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The Methyl Group as A Protecting Group for Arylthiols: A Mild and Efficient Method for the Conversion of Methyl Aryl Sulfides to Arylthiols

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Summary: Methyl aryl sulfides are converted in a mild, "one-pot", three step procedure via Pummerer rearrangement of the corresponding sulfoxides, and without purification of intermediates, to provide arylthiols in excellent yields.

In many respects the methylthioether is an ideal protecting group for arylthiols. Thus, the function is particularly stable to a wide variety of reaction conditions and is readily introduced either by simple alkylation of the corresponding thiols with methyl iodide or the methylthio group as such may be easily introduced into aromatic systems in a number of ways, e.g. via reaction of methanethiol with aromatic halides under base or copper catalysis.[1] Also, a variety of thioanisol compounds are commercially available and such compounds can serve as versatile intermediates for further elaborations, particularly via electrophilic substitution reactions such as the Friedel-Crafts reaction. However, perhaps as a necessary corollary of the great stability of methylthioaryl ethers, considerable difficulties have encountered in attempting to remove this protecting group in the past. The vigorous conditions required for such deprotection, e.g. CH_3SNa/HMPA/heat[2], CH_3SeNa/HMPA/heat[3], or alkali metals in ammonia[4], methylamine[5] or ether[6], have served to severely limit its use as a general protecting group for arylthiols.

We wish to report here, a simple method for the conversion of thioanisols to the corresponding arylthiols which is particularly mild, selective and high yielding, and which we feel should make the methylthioether the protecting group of choice for arylthiols.

The method takes advantage of the ability of alkylaryl sulfoxides to undergo facile and of necessity, regiospecific Pummerer rearrangements to provide hemithioacetal acetates which are then readily hydrolyzed to provide the desired arylthiols[7]. The three step sequence depicted in Scheme 1 in general requires no purification of intermediates and can be carried out on a multigram scale, in less than two hours. A number of examples are collected in Table 1.

Scheme 1

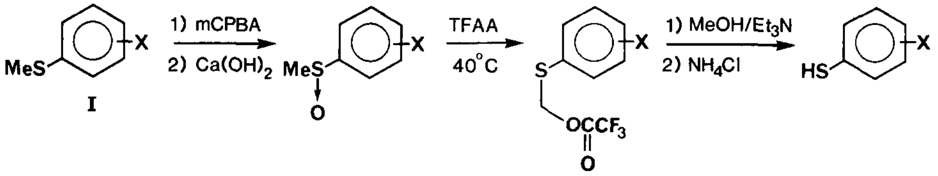
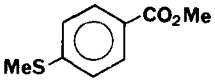
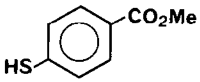
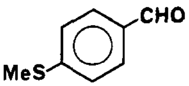
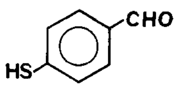
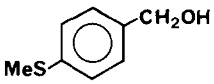
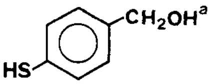
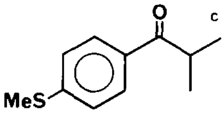
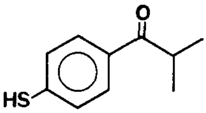
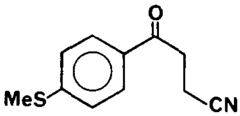
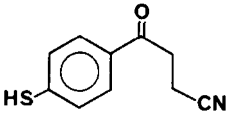
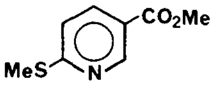
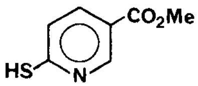
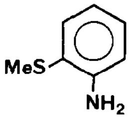
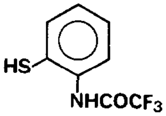


TABLE 1 Conversion of Thioanisols to Arylthiols

Entry	**I**	**Product**	**Yield of Thiol**	**Yield of Disulfide**	**mp (lit) of Disulfide**
1			97	(90)	124–125° (124–125°)[8]
2			100	(75)	105–106° (108°)[9]
3		 [a]	86	(–)[b]	128–130° (130–132°)[10]
4	 [c]		98	(86)	53–54°[d]
5			100	(86)	177–177.5°[d]
6			80	(–)	215–217°[d,e]
7	 [f]		90	(90)	124–125°[d]

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[a] Worked up with 2N NaOH instead of Et_3N/MeOH in step 3.

[b] The isolated thiol was essentially pure, a small portion was converted to the disulfide for characterization purposes.

[c] Prepared from thioanisol via Friedel-Crafts reaction ($AlCl_3$-$ClCOCH(CH_3)_2$).

[d] All unknown products were fully characterized and gave acceptable elemental analyses.

[e] mp of arylthiol.

[f] Amino function trifluoroacetylated prior to normal reaction sequence.

If the deprotected thiol is to be subsequently reacted with an electrophile, the final hydrolysis can be carried out in the presence of the electrophile and the free thiol need not be isolated.[11] As can be seen from the table, the method is compatible with a wide variety of functional groups. However, in some cases, care must be taken to avoid side reactions. In the case of 4-formylthioanisol (entry 2) the formyl group is converted to the corresponding geminal bis-trifluoroacetate during the Pummerer rearrangement. This product is quite unstable and polymerizes if allowed to hydrolize under acidic conditions (i.e. the material polymerizes even on dissolving in methanol).[12] However, if dissolved in the recommended methanol- triethylamine mixture such that the reaction is never allowed to become acidic, then the desired product is obtained in excellent yield. In the deblocking of 4-hydroxymethylthioanisol (entry 3), the Pummerer reaction provides the expected rearrangement product but with the alcohol group trifluoroacetylated ($CF_3COOCH_2SC_6H_4CH_2OCOCF_3$). This product on normal triethylamine-methanol treatment forms mainly polymers, apparently due to intermolecular reaction of the liberated thiolate anion with the benzylic trifluoroacetate. A similar polymer is obtained on treatment with 5% aqueous $NaHCO_3$. However, when treated in methanol with 2N NaOH, followed by acidification, the desired thiol is obtained in excellent yield. As can be seen from entry 6, the presence of a basic pyridine ring causes no complications. However, in the case of o-aminothioanisol (entry 7) the amino function must be protected (e.g. by dissolving in trifluoroacetic anhydride and evaporation to dryness to provide the corresponding N-trifluoroacetate) prior to being submitted to the normal sequence. Some demonstration of the synthetic utility of thioanisols is exemplified by entry 5. The substrate is readily prepared in about 60% yield from the commercially available 4-methylthiobenzaldehyde via Stetter reaction[13] with sodium cyanide and acrylonitrile. Subsequent deblocking provides the desired thiol in two steps from commercial materials.

In a representative example, methyl 4-(methylthio)benzoate (5mM) was oxidized (0°C, 1 eq. mCPBA, $CHCl_3$, 1 hr). Stirring the mixture with $Ca(OH)_2$ (R.T., 1.5 eq., 15 min) followed by filtration and evaporation gave the essentially pure sulfoxide which was dissolved in trifluoroacetic anhydride [14,15] (10 mL, reflux, 30 min). The volatile components were removed by evaporation and the residue was dissolved in methanol-triethylamine (1:1, 100 mL) and evaporated to dryness.[16] The residue was dissolved in chloroform, washed with NH_4Cl (sat.), dried and evaporated to dryness to provide methyl 4-mercaptobenzoate (820 mg, 97.5%). For the purpose of full characterization and determination of purified isolated yield, the thiol was converted to the corresponding disulfide (shaking a $CHCl_3$ solution with excess aqueous KI_3 followed by washing with Na_2SO_3, drying, evaporation and recrystallization (EtOAc-hexane)) in 90% overall yield, mp 124 - 125° (lit mp 124-125°[8]).

In conclusion, thioanisols can be deblocked in this three-step, "one-pot" procedure in high yields. The conditions are extremely mild and specific for the blocking group and are compatible with a wide variety of functional groups. The ready availability and reactivity of thioanisols should make this the protecting group of choice for arylthiols.

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7. Similar methodology has been used in the past for the synthesis of aldehydes from alkylphenylsulfoxides however the fate of the sulfur component has not been investigated. H. Sugihara, R. Tankiaga and A. Kaji, Synthesis, 881 (1978).
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11. It must be noted that a molar equivalent of formaldehyde is liberated and can serve to complicate subsequent reactions.
12. It appears from NMR analysis that the major product of methanol treatment is a dimeric hemithioacetal
13. H. Stetter and M. Schreckenberg, Chem. Ber., 107, 210 (1974).
14. Acetic anhydride can be used but higher temperatures (80-90°) are required and the reaction is somewhat slower. Also, more vigorous conditions are required in the subsequent hydrolytic step.
15. Although in general, we have employed neat TFAA in this step, the reaction can be effected with 1.2-2 equivalents of anhydride in CH_2Cl_2 or $CHCl_3$ (40°C, 30 min).
16. Aqueous Na_2CO_3 or 1N NaOH treatment can also be used if the molecule is not base sensitive.

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