A Simple, Fast and Chemoselective Method for the Preparation of Arylthiols

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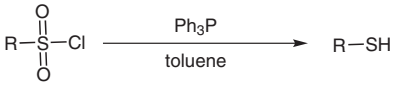
Abstract: An efficient and convenient method for the synthesis of arylthiols by reaction of sulfonyl chlorides with triphenylphosphine in toluene is reported.

Key words: thiols, arylsulfonyl chloride, triphenylphosphine, chemoselectivity, reductions

General strategies for the synthesis of arylthiols[1] include transition-metal-mediated electrophilic or nucleophilic substitution, followed by dealkylation to the arylthiol.[2] Another method is thiolation of haloaryls using metal sulfides such as sodium hydrogen sulfide[3] or disodium disulfide,[4] however, this method is only useful when the aryl ring contains an electron-withdrawing group, whereas alkanethiolate salts can be used for thiolation of non-activated arenes.[5a] Nucleophilic substitution of aryl iodides with thiourea in the presence of a transition-metal catalyst gives *S*-arylisothiouronium salts which, after hydrolysis, afford the thiol.[5b] For the synthesis of alkoxyarylthiols or aminoarylthiols (Herz reaction), disulfur dichloride has been used with various metal salts.[6] Mono-halogen substituted arylthiols have been prepared using polysulfide.[7] Catalytic reaction of phenol with hydrogen sulfide in the gas phase has also been used.[8] Arylthiols have also been prepared from phenol by a Newman–Kwart rearrangement,[9] and anilines through Leukart thiophenol synthesis.[10]

Besides the above methods, industrially more viable processes for the synthesis of thiophenols employ sulfonic acid and its derivatives. Arylsulfonyl chlorides are readily accessible compounds that can be easily synthesized by chlrosulfonation of aryl compounds.[11] Available methods for the conversion of arylsulfonyl chlorides into arylthiols[12a] use reducing agents such as: Zn/acid,[12b] $LiAlH_4$,[12c] Red P/I_2/AcOH,[12d] PH_3/base,[12e] Sn(II)/acid,[12f] Pt/H_2,[12g] $NaBH_4$/$AlCl_3$,[12h] and metal sulfide/H_2/pressure.[12i] However, most of these systems suffer from some disadvantages such as the use of hazardous and toxic chemicals such as phosphine, harsh reaction conditions, difficulties in the isolation of products, the formation of side-products, low yields, and use of expensive reagents such as lithium aluminum hydride.

The easy oxygenation of triphenylphosphine is well defined in Wittig, Mitsunobu and many other reactions. This reducing agent works well in the presence of other functional groups such as nitro groups, halogens, carboxylic acids, and ketones. The ease of preparation of arylsulfonyl chlorides, together with the activity profile of triphenylphosphine, led us to develop a method for the preparation of arylthiols from the corresponding arylsulfonyl chlorides as shown in Scheme1.



R = aryl, heteroaryl, etc.

Scheme 1 Reduction of arylsulfonyl chlorides to arylthiols

In preliminary experiments, we performed a reaction with 4-methylbenzenesulfonyl chloride as described in the experimental general procedure. Thus, the required amount of triphenylphosphine was added cautiously in portions to a solution of 4-methylbenzenesulfonyl chloride in toluene. A high exotherm was observed and solid separated out; both were indicative of the progress of the reaction. After workup, practically pure product was obtained.

The reaction was carried out in different solvents such as: xylene, toluene, chloroform, and dichloromethane, using 4-methylbenzenesulfonyl chloride as a model substrate. Yields were found to be almost identical in all solvents [xylene (88%), toluene (89%), chloroform (86%), and dichloromethane (85%)] and the rate of the reaction was not affected.

The chemoselectivity of the method was demonstrated using substrates containing different functional groups. Triphenylphosphine is known to be compatible with other reducible functional groups such as halogens, carboxylic acids and ketones, however, it is known to deoxygenate nitro groups in aromatic systems under certain conditions.[13] In order to establish the generality and chemoselectivity of the reaction, substrates containing these functionalities were subjected to the reaction conditions and the results are summarized in Table 1. It is noteworthy that, in all cases, irrespective of substitution, the reaction proceeded rapidly and was complete within 15 minutes. Under these reaction conditions the nitro group remained intact (entries 11–13).

In conclusion, we have developed an efficient and simple method for the preparation of arylthiols from the corresponding arylsulfonyl chlorides. The advantages of this method are: operational simplicity, good yields, short re-

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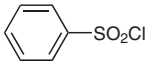
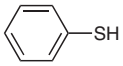
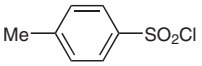
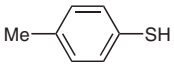
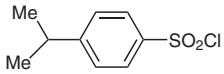
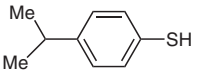
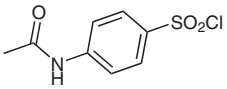
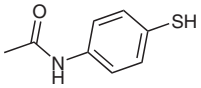
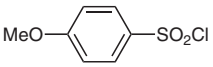
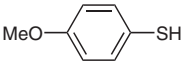
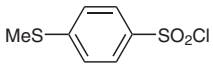
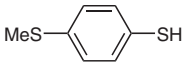
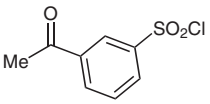
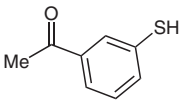
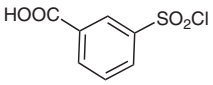
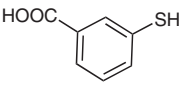
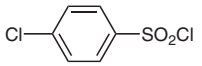
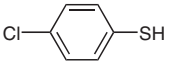
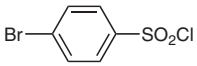
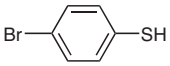
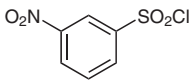
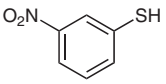
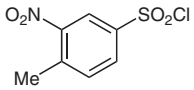
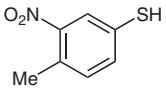
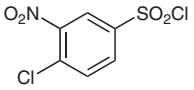
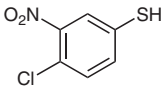
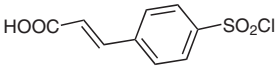
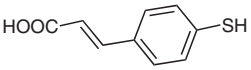
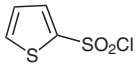
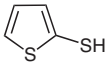
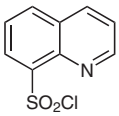
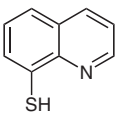
Table 1 Reduction of Arylsulfonyl Chlorides to Arylthiols Using Triphenylphosphine[a]

Entry	Starting material	Product[14]	Yield (%)
1			94
2			89
3			78
4			79
5			73
6			75
7			71
8			73
9			87
10			85
11			82
12			77
13			71
14			80
15			85
16			75

[a] Reaction conditions: substrate (5 mmol), Ph_3P (3.0 equiv), anhyd toluene.

action times, an easy workup procedure, and the chemoselectivity achieved. The disadvantage of the method is that it requires the use of three equivalents of triphenylphosphine, which is not atom-efficient.

All reagents were obtained from commercial suppliers and used without further purification. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} plates. ^1H NMR spectra were obtained using a JEOL FT-NMR spectrometer operating at 300 MHz in $CDCl_3$. TMS was used as internal standard and all coupling constants were reported in hertz (Hz). IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer using KBr for solid samples and $CHCl_3$ for liquid samples. Mass spectra were recorded on a Finnigan Mat 1020B using EI at 70 eV for ionization. Melting points were recorded on a Thermonik apparatus (using an oil heating system) from Campbell Electronics.

Synthesis of Arylthiols; General Procedure[14]

To a solution of arylsulfonyl chloride (5 mmol) in anhyd toluene (30 mL) in a three-neck round-bottom flask with a nitrogen inlet, reflux condenser, and calcium chloride guard tube, was added Ph_3P (15 mmol) in portions (CAUTION: reaction is highly exothermic and may start refluxing). The reaction was stirred for 10 min and allowed to cool to below 50 °C. H_2O (5 mL) was added and the mixture was stirred for 10 min. The aqueous layer was discarded and the organic layer was extracted with 10% NaOH (2 × 15 mL). The alkaline aqueous extract was washed with toluene (2 × 10 mL), acidified with dilute HCl and extracted with CH_2Cl_2 (2 × 15 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to give practically pure arylthiol.

4-Methyl-3-nitrobenzenethiol (Entry 12)

Oil.

IR ($CHCl_3$): 2576, 1514, 1335 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.08 (s, 1 H), 7.66–7.22 (m, 2 H), 3.48 (s, 1 H), 2.56 (s, 3 H).

MS (EI): *m*/*z* = 169 [M^+], 152, 121, 97, 77.

Anal. Calcd for $C_7H_7NO_2S$: C, 49.69; H, 4.17; N, 8.28. Found: C, 49.70; H, 4.07; N, 8.32.

4-Chloro-3-nitrobenzenethiol (Entry 13)

Yellow solid; mp 53–55 °C (Lit.[15] yellow solid).

IR (KBr): 2559, 1509, 1335 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.20 (m, 3 H), 3.44 (s, 1 H).

Anal. Calcd for $C_6H_4ClNO_2S$: C, 38.00; H, 2.13; N, 7.39. Found: C, 37.89; H, 2.30; N, 7.32.

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