A Simple Synthesis of Alkoxyaryl Alkyl Sulphides from Dichlorobenzene Derivatives

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The synthesis of alkoxyaryl alkyl sulphides (thioethers) does not present difficulties, but it requires a series of sometimes tedious steps. Thus, for instance, the methoxyphenyl methyl sulphides are prepared by methylation[1] of the methoxythiophenols which can be obtained either from the methoxyanilines[2] or from the sulphonyl chlorides[3]. The latter method is limited to substrates which undergo electrophilic substitution by chlorosulphonic acid. The preparation of thiophenols from anilines is performed via conversion of the diazonium salts into aryl ethyl xanthates which are then hydrolyzed or reduced by lithium aluminum hydride[2]. The procedure described here is considerably advantageous over the existing methods since the title compounds can be conveniently obtained in high yields from readily available starting products.

We have recently reported that unactivated aryl halides react easily with sodium alkanethiolates to give aryl alkyl sulphides if hexamethylphosphoric triamide (HMPT) is used as solvent[4-7]. These reactions proceed via an S_NAr mechanism[7]. It was also demonstrated that the alkylthio function activates the nucleophilic substitution of chlorine[7] and nitro[8] groups by thiolate anion; utilizing this fact we have now elaborated a synthesis of alkoxyaryl alkyl sulfides from dichlorobenzene derivatives. The method consists of two consecutive nucleophilic aromatic substitutions, first by sodium alkanethiolates and then by sodium alkoxides[9].

The reactions of dichlorobenzenes **(1)** with sodium alkanethiolates in hexamethylphosphoric triamide at 100°C give good yields of the monosubstituted products, chloroaryl alkyl sulphides **(2).** Minor amounts of disubstitution products are also formed in some cases (runs c and f in Table 1) but these products can be easily separated by column chromatography.

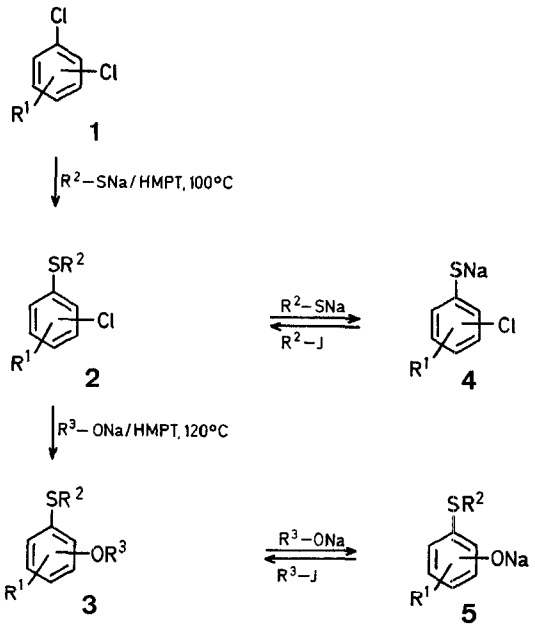

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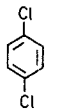
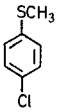
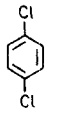
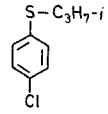
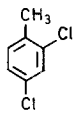
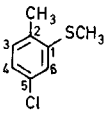
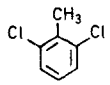
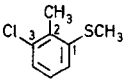
Table 1. Reaction of Dichlorobenzenes and Dichlorotoluenes (**1**; 20 mmol) with Sodium Alkanethiolates (30 mmol) in Hexamethylphosphoric Triamide (30 ml) at 100 °C

Run	Educt **1**	R^2	Reaction time [h]	Product **2**[a]	Yield[b] [%]	m.p. or b.p./torr [°C]	Molecular formula[c] or b.p./torr [°C] reported	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
a		CH_3	2.5		81	b.p. 119–121°/18	116°/14[11]	7.5–6.9 (m, 4H); 2.45 (s, 3H, S—CH_3)
b		CH_3	0.5		92	b.p. 108–109°/18	107°/15[12]	7.2–6.9 (m, 4H); 2.4 (s, 3H, S—CH_3)
c		CH_3	0.5		70[d]	b.p. 115–116°/18	110°/15[12]	7.25, 6.9 (AA'BB', 4H); 2.35 (s, 3H, S—CH_3)
d		i-C_3H_7	0.5		85	b.p. 117–118°/18	117–118°/18[7]	7.25 (s, 4H); 3.3 [sept, 1H, S—C<u>H</u>$(CH_3)_2$]; 1.2 [d, 6H, J=7 Hz, S—CH$(C\underline{H}_3)_2$]
e		CH_3	0.75		76[e]	—[f] (m.p. 102–104°)[g]	C_8H_9ClS (172.7)	7.1–6.9 (m, 3H); 2.4 (s, 3H, S—CH_3); 2.2 (s, 3H, CH_3)
f		CH_3	0.5		86[h]	—[f] (m.p. 96–98°)[i]	C_8H_8ClS (172.7)	7.2–6.9 (m, 3H); 2.4 (s, 3H, S—CH_3); 2.35 (s, 3H, CH_3)

[a] The products were identified by their ^{1}H-N.M.R. spectra and by comparison of their physical properties with those reported in the literature.

[b] Yields (based on **1**) of product isolated by column chromatography.

[c] The microanalyses of the new compounds and of their derivatives mentioned in the footnotes were in good agreement with the calculated values: C, ±0.27; H, ±0.21; S, ±0.18.

[d] *1,4-Bis[methylthio]-benzene*[6] was also formed.

[e] A 6% yield of *3-chloro-4-methylphenyl methyl sulphide* was also obtained as an oil.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ=7.3–6.95 (m, 3H); 2.45 (s, 3H, S—CH_3); 2.3 ppm (s, 3H, CH_3).

3-Chloro-4-methylphenyl methyl sulphone was obtained by oxidation with H_2O_2/AcOH; m.p. 87–89 °C.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ=7.85 (d, J=2 Hz, 2-H); 7.65 (dd, J=7.8 and 2 Hz, 6-H); 7.35 (d, J=7.8 Hz, 5-H); 3.0 (s, 3H, SO_2—CH_3); 2.4 ppm (s, 3H, CH_3).

[f] Oil; b.p. not determined.

[g] m.p. of *5-chloro-2-methylphenyl methyl sulphone* which was obtained by oxidation with H_2O_2/AcOH.

^{1}H-N.M.R. ($CDCl_3$/TMS) of this sulphone: δ=7.95 (d, J=2 Hz, 6-H); 7.45 (dd, J=7.8 and 2 Hz, 4-H); 7.25 (d, J=7.8 Hz, 3-H); 3.05 (s, 3H, SO_2-CH_3); 2.65 ppm (s, 3H, CH_3).

[h] A 7% yield of *2-methyl-3-methylthiobenzenethiol* was also obtained; m.p. 44–45 °C.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ=7.3–6.9 (m, 3H); 2.5 (s, 6H, S—CH_3, CH_3); 2.45 ppm (s, 1H, SH).

S-Methylation of the benzenethiol with methyl iodide gave 2,6-bis[methylthio]-toluene.

^{1}H-N.M.R. ($CDCl_3$/TMS): δ=7.25–6.8 (m, 3H); 2.4 (s, 6H, 2S—CH_3); 2.35 ppm (s, 3H, CH_3).

Oxidation of the bis-thioether with H_2O_2/AcOH gave *2,6-bis[methylsulphonyl]-toluene;* m.p. 204–205 °C.

^{1}H-N.M.R. (DMSO-d_6/TMS): δ=8.3 (d, J=7.8 Hz, 3-H, 5-H); 7.75 (t, J=7.8 Hz, 4-H); 3.35 (s, 6H, $2SO_2$—CH_3); 3.0 ppm (s, 3H, CH_3).

[i] m.p. of *3-chloro-2-methylphenyl methyl sulphone* which was obtained by oxidation with H_2O_2/AcOH.

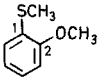
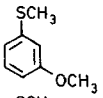
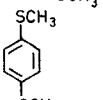
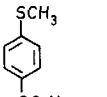
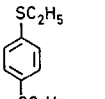
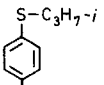
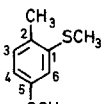
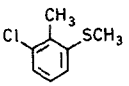
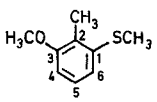
^{1}H-N.M.R. ($CDCl_3$/TMS): δ=7.9 (dd, J=7.8 and 1.5 Hz, 6-H); 7.6 (dd, J=7.8 and 1.5 Hz, 4-H); 7.25 (t, J=7.8 Hz, 5-H); 3.1 (s, 3H, SO_2—CH_3); 2.75 ppm (s, 3H, CH_3).

Further, some dealkylation of the methylthio group may occur[5] but the thiophenols **4** thus formed can be easily reconverted into the sulphide by adding methyl iodide to the reaction mixture prior to work-up. In the case of 2,4-dichlorotoluene, substitution takes place almost exclusively at the 2-position, the 4-substitution product (methyl 3-chloro-4-methylphenyl sulphide) being formed only in very small amounts.

The chloroaryl alkyl sulphides **2** react with excess sodium alkoxide in hexamethylphosphoric triamide at 120 °C to afford the alkoxyaryl alkyl sulphides **3** in good yields. Under the experimental conditions employed, compounds **3** are dealkylated to some extent to give the corresponding phenols **5**; it is therefore necessary to add alkyl iodides to the reaction mixtures to reconvert the phenols **5** into the ethers **3**. It is interesting to note that this dealkylation process occurs selectively at the alkoxy function and does not involve the alkylthio group.

The reaction of 4-chlorophenyl isopropyl sulphide (Table 2, run l) with sodium ethoxide afforded, after treatment with ethyl iodide, the desired 4-ethoxyphenyl isopropyl sulphide together with considerable amounts of 4-chlorophenyl ethyl sulphide, which obviously originates from 4-chlorobenzenethiol. The formation of this compound indicates that the nucleophilic substitution of the Cl-atom is in competition with

Table 2. Reactions of Chloroaryl Alkyl Sulphides (**2**; 10 mmol) with Sodium Alkoxides (80 mmol) in Hexamethylphosphoric Triamide (30 ml) at 120 °C

Run	Educt **2**	R^3	Reaction time [h]	Product **3**[a]	Yield[b] [%]	m.p. or b.p./torr [°C]	Molecular formula[c] or Lit. data [°C]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
g		CH_3	12		78	b.p. 123–125°/18	b.p. 125°/15[13]	7.1–6.5 (m, 4H); 3.75 (s, 3H, OCH_3); 2.3 (s, 3H, S—CH_3)
h		CH_3	10		70	b.p. 125–127°/18	b.p. 118–119°/10[14]	7.2–6.5 (m, 4H); 3.65 (s, 3H, OCH_3); 2.35 (s, 3H, S—CH_3)
i		CH_3	15		80	b.p. 128–130°/18	b.p. 90–95°/2[15]	7.2, 6.75 (AA'BB', 4H); 3.7 (s, 3H, OCH_3); 2.4 (s, 3H, S—CH_3)
j		C_2H_5	10		65	—[d] (m.p. 87–89°)[e,f]	(m.p. 89–89.5°)[e,16]	7.2, 6.75 (AA'BB', 4H); 3.95 (q, 2H, O—CH_2—CH_3); 2.4 (s, 3H, S—CH_3); 1.35 (t, 3H, O—CH_2—CH_3)
k		C_2H_5	10		80	—[d] (m.p. 40–41°)[e,g]	(oil)[e,16]	7.25, 6.75 (AA'BB', 4H); 3.95 (q, 2H, O—CH_2—CH_3); 2.8 (q, 2H, S—CH_2—CH_3); 1.4 (t, 3H, O—CH_2—CH_3); 1.25 (t, 3H, S—CH_2—CH_3)
l		C_2H_5	1		60[h]	—[d] (m.p. 80–81°)[e,i]	$C_{11}H_{16}OS$ (196.3)	7.25, 6.7 (AA'BB', 4H); 3.9 (q, 2H, O—CH_2—CH_3); 3.1 [sept, 1H, S—$CH(CH_3)_2$]; 1.35 (t, 3H, O—CH_2—CH_3); 1.2 [d, 6H, S—$CH(CH_3)_2$]
m		CH_3	30		61	—[d,j]	$C_9H_{12}OS$ (168.3)	7.0 (d, J=8,5 Hz, 3-H); 6.75 (d, J=2.5 Hz, 6-H); 6.55 (J=8.5 and 2.5 Hz, 4-H); 3.7 (s, 3H, OCH_3); 2.4 (s, 3H, S—CH_3); 2.25 (s, 3H, CH_3)
n		CH_3	30		73	—[d] (m.p. 102–104°)[e,k]	$C_9H_{12}OS$ (168.3)	7.1 (t, J=7.8 Hz, 5-H); 6.8 (d, J=7.8 Hz, 4-H); 6.6 (d, J=7.8 Hz, 6-H); 3.8 (s, 3H, OCH_3); 2.4 (s, 3H, S—CH_3); 2.25 (s, 3H, CH_3)

[a] The products were identified by their ^{1}H-N.M.R. spectra and by comparison of their physical properties with those reported in the literature.

[b] Yield (based on **2**) of product isolated by column chromatography.

[c] See footnote c of Table 1.

[d] Oil; b.p. not determined.

[e] m.p. of corresponding sulphone which is obtained by oxidation with H_2O_2/AcOH.

[f] ^{1}H-N.M.R. ($CDCl_3$/TMS) of *4-ethoxyphenyl methyl sulphone:* δ=7.85, 6.9 (AA'BB', 4H); 4.1 (q, 2H, O—CH_2—CH_3); 3.0 (s, 3H, SO_2—CH_3); 1.4 ppm (s, 3H, O—CH_2—CH_3).

[g] ^{1}H-N.M.R. ($CDCl_3$/TMS) of *4-ethoxyphenyl ethyl sulphone:* δ=7.75, 6.95 (AA'BB', 4H); 4.1 (q, 2H, O—CH_2—CH_3); 3.05 (q, 2H, SO_2—CH_2—CH_3); 1.4 (t, 3H, O—CH_2—CH_3); 1.25 ppm (t, 3H, SO_2—CH_2—CH_3).

[h] A 30% yield of *4-chlorophenyl ethyl sulphide* was also obtained. ^{1}H-N.M.R. ($CDCl_3$/TMS): δ=7.15 (s, 4H); 2.85 (q, 2H, S—CH_2—CH_3); 1.25 ppm (t, 3H, S—CH_2—CH_3).

[i] ^{1}H-N.M.R. ($CDCl_3$/TMS) of *4-ethoxyphenyl isopropyl sulphone:* δ=7.75, 6.95 (AA'BB', 4H); 4.1 (q, 2H, O—CH_2—CH_3); 3.1 [sept, 1H, SO_2—$CH(CH_3)_2$]; 1.4 (t, 3H, O—CH_2—CH_3); 1.25 ppm [d, 6H, SO_2—$CH(CH_3)_2$].

[j] ^{1}H-N.M.R. ($CDCl_3$/TMS) of *5-methoxy-2-methylphenyl methyl sulphone* (oil): δ=7.55 (d, J=2.5 Hz, 6-H); 7.25 (d, J=8.5 Hz, 3-H); 7.0 (dd, J=8.5 and 2.5 Hz, 4-H); 3.85 (s, 3H, O—CH_3); 3.05 (s, 3H, SO_2—CH_3); 2.6 ppm (s, 3H, CH_3).

[k] ^{1}H-N.M.R. ($CDCl_3$/TMS) of *3-methoxy-2-methylphenyl methyl sulphone:* δ=7.6 (dd, J=7.8 and 2.0 Hz, 6-H); 7.3 (t, J=7.8 Hz, 5-H); 7.05 (dd, J=7.8 and 2.0 Hz, 4-H); 3.85 (s, 3H, O—CH_3); 3.05 (s, 3H, SO_2—CH_3); 2.55 ppm (s, 3H, CH_3).

the dealkylation of the sulphide moiety. This latter process was not observed with the methyl and ethyl sulphides and it can therefore be assumed that the dealkylation proceeds via elimination rather than via aliphatic nucleophilic substitution[5]. This dealkylation is observed only with strongly basic alkoxide ions; if, in fact, alkanethiolate anions are used as nucleophiles the only reaction observed with 4-chlorophenyl isopropyl sulphide is substitution of the Cl-atom[7]. The elimination reaction represents a limitation of the present method which is therefore not expected to give good results with chloroaryl alkyl sulphides **2** having branched alkyl groups. In all the other cases, the method described here is advantageous over other

methods. A further point of interest is represented by the fact that compounds **3** can be selectively dealkylated at the alkoxy or at the alkylthio functions and can therefore be used for a convenient synthesis of alkylthio-phenols or of alkoxybenzenethiols[10].

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.

2-Chlorophenyl Methyl Sulphide; Typical Procedure:
A solution of 1,2-dichlorobenzene (2.94 g, 20 mmol) and sodium methanethiolate[6] (2.1 g, 30 mmol) in hexamethylphosphoric triamide (30 ml) is stirred, under nitrogen, for 2.5 h at 100 °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 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 2-chlorophenyl methyl sulphide; yield: 2.57 g (81%); b.p. 119–121 °C/18 torr (Ref.[11], b.p. 116 °C/14 torr).

2-Methoxyphenyl Methyl Sulphide; Typical Procedure:
A solution of 2-chlorophenyl methyl sulphide (1.58 g, 10 mmol) and sodium methoxide (4.32 g, 80 mmol) in hexamethylphosphoric triamide (30 ml) is stirred, under nitrogen, for 12 h at 120 °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 (a single spot on T.L.C.) is further purified by column chromatography on silica gel using light petroleum as eluent to give pure 2-methoxyphenyl methyl sulphide; yield: 1.2 g (78%); b.p. 123–125 °C/18 torr (Ref.[13], b.p. 125 °C/15 torr).

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