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EFFICIENT ROUTE FOR THE PREPARATION OF BENZYLOXY-SUBSTITUTED BENZENESULFONYL CHLORIDES FROM MERCAPTOPHENOLS

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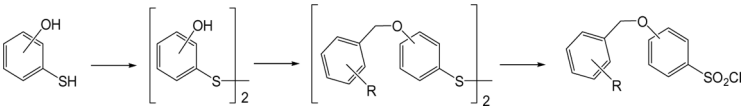
GRAPHICAL ABSTRACT



Abstract *A consistently high-yielding route has been developed for the preparation of benzyloxybenzenesulfonyl chlorides from mercaptophenols. This route allows rapid preparation of intermediates for array chemistry.*

Keywords Aromatic compounds; disulfides; mercaptophenols; sulfonyl chlorides

INTRODUCTION

As part of our research, we sought an efficient route to a range of benzyloxy-substituted benzenesulfonyl chlorides of structure **1** (Scheme 1). These were required as key building blocks for array chemistry and also as protected phenolic sulfonyl chloride precusors. Few examples of benzyloxy-substituted aromatic sulfonyl chlorides are exemplified in the literature, and the current methods do not fully explore the rapid preparation of a range of substituted benzyloxy analogs across *ortho*, *meta*, and *para* isomers.[1,2] The current literature routes include formation of aromatic sulfonyl chloride from aromatic halides via formation of Grignard intermediates[3] or halogen–metal exchange.[4] These methodologies allow to access sulfonyl chlorides with good to moderate yields,[5] with the limitation of requiring halogenated starting materials. Alternatively, direct chlorosulfonation with chlorosulfonic acid gives *para*-substituted analogs; unfortunately we have found this reaction to be very capricious. All three mercaptophenol isomers **2** are readily available and were therefore considered to be a suitable starting point. However, direct

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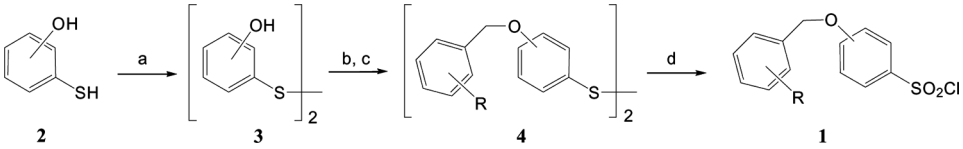

Scheme 1. Reagents and conditions: (a) I_2–MeOH, (b) NaH–DMF, (c) $ArCH_2Br$–DMF, (d) Cl_2–AcOH–H_2O or NCS–AcOH–H_2O.

alkylation of mercaptophenols gives the corresponding S-alkyl derivative.[6] We envisaged that formation of the corresponding disulfide would enable selective alkylation at oxygen and the disulfide could then be oxidatively cleaved to the corresponding sulfonyl chloride. Thus we explored the possibility of preparing benzyloxybenzenesulfonylchoride by the route shown in Scheme 1.

The methodology reported herein has been successfully used in some of our previous work.[7] Furthermore, there are other methods of accessing sulfonyl chlorides from disulfides.[8,9]

RESULTS AND DISCUSSION

All of the disulfides of structure **3** are known and were prepared from the corresponding mercaptophenols by treatment with iodine in methanol.[10] Alkylation of these disulfides using sodium hydride in dimethylformamide (DMF) gave the bis-*O*-alkylated products **4** in excellent yields (Table 1), providing the amount of alkylating agent was limited to 2.2 equivalents. If excess alkylating agent was used, the secondary alkylation occurred at sulfur. Treatment of the disulfide with either chlorine[11] or *N*-chlorosuccinimide (NCS)[12,13] in a mixture of acetic acid and water gave the desired sulfonyl chloride (Table 1). Consistently good yields were obtained for the *meta* and *para* isomers whereas yields were slightly reduced for the *ortho*

Table 1. Sulfonyl chlorides prepared using this methodology

			Sulfonyl chloride formation[a]	
R	Isomer	Alkylation step[a] yield (%)	Reagent	Yield (%)
4-F	*para*	100	Cl_2	94
"	"		NCS	93
3-F	"	80	"	90
2-F	"	70	"	83
4-Me	"	82	"	97
2,4-diF	"	87	"	93
3,4-diF	"	79	"	91
4-Br	"	82	"	85
4-CF_3	"	87	"	87
4-F	*meta*	86	"	98
4-Cl	"	82	"	78
4-F	*ortho*	93	"	65
4-Cl	"	96	"	65

[a]NMR and mass spectral data were fully consistent for the structures shown.

isomers, presumably because of steric hindrance, though no attempts were made to optimize conditions for this isomer.

All the sulfonyl chlorides prepared were reacted with a diverse range of amines using standard literature conditions[14] in an array format, giving the corresponding sulfonamides in >80% yield.

CONCLUSIONS

In summary, this methodology gives excellent yields to access benzyloxy-substituted benzenesulfonyl chlorides and has the potential to be applied to the preparation of further homologated analogs. For example, we have shown that equally good yields can be obtained by substituting $Ar(CH_2)_3Br$ or $Ar(CH_2)_2Br$ for benzyl bromide.

EXPERIMENTAL

Typical Experimental Procedure for Benzylation of Hydroxyphenyl Disulfides Bis-[3-(4-fluorobenzyloxy)-phenyl]-disulfide

To a solution of *bis*-(3-hydroxyphenyl)-disulfide (0.84 g, 3.4 mmol) in DMF (15 mL) was added sodium hydride 60% in oil (0.28 g, 7.0 mmol). The solution was stirred for 10 min when 4-fluorobenzyl bromide (1.32 g, 7 mmol) was added, and the solution stirred for another 16 h, poured onto water, and extracted with ethyl acetate. The organic extracts were washed with dilute sodium hydroxide solution and then brine and evaporated. Chromatography on silica gel eluting with 10% ethyl acetate in hexane gave the desired *bis*-[3-(4-fluorobenzyloxy)-phenyl]-disulfide as a white solid (1.34 g, 86% yield). Mass spectrum 467 (M^+); ^1H NMR: $CDCl_3$ 4.96 (4H, s), 6.83, (2H, m), 6.8–7.1 (8H, m), 7.2 (2H, m), 7.35 (4H, m).

Typical Experimental Procedure for Conversion of the Disulfides to Sulfonyl Chlorides 3-(4-Fluorobenzyloxy)-benzenesulfonyl Chloride

A solution of *bis*-[3-(4-fluorobenzyloxy)-phenyl]-disulfide (1.3 g, 2.8 mmol) in glacial acetic acid (20 mL) and water (5 mL) was cooled in an ice-water bath. *N*-Chlorosuccinimide (1.9 g, 14 mmol) was added with stirring, and the solution was allowed to warm to room temperature over 2 h. The reaction was then poured into water and extracted with ethyl acetate. The organic extract was washed with brine, dried with Na_2SO_4, filtered, and evaporated to give the title compound as a white solid (1.65 g, 85% yield). ^1H NMR: $CDCl_3$ 5.10 (2H, s), 7.08, (2H, m), 7.32 (1H, m), 7.44 (2H, m), 7.51 (1H, m), 7.55 (1H, m), 7.66 (1H, m).

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