which is weaker than *tert*-butoxide can change this reaction from the dehydronaphthalene mechanism to direct nucleophilic substitution. This is shown by the fact that the reaction of bromanaphthalene with *tert*-butoxide (pK 29.2)[14] gave the dehydronaphthalene mechanism;[4] with *n*-butoxide (pK probably the same as *n*-propyl alcohol = 28.0),[14] both dehydronaphthalene and direct nucleo-

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(2) National Defense Education Act Fellow, 1967–1970.

(3) R. H. Hales, J. S. Bradshaw, and D. R. Pratt, *J. Org. Chem.*, **36**, 314 (1971).

(4) J. S. Bradshaw and R. H. Hales, *ibid.*, **36**, 318 (1971).

(5) A. J. Parker, "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, p 103.

(6) A. J. Parker, "Advances in Physical Organic Chemistry," Vol. 5, V. Gold, Ed., Academic Press, London, 1965, p 173.

(7) G. Bartoli and P. E. Todesco, *Tetrahdron Lett.*, 4867 (1968).

(8) J. Miller and K. W. Kong, *Aust. J. Chem.*, **18**, 117 (1965).

(9) See also J. Miller, "Aromatic Nucleophilic Substitution," Elsevier, New York, N. Y., 1968, pp 180–233.

(10) P. Caubere and B. Loubinoux, *Bull. Soc. Chim. Fr.*, 3008 (1968).

(11) P. Caubere and M.-F. Hochu, *ibid.*, 2854 (1969).

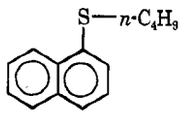
(12) See, for example, J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 220.

(13) See J. Miller, ref 9, pp 137–176, for specific examples.

(14) See J. F. Coetzee and C. D. Ritchie, "Solute-Solvent Interactions," Marcel Dekker, New York, N. Y., 1969, Chapter 4.

TABLE I

REACTION OF FLUORO- AND BROMONAPHTHALENE WITH SODIUM *n*-BUTYL AND *tert*-BUTYL MERCAPTIDES IN DIMETHYL SULFOXIDE[a]



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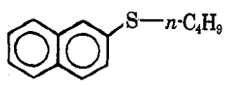

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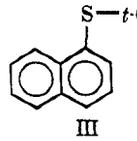
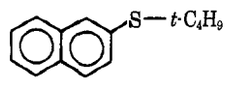


III



IV

Run	Registry no.	ArX	Registry no.	RS⁻	Time, hr	Conversion, %	Product yield, %[b] I	II	III	IV	Remarks
1	321-38-0	1-F	20733-16-8	*n*-Bu	1	96	83				Initial run gave 47%
2	323-09-1	2-F		*n*-Bu	1	80		51			
3	90-11-9	1-Br		*n*-Bu	1	80	96				Initial run gave 66%
4	580-13-2	2-Br		*n*-Bu	1	86		67			
5		1-F	20733-19-1	*t*-Bu	24	61			73		
6		2-F		*t*-Bu	24	55				48	
7		1-Br		*t*-Bu	24	41			54		Initial run gave 44%
8		2-Br		*t*-Bu	24	56				57	Initial run gave 47%

[a] A ratio of 1 mol of substrate, 2 mol of mercaptide, 3 mol of mercaptan, 15 mol of DMSO and 2 mol of methanol was used in all reactions. [b] Registry numbers: I, 5826-44-2; II, 5826-43-1; III, 25752-97-0; IV, 32689-97-7.

philic substitution were observed;[4] and with methoxide (pK 27.0),[14] only direct nucleophilic substitution was found.[15] It appears that relatively small changes in the pK can greatly affect this reaction. The fact that even *tert*-butyl mercaptide gave direct nucleophilic substitution (as contrasted to the oxide reactions[4]) probably means that the pK of *tert*-butyl mercaptan is less than 27.

Experimental Section

Materials and Apparatus.—The halonaphthalenes in this study were used as received: 1- and 2-bromonaphthalenes from J. T. Baker, 1-fluoronaphthalene from Aldrich Chemical, and 2-fluoronaphthalene from PCR Inc. The thiols were used as obtained from Aldrich Chemical. Sodium methoxide (Matheson, Coleman and Bell) was stored in a sealed container and used as received. J. T. Baker Reagent Grade dimethyl sulfoxide (DMSO) was passed through silica gel and stored over Linde 4A molecular sieves (Alfa Inorganic Chemical Co.).

All reaction runs were analyzed and the products were isolated using a Varian Aerograph 202-B temperature-programming vapor-phase chromatograph (vpc). All infrared (ir) spectra were obtained on a Perkin-Elmer 457 spectrophotometer. A Varian A-60A spectrometer[16] was used to obtain the nuclear magnetic resonance (nmr) spectra.

1-Fluoronaphthalene–*n*-Butyl Mercaptide Reaction (Run 1).—A stirred mixture of 11.25 g (0.125 mol) of *n*-butyl mercaptan, 2.7 g (0.05 mol) of sodium methoxide, and 78.0 g (0.375 mol) of DMSO was heated to 80° in a 100-ml, three-necked, round-bottom flask equipped with a reflux condenser, thermometer, addition funnel, heating mantle, and magnetic stirrer. 1-Fluoronaphthalene (3.65 g, 0.025 mol) was added and the stirred mixture was heated and refluxed (110°) for 1 hr. The reaction mixture was then added to 100 ml of ice water and extracted four times with 100-ml portions of ethyl ether. The combined ether extracts were washed with aqueous sodium hydroxide and dried over anhydrous magnesium sulfate. The oily residue (4.36 g) left after the ether was evaporated was the neutral fraction.

The aqueous layer from the reaction mixture was acidified and extracted with ethyl ether After drying and evaporation, the ether extract yielded less than 20 mg of an oily liquid. This same amount of material was found in the acidic layer of every run. The yield was so small that this material was not analyzed.

The neutral fraction was separated on the vpc using a 6 ft × 0.25 in. column packed with a mixture of 6% Carbowax 20M and 6% SE-30 on 60–80 mesh Chromosorb G, acid washed, at 200°. Analysis was done using 1-bromo-4-methylnaphthalene as an internal standard[17] for the *n*-butyl sulfide products and 1,4-dimethylnaphthalene as an internal standard for the *tert*-butyl sulfide products. The vpc was temperature programmed from 80 to 200° at a rate of 12° per minute.

Three compounds were isolated from the reaction mixture. These proved to be di-*n*-butyl disulfide[18] [*Anal.* Calcd for $C_8H_{18}S_2$: C, 53.87; H, 10.17; S, 35.95. Found: C, 53.85; H, 10.03; S, 35.78],[20] $n^{29}D$ 1.4918 (lit.[21] $n^{20}D$ 1.4926), 1-fluoronaphthalene (30%), and *n*-butyl 1-naphthyl sulfide (I, 47%, $n^{29}D$ 1.6044). The *n*-butyl 1-naphthyl sulfide exhibited ir bands at 3055, 2955, 2930, 2875, 1590, 1560, 1500, 1460, 1380, 1260, 1215, 1200, 1025, 975, 790, 770, and 665 cm^{-1} and the following nmr peaks: δ 8.4 (m, 1), 7.3–7.8 (m, 6), 2.95 (t, 2), 1.40–1.80 (m, 4), 0.95 (t, 3). *Anal.* Calcd for $C_{14}H_{18}S$: C, 77.73; H, 7.46; S, 14.82. Found: C, 77.65; H, 7.57; S, 14.82.

2-Fluoronaphthalene–*n*-Butyl Mecaptide Reaction (Run 2).—This reaction was carried out in the same manner as the 1-fluoronaphthalene reaction except that a small portion of the DMSO was used to dissolve the 2-fluoronaphthalene in order to facilitate the addition. The reaction yielded 20% recovered 2-fluoronaphthalene and *n*-butyl 2-naphthyl sulfide (II, 51%, $n^{29}D$ 1.6196). Compound II exhibited ir bands at 3080, 2960, 2930, 2870, 1625, 1590, 1570, 1500, 1460, 1430, 1380, 1335, 1270, 1220, 1190, 1130, 1070, 1015, 960, 940, 880, 850, 810, 740, and 600 cm^{-1} and the following nmr peaks: δ 7.10–7.80 (m, 7), 2.90 t, 2), 1.20–1.90 (m, 4), 0.90 (t, 3). *Anal.* Calcd for $C_{14}H_{18}S$: C, 77.73; H, 7.46; S, 14.82. Found: C, 78.00; H, 7.50; S, 14.96.

1-Bromo- and 2-Bromonaphthalene–*n*-Butyl Mercaptide Reactions (Runs 3 and 4).—These reactions were carried out the same as runs 1 and 2. The conversions and yields are given in Table I.

1-Fluoronaphthalene–*tert*-Butyl Mercaptide Reaction (Run 5).—This reaction was carried out the same as run 1 except that *tert*-butyl mercaptan was used and the reaction was refluxed at 95° for 24 hr. The products of this reaction proved to be di-*tert*-butyl disulfide (the ir spectrum of this material was similar to that of the di-*n*-butyl disulfide product) and *tert*-butyl 1-naphthyl sulfide (III, 73%, mp 53.5–55°). The ir spectrum for III exhibited bands at 3070, 3050, 2960, 2940, 2920, 2900, 2860, 1590, 1560, 1500, 1470, 1455, 1390, 1380, 1365, 1325, 1250, 1215, 1200, 1165, 1155, 1135, 1060, 1020, 975, 955, 865, 800, 775, 735, 670, 630, and 580 cm^{-1}. The nmr spectrum for III contained peaks at δ 8.60–8.80 (m, 1), 7.10–7.80 (m, 6), and 1.20 (s, 9). *Anal.* Calcd for $C_{14}H_{18}S$: C, 77.73; H, 7.46; S, 14.82. Found: C, 77.96; H, 7.46; S, 14.92.

(15) J. S. Bradshaw and E. Y. Chen, unpublished observations.

(16) The Varian A-60A spectrometer was purchased under the National Science Foundation Grant GP-6837.

(17) A. B. Littlewood, "Gas Chromatography, Principles, Techniques and Applications," Academic Press, New York, N. Y., 1962, p 246.

(18) This product was isolated when the reaction mixture without 1-fluoronaphthalene was subjected to the same conditions and work-up. Indeed, mercaptans are easily oxidized to disulfides.[19]

(19) T. J. Wallace, A. Schriesheim, and W. Bartok, *J. Org. Chem.*, **28**, 1311 (1963).

(20) C–H–S analysis was performed by M-H-W Laboratories, Garden City, Mich.

(21) R. C. West, Ed., "Handbook of Chemistry and Physics," 50th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1969–1970, p C-273.

2-Fluoronaphthalene–*tert*-Butyl Mercaptide Reaction (Run 6). This reaction was carried out in the same manner as run 5. *tert*-Butyl 2-naphthyl sulfide (IV, 48%, mp 58.5–59.5°) was the only aromatic product. Compound IV exhibited ir bands at 3060, 3040, 2980, 2960, 2940, 2920, 2900, 2860, 1585, 1470, 1455, 1360, 1350, 1340, 1270, 1240, 1220, 1170, 1150, 1130, 1075, 1020, 965, 950, 900, 865, 825, 745, 650, and 635 cm^{-1} and the following nmr peaks: δ 7.98 (m, 1), 7.25–7.80 (m, 6), and 1.30 (s, 9). *Anal.* Calcd for $C_{14}H_{16}S$: C, 77.73; H, 7.46; S, 14.82. Found: C, 77.68; H, 7.24; S, 14.58.

1-Bromo- and 2-Bromonaphthalene–*tert*-Butyl Mercaptide Reactions (Runs 7 and 8).—These reactions were carried out the same as runs 5 and 6. The conversions and yields are listed in Table I.

Registry No.—DMSO, 67-68-5.

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The Specific Deuteration of the Camphor Skeleton. Reduction of Chlorosulfoxides[1]

G. C. JOSHI[2] AND E. W. WARNHOFF*

Department of Chemistry, University of Western Ontario, London, Canada

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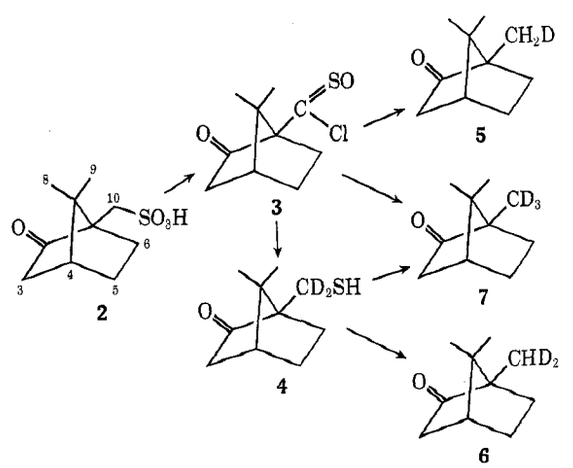
A convenient and inexpensive method has been developed for preparation of 9- and 10-deuterated camphors by the stepwise reduction of the corresponding chlorosulfoxide (oxythio acyl chloride) with deuterated amalgamated aluminum and/or Raney nickel. Simple procedures for stereoselective deuteration of camphor at C-3, C-4, C-5, and C-6 are also described.

For a proposed study of the stereochemistry of halogenation of camphor (**1**) and its enol derivatives, the analysis of product mixtures was to be done by nmr spectroscopy, a technique which had proved invaluable in a similar study with 3-keto steroid derivatives.[3] In particular, the chemical shifts of the C-8 methyl group and the C-3 and C-4 protons were to be used to assign halogen stereochemistry in the products. Therefore, it was essential to be certain which of the three methyl peaks belonged to C-8 in each of the compounds involved, and for this purpose deuterium labeling of methyl groups was the logical tool. Rather than deuterate the C-8 methyl group,[4] it appeared from the known chemistry of camphor to be easier and more generally useful to label the C-9 and C-10 methyl groups. Of the three reported procedures[6] for so doing, (a) reduction of the appropriate carboxylic acid to the primary alcohol and thence by way of hydride reduction of the tosylate to a methyl group,[6a,b] (b) zinc reduction of the C-9 primary bromide,[6c] and (c) hydride reduction of the appropriate primary sulfonyl chloride to a methyl group,[6d] two (a and c) require the use of the expensive lithium aluminum deuteride, while the third (b) gives a fragmentation side product.

Therefore, a convenient, inexpensive three- or four-step method has been developed for the incorporation of one, two, or three deuterium atoms into the C-9 and C-10 methyl groups of camphor.[1] The method involves the previously unreported stepwise reduction of the chlorosulfoxide group (oxythio acyl chloride or thioacyl chloride *S*-oxide) in the readily available camphor-10-chlorosulfoxide (**3**) and 3-*endo*-bromocamphor-9-chlorosulfoxide (**9**) with the cheapest source of deuterium, deuterium oxide. Since our halogenation study also required deuterium at C-4, it seemed worthwhile to develop practical procedures for stereoselective deuteration of C-6, C-5, and C-3 as well.

Very recently, Rodig and Sysko[7] have reported a nine-step synthesis of racemic camphor from norbornanone. Their synthesis has the advantage of allowing C labeling as well as H labeling of the methyl groups, but for H labeling it has the disadvantages, compared to the presently described synthesis, of being longer, of giving racemic camphor, and of not readily permitting the preparation of 9- or 10-mono- or dideuteriocamphor. Thus the two syntheses are complementary.

Our 10-methyl deuteration begins with conversion of the commercially available sulfonic acid **2** *via* the



sulfonyl chloride into the chlorosulfoxide **3** by the pyridine–toluenesulfonyl chloride procedure.[8] The chlorosulfoxide could now be reduced in stages by a suitable combination of two neutral reagents: (a) Raney nickel (Ra Ni) and (b) amalgamated aluminum (Al/Hg) with or without deuterium oxide. Raney nickel was found to reduce the chlorosulfoxide all the

(1) Presented in part at the 51st Canadian Chemical Conference, Vancouver, 1968, and taken from the Ph.D. Thesis of G. C. J., 1968.

(2) Commonwealth Scholar, 1964–1968; Defence Research Laboratory (Materials), Kanpur, India.

(3) E. W. Warnhoff, *J. Org. Chem.*, **28**, 887 (1963).

(4) In principle, the C-10 methyl group of *d*-camphor could be labeled and then transformed into the C-8 methyl group of *l*-camphor by racemization and resolution,[5] but this procedure promised to be more tedious than the one adopted and would have given at most 50% yield per cycle.

(5) A. M. T. Finch and W. R. Vaughan, *J. Amer. Chem. Soc.*, **87**, 5520 (1965); *ibid.*, **91**, 1416 (1969).

(6) (a) J. D. Connelly and R. McCrindle, *Chem. Ind. (London)*, 379 (1965); (b) W. L. Meyer and A. P. Lobo, *J. Amer. Chem. Soc.*, **88**, 3181 (1966); W. L. Meyer, A. P. Lobo, and R. N. McCarty, *J. Org. Chem.*, **32**, 1754 (1967); (c) K. M. Baker and B. R. Davis, *Tetrahedron*, **24**, 1655 (1968); (d) D. R. Dimmel and J. Wolinsky, *J. Org. Chem.*, **32**, 410 (1967).

(7) O. R. Rodig and R. J. Sysko, *J. Org. Chem.*, **36**, 2324 (1971).

(8) J. Strating, *Recl. Trav. Chim. Pays-Bas*, **83**, 94 (1964).