Synthesis of α-Haloalkyl Aryl Ethers from O,S-Acetals

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α-Haloalkyl aryl ethers are prepared under mild conditions in high yields by selective cleavage of O,S-acetals using sulfuryl chloride or bromine. The intermediate O,S-acetal is prepared from the phenol by O-alkylation using a readily accessible α-haloalkyl aryl thioether.

The methods reported for the synthesis of α-haloalkyl aryl ethers are either inconvenient and laborious, or they lack generality.1 We very recently reported on a much improved synthesis of chloromethoxybenzenes by chlorotris(triphenylphosphine)rhodium(I) catalytic decarboxylation of phenoxacycl chloride.2 The decarboxylation requires heating (150 – 170°C), however, which excludes heat sensitive substrates. In our continued search for improvements in the synthesis of α-haloalkyl aryl ethers under mild conditions, we have investigated cleavage reactions of carbon – sulfur bonds which represent an important type of reaction in organic synthesis.3*

* Protection of primary hydroxyl groups as methythioethyl ethers;3b benzylthiomethyl as an S-protecting group;3c thioacetalization with bromodiethyl sulfonium bromide;3d thioacetalization with soft acid metal salts;3e synthesis of sulfanyl chlorides;3f synthesis of sulfanyl chloride;3e,3h transformation of thioethers into ethers by thallium(III) nitrate.3i

The substitution of the phenylthio group by a halogen has been demonstrated in the synthesis of N-(α-chloroalkyl)phthalimides from N-[α-phenylthioalkyl]phthalimides on treatment with sulfuryl chloride at room temperature.4 Because divalent oxygen is a hard base and divalent sulfur is a soft base,5 it was expected that the carbon – sulfur bond in O,S-acetals could be selectively cleaved under mild reaction conditions to give an α-haloalkyl ether and its complementary sulfonyl halide using reagents like sulfuryl chloride or chlorine.

On treatment of the O,S-acetals 3a – 3g with equimolar amounts of sulfuryl chloride or bromine at room temperature in dichloromethane or tetrachloromethane, the carbon – sulfur bond was selectively cleaved in the course of a few minutes to give the α-haloalkyl aryl ethers 4a – 4i and the sulfonyl halide 5 (Scheme 1, Table 1). The highly reactive sulfonyl halides were trapped by the reaction with an olefin in situ to give a high boiling liquid from which the α-haloalkyl aryl ethers could be separated by distillation; yield of adduct 73 – 97%. Cyclohexene was used as the trapping agent for sulfonyl chlorides, whereas styrene was used for the bromides since the bromocyclohexane adduct was found to condistil with the α-bromoalkyl aryl

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\begin{align*}
\text{ArOH} + \text{Br(CI)CHSAr'} & \xrightarrow{\text{1-BuOK, DMF}} \text{ArOCHSAr'} & \xrightarrow{\text{50%Et2O/CH2Cl2}} \text{ArOCHX} + \text{XSAr'} \\
1 & 2 & 3 & 4 & 5
\end{align*}
\]

\[
\text{PhOCHSPh} \xrightarrow{\text{Me}} \text{PhSCHSPh + PhOCHOPh}
\]

\[
3g \quad \text{6} \quad \text{7}
\]

Scheme 1.
**Table 1. Yields in the synthesis of α-haloalkyl aryl ethers 4 and intermediate O,S-acetals 3.**

<table>
<thead>
<tr>
<th>Ar</th>
<th>R</th>
<th>Ar'</th>
<th>X</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Ph</td>
<td>H</td>
<td>4-CIPh</td>
<td>64</td>
</tr>
<tr>
<td>b</td>
<td>4-MePh</td>
<td>H</td>
<td>4-CIPh</td>
<td>58</td>
</tr>
<tr>
<td>c</td>
<td>4-CIPh</td>
<td>H</td>
<td>4-CIPh</td>
<td>64</td>
</tr>
<tr>
<td>d</td>
<td>3-CF₃Ph</td>
<td>H</td>
<td>4-CIPh</td>
<td>64</td>
</tr>
<tr>
<td>e</td>
<td>4-AcPh</td>
<td>H</td>
<td>4-CIPh</td>
<td>68</td>
</tr>
<tr>
<td>f</td>
<td>2-naphthyl</td>
<td>H</td>
<td>4-CIPh</td>
<td>57</td>
</tr>
<tr>
<td>g</td>
<td>Ph</td>
<td>Me</td>
<td>Ph</td>
<td>47</td>
</tr>
<tr>
<td>h</td>
<td>Ph</td>
<td>H</td>
<td>4-CIPh</td>
<td>86</td>
</tr>
<tr>
<td>i</td>
<td>4-MePh</td>
<td>H</td>
<td>4-CIPh</td>
<td>75</td>
</tr>
</tbody>
</table>

ethers 4ₕ and 4ᵢ. In ¹H NMR there is a downfield shift of ca. 0.5 ppm from the methylene protons of the O,S-acetals 3 (δ 5.1–5.4) to the corresponding protons of the α-halo ethers 4. The α-bromo ethers 4ₕ and 4ᵢ easily decompose when heated and become highly coloured in storage, even in the cold.

From Table 1 it is seen that α-haloalkyl aryl ethers 4 with both electron attracting and donating substituents in the aryl moiety can be synthesized by this method. Furthermore, the nature of the aryl substituents appears to have little influence on the yields of the reaction. Thus satisfactory yields were obtained for the compounds 4ₑ, 4ᵢ and 4₇ which were difficult to prepare by the previously reported method of catalytic decarboxylation of phenoxyacetyl chlorides.²

The cleavage reaction of 3 is very rapid at room temperature and no product from α-halogenation of the O,S-acetal 3 was seen. This is noticeable since in the reaction of the S,S-acetal 1,3-dithiane with sulfuryl chloride the main product is 2-chloro-1,3-dithiane, and the product due to carbon–sulfur bond cleavage is only present as a minor impurity.⁶

The O,S-acetals 3 were prepared by the reaction between potassium phenolates 1 and readily available α-haloalkyl aryl sulfides 2. (Table 1; 3) The O,S-acetals were stable compounds except for the product 3₇ derived from acetaldehyde. 3₇ could be distilled, but the distillate invariably contained some of the corresponding dithioacetal 6. ¹H NMR showed that the distillate of 3₇ in storage at 5 °C after 14 days had lost the quartet at δ 5.50 (CHMe); a new quartet was present at δ 4.48 due to the dithioacetal 6, and another quartet at δ 5.86 due to the acetal 7. Corresponding shifts in the signals from the protons of the methyl group were also observed.

On further storage for 2 weeks the signals from the acetal 7 gradually disappeared again; the thioacetal 6 was then isolated for identification.

The instability of 3₇ can in part be explained by the phenomenon termed “symbiosis” which means that ligands of the same hardness or softness tend to flock together on the same acceptor atom.⁵ Hence both 6 and 7, according to the HSAB principles, are expected to be thermodynamically more stable than 3₇, which has a combination of hard and soft ligands on the same centre.

The disproportionation was not observed for the formyl derived O,S-acetals 3ₐ–3ₖ in storage. In principle, however, the same reaction is to be expected but was not further pursued. Elimination of the phenoxy or phenyllithio group with the formation of a cationic structure may be the initial step, in which case the added stabilization of this species from the methyl derivative 3₇ may explain in part the differences in stability between 3ₐ–3ₖ and 3₇. Alternatively, the reaction may proceed via a vinyl phenyl ether (thioether) intermediate after initial elimination of thiophenol (phenol) from 3₇.

**EXPERIMENTAL**

_Procedure for the synthesis of the O,S-acetals 3ₐ–3ₖ._ 1-Bromomethylthio-4-chlorobenzene ⁷ (20 mmol) was added to a solution of the potassium phenolate (20 mmol) in DMF (50 ml). The mixture was stirred at 80° for 1–2 h before the solvent was distilled off. The residue was triturated with water, extracted into ether and washed with water (4 ×). The dried (MgSO₄) solution was evaporated and the residue distilled or recrystallized. 3ₐ: B.p. 110 – 112 °C/0.01 mmHg.⁸ Anal. C₁₃H₁₁Cl₂OS: C, H. ¹H NMR (CDCl₃): δ 5.32 (CH₃), 6.7 – 7.4 (Ar). MS [70 eV, m/z

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(% rel. int.): 250 (15, M), 159(35), 158(8), 157(100), 77(16), 45(26). 3b: M.p. 43 – 44 °C (light petroleum).

Anal. C_{13}H_{11}ClO_3: C, 58.1, H, 4.49. H NMR (CDCl_3): δ 2.23 (CH_3), 5.30 (CH_2), 6.7 – 7.4 (CH, Ar). MS [70 eV, m/z (% rel. int.): 264 (15, M), 159(36), 158(9), 157(100), 121(5), 91(11), 45(26). 3c: B.p. 135 – 140 °C/0.01 mmHg. Anal. C_{13}H_{11}ClO_3: C, 58.1, H, 4.49. H NMR (CDCl_3): δ 5.30 (CH_2), 6.7 – 7.4 (Ar). MS [70 eV, m/z (% rel. int.): 264 (15, M), 159(36), 158(9), 157(100), 121(5), 91(11), 45(26). 3d: B.p. 118 – 122 °C/0.01 mmHg. H NMR (CDCl_3): δ 5.30 (CH_2), 6.7 – 7.4 (Ar). MS [70 eV, m/z (% rel. int.): 264 (15, M), 159(36), 158(9), 157(100), 121(5), 91(11), 45(26). 3e: B.p. 150 – 155 °C/0.01 mmHg. H NMR (CDCl_3): δ 5.30 (CH_2), 6.7 – 7.4 (Ar). MS [70 eV, m/z (% rel. int.): 264 (15, M), 159(36), 158(9), 157(100), 121(5), 91(11), 45(26). 3f: B.p. 135 – 140 °C/0.01 mmHg. H NMR (CDCl_3): δ 5.30 (CH_2), 6.7 – 7.4 (Ar). MS [70 eV, m/z (% rel. int.): 264 (15, M), 159(36), 158(9), 157(100), 121(5), 91(11), 45(26). 3g: B.p. 118 – 122 °C/0.01 mmHg. H NMR (CDCl_3): δ 5.30 (CH_2), 6.7 – 7.4 (Ar).

**Procedure for the synthesis of the α-bromoalkyl aryl ethers 4h and 4i:** Bromine (10 mmol) in dry tetrachloromethane (10 ml) was added dropwise during 20 min at room temperature to a solution of the O,S-acetyl in dry tetrachloromethane (40 ml). The mixture was stirred for 1 h at room temperature before styrene (10 mmol) in dry tetrachloromethane (10 ml) was added dropwise during 15 min at 5 °C. The mixture was stirred for 1 h at room temperature before the solvent was distilled off, and the residue distilled under vacuum. 4h: B.p. 110 – 112 °C/20 mmHg. H NMR (CDCl_3): δ 5.92 (CH_2), 6.5 – 7.4 (Ar). MS [70 eV, m/z (% rel. int.): 188(186(6,6), M), 142(11), 107(100), 104(14), 94(11), 79(15), 77(70). 4i: B.p. 48 – 52 °C/0.01 mmHg. H NMR (CDCl_3): δ 2.28 (4-Me), 5.91 (CH_2), 6.8 – 7.3 (Ar). MS [70 eV, m/z (% rel. int.): 202(200(7,7, M) 188(8), 186(15), 185(86), 184(88), 183(81), 121(53), 107(55), 104(100), 103(51), 91(32), 77(47). The 1-bromo-1-phenyl-2-(4-chlorophenylthio)ethane had m.p. 47 – 49 °C (light petroleum).

**REFERENCES**


(4-Chlorophenylthio)ethane had b.p. 118 – 122 °C/0.01 mmHg.

2-Chloromethoxyphthalalene 4f: Procedure as above, but the sulfonyl chloride was trapped with styrene; b.p. 82 – 95 °C/0.03 mmHg. H NMR (CDCl_3): δ 5.87 (CH_2), 7.0 – 7.7 (Ar). The 1-chloro-1-phenyl-2-(4-chlorophenylthio)ethane had b.p. 120 – 135 °C/0.05 mmHg.

(1-Chloroethoxy)benzene 4g. Procedure as above; b.p. 94 – 96 °C/20 mmHg. H NMR (CDCl_3): δ 1.96 (d, CH_3, J 5 Hz), 6.13 (q, CH, J 5 Hz), 6.8 – 7.3 (Ar). MS [70 eV, m/z (% rel. int.): 158/156 (3,9, M), 135(8), 121(48), 120(64), 94(100), 91(56), 77(47). The 1-chloro-2-phenylthio-cyclohexane had b.p. 98 – 100 °C/0.01 mmHg.
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