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Direct synthesis of thioethers from sulfonyl chlorides and activated alcohols

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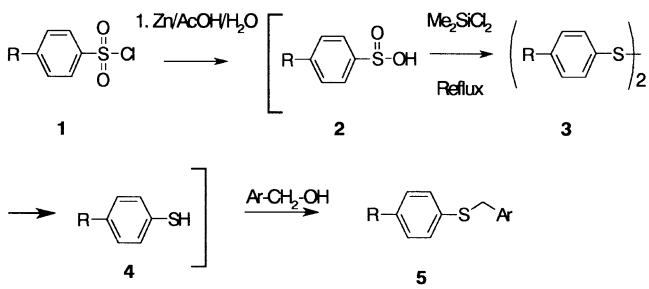
Abstract—An efficient, safe one-pot synthesis of thioethers from aromatic sulfonyl chlorides and activated alcohols has been developed under non-aqueous conditions.

Formation of thioethers is an important synthetic process typically carried out by coupling the corresponding thiols with an activated derivative of the alcohol in the presence of base, or alternatively by a Lewis acid-catalyzed reaction with activated alcohols.[1–4] Recent reports have shown that these thiols can be obtained in good yields and purity via a zinc–dichlorodimethylsilane–dimethylacetamide-mediated reduction of aryl sulfonyl chlorides.[5] In the course of our work, we required a method of reducing the sulfonyl chlorides and utilizing them directly in the formation of thioethers. Although it is reported that the zinc–dichlorodimethylsilane reduction occurs via a Vilsmeyer type activated intermediate[5] we found a safe and efficient reduction procedure in ethyl acetate alone that allows for the one-pot synthesis of thioethers. It was found that step-wise addition of the sulfonyl chloride **1** followed by dichlorodimethylsilane to a pre-activated mixture of zinc and acetic acid provides a safe method for obtaining the intermediate thiol **4** in this extremely exothermic reaction.[6] The crude, unisolated thiol is then treated directly with various alcohols to provide the corresponding thioethers **5** in high yield and purity after aqueous work-up (see Scheme 1). Selected examples of this process have been run on a kilogram scale, without incident by following the step-wise reduction procedure.

The results of the experiments are summarized in Table 1. As can be seen, the nature of both the sulfonyl chloride and alcohol effect the rate of reaction.[1] The rate of the reduction to the intermediate thiol and the rate of coupling are controlled by different factors. As expected, the reduction rate is determined by substitution on the sulfonyl chloride. For instance, the reduction proceeds faster for substrates with *para*-alkoxy substituents than for the *para*-triflouromethyl group, due most likely to the electron donating effect of the *para*-alkoxy group. In fact, some substrates including 4-chlorosulfonyl benzoic acid and 2,4,6-isopropylbenzene sulfonyl chloride failed to give productive yields on the reduction stage due either to a slow rate of reaction or side product formation. Phenethyl alcohol and *para*-nitro benzyl alcohol failed to give productive reactions in the coupling stage due to their inability to form stable carbonium ions under these conditions. In all the successful reductions the sulfinic acid intermediate **2** is formed rapidly after addition of the sulfonyl chloride to the pre-activated zinc (as judged by HPLC). Likewise, the conversion of this sulfinic acid to the disulfide **3** is rapid upon addition of the dichlorodimethylsilane. The slowest step in the reduction is conversion from the intermediate disulfide to the thiol as monitored by HPLC. Temperature also plays an important role in the reduction to the thiol. In our early work, the dichlorodimethylsilane was added at 60°C, and the reduction would take up to 5 h for the



Scheme 1.

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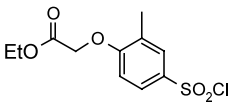
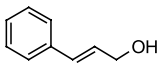
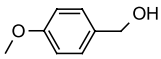
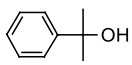
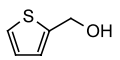
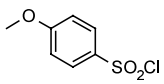
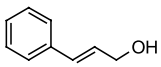
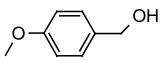
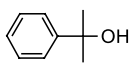
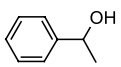
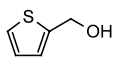
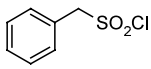
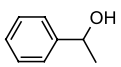
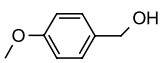
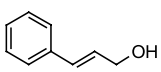
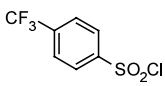
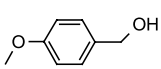
Table 1. Coupling of aromatic sulfonyl chlorides and activated alcohols

Ar-SO_2Cl	Ar-CH_2-OH	Yield[a]	Time[b] (t_1/t_2)	Entry
		49%	1h/ 16h	1a
		74%	45min/ 1h	1b
		87%	45min/ 5min	1c
		34%	40min/ 1.5h	1d
		58%	1h/ 45min	2a
		67%	1h/ 1h	2b
		80%	1h/ 1min	2c
		77%	50min/ 2h	2d
		70%	0.5h/ 0.5h	2e
		78%	16h/ 2h	3a
		50%	16h/ 1h	3b
		40%	16h/ 1h	3c
		79%	16h/ 0.5h	4a

[a] Isolated yields.
[b] t_1 is the time required for reduction to the thiol intermediate, t_2 is the time required for coupling.

activated sulfonyl chlorides to go to completion. However, when the temperature was increased to 85°C, the reduction time was reduced to under an hour.

In conclusion we have developed a safe and efficient one-pot synthesis of thioethers via a direct reduction/coupling of aromatic sulfonyl chlorides to activated alcohols with typical yields in the range of 34–87%. Based on reaction calorimetry data, the reduction stage is highly exothermic, however by using the two stage addition controlled process we have described here, the reaction can be run safely even on large scale. By utilizing the in-situ generated thiol directly, this process avoids problems associated with isolation and storage of these intermediates.

Typical experimental procedure

Under an N_2 atmosphere, zinc (1.103 g, 16.9 mmol), followed by ethyl acetate (12 mL) was added to a round-bottomed flask and the mixture was stirred mechanically and heated to 40°C. Acetic acid (0.551 mL, 9.6 mmol) and water (0.174 mL, 9.6 mmol) were then added and the temperature was increased to 60°C. 4-Methoxybenzenesulfonyl chloride (1 g, 4.8 mmol, dissolved in 3 mL of ethyl acetate) was then added over a period of 5 min, and the temperature was then increased to 85°C. Dichlorodimethylsilane (1.71g, 13.3 mmol) was then added over 10 min and the solution was allowed to stir for 30 min. 2-Thiophenemethanol (0.550 g, 4.8 mmol) was then added and the reaction was stirred for an additional 30 min. The reaction was then cooled to ambient temperature and extracted with water (2×10 mL) followed by 50% brine (2×10 mL). The water and brine extracts were then backwashed with ethyl acetate (10 mL) and the combined organic fractions were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The compound was then purified on silica gel by flash column chromatography eluted with a hexanes:dichloromethane gradient (95–65% hexane solution) to provide compound **2e**.[7]

Acknowledgements

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References

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6. For example, reduction of **1** has a predicted adiabatic temperature rise of 124°C based upon reaction calorimetry.
7. ^1H, ^{13}C NMR, and elemental analysis for all compounds are in accordance with assigned structures. Spectroscopic data for compound **2e** is as follows: ^1H NMR (300 MHz, DMSO-d_6) δ 3.73 (s, 3H), 4.33 (s, 2H), 6.8 (m, 4H) 7.3 (m, 3H).^{13}C NMR (75 MHz, DMSO-d_6) δ 159.4, 142.0, 133.5, 127.4, 127.1, 126.0, 125.9, 115.4, 55.9, 34.4. Anal calcd for $C_{12}H_{12}OS_2$: C, 60.98; H, 5.12; O, 6.77; S, 27.13. Found: C, 61.07; H, 5.33; S, 26.92.