The Displacement of Nitrite Ion in Nitrobenzenes by Sodium Thiolates[1]

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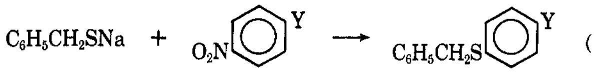
The reaction of sodium α-toluenethiolate or sodium 1-dodecanethiolate with substituted nitrobenzenes in *N*,*N*-dimethylformamide led to the production of alkyl aryl sulfides by displacement of the nitro group. The reaction was successful with ethyl *p*-nitrobenzoate and $C_6H_5CH_2S^-$, with methyl *o*-nitrobenzoate, *p*-nitrobenzaldehyde, and *p*-nitrobenzonitrile and $CH_3(CH_2)_{11}S^-$, and with methyl *p*-nitrobenzoate and *p*-nitrobenzophenone with both thiolate salts. The effect of concentration, solvent, and temperature on the yield was investigated.

Recently, we discovered that sodium α-toluenethiolate and methyl *p*-nitrobenzoate react, with loss of nitrite ion, to form methyl *p*-(benzylthio)benzoate (eq 1, compound **1**). The literature contains few examples of the synthesis of aromatic sulfides by nucleophilic substitution upon substrates containing functional groups.[2] There are only a small number of reported cases in which a nitro group has been replaced from disubstituted benzenoid hydrocarbons,[3-10] even though it is one of the most labile substituents.[11,12] This is no doubt due to the fact that it also has a very strong activating effect toward nucleophilic displacement of other substituents on an aromatic nucleus. With two exceptions,[3,4] only dinitro compounds are reported to have undergone loss of nitrite ion. The formation of **1** was thus unusual and an investigation of this reaction as a method of preparing substituted aryl sulfides was undertaken.

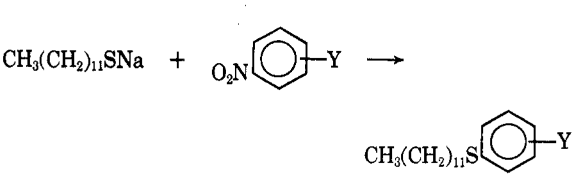
Results

Initial experiments were carried out using the sodium salt of α-toluenethiol (benzyl mercaptan) as the nucleophile and various para-substituted nitrobenzenes as substrates. Successful syntheses are outlined in eq 1. Attempts to prepare sulfides from *p*-nitrobenzamide and from *p*-nitrobenzaldehyde using sodium α-toluenethiolate in refluxing DMF (*N*,*N*-dimethylformamide) failed. It was then assumed that the α-toluenethiolate anion might be susceptible to oxidation at the benzyl carbon, preventing the success of the synthesis with certain substrates. Sodium 1-dodecanethiolate, of comparable nucleophilicity,[13] was therefore chosen for use in further experiments. Syntheses of sulfides which were accomplished with this salt are shown in eq 2.



(1)

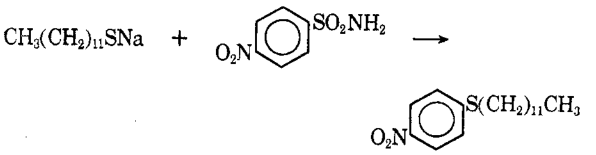
1, Y = CO_2CH_3
2, Y = $CO_2C_2H_5$
3, Y = $C_6H_5C{=}O$



(2)

4, Y = *p*-CO_2CH_3
5, Y = *p*-$C_6H_5C{=}O$
6, Y = *p*-CN
7, Y = *p*-CHO
8, Y = *o*-CO_2CH_3

The reaction of *p*-nitrobenzenesulfonamide and sodium 1-dodecanethiolate yielded dodecyl *p*-nitrophenyl sulfide (eq 3) *via* replacement of the sulfonamide function.



(3)

Oxidation of the thiolate anion can be the major reaction, as demonstrated by the conversion of sodium 1-dodecanethiolate to dodecyl disulfide when the salt was treated with methyl *m*-nitrobenzoate, or when it reacted with *p*-nitrobenzamide. Products from the reactions of various nitrobenzenes are summarized in Table I.

Relative Reactivity of Nitro Compounds.—An evaluation of the effectiveness of substituents in promoting the displacement of the nitro group may be made from Table I, comparing the formation of compounds **4, 5, 6,** and **7,** and of compounds **2** and **3** at the same concentration, temperature, and reaction time. These results, combined with the fact that the formation of the aldehyde **7** was successful at 25° while sodium 1-dodecanethiolate was oxidized to dodecyl disulfide by *p*-nitrobenzamide at 25°, lead to two similar orders of reactivity for para-substituted nitro compounds. These orders are, for $C_6H_5CH_2S^-$, $C_6H_5C{=}O > CO_2C_2H_5$; for $CH_3(CH_2)_{11}S^-$, $CN > C_6H_5C{=}O > CO_2CH_3 > CHO > CONH_2$. It is not unexpected that this does not parallel the established order for aromatic nucleophilic substitution,[14,15] since side reactions such as nucleophilic attack on the functional group or reduction of the nitro substituent are certain to compete effectively. The order given may be regarded as an empiri-

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[1] Supported by grants from the Central Fund for Research, Pennsylvania State University.

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TABLE I

REACTION CONDITIONS FOR SULFIDE PREPARATIONS IN *N*,*N*-DIMETHYLFORMAMIDE[a]

Nitrobenzene substituent	Sodium thiolate	Mol of reactants	Time, hr	Yield %	Procedure
p-CO_2CH_3	α-Toluene	0.034	1	36	A[b,c]
p-CO_2CH_3	α-Toluene	0.017	4	39	C[c]
p-$CO_2C_2H_5$	α-Toluene	0.010	2	10	A
p-$C_6H_5C{=}O$	α-Toluene	0.010	2	31	A
p-CO_2CH_3	Dodecyl	0.020	2	31	B
p-CO_2CH_3	Dodecyl	0.010	2	14	A
p-$C_6H_5C{=}O$	Dodecyl	0.010	2	31	A
p-CN	Dodecyl	0.010	2	53	A
p-CHO	Dodecyl	0.010	2	0	A
p-CHO	Dodecyl	0.040	48	53	D[d]
p-$CONH_2$	Dodecyl	0.010	2	0	A
p-$CONH_2$	Dodecyl	0.010	24	0[e]	D[d]
p-SO_2NH_2	Dodecyl	0.010	2	0[f]	A
p-SO_2NH_2	Dodecyl	0.010	48	0[g]	D[d]
o-CO_2CH_3	Dodecyl	0.050	48	23	D[d,h]
m-CO_2CH_3	Dodecyl	0.050	48	0[i]	D[c,d]

[a] All reactions were carried out using 50 ml of DMF unless otherwise noted. [b] Reaction open to air. [c] 100 ml of DMF used. [d] At 25°; other reactions at 155°. [e] 29% yield of dodecyl disulfide, based on moles of thiolate. [f] 30% yield of dodecyl *p*-nitrophenyl sulfide. [g] 33% yield of dodecyl *p*-nitrophenyl sulfide. [h] 75 ml of DMF used. [i] 54% yield of dodecyl disulfide.

cal one which includes side reactions peculiar to each compound.

Effect of Reaction Conditions.—A study of the effect of concentration, temperature, and reaction time is contained in Table II.

TABLE II

FORMATION OF METHYL *p*-(DODECYLTHIO)BENZOATE IN *N*,*N*-DIMETHYLFORMAMIDE[a]

Expt	Mol of reactants	Time, hr	Yield, %
I	0.010	2	7[b,c]
II	0.010	2	13[c,d]
III	0.010	2	14[c-e]
IV	0.010	48	26[d,f]
V	0.020	2	31[b,c]
VI	0.050	48	12[d,f]

[a] All reactions in 50 ml of solvent except experiment VI which was carried out in 75 ml. [b] Thiolate salt formed *in situ* (procedure B). [c] At 155°. [d] Thiolate salt prepared previously (procedure A). [e] Reaction open to air. [f] At 25°.

Comparison of experiments I and II shows that use of previously prepared thiolate salt results in increased yield, compared to *in situ* formation. Increasing the concentrations of the reactants increased the yield for reactions at 155° (experiments I and V). A similar increase in yield was not obtained in reactions carried out at room temperature (experiments IV and VI). The displacement is favored at low concentrations by a long reaction time at 25° (experiment IV) rather than a few hours at reflux (155°) (experiment II). There was no difference in the yields when the reaction was open to air (experiment III) compared to the same conditions under a nitrogen atmosphere (experiment II). Table I shows that there was only a small reduction in the yield of methyl *p*-(benzylthio)benzoate due to exposure to air. We conclude that oxidation of the thiolate anion by atmospheric oxygen is not an important side reaction, if it occurs at all.

Effect of Solvent.—Table III shows the effect of three solvents upon the reaction of sodium 1-dodecanethiolate and methyl *p*-nitrobenzoate. Dimethyl sulfoxide showed no advantage over *N*,*N*-dimethylformamide although it is nearly four times as effective in promoting the reaction between *p*-dinitrobenzene and piperidine.[16] Oxidation of the thiolate anion to dodecyl disulfide occurred readily in sulfolane.

TABLE III

PER CENT YIELDS OF PRODUCTS OF THE REACTION OF SODIUM 1-DODECANETHIOLATE AND METHYL *p*-NITROBENZOATE IN VARIOUS SOLVENTS[a]

Products	DMF	DMSO[b]	Sulfolane[c]
Methyl *p*-(dodecylthio)benzoate	14	14	0
Dodecyl disulfide	0	0	43

[a] All data for 140°, reaction time 2 hr, initial concentration 0.20 *M*. [b] Dimethyl sulfoxide. [c] Tetramethylene sulfone.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are corrected. Boiling points are uncorrected. Infrared spectra were measured in a Perkin-Elmer 237B grating spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Sulfolane used was Sulfolane-W, a gift from Shell Chemical Co. Other solvents were commercial reagent grade products. Preparation of sodium α-toluenethiolate, sodium 1-dodecanethiolate, and *p*-nitrobenzophenone is described below. Other organic compounds used were highly quality commercial products. The boiling point of the petroleum ether used is 30–60°. Baker silica gel was used for column chromatography.

Unless otherwise noted all reactions were carried out under nitrogen. Nitrogen was passed through the apparatus while it was flamed dry and for 10 min thereafter. Following the addition of the solvent and all reactants, nitrogen was passed in for 10 min, maintaining a flow rate sufficient to flush the apparatus thoroughly. Procedures used for the isolation of the crude products from various reactions are outlined below.

Procedure A.—The nitro compound, the thiolate salt, and the solvent were heated and then maintained at an elevated temperature. At the end of the reaction period the solvent was removed *in vacuo*.

Procedure B.—The thiol was dissolved in the solvent and heated with an equimolar amount of sodium metal until the reaction was completed. The solution was cooled, the nitro compound was added, and the mixture was then heated to the desired temperature. After the reaction was completed, the solvent was removed at reduced pressure.

Procedure C.—The thiolate was formed *in situ* as in procedure B. Isolation of the crude product was accomplished by the addition of water (twice the volume of the solvent used).

Procedure D.—The nitro compound, the thiolate salt, and the solvent were stirred at room temperature. Addition of water (twice the volume of the solvent used) resulted in separation of the product mixture.

Methyl *p*-(Dodecylthio)benzoate (4) (Tables II, III).—Extraction of the residue from evaporation using 50 ml of boiling methanol gave the crude ester, typical mp 62–64° after one recrystallization from petroleum ether.

Dodecyl Disulfide (Table III).—The crude residue was boiled with 50 ml of methanol and the hot solution was filtered from an oil, which crystallized upon standing. The product was recrystallized from 1-propanol, mp 32.0–34.0° (lit.[17] mp 34°).

Methyl *p*-(Benzylthio)benzoate (1).—One recrystallization of the impure product from methanol yielded 1.7 g (39%) of the ester, mp 88.4–90.4°, ir (CCl_4) 1725 cm^{-1}. An analytical sample was obtained after three additional recrystallizations, mp 90.4–91.9°.

Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46; S, 12.41. Found: C, 69.63; H, 5.60; S, 12.55.

Ethyl *p*-(Benzylthio)benzoate (2).—The product was dissolved in 50 ml of ether, and the solution was filtered, extracted with

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water, and dried ($MgSO_4$). Evaporation of the ether yielded an oil which solidified upon standing. The solid was taken up in 10 ml of benzene and chromatographed on 30 g of silica gel, eluting with benzene in fractions of 15 ml. The product was contained in fractions 9, 10, and 11: 0.30 g (10%), mp 54–56°; ir (CCl_4) 1715 cm^{-1}. Two recrystallizations from petroleum ether gave an analytical sample, mp 57.0–57.8° (lit.[18] mp 60°).

Anal. Calcd for $C_{16}H_{16}O_2S$: S, 11.77. Found: S, 11.72.

p-**(Benzylthio)benzophenone (3).**—The crude solid was dissolved in 50 ml of ether and filtered, and the filtrate was evaporated. The residue was recrystallized from methanol to give 0.95 g (31%) of **3**, mp 81.5–84.0°, ir (CCl_4) 1650 cm^{-1}. Four more recrystallizations from methanol afforded the pure ketone, mp 84.5–85.4°.

Anal. Calcd for $C_{20}H_{16}OS$: C, 78.91; H, 5.30; S, 10.53. Found: C, 79.07; H, 5.41; S, 10.74.

Methyl *p*-(Dodecylthio)benzoate (4) (Table I, 0.020 Mol).—The impure product was extracted with 140 ml of boiling methanol and the resulting solid was recrystallized from petroleum ether to give the ester: 2.1 g (31%); mp 62.9–65.4°; ir (CCl_4) 1720 cm^{-1}. Four more recrystallizations from petroleum ether gave pure **4**, mp 63.9–65.4°.

Anal. Calcd for $C_{20}H_{32}O_2S$: C, 71.37; H, 9.59; S, 9.53. Found: C, 71.55; H, 9.55; S, 9.33.

p-**(Dodecylthio)benzophenone (5).**—The residue was boiled with 35 ml of petroleum ether, yielding a crude product which was crystallized from methanol: 1.2 g (31%) of **5**; mp 45.7–46.7°; ir (CCl_4) 1650 cm^{-1}. Two further recrystallizations from methanol yielded pure product, mp 45.7–46.5°.

Anal. Calcd for $C_{25}H_{34}OS$: C, 78.48; H, 8.96; S, 8.38. Found: C, 78.65; H, 8.92; S, 8.31.

p-**Dodecylthiobenzonitrile (6).**—Extraction of the product with 50 ml of boiling methanol gave a solid which after recrystallization, twice from methanol, once from petroleum ether, yielded 1.6 g (53%) of **6**: mp 46.9–48.5°; ir (CCl_4) 2230 cm^{-1}; mp 48.5–49.2° after two more recrystallizations from petroleum ether.

Anal. Calcd for $C_{19}H_{29}NS$: C, 75.19; H, 9.63; N, 4.62; S, 10.57. Found: C, 75.05; H, 9.76; N, 4.60; S, 10.45.

p-**(Dodecylthio)benzaldehyde (7).**—Two recrystallizations of the crude product from methanol gave 6.5 g (53%) of the yellow aldehyde, mp 31.0–33.5°, ir (CCl_4) 1700 cm^{-1}.

A semicarbazone of **7** was prepared which was recrystallized from methanol and then several times from methanol–toluene, mp 185.7–186.9°.

Anal. Calcd for $C_{20}H_{33}N_3OS$: C, 66.06; H, 9.15; N, 11.56; S, 8.82. Found: C, 66.19; H, 9.23; N, 11.50; S, 8.60.

Methyl *o*-(Dodecylthio)benzoate (8).—The residue was dissolved in 100 ml of ether and filtered, and the filtrate was dried ($MgSO_4$) and evaporated. The solid was distilled, yielding 3.9 g (23%) of ester, bp 206–208° (0.65 mm). Three recrystallizations from methanol and three from petroleum ether gave pure product, mp 40.3–41.0°, ir (CCl_4) 1720 cm^{-1}.

Anal. Calcd for $C_{20}H_{32}O_2S$ C, 71.37; H, 9.59; S, 9.53. Found: C, 71.19; H, 9.40; S, 9.68.

p-**Nitrobenzenesulfonamide and Sodium 1-Dodecanethiolate.**—The residue from the reaction carried out at 155° was extracted with 50 ml of boiling methanol, yielding a solid which was recrystallized from methanol, 0.98 g (30%) of dodecyl *p*-nitrophenyl sulfide, mp 45.0–49.0°. After three recrystallizations from 1-propanol, mp 48.3–49.4° (lit.[19] mp 47°).

Anal. Calcd for $C_{18}H_{29}NO_2S$: C, 66.83; H, 9.04; N, 4.33; S, 9.91. Found: C, 66.81; H, 8.94; N, 4.31; S, 9.92.

p-**Nitrobenzamide and Sodium 1-Dodecanethiolate.**—The impure product was boiled with 50 ml of methanol and the hot solution was filtered from an oil. The oil solidified readily and was recrystallized from 1-propanol yielding dodecyl disulfide as white flakes, 0.58 g (29%), mp 31.1–33.3° (lit.[17] mp 34°). The identity of the product was confirmed by mixture melting point and by comparison of the infrared spectrum with that of an authentic sample which was prepared by the oxidation of sodium 1-dodecanethiolate with aqueous iodine–potassium iodide.

Methyl *m*-Nitrobenzoate and Sodium 1-Dodecanethiolate.—The mixture of solids obtained was boiled with 40 ml of methanol. The solution was decanted from an insoluble oil which solidified upon standing, 5.5 g (54%) of dodecyl disulfide, mp 31.0–33.0° (lit.[17] mp 34°). The identity of the product was confirmed by mixture melting point and by comparison of its infrared spectrum with that of an authentic sample.

Sodium 1-Dodecanethiolate.—Sodium metal (6.90 g, 0.300 g-atom) was converted to sodium methoxide by reaction with 100 ml of methanol. 1-Dodecanethiol (70.5 g, 0.349 mol) was added to the solution and the thiolate salt was isolated by evaporation of the methanol *in vacuo*. The solid was triturated with 200 ml of absolute ether, suction-filtered, stirred with 100 ml of absolute ether, and suction-filtered again. The salt was dried for 30 min at 30 mm and 100°, 65 g (97%). The product was analyzed by titrating a methanol solution with aqueous iodine. Purity by this method was at least 99%.

Sodium α-toluenethiolate was prepared and analyzed as described for sodium 1-dodecanethiolate. A total of 41 g (93%) of the salt was isolated; purity was at least 99%.

p-**Nitrobenzophenone.**—Aluminum chloride (16 g, 0.12 mol) was added in portions during 15 min to a refluxing mixture of 18.6 g (0.100 mol) of *p*-nitrobenzoyl chloride and 87.9 g (1.13 mol) of benzene. Refluxing was then continued for 65 min after which the mixture was poured onto 44 g of ice in 70 ml of 45% hydrochloric acid. The crude product was suction-filtered and recrystallized from glacial acetic acid, 11.3 g (50%), mp 136.8–137.7° (lit.[20] mp 135–137°).

Registry No.—Sodium α-toluenethiolate, 3492-64-6; sodium 1-dodecanethiolate, 26960-77-0; **1**, 26960-78-1; **3**, 26960-79-2; **4**, 26960-80-5; **5**, 26960-81-6; **6**, 26960-82-7; **7**, 26960-83-8; **7** semicarbazone, 26960-84-9; **8**, 26960-80-5.

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