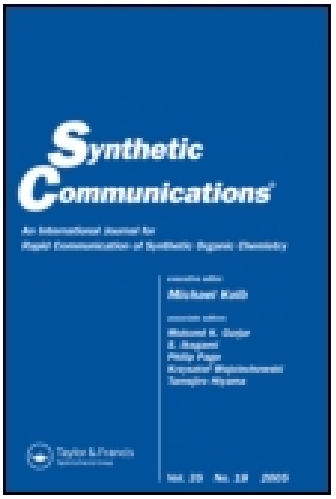

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One-Pot, Catalyst-Free, Facile, and Efficient Sulfenylation of Electron-Rich Substrates with a Mild Sulfenium Carrier Azobenzene-2-sulfenyl Bromide

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ONE-POT, CATALYST-FREE, FACILE, AND EFFICIENT SULFENYLATION OF ELECTRON-RICH SUBSTRATES WITH A MILD SULFENIUM CARRIER AZOBENZENE-2-SULFENYL BROMIDE

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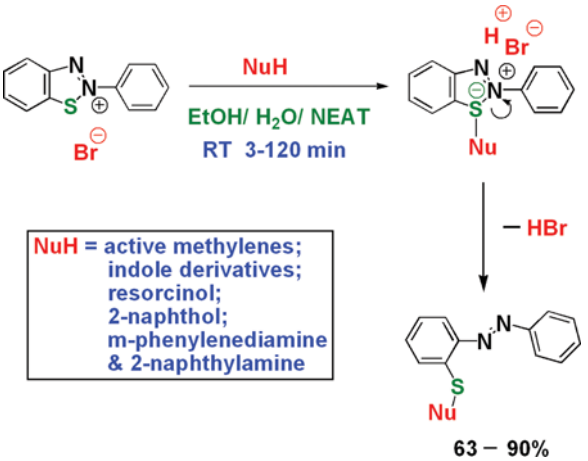
GRAPHICAL ABSTRACT



Abstract *One-pot, catalyst-free, facile, and efficient sulfenylations of resorcinol, 1,3-diaminobenzene, 2-naphthol, 2-aminonaphthalene, indole, pentane-2,4-dione, etc., in aqueous and ethanolic solution by a mild sulfenium carrier azobenzene-2-sulfenyl bromide are described. Efficient sulfenylating reagent, mild reaction conditions, and excellent yields make this method quite simple, convenient, and practical.*

Supplemental materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *to view the free supplemental file.*

Keywords Aqueous medium synthesis; azobenzene-2-sulfenyl bromide; azo-sulfur interaction; hypervalent episulfonium ion; sulfenylation

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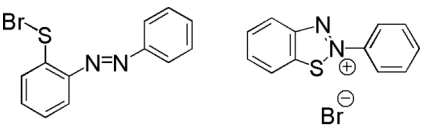
INTRODUCTION

Sulfenylation of electron-rich compounds such as 1-naphthol, resorcinol, 2-naphthylamine, and indole have versatile synthetic and pharmaceutical utility. 3-Sulfenylindoles are of particular interest as the precursor of anti-HIV active compounds,[1,2] antinociceptive active compounds,[3] 5-lipoxygenase inhibitors,[4] and organic nonlinear optical materials.[5] Again sulfenylated 2-naphthols could be used as agricultural chemicals for powdery mildew.[6] Divalent organosulfur compounds, especially alkane and arene sulfenyl chlorides, and their sulfenylation reactions have been extensively studied over the past three decades.[7–15] Although many useful methods for the sulfur–carbon bond formation have been reported using a variety of reagents such as disulfide,[16] thiols in the presence of iodine,[17,18] *N*-chlorosuccinimide,[19] phenyliodine (III) bis-(trifluoroacetate),[20] and vanadium catalyzed thiol under molecular oxygen[21] most of them require hazardous solvents, severe reaction conditions, and long reaction times.

Quantum mechanical calculations[22] have shown that the ground-state electronic configuration of sulfenium cation is a high-energy triplet state for which sulfenylation reactions involving such intermediates should be highly endothermic. The reactive species, sulfenium cation, exists as a sulfenium cation carrier species, where it is stabilized by an external (nucleophilic solvent) or an internal nucleophilic group. Conductometric and spectroscopic studies of 2,4-dinitrobenzene sulfenyl chloride have revealed the existence of strong intramolecular interaction between sulfenyl sulfur and the *ortho* nitro group.[23] Again aromatic sulfenyl chlorides undergo solvolytic cleavage in hydroxylic solvents even at room temperature,[24] so these electrophilic sulfenyl reagents cannot be employed in aqueous medium sulfenylation reactions.

In this article, catalyst-free, one-pot sulfenylation of electron-rich substrates with a mild sulfenium carrier azobenzene-2-sulfenyl bromide (ABS-Br) is presented. ABS-Br belongs to the class of *ortho* mercapto-azo compounds[25–28] which have been mentioned in the synthesis of sulfonamides,[29] sulfenylation of resorcinol[30] and ketones,[31] and oxidation of amino acids.[32] Some exceptional features such as thermal stability, crystalline nature, and nonreactive solubility in water and ethanol encourage us to take ABS-Br as sulfenylating agent. The unusual stability can be attributed to the existence of a strong *ortho* azo-sulfur interaction[33] 1b (Fig. 1) in the molecule of the compound. This *ortho* azo-sulfur interaction arises as a result of the flow of electron density from proximate *ortho*-azo group to the low-energy lowest unoccupied molecular orbital (LUMO) of sulfenyl sulfur atom.

However, in spite of the strong *ortho* azo-sulfur interaction, its sulfenylating ability has not been totally sacrificed, as evident from its application as selective reagent for polypeptides and proteins[34] and for sulfenylation of alkyl methyl ketones and phenolics.[35]



1a 1b

Figure 1. Thiadiazolium salt structure azobenzene-2-sulfenyl bromide.

RESULTS AND DISCUSSION

The intramolecular cyclization of the azobenzene-2-sulfenyl bromide **1b** was due to the interaction between low-energy LUMO of sulfenyl sulfur atom and the *ortho*-azo group. It was expected that external nucleophiles stronger than the phenylazo group should be able to attack the sulfur atom of the **1b** and could cause a ring opening of the compound. This was possible because the sulfur atom of **1b** remains attached to a quaternary nitrogen atom and is also capable of expanding its octet to receive a pair of electrons, so **1b** should behave as a sulfenium carrier to take part in electrophilic sulfenylation reactions with electron-rich substrates. Because of the solubility of **1b** in water, all the reactions were performed in water, ethanol, or neat. The results are summarized in Table 1.

In the catalyst-free aqueous medium reactions between equimolar quantities of ABS-Br and water-soluble, electron-rich substrates such as resorcinol **2a** and m-phenylenediamine **2b**, sulfenylation took place at the *para*-position to give water-insoluble sulfenylated products via episulfonium ion intermediate **3** (Scheme 1).

In the case of 2-naphthol, the sulfenylation reaction proceeded very slowly in ethanol and took more than 24 h for completion, but when 2-naphthol was pasted with **1b** in the solid state, we got the desired α -sulfenylated product in 10 min. Sulfenyl halides had special reactivity toward indole nucleus in tryptophan,[36] so we employed **1b** for sulfenylation of indole **5** and 3-methylindole in water. Here, **1b** rapidly reacted with **5** to give β-thioarylated product **7** via indolenine form **6** (Scheme 2), whereas in the case of 3-methylindole, α -thioarylation took place.

In the case of active methylene compounds such as acetyl acetone **8** and 5,5-dimethyl-1,3-cyclohexanedione (dimedone), sulfenylation by **1b** in solid state (neat) took place via the enolic form of the substrates as shown in Scheme 3.

So, ABS-Br was found to be a suitable reagent for catalyst-free, one-pot sulfenylation (carbon–sulfur bond formation) of electron-rich substrates in ethanol, water, or solid (neat) at room temperature. In addition, simple workup, mild reaction conditions, comparative yields, and short reaction times make this method quite simple, convenient, and practical over the existing methods in the literature.

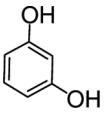
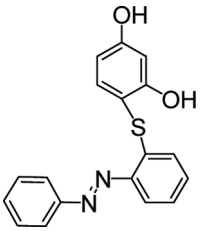
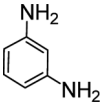
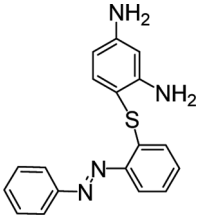
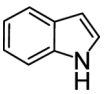
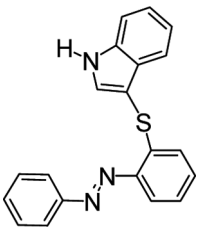
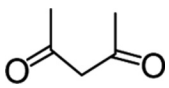
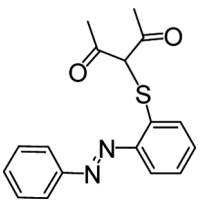
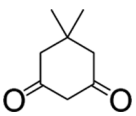
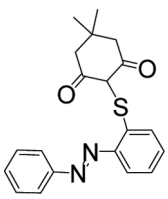
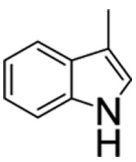
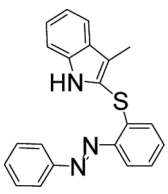
EXPERIMENTAL

Melting points were recorded on a Veego melting-point apparatus and were uncorrected. CHN analyses were recorded on a Perkin-Elmer Series II CHNS/O analyzer. Infrared (IR) spectra were recorded on an IR-affinity-I FTIR spectrometer (Shimadzu) as KBr Pellet. ^{1}H and ^{13}C NMR spectra were recorded on Ultrasonic Bruker 300-MHz FT NMR spectrometer, using tetramethylsilane (TMS) as internal standard and $CDCl_3$ as solvent. All the chemicals used were from Merck. Azobenzene-2-sulfenyl bromide was synthesized as described by Burawoy and Vellins.[28]

General Procedure for Sulfenylation of Electron-Rich Substrates

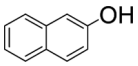
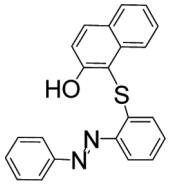
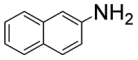
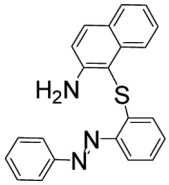
A solution of the substrates (1 mmol) in 5 mL water or ethanol [for neat, solid substrate taken in agate mortar] was added dropwise to a clear solution of

Table 1. Reactions of ABS-Br (**1b**) with electron-rich substrates

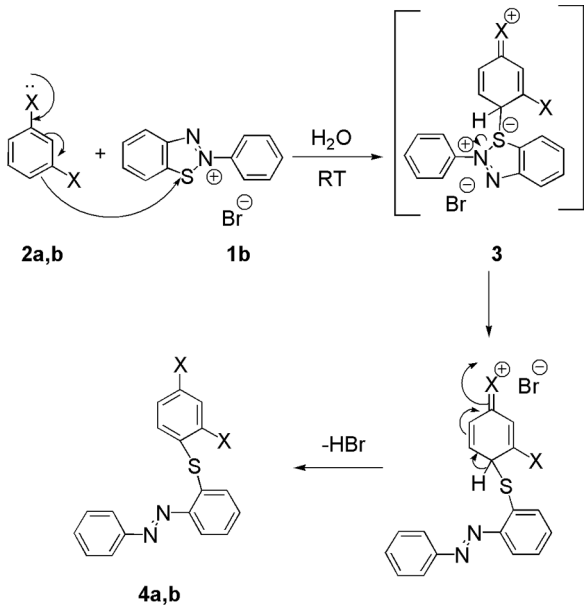
Entry	Substrate	Reaction medium	Product	Time (min)	Yield (%)
1		H_2O		5	77
2		H_2O		5	82
3		H_2O		15	77
4		Neat		3	89
5		Neat		3	88
6		H_2O		15	63

(*Continued*)

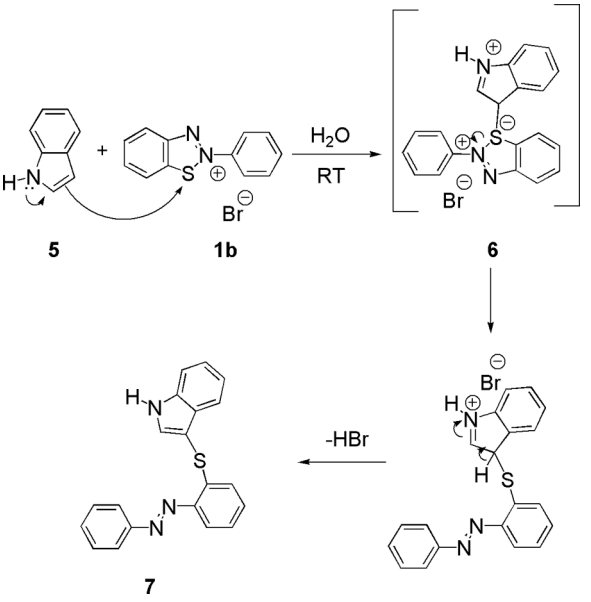
Table 1. Continued

Entry	Substrate	Reaction medium	Product	Time (min)	Yield (%)
7		Neat		10	90
8		EtOH		120	72

azobenzene-2-sulfenyl bromide (1 mmol, 0.292 g) in 25 mL water or ethanol [for neat reaction condition, solid azobenzenes-2-sulfenyl bromide was used]. The mixture was then further stirred (ground for neat reaction) at room temperature until the completion. The precipitate formed was filtered, washed with water, dried, and recrystallized from ethanol. [For reaction in ethanol, solvent was evaporated in vacuum and the pasty residue was chromatographed on a column of silica gel using dichloromethane–petroleum ether (1:4) as the eluent.]



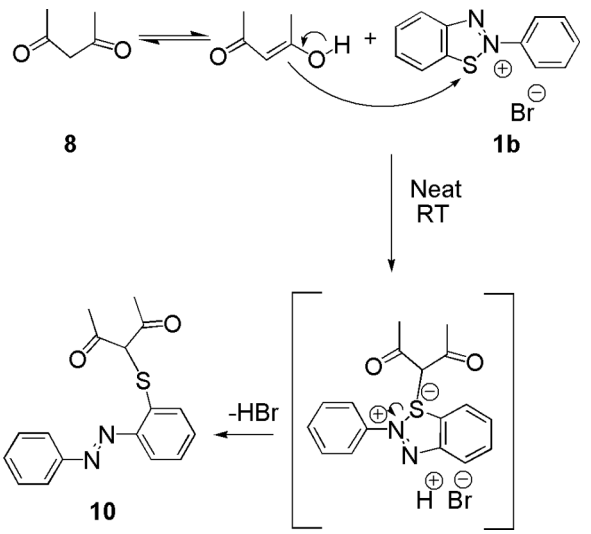
Scheme 1. Proposed pathway to the formation of sulfenylated resorcinol and m-phenylenediamine.



Scheme 2. Aqueous medium sulfenylation of indole by azobenzene-2-sulfenyl bromide.

Azobenzene-2-sulfenyl Bromide[28] (1b of Fig. 1)

Yellow crystal. Mp 220–222 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.6 (2H, d, $J = 8.1$ Hz), 8.5 (1H, d, $J = 8.1$ Hz), 8.1 (2H, d, $J = 6.6$ Hz), 7.9–8.0 (2H, m), 7.6 (3H, d, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$, 300 MHz): 122.5, 125.7, 128.8, 130.6, 130.8, 133.1, 134.1, 140.2, 145.2, 151.1; IR (KBr) (ν_{max}/cm^{-1}): 2997.3 (C-H str),



Scheme 3. Proposed pathway to the formation of mono-sulfenylated acetyl acetone.

1598.3 (N=N str.), 1365.6 (Ar. C-N str.), 763.8 (C-S str). Anal. calcd. for $C_{12}H_9BrN_2S$: C, 49.16; H, 3.09; N, 9.55. Found: C, 49.0; H, 3.1; N, 9.4.

2,4-Dihydroxyphenyl-o-phenylazophenyl Sulfide[35] (Table 1, entry 1)

Orange powder. Mp 173–174 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.52–6.59 (1H, m), 6.9 (2H, s), 7.2 (1H, s), 7.4–7.5 (4H, m), 7.7 (1H, m), 8.0 (2H, m); ^{13}C NMR ($CDCl_3$, 300 MHz): 102.7, 107.1, 109.3, 117.2, 123.2, 126.4, 127.5, 129.2, 131.5, 131.7, 138.3, 149.0, 152.6, 159.1, 159.4; IR (KBr) (ν_{max}/cm^{-1}): 3367.71 (s, OH str.), 2931.80 (w, ArH), 1598.99 (N=N str.). Anal. calcd. for $C_{18}H_{14}N_2O_2S$: C, 67.08; H, 4.34; N, 8.69. Found: C, 66.90; H, 4.30; N, 8.62.

2-Hydroxynaphthyl-1-(o-phenylazophenyl) Sulfide[35] (Table 1, entry 7)

Red powder. Mp 152–153 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.7 (1H, s), 6.6 (1H, d, $J = 8.1$), 7.086–7.136 (1H, m), 7.2 (1H, t, $J = 7.5$), 7.326–7.438 (3H, m), 7.5–7.6 (4H, m), 7.7 (1H, d, $J = 7.8$), 7.8 (1H, d, $J = 8.1$), 8.6 (2H, m), 8.3 (1H, m); ^{13}C NMR ($CDCl_3$, 300 MHz): 107.8, 117.1, 117.2, 123.3, 123.9, 124.7, 126.3, 127.1, 128.0, 128.6, 129.3, 129.5, 131.5, 131.7, 132.8, 135.7, 137.3, 149.3, 152.7, 157.4; IR (KBr) (ν_{max}/cm^{-1}): 3392.79 (s, OH str.), 2935.66 (w, ArH), 1597.06 (N=N str.). Anal. calcd for $C_{22}H_{16}N_2OS$: C, 74.20; H, 4.52; N, 7.86. Found: C, 74.09; H, 4.7; N, 7.72.

2-Aminonaphthyl-1-(o-phenylazophenyl) Sulfide (Table 1, Entry 8)

Red powder. Mp 118–119 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.0 (2H, s), 6.6 (1H, d, $J = 6.9$ Hz), 7.0–7.1 (3H, m), 7.2–7.3 (1H, m), 7.4–7.5 (4H, m), 7.7–7.8 (3H, m), 8.0 (2H, d, $J = 8.1$ Hz), 8.3 (1H, d, $J = 9.6$ Hz); ^{13}C NMR ($CDCl_3$, 300 MHz): 103.8, 117.0, 117.7, 122.6, 123.3, 124.2, 125.1, 125.7, 127.8, 128.4, 128.4, 129.2, 131.2, 131.5, 131.9, 136.8, 139.0, 148.8, 148.9, 152.8; IR (KBr) (ν_{max}/cm^{-1}): 3464.15, 3367.71 (s, NH str. for NH_2), 2926.01 (w, ArH), 1606.70 (N=N str.). Anal. calcd. for $C_{22}H_{17}N_3S$: C, 74.34; H, 4.82; N, 11.82. Found: C, 74.4; H, 4.8; N, 11.8.

CONCLUSIONS

In conclusion, we have successfully employed azobenzene-2-sulfenyl bromide as a mild electrophilic sulfenylating agent for the one-pot, catalyst-free sulfenylation of electron-rich substrates neat or in water or ethanol medium at room temperature. Simple workup, mild reaction conditions, comparative yields, and short reaction time make this method more simple, convenient, and practical than the existing methods in the literature.

SUPPORTING INFORMATION

Full experimental details and ^{1}H and ^{13}C NMR spectra can be found via the "Supplementary Content" section of this article's Web page.

ACKNOWLEDGMENTS

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