Simple Syntheses of Aryl Alkyl Thioethers and of Aromatic Thiols from Unactivated Aryl Halides and Efficient Methods for Selective Dealkylation of Aryl Alkyl Ethers and Thioethers

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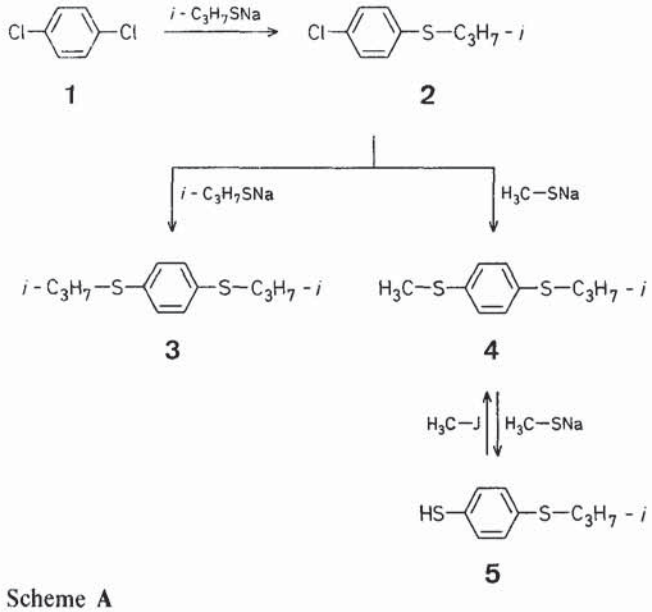
In a series of papers, we have recently described the synthesis of alkylthiobenzenes[1,2], alkoxybenzenes[3], and alkoxyaryl alkyl sulphides[4] by means of nucleophilic aromatic substitution reactions carried out on the unactivated halobenzenes or on the scarcely activated polyhalobenzenes and haloaryl alkyl sulphides. We have also described several methods to effect the selective dealkylation of these compounds to give thiophenols, phenols, or polymercaptobenzenes by means of sodium alkanethiolates, sodium alkoxides, or sodium[3,5-9]. All these processes are made possible by the use of hexamethylphosphoric triamide as solvent. This represents a limitation in view of the carcinogenic properties of this solvent.

We now report that all these reactions can also be effected with similar good results using dimethylformamide or dimethylacetamide as solvents. The new procedures therefore represent a substantial improvement. The range of application has been tested with several selected substrates (Tables). In most cases only the *p*-disubstituted compounds have been examined. Similar good results very likely can be obtained with the *o*- and *m*-isomers as it was found in previous works in hexamethylphosphoric triamide.

Nucleophilic aromatic substitutions of unactivated aryl halides: The nucleophilic aromatic substitutions carried out with the scarcely activated halobenzenes and excess sodium 2-propanethiolate (Table 1, runs 2, 3, 4) gave good yields of the benzene derivatives, in which all the chlorine atoms had been substituted by the isopropylthio group. In the case of *p*-dichlorobenzene **(1)**, the use of lower amounts of the nucleophile (run 1) gives rise to a mixture of the mono-substituted **(2)** and the disubstituted product **(3)** together with unreacted starting compound (20%), indicating that the substitutions in the *p*-dichlorobenzene and in the *p*-chlorophenyl isopropyl sulphide **(2)** occur with comparable rates (Scheme **A**).

Sodium methanethiolate and sodium ethanethiolate react with **2** to give the 1,4-bis[alkylthio]benzenes corresponding to **4** (Table 1, runs 5 and 6). These, however, can in part further react at the primary alkylthio group to give the corresponding thiophenols **5.** Methyl or ethyl iodide was therefore added to the reaction mixtures to reconvert **5** into **4** (Scheme **A**).



Scheme **A**

Methoxyphenyl alkyl sulphides can be obtained by the reaction of the chlorophenyl alkyl sulphides with sodium methoxide. In these cases, displacement of the chlorine atom is in competition with the nucleophilic aliphatic substitution at the methylthio group or with the elimination reaction at the isopropylthio group so that some *p*-chlorothiophenol is also obtained from the reactions of *p*-chlorophenyl methyl sulphide and *p*-chlorophenyl isopropyl sulphide with sodium methoxide (Table 1, runs 7 and 8).

Selective dealkylations of bis[alkylthio]benzenes, bis[alkoxy]benzenes and of alkoxyaryl alkyl sulphides can be effected by nucleophilic aliphatic substitutions with sodium methanethiolate, by elimination with potassium *t*-butoxide, and by electron transfer with sodium.

Selective dealkylations by nucleophilic aliphatic substitution: With sodium methanethiolate, the reaction with *p*-isopropylthiophenyl methyl sulphide **(4)** or *p*-isopropoxyphenyl methyl ether occurs selectively at the primary alkyl group to give *p*-(isopropylthio)-thiophenol and *p*-(isopropoxy)-phenol, respectively (Table 1, run 9 and 10). As already observed in hexamethylphosphoric triamide, the reaction of *p*-methoxyphenyl methyl sulphide with methanethiolate gives selectively *p*-(methylthio)-phenol (run 11). It has been recently reported, that the use of sodium diethylamide in hexamethylphosphoric triamide/xylene gives *p*-(methoxy)-thiophenol instead[10]. The same process can also be effected by using sodium. Thus, the appropriate choice of the reagents permits the selective dealkylation of the methoxy or the methylthio groups in methoxythioanisoles.

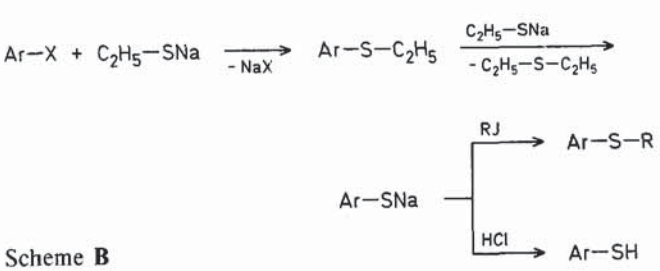
Selective dealkylations by elimination: The elimination reactions were effected by sodium methoxide in hexamethylphosphoric triamide. The same reactions in dimethylformamide were very slow and gave rise to mixtures of products. We have found that, in dimethylformamide, the best reagent to dealkylate aryl alkyl ethers or sulphides via elimination is potassium *t*-butoxide. In this way *p*-isopropylthiophenyl methyl sulphide

or *p*-isopropoxyphenyl methyl ether give *p*-methylthio-thiophenol or *p*-methoxyphenol, respectively (Table 1, runs 12 and 13). Interestingly, when the same reaction is applied to *p*-isopropoxyphenyl isopropyl sulphide the elimination takes place selectively at the alkoxy function to give *p*-isopropylthio-phenol (run 14).

Selective dealkylations by electron transfer: The dealkylation of aryl alkyl ethers and thioethers promoted by sodium cannot be effected in dimethylformamide. We have now found that also in this case the use of hexamethylphosphoric triamide can be avoided. The solvent employed for these reactions is the dimethylacetamide which can also be employed for all the other reactions reported above. When a solution of 1,2-bis[isopropylthio]benzene or 1,3,5-tris[isopropylthio]benzene in dimethylacetamide is treated with sodium, 1,2-benzenedithiol or 1,3,5-benzenetrithiol was obtained in good yield (Table 1, runs 15 and 16). The two starting products were prepared *in situ*. Thus, this method represents a very useful one-pot synthesis of poly(mercapto)benzenes from poly(chloro)benzenes. As already observed in hexamethylphosphoric triamide, the 1,2,4-trimethoxybenzene is selectively dealkylated at position 2 (run 18). Finally, treatment of methoxythioanisole with sodium gives the *p*-methoxythiophenol (run 17) by selective dealkylation of the methylthio group.

In conclusion, the results presented indicate that all the reactions previously described can be effected in dimethylformamide or dimethylacetamide with similar good results. The new procedures therefore represent a substantial practical improvement in respect to the previously described methods. The mechanistic aspects of these reactions have been already pointed out in the previous works[1-9] and can be directly applied to the reactions described in the present paper. Of particular interest are the three methods of dealkylation using sodium alkanethiolate, sodium alkoxide, or sodium. These are, in fact, complementary and the appropriate choice of the reagent permits selective dealkylation of the desired alkoxy or alkylthio group from aromatic substrates containing two or more different alkoxy groups, two different alkylthio groups, or an alkoxy and an alkylthio group.

Synthesis of aromatic thiols from unactivated aryl halides: A convenient one-pot synthesis of aromatic thiols from unactivated aryl halides can be effected by refluxing a solution of the aryl halide and sodium ethanethiolate in dimethylformamide. This synthesis is based on two interesting consecutive reactions: a nucleophilic aromatic substitution which occurs on the unactivated aryl halide and which affords the aryl ethyl sulphide, followed by a nucleophilic aliphatic substitution which effects the cleavage of these sulphides to afford the arenethiolate anions (Scheme **B**).



Scheme **B**

In respect to the previously described method[1,2,5], the above procedure has two major advantages: (a) the carcinogenic hexamethylphosphoric triamide is replaced by the less expensive dimethylformamide which can also be recovered easily by vacuum distillation and (b) ethanethiol is cheaper and easier to handle than methanethiol.

At the end of the reaction, the solution containing the sodium arenethiolates can be treated with dilute hydrochloric acid to obtain the thiophenols or directly used for further reactions. In some cases, we treated the cooled reaction mixture with an alkyl iodide in order to form an aryl alkyl sulphide, which could be more easily isolated than the corresponding thiophenol. No substantial differences can be observed between the results obtained and those reported. It is thus clear that the present procedure is much more convenient than that previously described and moreover it presents several advantages in respect to other methods described in the literature for the synthesis of aromatic thiols[11]. As indicated, this method is also useful for the preparation of mercaptopyridines and mercaptoquinolines and, very likely, can be applied to other heteroaromatic compounds (Table 2).

T.L.C. analyses were effected on Merck DC-Plastikfolien Kieselgel 60 F 254 using light petroleum as eluant. The purity of the products obtained after column chromatography was checked by G.L.C. analysis using a Hewlett-Packard 5830A chromatograph with a 20 in. 10% UCW 982 column and resulted to be in every case greater than 95%. The ^{1}H-N.M.R. spectra were recorded using a 90 MHz Varian EM 390 instrument.

1,4-Bis[isopropylthio]benzene (3); Typical Procedure for Runs 1–6 (Table 1):

A solution of 1,4-dichlorobenzene (1.47 g, 10 mmol) and sodium 2-propanethiolate[1] (4.9 g, 50 mmol) in dimethylformamide (30 ml) is stirred under nitrogen for 17 h at 100°C. The progress of the reaction is monitored by T.L.C. and G.L.C. The mixture is cooled, poured into water (100 ml) and extracted with ether (3 × 50 ml). The organic layer is washed with water (2 × 50 ml), dried with sodium sulphate, and evaporated. The residue (a single spot on T.L.C.) is chromatographed through a silica gel column using light petroleum as eluent, to give pure 1,4-bis[isopropylthio]benzene; yield: 1.83 g (91%); b.p. 168–169°C/18 torr (Ref.[1], b.p. 167–169°C/18 torr).

4-Methoxyphenyl Methyl Sulphide; Typical Procedure for Runs 7, 8 (Table 1):

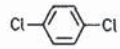
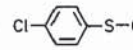
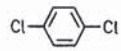
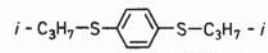
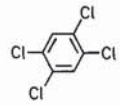
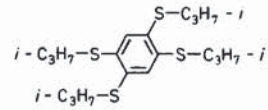
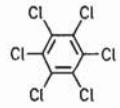
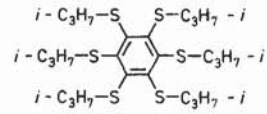
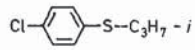
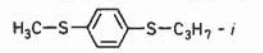
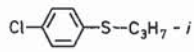
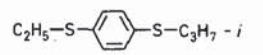
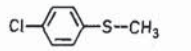
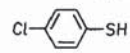
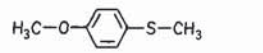
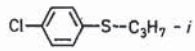
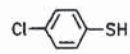
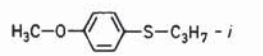
A solution of 4-chlorophenyl methyl sulphide (1.58 g, 10 mmol) and sodium methoxide (4.32 g, 80 mmol) in dimethylformamide (30 ml), is stirred under nitrogen for 22 h at 160°C. The progress of the reaction is monitored by T.L.C. The mixture is cooled and methyl iodide (0.7 g, 5 mmol) is added with stirring. The mixture is then poured into water (150 ml) and extracted with ether (3 × 50 ml). The organic phase is washed with water (2 × 50 ml), dried with sodium sulphate, and evaporated. The residue is chromatographed through a silica gel column using light petroleum as eluent to give 4-chlorophenyl methyl sulphide (0.12 g, 8%) and pure 4-methoxyphenyl methyl sulphide; yield: 1.03 g (67%); b.p. 123–124°C/18 torr (Ref.[4], b.p. 123–125°C/18 torr).

4-(Ethylthio)-phenyl Isopropyl Sulphide; Typical Procedure for Runs 9–11 (Table 1):

A solution of 4-(methylthio)-phenyl isopropyl sulphide (1.98 g, 10 mmol) and sodium methanethiolate[1] (3.5 g, 50 mmol) in dimethylformamide (30 ml) is stirred under nitrogen at 160°C for 1.5 h. The progress of the reaction is followed by T.L.C. The mixture is cooled and excess ethyl iodide (5 ml) is added. The mixture is poured into water (150 ml) and extracted with ether (3 × 50 ml). The organic layer is washed with water, dried with sodium sulphate, and evaporated. The residue (a single spot by T.L.C.) is chromatographed through a silica gel column using light petroleum as eluent, to give pure 4-(ethylthio)-phenyl isopropyl sulphide; yield: 2.0 g (95%); colourless liquid[6]. Bis-sulphone: m.p. 118–119° (Ref.[1,6], m.p. 117–118°C).

In the runs 10 and 11, no methyl iodide was added to the reaction mixture and the products were isolated as phenols[7,8] by pouring the reaction mixture into 0.1 normal hydrochloric acid (150 ml).

Table 1. Synthesis and Dealkylation of Aryl Alkyl Ethers and Thioethers (10 mmol) in Dimethylformamide (30 ml)

Run	Substrate	Reagent	Product[a]	Reaction Conditions			Yield [%][b]		Reference
				Equiv. of Reagent	Temp. [°C]	Time [h]	found	reported	
1		*i*-C_3H_7–SNa		1.5	100	14	57	72	1
1; 2		*i*-C_3H_7–SNa		1.5; 5	100; 100	14; 17	20; 91	7; 96	1
3		*i*-C_3H_7–SNa		8	100	1	95	75	2
4		*i*-C_3H_7–SNa		12	100	0.25	93	95	2
5		H_3C–SNa		3	100	17	79[c]	60	1
6		C_2H_5–SNa		3	100	18	94[d]	95	1
7		H_3C–ONa	 + 	8	160	22	8[e]	—	
							67	80	4
8		H_3C–ONa	 + 	7	160	5	28[e]	30[f]	4
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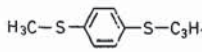
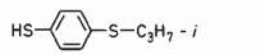
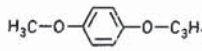
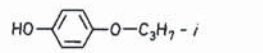
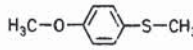
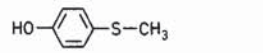
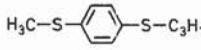
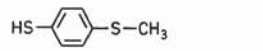
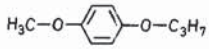
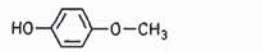
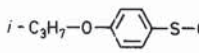
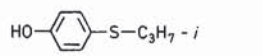
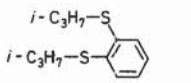
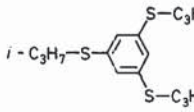
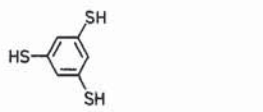
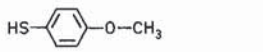
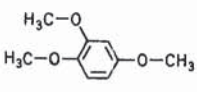
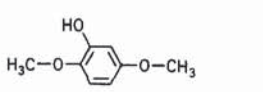
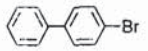
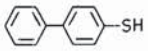
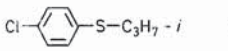
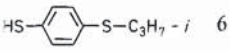
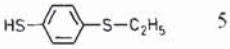
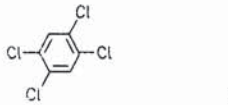
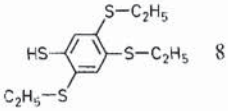
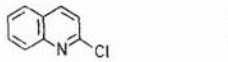
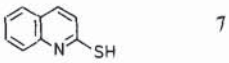
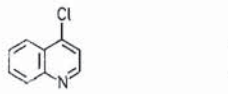
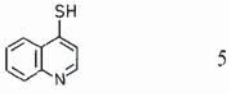
9		H_3C–SNa		5	160	1.5	95[g]	95	6
10		H_3C–SNa		5	160	2.5	93	93	8
11		H_3C–SNa		5	160	1.5	90	85	7
12		*t*-C_4H_9–OK		5	160	6	74[g]	87	6
13		*t*-C_4H_9–OK		5	160	15	86	65	8
14		*t*-C_4H_9–OK		7	160	6	69	75	8
15		Na		7	100[h]	15	93	89	9
16		Na		10	100[h]	16	84	90	9
17		Na		5	100[h]	15	66[g]	85	7
18		Na		6	100[h]	4	95	87	8

[a] Products identified by comparison of physical properties and ^{1}H-N.M.R. spectra with those reported in the references given.
[b] Yield of product isolated by column chromatography.
[c] Methyl iodide is added to the reaction mixture before work-up.
[d] Ethyl iodide is added to the reaction mixture before work-up.
[e] Product isolated as the methyl sulphide by adding methyl iodide to the cooled reaction mixture.
[f] Reaction carried out in hexamethylphosphoric triamide with sodium ethoxide.
[g] Product isolated as the ethyl sulphide by adding ethyl iodide to the cooled reaction mixture.
[h] Reaction carried out in dimethylacetamide.

Table 2. Synthesis of Aromatic Thiols from Aromatic Halides (10 mmol) and Sodium Ethanethiolate in Refluxing Dimethylformamide (30 ml)

Aromatic Halide	Aromatic Thiol[a]	Equiv. of $NaSC_2H_5$	Reaction Time [h]	Yield [%]		m.p. [°C] or b.p. [°C]/torr		^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
				found[b]	reported	found	reported	
		10	23	78	90[5]	168–169°/ 760	169°/ 760[12]	—
		6	22	67	96[5]	111–112°[c]	111°[13]	—
		6	22	95	90[5]	165–167°/ 18	166–168°/ 20[14,d]	2.5 (s, 3H); 7.1–7.7 (m, 6H); 8.1–8.25 (m, 1H)[e]
		5	4	94	88[5]	79–80°	79–80°[16]	3.5 (s, 1H); 7.0–7.7 (m, 7H)
		6	24	95[c]	90[5]	138–139°[f]	139–140°[1,f]	see Ref.[1]
		5	17	80[c,g]	—	171–173°[f]	171–173°[6,f]	see Ref.[6]
		8	1	75	85[2]	136–137°/ 0.05	130–131°/ 0.01[2]	see Ref.[2]
		5	16	70[c]	—	43–45°[d]	47°[15,d]	2.4 (s, 3H); 6.9–7.1 (m, 2H); 8.2–8.4 (m, 2H)[e]
		7	7	81[c]	—	58–59°[d]	58–59°[15,d]	2.6 (s, 3H); 6.95 (d, J=8.5 Hz, 1H); 6.9–7.6 (m, 4H); 7.8 (d, J=8.5 Hz, 1H)[e]
		5	6	80	80[5]	159–163°[c]	158–162°[15]	4.7 (s, 1H); 7.2–7.7 (m, 7H); 8.7 (m, 1H)[h]

[a] Products identified by ^{1}H-N.M.R. spectroscopy and by comparison of their physical data with those reported in the literature.
[b] Yield of product isolated by column chromatography.
[c] Product isolated as the methyl sulphide by adding methyl iodide to the cooled reaction mixture.
[d] m.p. or b.p. of the methyl sulphide.
[e] ^{1}H-N.M.R. spectrum of the methyl sulphide.
[f] m.p. of the corresponding bis-sulphone obtained by oxidation with hydrogen peroxide/acetic acid.
[g] A 4% yield of *p*-chlorothiophenol (isolated as *p*-chlorophenyl methyl sulphide) was also obtained.
[h] In CD_3OD.

4-(Methylthio)-phenyl Ethyl Sulphide; Typical Procedure for Runs 12–14 (Table 1):

A solution of 4-(methylthio)-phenyl isopropyl sulphide (1.98 g, 10 mmol) and potassium *t*-butoxide (5.6 g, 50 mmol) in dimethylformamide (30 ml) is stirred under nitrogen at 160°C for 6 h. The progress of the reaction is monitored by T.L.C. The mixture is cooled and excess ethyl iodide (5 ml) is added. The mixture is poured into water (150 ml) and extracted with ether (3 × 50 ml). The organic layer is washed with water, dried with sodium sulphate, and evaporated. The residue (a single spot by T.L.C.) is chromatographed through a silica gel column using light petroleum as eluent, to give pure 4-(methylthio)-phenyl ethyl sulphide; yield: 1.35 g (73%); colourless liquid[6]. Bissulphone: m.p. 171–173°C (Ref.[6], m.p. 171–173°C).

In the runs 13 and 14, no ethyl iodide was added to the reaction mixture and the products were isolated as phenols[8] by pouring the reaction mixture into 0.1 normal hydrochloric acid (150 ml).

1,2-Dimercaptobenzene; Typical Procedure for Runs 15–18 (Table 1):

A solution of 1,2-dichlorobenzene (1.47 g, 10 mmol) and sodium 2-propanethiolate (4.9 g, 50 mmol) in dimethylacetamide (30 ml) is stirred under nitrogen at 100°C for 24 h. The progress of the reaction is monitored by T.L.C. After this time, all the starting compound has been consumed and the solution contains the 1,2-bis[isopropylthio]benzene. Small pieces of sodium (1.6 g, 0.07 mol) are added and the mixture is stirred under nitrogen at 100°C for 15 h. The progress of the reaction is monitored by T.L.C. The mixture is cooled, poured into 0.1 normal hydrochloric acid (150 ml) and extracted with ether (3 × 50 ml). The organic layer is washed with water, dried with sodium sulphate, and evaporated. The residue is pure 1,2-dimercaptobenzene; yield: 1.32 g (93%); b.p. 92–94°C/5 torr (Ref.[9], b.p. 85–87°C/4 torr).

β-Mercaptonaphthalene; Typical Procedure (Table 2):

A solution of β-bromonaphthalene (2.07 g, 10 mmol) and sodium ethanethiolate[1] (4.2 g, 50 mmol) in dimethylformamide (30 ml) is stirred under nitrogen under reflux for 4 h. The progress of the reaction is monitored by T.L.C. The mixture is cooled and most of the dimethylformamide is distilled off in vacuum. The residue is poured into 0.1 normal hydrochloric acid (150 ml) and extracted with ether (3 × 50 ml). The organic layer is washed with water, dried with sodium sulphate, and evaporated. The residue is chromatographed through a silica gel column to give pure β-mercaptonaphthalene; yield: 1.5 g (94%); m.p. 79–80°C (Ref.[16], m.p. 79–80°C).

^{1}H-N.M.R. ($CDCl_3$): δ = 3.50 (s, 1H); 7.0–7.7 ppm (m, 7H).

To isolate *4-mercaptoquinoline*, the residue after distillation of dimethylformamide, is treated with ammonium chloride solution and then with dilute hydrochloric acid to pH 5.5. The yellow solid is extracted with chloroform. Alternatively, the mixture is treated with methyl iodide to give *4-methylthioquinoline*, yield: 93%; m.p. 68–69°C (Ref.[15], m.p. 70–72°C).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.40$ (s, 3 H); 6.80 (d, 1 H, $J = 4.5$ Hz); 7.2–7.6 (m, 2 H); 7.8–8.05 (m, 2 H); 8.5 ppm (d, 1 H, $J = 4.5$ Hz).

In order to isolate the methyl sulphides (see Table 2), methyl iodide (5 ml) is added to the mixture after distillation of the solvent. The residue is then poured into water and worked up in the usual way.

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