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LETTERS

Efficient Formation of Aromatic Thiols From Thiomethylated Precursors

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Abstract: As a model study, a series of linear and branched *p*-phenylene and *m*-phenylene sulfides, functionalized by a thiomethyl group, were deprotected to thiols while using various alkyl thiolates at 160°C in DMF. Many complex aromatic thiols were obtained in almost quantitative yields from a trivial purification and without significant contamination by disulfides. This methodology is reliable, efficient and has been optimized on several substrates. © 1999 Published by Elsevier Science Ltd. All rights reserved.

In spite of their strong and often unpleasant odors, thiols make an important contribution to flavours. For instance, they contribute to the aroma of roast meat, coffee, grapefruits, etc..[1] Thiols are of prime importance in the processes of life because of their redox properties and nucleophilicity. However, their synthesis often suffers from oxidation to various by-products, including disulfides, which causes problems in the purification and the yields (often less than 70-80%).[2]

We have briefly described one of the best methods for making aromatic thiols.[3] It is based on the deprotection of thiomethylated aromatics, which are commercial or easily prepared. In this work, we have optimized our procedures and made several tests on a large collection of substrates and thiolates. New conditions, observations, comparison to other methods and optimization provided a major breakthrough to the useful, clean and almost quantitative formation of aromatic thiols. It was needed because the method of Tiecco et al. with MeSNa gave us incomplete reactions, often with unseparable starting materials and products.[4]

$$\text{Ar-S-Me} \xrightarrow[\text{DMF, 160°C, 4 hrs}]{\text{1) t-BuSNa (2.0)}} \text{Ar-SH}$$

$$\text{2) HCl}_{\text{(aq)}} \qquad \text{(95-99\%)}$$

In Table 1, we compared the deprotection of thiomethyl groups with MeSNa, iPrSNa and tBuSNa. It was systematically found that MeSNa gives incomplete reactions and lower yields, regardless of solvents, temperatures and excess of reagents used (Entries no 7, 9 and 11). iPrSNa gave moderate yields (Table 1; Entries no 3, 6, 10 and Table 2; Entries no 1, 6), but the best reagent was tBuSNa. It consistently produced over 95% yield of thiol without significant by-products. In Entries 1 and 2 (Table 1), a combination of thiolate reagents (tBuSNa, iPrSNa) and substrates (EtSAr) were tried, but steric hindrance and kinetics did not favor thoses pairs. Deprotection of OMe group is also achievable with this procedure (Entries 5,6,7, 10, 11).

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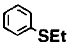
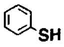
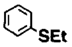
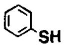
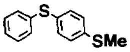
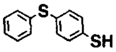
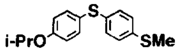
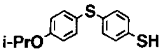
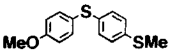
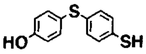
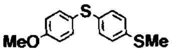
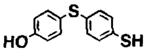
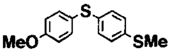
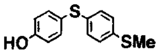
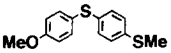
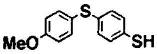
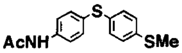
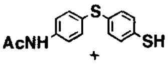
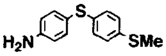
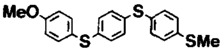
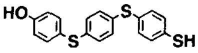
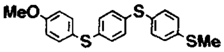
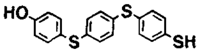
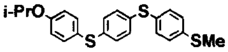
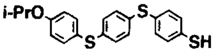
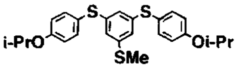
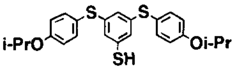
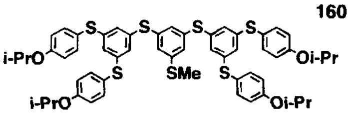
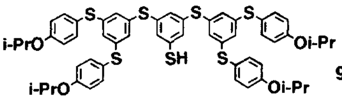
Table 1. Synthesis of Aromatic Thiols[a]

ENTRY NO	ARYL METHYL SULFIDE	T (°C)[c]	THIOLATE (Equiv)	TIME (hr)	AROM. THIOL	YIELD[b] (%)
1		160	i-PrSNa (6.0)	24		Mixtures (starting material)
2		160	t-BuSNa (6.0)	24		Traces
3		160	i-PrSNa (5.0)	2.0		93% [e]
4		160	t-BuSNa (2.0)	4.0		95% (80%[e])
5		160	t-BuSNa (4.0)	4.0		90%
6		160	i-PrSNa (10.0)	20		68%
7		200[d]	MeSNa (16.0)	2.0		25%
8		160	Na/NH$_3$ (5.0)	6.0		Mixtures
9		160	MeSNa (5.0)	20	 +	16%
						16%
10		160	i-PrSNa (5.0)	2.5		70% [e]
11		200[d]	MeSNa (15.0)	17		48% ref 3a
12		160	t-BuSNa (2.0)	4.0		95% (75%[e])
13		160	t-BuSNa (5.0)	4.0		99%
14		160	t-BuSNa (5.0)	4.0		99%

a: Thiols were characterized by ^{1}H, ^{13}C and LRes MS (EI)

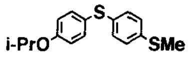
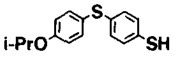
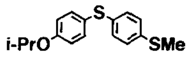
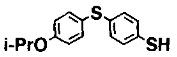
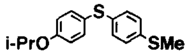
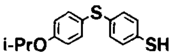
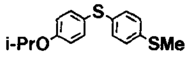
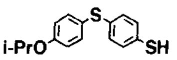
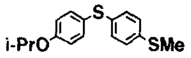
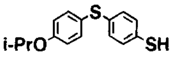
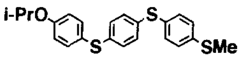
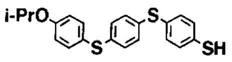
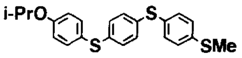
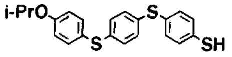
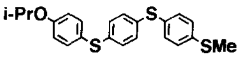
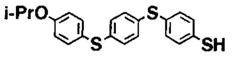
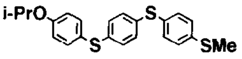
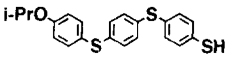
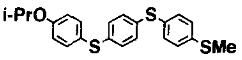
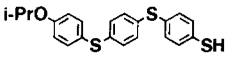
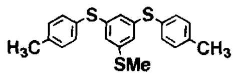
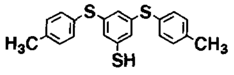
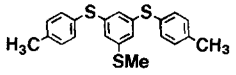
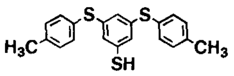
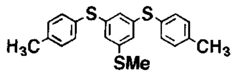
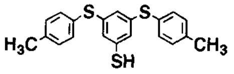
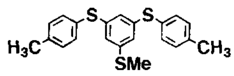
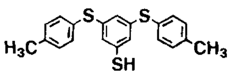
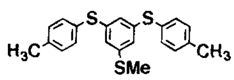
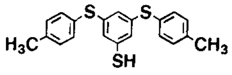
b: isolated yields

c: DMF as solvent

d: N-methyl-2-pyrrolidone as solvent

e: Yields in parenthesis refer to i-PrSNa (5.0) as in ref. 3a

Table 2. Optimization of the Conditions for Making Thiols[a]

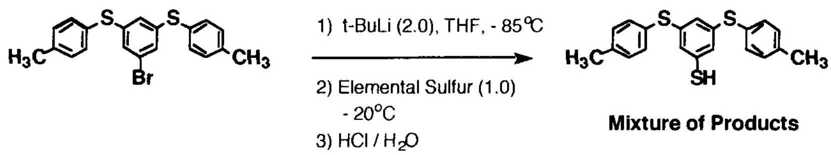
ENTRY NO	ARYL METHYL SULFIDE	T (°C)	THIOLATE (Equiv)	TIME (hr)	AROM. THIOL	YIELD[b]
1		160	i-PrSNa (5.0)	3.0		80%
2		160	t-BuSNa (5.0)	2.0		96%
3		160	t-BuSNa (3.0)	3.0		> 95%
4		160	t-BuSNa (2.0)	4.0		95%
5		160	t-BuSNa (1.5)	8.0		Incomplete
6		160	i-PrSNa (5.0)	2.5		75%
7		160	t-BuSNa (5.0)	2.0		96%
8		160	t-BuSNa (3.0)	3.0		> 95%
9		160	t-BuSNa (2.0)	4.0		95%
10		160	t-BuSNa (1.5)	12		Incomplete
11		160	t-BuSNa (5.0)	4.0		99%
12		160	t-BuSNa (3.3)	3.5		Complete
13		160	t-BuSNa (2.25)	3.75		Complete
14		160	t-BuSNa (1.7)	4.0		Complete
15		160	t-BuSNa (1.1)	22		Incomplete

a: Thiols were characterized by ^1H, ^{13}C and LRes MS (EI), b: DMF as solvent

Optimization of the conditions with 3 substrates is shown in Table 2. The best procedure involves 2.0 equiv. of tBuSNa at 160°C in dry DMF for 4 hrs. Less than 2.0 equiv. of tBuSNa could give erratic results (Table 2; Entries 5,10 and 15). The method is applicable to several substrates and scaling up to multiple grams was achieved (see experimental procedure on 10 g.). Some observations are important: a) the reactions are run under N_2 at high temperatures but there is no need to degas the mixture for preventing the oxidation of the thiolate formed; an excess of tBuSNa probably acts as an antioxidant by reacting first with traces of oxidizing agent (such as O_2), b) DMF must be dry (distilled over CaH_2, kept over 3Å sieves, activated at 250°C for 3 hrs under vacuum), c) tBuSNa is a commercial solid which does not produce a strong odor, d) when the reaction is over, it is necessary to cool down the mixture to R.T. or 0°C, use an abundant flow of N_2, and poor in the concentrated acid at once. Otherwise, disulfides are spontaneously produced in the air from the oxidation of thiolate anions at high temperatures, e) the volatile by-product tBuSMe is normally not present after evaporation of the solvent under vacuum, f) the final purification was simplified to a quick filtration over a plug of SiO_2 for removing most of the salts.

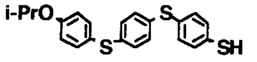
The mechanism of these demethylations remains a curiosity but it might involve an S_N2 reaction. However, a thermodynamic exchange of methyl groups seems to play a role with MeSNa at 160°C; whereas bulkier tBuSNa and iPrSNa would generate less reactive iPrSMe and tBuSMe, toward S_N2 reactions.

In short, our strategy easily introduced an Ar-S bond from MeSNa and an aryl halide, and our method of deprotection makes it practical to generate thiols. Otherwise, major impurities are often found when using classical methods of aromatic thiol formation. A convincing example is shown below:



Our procedure provides the same thiol in 99% yield (Entry 11, Table 2).

Optimized procedure: To an oven-dried 250-mL flask, connected to a condenser and cooled under N_2, was added *i*-PrOPhSPhSPhSMe (10.00 g.; 25.00 mmol), followed by commercial tBuSNa (5.63 g.; 50.0 mmol). Dry DMF (80 mL) was injected via a syringe while stirring vigorously. An oil bath was heated at 160°C and the flask was partially immersed into it. The transparent solution became slightly dark. After 4 hrs, the flask was cooled in an ice-bath for 45 min.. A strong stream of N_2 was passed in the flask and an aqueous 3M solution of HCl (150 mL) was rapidly added to the mixture until pH is about 1. A paste was formed. This mixture was transferred into a 2-L erlenmeyer flask containing 3M HCl (850 mL). The original flask was rinsed with CH_2Cl_2 (100 mL). The two phases were stirred for 30 min. and the organic one was separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 50 mL). The organic phases were collected and dried over Na_2SO_4. After a filtration, the solvent was evaporated under vacuum and a light yellow solid was obtained. Dissolution in a minimal amount of CH_2Cl_2 and a filtration on a plug of SiO_2 with EtOAc/Hex (5/95) as eluent, provided the expected white thiol below as a sufficiently pure solid (9.17 g.; 24.0 mmol; 95% yield).



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