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Firdous Imran Ali <sup>a</sup>, Imran Ali Hashmi <sup>a</sup>, Bina S. Siddiqui <sup>b</sup> & Munawwer Rasheed <sup>a</sup>

<sup>a</sup> Department of Chemistry, University of Karachi, Karachi, Pakistan

<sup>b</sup> H.E.J. Research Institute of Chemistry, University of Karachi, International Center for Chemical Sciences, Karachi, Pakistan

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## Simple Method for the Preparation of Symmetrical Alkyl and Aryl Disulfides with Alkyl Sulfonyl Halides in Nitrogenous Base

**Firdous Imran Ali and Imran Ali Hashmi**

Department of Chemistry, University of Karachi, Karachi, Pakistan

**Bina S. Siddiqui**

H.E.J. Research Institute of Chemistry, University of Karachi,  
International Center for Chemical Sciences, Karachi, Pakistan

**Munawwer Rasheed**

Department of Chemistry, University of Karachi, Karachi, Pakistan

**Abstract:** In the present study, the reaction of thiols with alkyl sulfonyl halides was carried out in a nitrogenous base to compare the reactivity of -SH with that of -OH, which, however, led to the formation of disulfides. The reaction achieved as a result offers the use of an inexpensive reagent, quantitative yields of the product, and simplicity for the formation of the S-S bond.

**Keywords:** disulfides, methanesulfonyl chloride, pyridine, thiols

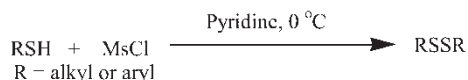
### INTRODUCTION

Diaryl and dialkyl disulfides have achieved much attention because of their application in many important synthetic reactions, for instance, synthesis of nucleotide derivatives,<sup>[1]</sup> addition of substituted alkenes to vinylcyclopropane,<sup>[2]</sup> conversion of hydroxy acids into lactones,<sup>[3]</sup> and several other syntheses.<sup>[4–7]</sup> Disulfides play a vital role in living systems.<sup>[8,9]</sup> In the

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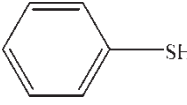
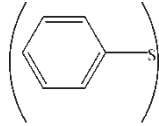
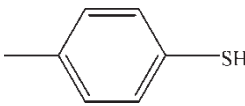
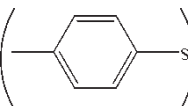
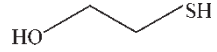
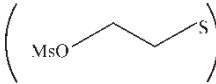
Address correspondence to Firdous Imran Ali, Department of Chemistry, University of Karachi, Karachi, Pakistan. E-mail: firdousilyas@yahoo.com

present article, we are reporting disulfide formation from thiols on their reaction with methanesulfonyl chloride in pyridine at 0°C, in almost theoretical yield. The present reaction offers the use of an inexpensive reagent, quantitative yields of the product, and simplicity. The scope of the reagent can be measured from the wide range of substrates entered in Table 1. In all cases, mild conditions have been used.

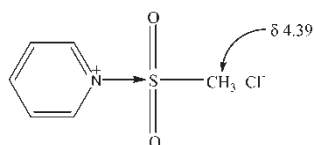


A great deal of synthetic work has already been carried out for the formation of disulfides from thiols<sup>[10–18]</sup> and other reagents.<sup>[19–21]</sup> In 1988, Langer et al. reported the formation of disulfides with methanesulfonyl chloride in the presence of 2,4,6-tribromophenol as catalyst using NaH as base. The reaction is suggested to proceed via 2,4,6-tribromosulfonate formation followed by the attack of mercaptide ion.<sup>[22]</sup> Our procedure uses the reduction of acyl ammonium salt (mesyl pyridinium chloride) with mercaptide anions (Scheme 1) in analogy with the formation of acyl ammonium salt reported earlier.<sup>[23]</sup> The formation of the mesyl pyridinium

**Table 1.** Synthesis of symmetrical aryl and alkyl disulfides with mesyl chloride in pyridine

Entry	Substrate	Product	Yield (%)	Time (min)
1			100	15
2			95	20
3			65	15
4	C <sub>2</sub> H <sub>5</sub> SH	(C <sub>2</sub> H <sub>5</sub> S) <sub>2</sub>	78	25
5	n-C <sub>3</sub> H <sub>7</sub> SH	(n-C <sub>3</sub> H <sub>7</sub> S) <sub>2</sub>	70	30
6	iso-C <sub>3</sub> H <sub>7</sub> SH	(iso-C <sub>3</sub> H <sub>7</sub> S) <sub>2</sub>	76	25
7	n-C <sub>4</sub> H <sub>9</sub> SH	(n-C <sub>4</sub> H <sub>9</sub> S) <sub>2</sub>	91	30
8	n-C <sub>6</sub> H <sub>13</sub> SH	(n-C <sub>6</sub> H <sub>13</sub> S) <sub>2</sub>	89	25

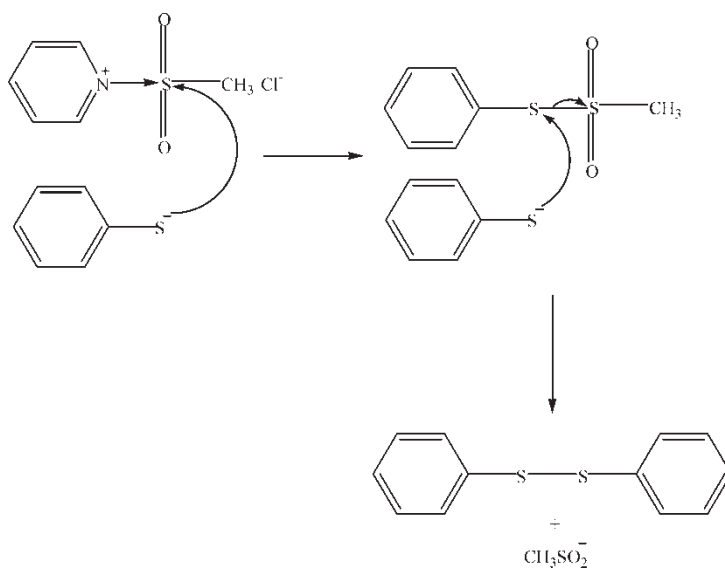
chloride was supported by  $^1\text{H}$  NMR spectroscopic studies. Methanesulfonyl chloride was added to a cold solution ( $0^\circ\text{C}$ ) of  $\text{C}_5\text{D}_5\text{N}$ , and its  $^1\text{H}$  NMR spectra were recorded five times, each with an interval of 2 min for 10 min. Each time, the signal of  $-\text{SO}_2\text{CH}_3$  was observed at the same chemical shift, that is,  $\delta$  4.39 as against  $-\text{SO}_2\text{CH}_3$  of  $\text{MsCl}$  alone at  $\delta$  3.7;<sup>[24]</sup> in  $\text{CD}_3\text{OD}$ , it appeared at  $\delta$  3.03, which shifted to  $\delta$  3.88 after the addition of tributyl amine.



The formation of disulfides proceeded well with nitrogenous bases, whereas in the case of nonnitrogenous base, the thiophenol was recovered as such (Table 2).

Reaction with different alkyl sulfonyl and aryl sulfonyl halides showed that other alkyl sulfonyl halides react in the same way as mesyl chloride, whereas with aryl halides the desired results were not achieved and the starting material was recovered unchanged (Table 3).

The general applicability of the reaction was observed on elaborating the reaction to various thiols and thiophenols (entries 2–8, Table 1). In each case, a solution of thiol or thiophenol (1 mmol) in anhydrous pyridine (1.2 mmol)



**Scheme 1.** Proposed mechanism of disulfide formation.

**Table 2.** Effect of bases on phenyl disulfide formation

Substrate	Base	Temp. (°C)	Time	Yield (%)
1	Pyridine	0	15 min	100
2	Lutidine	0	5 min	100
3	Diisopropyl amine	10	20 min	98
4	Tributyl amine	0	25 min	100
5	Trimethyl amine (acetonitrile)	rt <sup>a</sup>	72 h	95
6	Potassium <i>t</i> -butoxide (n-BuOH)	0–rt	72 h	0

<sup>a</sup>rt = Room temperature.

was treated with methanesulfonyl chloride (1.2 mmol) at 0°C. The reaction time required for completion of the reaction was monitored through thin-layer chromatography (TLC) and found variable. All products were identified by comparing their physical and spectroscopic data with those published in literature.<sup>[4,5]</sup>

The phenols were also treated with the same reagent under the same conditions, but their dimers were not obtained as observed in the case of thiols.

## EXPERIMENTAL

### General

All chemicals were purchased from Aldrich. TLC was carried out on homemade silica-gel (GF<sub>254</sub>) plates; <sup>1</sup>H NMR were recorded in CDCl<sub>3</sub> on a Bruker Aspect 3000 AM 300 spectrophotometer, Bruker Aspect 4000 AM 400, and AMX 500 spectrophotometer, operating at 300, 400, and 500 MHz, respectively.

### Representative Procedure for Disulfide Formation of Thiophenol

A solution of the thiophenol (**1**) (100 mg, 0.219 mmol) in anhydrous pyridine (2 ml, 0.3 mmol) was treated with methanesulfonyl chloride (0.041 ml,

**Table 3.** Effect of different sulfonyl halides on phenyl disulfide formation

Substrate	Sulfonyl halide	Temp. (°C)	Time	Yield (%)
1	Methanesulfonyl chloride	0	15 min	100
2	Ethanesulfonyl chloride	0	10 min	100
3	Toluenesulfonyl chloride	rt	72 h	0
4	1-Naphthylsulfonyl chloride	rt	72 h	0

0.54 mmol) at 0°C, and the reaction was monitored by TLC. After 10 min, **1** was almost completely consumed, and white precipitates were obtained. The reaction product was poured into ice-cold water, and the crystals of diphenyl disulfide obtained were filtered, washed several times with ice-cold water, and air dried. Other products (entries 2–8) were obtained upon usual workup. (The reaction mixture was partitioned between water and ethyl acetate; the ethyl acetate phase was washed, dried, and evaporated under reduced pressure.)

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