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SELECTIVE CLEAVAGE OF THE CARBON–SULPHUR AND CARBON–OXYGEN BONDS IN METHOXYTHIOANISOLES

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Abstract—Selective cleavage of thioether or ether functions in methoxythioanisoles in hexamethylphosphoramide (HMPA) with sodium gives methoxythiophenols by cleavage of the carbon–sulphur bond. Reactions with sodium isopropanethiolate give instead the thiomethoxyphenols by dealkylation of the methoxy function. When the methoxythioanisoles were treated first with sodium isopropanethiolate and then with sodium complete dealkylation was achieved with formation of mercaptophenols. The present methods have considerable advantages over existing procedures for the synthesis of methoxythiophenols, thiomethoxyphenols and mercaptophenols. The mechanistic implications of the reactions investigated are also discussed.

The selective dealkylation of aryl alkyl ethers is a synthetically important process which presents some difficulty and several different methods, which do not interfere with other functional groups, have therefore been developed.[1–5] Similar problems are encountered in the case of aryl alkyl thioethers for which we have recently described two methods of dealkylation.[6–8] The presence of both an alkoxy and thioalkoxy function in the same molecule presents further problems which have not been investigated so far. With this kind of compound it would be obviously desirable to discover methods by which one could selectively dealkylate the alkoxy or the thioalkoxy groups and also effect the dealkylation of both functions. We have investigated these problems and in the present

$$\mathrm{Ar(OH)SH} \leftarrow \mathrm{Ar(OMe)SMe} \begin{cases} \nearrow \mathrm{Ar(OH)SMe} \\ \searrow \mathrm{Ar(OMe)SH} \end{cases}$$

paper we describe the procedures by which all these processes can be realized with great selectivity and efficiency.

The aromatic substrates selected for the present study were the simple methoxythioanisoles, (1)–(5), for which we have recently reported a simple and efficient synthesis starting from the corresponding dichlorobenzene derivatives.[9]

RESULTS

The reactions of the methoxythioanisoles (1)–(5) with 2.5 equivalents of sodium in HMPA at 100° for 2.5 h, gave the sodium salts of the methoxythiophenols (eqn 1).

$$\mathrm{Ar(OMe)SMe} \xrightarrow{\mathrm{Na}} \mathrm{Ar(OMe)SNa} \xrightarrow{\mathrm{EtI}} \mathrm{Ar(OMe)SEt} \quad (1)$$

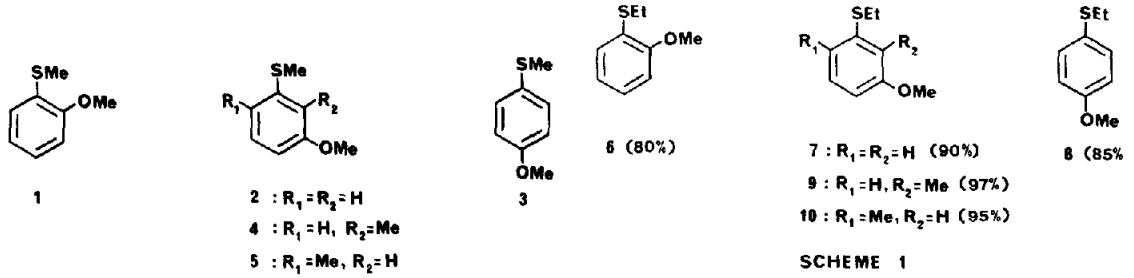
The thiophenols can be obtained by treatment with acid, or the thiolates can be directly used for further reactions. In order to make the separation of the reaction products easier, ethyl iodide was added to the final reaction mixtures (eqn 1) and the (ethyltio)anisoles (6)–(10) were obtained (Scheme 1); reaction yields, based on isolated products after column chromatography, are indicated in parentheses.

In the cases of o-(1) and m-methoxythioanisoles (2) small amounts (*ca.* 5%) of compounds (16) and (17) respectively were also obtained, indicating that to a small extent the sodium thiophenoxides have also suffered dealkylation of the methoxy group. Indeed the use of larger amounts of sodium and much longer reaction times produces an increase of (16) and (17) although (6) and (7) still remain the major reaction products.

The reactions of the methoxythioanisoles (1)–(5) with 2.5 equivalents of sodium isopropanethiolate, in HMPA at 120° for 2.5 h, afforded the sodium salts of the (methylthio)phenols from which the phenols (11)–(15) were obtained by acidification (eqn 2).

$$\mathrm{Ar(OMe)SMe} \xrightarrow{\mathrm{Me_2CHSNa}} \mathrm{Ar(ONa)SMe} \xrightarrow{\mathrm{H^+}} \mathrm{Ar(OH)SMe}. \quad (2)$$

Reaction yields, based on isolated products, are reported in parentheses in Scheme 2. Small amounts (*ca.* 5%) of o- and m-methoxythiophenol were isolated from the reactions of (1) and (2) respectively, indicating that in these cases the dealkylation process is not completely selective. Other sodium alkanethiolates can be used with similar good results.



SCHEME 1

11 (88%) 12 : $R_1 = R_2 = H$ (88%) 13 (85%)
14 : $R_1 = H$, $R_2 = Me$ (82%)
15 : $R_1 = Me$, $R_2 = H$ (91%)

SCHEME 2

Finally, when the reaction mixtures containing the sodium(methylthio)phenoxides, obtained from (1)–(5) and the Me_2CHSNa as described above, are treated with excess sodium (6 equivalents) at 120° for 5–15 h, the sodium salts of the mercaptophenols are obtained (eqn 3). If desired these can be isolated by acidification; in the present case ethyl iodide was added to the reaction mixtures and the reaction products were isolated and identified as the (ethanethio)phenetoles (16)–(20). The results obtained and the reaction yields are collected in Scheme 3.

$$Ar(OMe)SMe \xrightarrow{Me_2CHSNa} Ar(ONa)SMe \xrightarrow{Na} Ar(ONa)SNa \xrightarrow{EtI} Ar(OEt)SEt \qquad (3)$$

DISCUSSION

The efficient and selective cleavages of carbon–oxygen and carbon–sulphur bonds in methoxythioanisoles described in this paper can be interpreted on the basis of two simple processes: a nucleophilic aliphatic substitution (eqns 2 and 3) and a dissociative electron transfer (eqns 1 and 3).

The nucleophilic cleavage of aryl methyl ethers by thiolate anions is now a well established S_N2 reaction which occurs easily in dipolar aprotic solvents.[1,2,10] We have recently shown that the same reagents can also effect the dealkylation of aryl alkyl sulphides when HMPA is used as solvent[6] and this reaction can be employed for a convenient synthesis of aromatic thiols.[7] In the case of the methoxythioanisoles (1)–(5) two electrophilic centres are therefore available for the nucleophilic attack by the isopropanethiolate anions: the methyl carbon atom linked to oxygen and that linked to sulphur. The results obtained (eqn 2) demonstrate that the nucleophilic attack occurs selectively at the methoxy group. This behaviour was already observed during the synthesis of the starting products (1)–(5).[9] This synthetically important result cannot find a straightforward interpretation. It is clear that in the present cases the nucleofugacity does not depend upon the pK_a of the conjugate acid of the two leaving ArS and ArO groups because this would favour substitution at the carbon atom of the methanethio function. Under the conditions employed therefore the basicity seems not to be an important criterium to establish the relative leaving ability of the ArS and the ArO groups. What is observed is that the arylthio group, which is a better nucleophile than the aryloxy, is a poorer leaving group. As a tentative explanation one can suggest that owing to the reaction medium employed and to the nature of the nucleophile, the transition state occurs early in the course of the reaction and that therefore the attack occurs preferentially at the more positive methyl carbon atom which is the one linked to the more electronegative oxygen atom. However, several other factors can be assumed to play an important role in making this substitution so selective and the qualitative results available so far do not justify to further speculate about this problem.

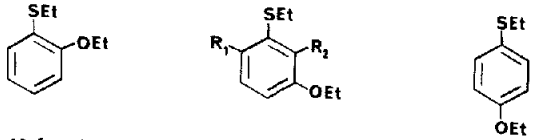
The reactions of methoxythioanisoles (1)–(5) with sodium lead to the cleavage of the carbon–sulphur bond (eqn 1). As it has been suggested in previous works on poly(alkanethio)benzenes,[8] it can be assumed that the interaction of the aromatic compound with sodium consists of an electron transfer from which the radical anions of (1)–(5) are formed (eqn 4); these reactive intermediates then evolve by dissociation to the sodium arenethiolate and methyl radicals (eqn 4).

$$Ar(OMe)SMe + Na \rightarrow [Ar(OMe)SMe]^{\cdot}Na^{+} \rightarrow Ar(OMe)SNa + Me^{\cdot} \qquad (4)$$

The preferred fragmentation at the C–S in respect to the C–O bond finds confirmation of the reported behaviour of the radical anions of methoxy substituted aryl sulphides[11] in which fragmentation of the carbon–oxygen bond was not observed.

The sodium salts of the methoxythiophenols, Ar(OMe)SNa, are not further reduced by sodium than to a very small extent. On the contrary, the sodium salts of the (methanethio)phenols, Ar(ONa)SMe, are easily cleaved by sodium to afford Ar(ONa)SNa, (eqn 3). This different behaviour is also confirmed by the fact that whereas the reaction of p-$C_6H_4(OMe)_2$ with excess sodium stops at the p-C_6H_4(OMe)ONa, the reaction of p-$C_6H_4(SMe)_2$ proceeds until both the alkanethio groups are dealkylated and gives the p-$C_6H_4(SNa)_2$. Thus the presence of the alkanethio function makes the molecule much more easily reducible, even if it is already an anion like the Ar(ONa)SMe or the Ar(SNa)SMe. Indeed, the fragmentation of the alkanethio groups, promoted by sodium, occurs at all the RS groups present in the molecule; thus, di-, tri-, tetra-, penta-, and hexamercaptobenzene are all formed in good yields from the reactions of excess sodium with the corresponding di-, tri-, tetra-, penta-, and hexa(alkanethio)benzene.[8] This behaviour is therefore peculiar to the sulphides and probably reflects the fact that the unpaired electron is accepted by the sulphur atom since this element can expand its electron surroundings by using d-orbitals.

A final comment deserves the synthetic aspect of the reactions described in this paper. Owing to the extremely simple experimental conditions, to the high reaction yields and to the easiness with which the starting products can be obtained,[9] the reactions reported in eqns (1)–(3) present several advantages over other existing methods for the synthesis of the methoxythiophenols,



16 (95%) 17 : $R_1 = R_2 = H$ (85%) 18 (97%)
19 : $R_1 = H$, $R_2 = Me$ (85%)
20 : $R_1 = Me$, $R_2 = H$ (90%)

SCHEME 3

thiomethoxyphenols, mercaptophenols and their alkyl derivatives. Moreover, the same reactions can be employed to effect the exchange of the alkyl groups of ether or thioether functions of an alkoxyaryl alkyl sulphide.

EXPERIMENTAL

Commercial HMPA was used without further purification. Sodium isopropanethiolate[6] and the methoxythioanisoles[9] (1)–(5) were prepared as described. Reaction products were identified by comparison of their physical and spectral properties with those reported in the literature and by ^{1}H-NMR spectra. NMR spectra were recorded, in $CDCl_3$ solutions, on a 90 MHz Varian EM 390 instrument.

The sulphones were prepared by oxidation with H_2O_2 in acetic acid and purified by crystallization from ethanol.

Synthesis of methoxythiophenols and of (ethanethio)anisoles (6)–(10)

General procedure A. To a stirred solution of the methoxythioanisoles (1)–(5) (0.01 mol) in HMPA (30 ml), kept under N_2 at 100°, small pieces of sodium (2.5 eq) were added. The progress of the reaction was monitored by tlc. After 2.5h the starting products were completely consumed. The mixture was cooled at room temperature and excess ethyl iodide was added. (To obtain the methoxyphenols the reaction mixtures were treated with dilute hydrochloric acid). The mixture was poured on water and extracted with ether; the organic layer was washed with water, dried over sodium sulphate and evaporated. The residue was purified by column chromatography on silica gel using light petroleum as eluant. Reaction yields are reported in Scheme 1.

Synthesis of (methanethio)phenols (11)–(15)

General procedure B. To a stirred solution of the methoxythioanisoles (1)–(5) (0.01 mol) in HMPA (30 ml), kept under nitrogen at 120°, sodium isopropanethiolate (2.5 eq) was added. The progress of the reaction was monitored by tlc. After 2.5 h the starting products were completely consumed. Excess hydrochloric acid was added and the mixture was worked up as described in procedure A. Purification by column chromatography was effected using a 95:5 mixture of light petroleum and ethyl ether. Reaction yields are reported in Scheme 2.

Synthesis of mercaptophenols and (ethanethio)phenetoles (16)–(20)

General procedure C. The reactions were carried out as described in B. To the reaction mixtures containing the sodium salts of the (methanethio)phenols small pieces of sodium (6 eq) were added. The progress of the reaction was monitored by tlc. After 5 to 15 h reactions were complete. After cooling to room temperature, excess ethyl iodide was added. (To obtain the mercaptophenols the reaction mixtures were treated with dilute hydrochloric acid). The mixtures were worked up as described in procedure A. Reaction yields are reported in Scheme 3.

The physical and NMR data of compounds (6)–(20) are reported below; the coupling constant of the ethyl groups was 7 Hz in every case.

The procedure employed for the synthesis of each compound is indicated in parentheses.

o-(ethanethio)anisole (6) (A). Colourless liquid (Lit[12] b.p. 130°/15 mm). δ 7.3-6.6 (m, 4H), 3.8 (s, 3H), 2.85 (q, 2H), 1.3 (t, 3H). *m-(Ethanethio)anisole* (7) (A). Colourless liquid (Lit[13] b.p. 125°/12 mm). δ 7.15 (m, 1H), 6.8 (m, 2H), 6.65 (m, 1H), 3.75 (s, 3H), 2.9 (q, 2H), 1.25 (t, 3H). *p-(Ethanethio)anisole* (8) (A). Colourless liquid (Lit[14] b.p. 76°/0.4 mm) δ 7.3 (m, 2H), 6.75 (m, 2H), 3.8 (s, 3H), 2.8 (q, 2H), 1.2 (t, 3H). *2-Methyl-3-(ethanethio)anisole* (9) (A). Colourless liquid. δ. 7.1 (t, H_5, J = 7.8 Hz), 6.85 (dd, H_6, J = 7.8 and 1.5 Hz), 6.6 (dd, H_4, J = 7.8 and 1.5 Hz), 3.75 (s, 3H), 2.85 (q, 2H), 2.25 (s, 3H), 1.3 (t, 3H). Sulphone, m.p. 44–5°. δ 7.6 (dd, H_4, J = 7.8 and 1.5 Hz), 7.3 (t, H_5, J = 7.8 Hz), 7.05 (dd, H_6, J = 7.8 and 1.5 Hz), 3.85 (s, 3H), 3.15 (q, 3H), 2.55 (s, 3H), 1.25 (t, 3H). *4-Methyl-3-(ethanethio)anisole* (10) (A). Colourless liquid. δ 7.0 (d, H_5, J = 7.5 Hz), 6.8 (d, H_2, J = 2.5 Hz), 6.55 (dd, H_6, J = 7.5 and 2.5 Hz), 3.75 (s, 3H), 2.85 (q, 2H), 2.25 (s, 3H), 1.3 (t, 3H). Sulphone, m.p. 101–2°. δ 7.45 (d, H_2, J = 2.5 Hz), 7.2 (d, H_5, J = 8 Hz), 7.0 (dd, H_6, J = 8 and 2.5 Hz), 3.8 (s, 3H), 3.15 (q, 2H), 2.6 (s, 3H), 1.25 (t, 3H). *o-(Methanethio)phenol* (11) (B). Colourless liquid (Lit[15] b.p. 104–5°/22 mm). δ 7.5-6.6 (m, 4H), 6.55 (s, 1H), 2.25 (s, 3H). *o-Methoxythiophenol* (B). Colourless liquid. δ 7.3–6.6 (m, 4H), 3.85 (s, 3H), 3.75 (s, 1H). *m-(Methanethio)phenol* (12) (B). Colourless liquid (Lit[16] b.p. 141.5°/8 mm). δ 7.1 (m, 1H), 6.75 (m, 2H), 6.6 (m, 1H), 5.55 (s, 1H), 2.4 (s, 3H). *m*-Methoxythiophenol (B). Colourless liquid. δ 7.1 (m, 1H), 6.8 (m, 2H), 6.65 (m, 1H), 3.75 (s, 3H), 3.4 (s, 1H). *p-(Methanethio)phenol* (13) (B). M.p. 84–5°. δ 7.15 (m, 2H), 6.7 (m, 2H), 5.0 (s, 1H), 2.4 (s, 3H). *2-Methyl-3-(methanethio)phenol* (14) (B). Colourless liquid. δ 6.95 (t, H_5, J = 7.8 Hz), 6.7 (dd, H_6, J = 7.8 and 1.2 Hz), 6.5 (dd, H_4, J = 7.8 and 1.2 Hz), 5.55 (s, 1H), 2.4 (s, 3H), 2.2 (s, 3H). *4-Methyl-3-(methanethio)phenol* (15) (B). M.p. 40–1° (Lit[17] m.p. 41). δ 6.9 (d, H_5, J = 7.8 Hz), 6.6 (d, H_2, J = 2.4 Hz), 6.45 (dd, H_6, J = 7.8 and 2.4 Hz), 5.55 (s, 1H), 2.35 (s, 3H), 2.2 (s, 3H). 2,4-Dinitrophenyl ether, m.p. 128–9°. δ 8.75 (d, $H_{3'}$, J = 3 Hz), 8.25 (dd, $H_{5'}$, J = 9 and 3 Hz), 7.0 (d, $H_{6'}$, J = 9 Hz), 7.15 (d, H_5, J = 7.8 Hz), 6.85 (d, H_2, J = 2.4 Hz), 6.75 (dd, H_6, J = 7.8 and 2.4 Hz), 2.45 (s, 3H), 2.35 (s, 3H). *o-(Ethanethio)phenetole* (16) (C). Colourless liquid (Lit[18] b.p. 248–50°/760 mm). δ 7.3–6.75 (m, 4H), 4.0 (q, 2H), 2.85 (q. 2H), 1.4 (t, 3H), 1.25 (t, 3H). *m-(Ethanethio)phenetole* (17) (C). Colourless liquid. δ. 7.1 (m, 1H), 6.8 (m, 2H), 6.6 (m, 1H), 3.9 (q, 2H), 2.85 (q, 2H), 1.35 (t, 3H), 1.25 (t, 3H). *p-(Ethanethio)phenetole* (18) (C). Colourless liquid (Lit[19] 110-112°/6 mm). δ 7.25 (m, 2H), 6.75 (m, 2H), 3.95 (q, 2H), 2.8 (q, 2H), 1.4 (t, 3H), 1.25 (t, 3H). Sulphone, m.p. 40–1° (Lit[19] oil). δ 7.75 (m, 2H), 6.95 (m, 2H), 4.1 (q, 2H), 3.05 (q, 2H), 1.4 (t, 3H), 1.25 (t, 3H). *2-Methyl-3-(ethanethio)phenetole* (19) (C). Colourless liquid. δ 7.0 (m, 1H), 6.85 (m, 1H), 6.6 (m, 1H), 4.0 (q, 2H), 2.9 (q, 2H), 2.3 (s, 3H), 1.4 (t, 3H), 1.25 (t, 3H). Sulphone, m.p. 48–9°. δ 7.55 (dd, H_4, J = 7.8 and 1.5 Hz), 7.25 (t, H_5, J = 7.8 Hz), 7.05 (dd, H_6, J = 7.8 and 1.5 Hz), 4.05 (q, 3H), 3.15 (q, 3H), 2.55 (s, 3H), 1.45 (t, 3H), 1.25 (t, 3H). *4-Methyl-3-(ethanethio)phenetole* (20) (C). Colourless liquid. δ 6.95 (d, H_4, J = 7.5 Hz), 6.75 (d, H_2, J = 2.5 Hz), 6.55 (dd, H_6, J = 7.5 and 2.5 Hz), 3.95 (q, 2H), 2.9 (q, 2H), 2.25 (s, 3H), 1.4 (t, 3H), 1.35 (t, 3H). Sulphone, m.p. 40–1°. δ 7.45 (d, H_2, J = 2.5 Hz), 7.2 (d, H_4, J = 7.5 Hz), 7.0 (dd, H_6, J = 7.5 and 2.5 Hz), 4.0 (q, 2H), 3.1 (q, 2H), 2.55 (s, 3H), 1.4 (t, 3H), 1.25 (t, 3H).

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