



# PTAB mediated open air synthesis of sulfonamides, thiosulfonates and symmetrical disulfanes



Debayan Sarkar<sup>\*</sup>, Manoj Kumar Ghosh<sup>a</sup>, Nilendri Rout

Department of Chemistry, National Institute of Technology, Rourkela, Odisha 769008, India

## ARTICLE INFO

### Article history:

Received 11 March 2018

Revised 7 May 2018

Accepted 8 May 2018

Available online 9 May 2018

### Keywords:

Sulfonamide

Thiosulfone

Disulfane

Gram-scale

Chiral pool

## ABSTRACT

A facile methodology has been described which has successfully simplified the generation of sulfonamides, thiosulfonates and symmetric disulfanes. This “trio” of reactions occur in an open air metal free atmosphere and has also been scaled up to grams making it suitable for commercialization. The reactions also have been successfully carried out with asymmetric variants, thus contributing to the chiral pool. The user friendly “trio” enables easy generation of these versatile sulfur analogues and the reaction condition employed depict an economic outline.

© 2018 Elsevier Ltd. All rights reserved.

## Introduction

Synthetic intrigues towards generation of new sulfur molecules have been a lucrative area to explore due to immense biological properties related to them.<sup>1</sup> The sulfonamides,<sup>2</sup> thiosulfonates<sup>3</sup> and disulfanes<sup>4</sup> are well explored motifs. Particularly in the last five years, the reports on sulfonamides and thiosulfonate synthesis have been voluminous. These motifs have also in widespread use as intermediates and reagents.<sup>5</sup>

In the recent past, sulfonamides have acted as versatile protecting groups, asymmetric ligands and organocatalysts<sup>6</sup> which has overhyped our interest on these particular class of synthetically challenging motifs.

The traditional approaches towards synthesis of sulfonamides involve sulphide oxidation and amide coupling of sulphonium halides with amines.<sup>7</sup> It would be a long tale out to enlist the synthetic attempts executed towards these directions. Metal free synthetic methodologies have always been preferred areas to explore due to facile environmental acceptance and cost effectiveness. Albeit, it was observed that these preferred metal free protocols to generate these sulfonamides were reported rarely.<sup>8</sup> Shi *et al.* reported an impressive cross-coupling reaction of aryl boronic acids to generate sulfonamides.<sup>7</sup> Recently, Xia *et al.* illustrated a NBS mediated direct *N*-sulfonylation of azoles with sodium sulfonates although it delivered minor substrate scope.<sup>9</sup> Use of *N*-halo

succinimide has not been generalized in these reactions as well as generating unwanted succinimide at the end of the reaction brands the protocol as uneconomic. Thiosulfonates and disulfanes are equally important bond generations due to their prominent presence in important biological proteins, antibiotics and anti-tumor agents.<sup>10</sup> The synthetic approaches include oxidation of sulfanes, coupling of sulfanes with sodium sulfinates and coupling of thiols with sulphonyl chlorides.<sup>11</sup> Metal catalysed approaches, have also been the main course of synthesis in the above case.<sup>10</sup> The Sinha group reported an ionic liquid based oxidative coupling of thiols to deliver sulfanes,<sup>12</sup> followed by the synthesis of unsymmetrical disulfanes by Witt *et al.* from the corresponding thiols and bis-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinanyl) disulfane, however both these protocols lacked the expected versatility in substrate scope.<sup>13</sup> In the course of reactions with generation of disulfanes, we found that the NMR data reported by Zhou *et al.*<sup>14</sup> were not inconsistency with the one we isolated. We were convinced that the S-N, S-S bond generation were very challenging to achieve and there has no common protocol available which could achieve these ‘Trio’ of operations. It would be a further realisation, if the pathway could be applied to a gram scale transformation employing an economic route which would also demonstrate substantial commercial importance (See [Figs. 1 and 2](#)).

Herein, we report a sustainable and economic metal free, open air one pot synthesis of sulfonamides, thiosulfonates and symmetric disulfanes, – employing Phenyl Trimethyl Ammonium Tribromide (PTAB) as the effective reagent. Enantiomerically pure sulfonamides have been synthesized with scaling up to grams in a single batch reaction.

<sup>\*</sup> Corresponding author.

E-mail address: [sarkard@nitrkl.ac.in](mailto:sarkard@nitrkl.ac.in) (D. Sarkar).

<sup>a</sup> Present address: University of Warsaw, 02-097, Poland.

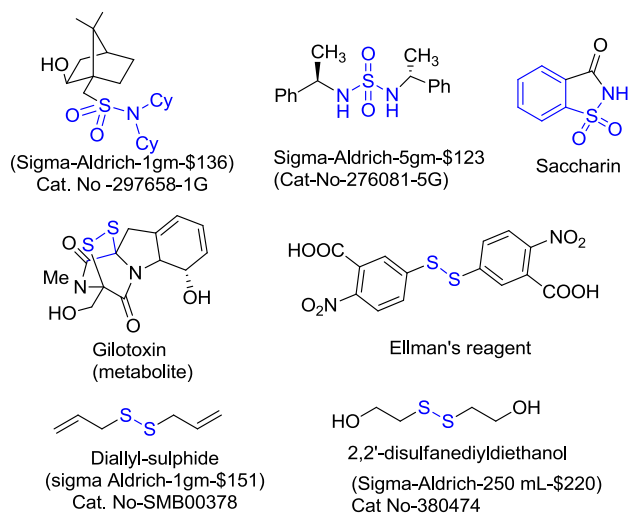


Fig. 1. Important sulfur analogues.

## Results and discussion

Preparation of sulfonamides from sodium sulfinate and amines. In the last few years, our group has been exploring the tribromide oxidations in dearomatization chemistry.<sup>17</sup> The excellent oxidative tendencies of tribromides in Oxidative dearomatization prompted us to focus on these tendencies on oxidative couplings in the S-N and S-S generation studies. In an initial attempt, the mixture of sodium benzene sulfinate (1a) with morpholine (2a) was treated with PTAB and THF as the solvent in open air atmosphere which delivered 4-(phenylsulfonyl)morpholine (3a) as the only product with 82% yield (Scheme 1).

The reaction required one equivalent of PTAB for completion of the reaction, although employing decreased equivalents did not hinder the rate of the reaction. To illustrate the synthetic potential of the stated methodology, wide range of amines were exposed to similar reaction conditions with a variety of sodium benzene sulfinate salts (Table 1) and in every case delivering the expected sulfonamides with moderate to excellent yields.

Enhanced nucleophilicity played a dominant role in the reaction as compared to the steric limitations. Secondary amines delivered better yields compared to primary and cyclic ones.

It was overwhelming to discover that generation of chiral(S)-4-methyl-N-(1-phenylethyl) benzene-sulfonamide (3k) and 1,2-diphenyldisulfane (6f) was scaled up to grams in a single batch (Schemes 2 and 3) in open air conditions, thus making it viable for industrial applications without trace of racemisation. With these results in hand, we planned to investigate the prospects for generation of thiosulfonates and disulfanes. Benzenesulfonates reacted efficiently with the thiols in similar reaction conditions to deliver the thiosulfonates and symmetrical disulfanes in an average ratio of 1:1 in almost all cases. The thiosulfonates and disulfanes were easily separated employing column chromatography and the purity was analysed by the semi-preparative HPLC. These oxidative PTAB mediated couplings were satisfactory in terms of excellent yields at ambient temperature and limited reaction time. In fact, the reaction time required for total completion was only 4–6 h. Reactions with sensitive cyclopropanes (3q & 3r) and halide substitutions (5b, 5j, and 5l) were also found satisfactory which was additional advantage over the use of N-halo succin-

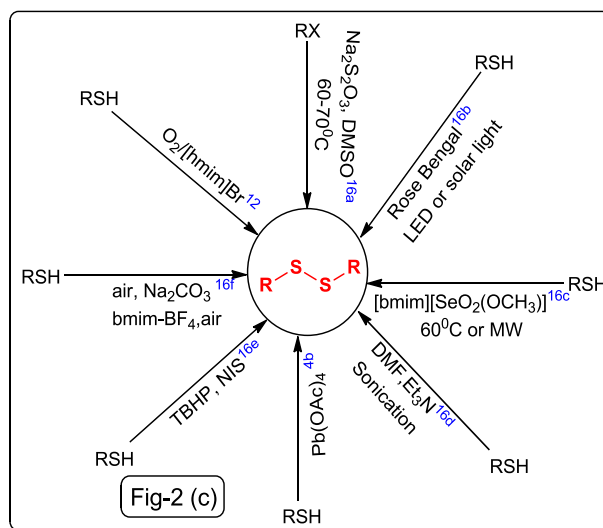
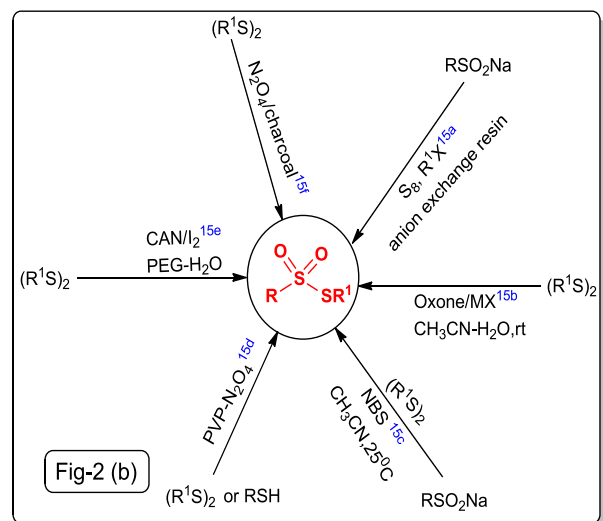
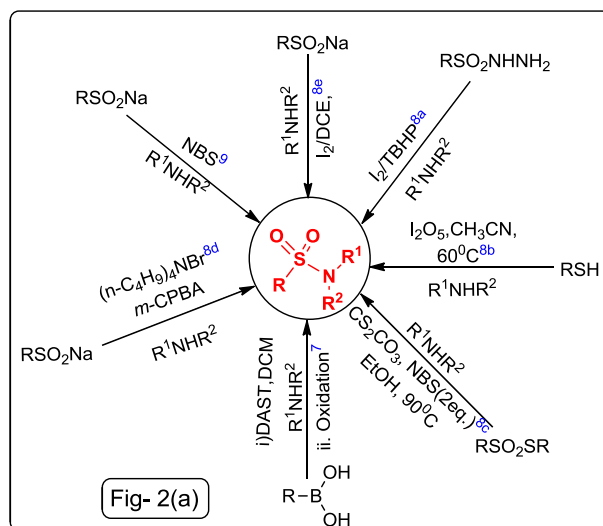


Fig. 2. Metal Free Protocols towards construction of (a) Sulfonamides (b) Thiosulfonates (c) Disulfanes (d) Schematic Presentation of the current Work. (See above-mentioned references for further information)

Download English Version:

<https://daneshyari.com/en/article/7829000>

Download Persian Version:

<https://daneshyari.com/article/7829000>

[Daneshyari.com](https://daneshyari.com)