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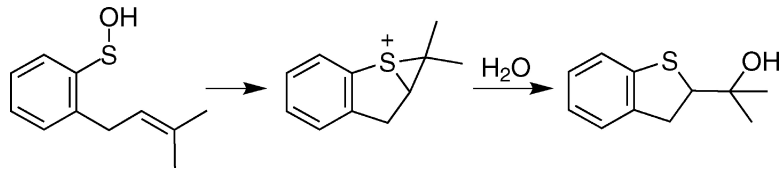

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Evidence for a Morin Type Intramolecular Cyclization of an Alkene with a Phenylsulfenic Acid Group in Neutral Aqueous Solution

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Sulfenic acids (RSOH) are among the most common sulfur-centered reactive intermediates generated in biological systems. Given the biological occurrence of sulfenic acids, it is important to explore the reactivity of these intermediates under physiological conditions. The Morin rearrangement is a synthetic process developed for the conversion of penicillin derivatives into cephalosporins that proceeds via nucleophilic attack of an alkene on a sulfenic acid intermediate. In its classic form, the Morin reaction involves initial elimination of a sulfenic acid from a cyclic sulfoxide, followed by intramolecular cyclization of the resulting alkene and sulfenic acid groups to generate an episulfonium ion intermediate that undergoes further reaction to yield ring-expanded products. On the basis of the existing literature, it is difficult to assess whether the reaction between an alkene and a sulfenic group can occur under mild conditions because the conditions required to generate the sulfenic acid from the sulfoxide precursor in the Morin reaction typically involve high temperatures and strong acid. In the work described here, β-sulfinylketone precursors were used to generate a "Morin type" sulfenic acid intermediate under mild conditions. This approach made it possible to demonstrate that the intramolecular cyclization of an alkene with a phenylsulfenic acid to generate an episulfonium ion intermediate can occur in neutral aqueous solution at room temperature.

Introduction

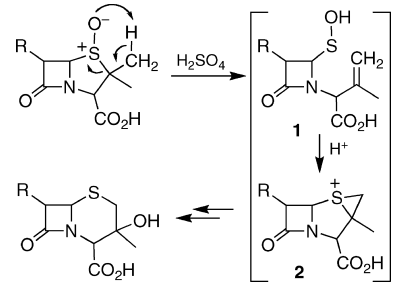
Sulfenic acids (RSOH) are among the most common sulfur-centered reactive intermediates generated in biological systems. For example, thiol groups on a wide variety of cellular proteins are converted to sulfenic acids under conditions of oxidative stress (*1–14*). In some cases, oxidation of key cysteine thiol residues to the corresponding sulfenic acids regulates protein function as part of normal hydrogen peroxide-mediated cell signaling processes (*6–12, 14*). Furthermore, sulfenic acids can be generated inside cells through the oxidation of low molecular weight thiols such as glutathione (*15–17*) and by the breakdown of drugs and other xenobiotics (*18–32*). Sulfenic acids are unstable, most commonly decomposing by reaction with nucleophiles (*15, 33–36*). For example, in biological systems, sulfenic acids often react with thiols to produce a disulfide linkage (eq 1) (*15, 37–40*).

$$\mathrm{RSOH} + \mathrm{R'SH} \rightarrow \mathrm{RSSR'} + \mathrm{H_2O} \qquad (1)$$

Given the biological occurrence of sulfenic acids, it may be interesting to explore the range of nucleophiles that can react with these intermediates under physiological conditions.

The Morin rearrangement is a synthetic transformation developed for the conversion of penicillin derivatives into cephalosporins that proceeds via nucleophilic attack of an alkene on a sulfenic acid intermediate (Scheme 1) (*36, 41–43*). In its classic form, the Morin reaction involves initial elimination of a sulfenic acid from a cyclic sulfoxide, followed by intramolecular cyclization of the resulting alkene and sulfenic acid groups to generate an episulfonium ion intermediate (**2**) that undergoes further reaction to yield ring-expanded products such as that shown in Scheme 1. On the basis of existing literature, it is difficult to assess whether the reaction between an alkene and a sulfenic group can occur under mild conditions because the conditions required to generate the sulfenic acid intermediate from the sulfoxide precursor in the Morin reaction typically involve high temperatures, strong acids, or the presence of reagents such as acetic anhydride (*36, 41–46*). In the work described here, we employed β-sulfinylketone precursors to generate a "Morin type" sulfenic acid intermediate under mild conditions. This approach made it possible to demonstrate that the intramolecular cyclization of an alkene onto a phenylsulfenic acid moiety to generate an episulfonium ion can occur in neutral aqueous solution at room temperature.

Scheme 1



Experimental Procedures

Materials. Reagents used were of highest purity available and were used without further purification unless otherwise noted. Materials were purchased from the following suppliers: HPLC grade solvents, Fisher; silica 60 (0.04−0.063 mm pore size) for column chromatography, Merck; and TLC plates coated with general purpose silica containing UV_{254} fluorophore, Aldrich Chemical Co.; all other chemicals were purchased from Aldrich Chemical Co.

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Water was distilled, deionized, and glass redistilled. All reactions were carried out under an atmosphere of nitrogen, unless otherwise noted. The oxidizing agent, dimethyl dioxirane (DMD), was freshly prepared as described (*47*). High-resolution mass spectrometry was performed at University of Illinois at Urbana−Champaign Mass Spectrometry facility (ESI and EI) or Washington University Mass Spectrometry facility (EI), and low-resolution mass spectrometry were performed at the University of Missouri−Columbia.

4-[2-(2-Bromo-phenylsulfanyl)ethyl]pyridine (3). This compound was prepared following the general method of Katrizky and co-workers (*48*). Commercially available 2-bromothiophenol (2 g, 10.6 mmol) was added to vinyl pyridine (1.6 g, 14.8 mmol) in benzene (30 mL). This mixture was refluxed overnight for 15 h. The solvent was removed under reduced pressure to give a thick, reddish brown oil. Purification of the crude compound by flash column chromatography using silica gel eluted with 2:1 hexane: ethyl acetate gave **3** (2.9 g, 95%, $R_f = 0.28$, in 2:1 hexane:ethyl acetate) as a thick, orange-brown oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.53 (d, 2H, $J = 4.5$ Hz), 7.57 (dd, 1H, 7.78 Hz), 7.27 (m, 2H), 7.15 (d, 2H), 7.05 (m, 1H), 3.20 (t, 2H), 2.97 (t, 2H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 149.89, 149.03, 142.02, 134.5, 133.06, 129.34, 129.33, 126.59, 126.57, 123.87, 122.30, 34.76, 33.96, 32.56, 25.76, 17.99 ppm. HRMS (ESI) calcd for $C_{13}H_{12}BrNS$ $[M + H]^+$, 292.9952; found, 292.9963.

4-{2-[2-(3-Methyl-but-2-enyl)phenylsulfanyl]ethyl}pyridine (4). Compound **3** (500 mg, 1.7 mmol) in THF (20 mL) was placed in a flame-dried, argon-flushed flask. The flask was cooled to −100 °C in an ether−liquid nitrogen bath. To this cooled solution, *n*-butyllithium (0.82 mL of a 2.5 M solution in hexane, 2.04 mmol) was added. The color of the solution turned dark orange yellow, and it was allowed to stir for 10 min at this temperature. Prenyl bromide (1.37 mL, 11.9 mmol) was added to this mixture, and the temperature was raised to −60 °C. The mixture was allowed to stir at this temperature for 45 min. During this time, the dark orange yellow reaction mixture turned pale yellow. The reaction was quenched with 10% HCl (20 mL), and the aqueous layer was extracted with ether (3 × 20 mL) to remove any unreacted prenyl bromide or **4**. The aqueous layer was then carefully brought to pH 7 by addition of 30% NaOH (8 mL). Care must be taken at this step because addition of too much sodium hydroxide can result in decomposition of the product. The product was extracted into ethyl acetate (3 × 20 mL). The organic layer was washed with water (2 × 20 mL) followed by brine (2 × 20 mL) and then dried over anhydrous sodium sulfate to give **4** (201 mg, 42%, $R_f = 0.37$, in 1:1 hexane:ethyl acetate) as a pale brown oil. No further purification of this compound was necessary. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.51 (d, 2H, $J = 5.43$ Hz), 7.34 (m, 1H), 7.17 (m, 5H), 5.24 (m, 1H), 3.44 (d, 2H, $J = 7.13$ Hz), 3.15 (t, 2H), 2.91 (t, 2H), 1.72 (d, 6H, $J = 6.23$ Hz) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 149.71, 148.79, 141.73, 134.29, 132.88, 129.10, 129.01, 126.39, 126.32, 123.67, 122.06, 34.52, 33.69, 32.34, 25.59, 17.8 ppm. HRMS (ESI) calcd for $C_{18}H_{21}NS$ $[M + H]^+$, 284.1473; found, 284.1474.

3-[2-(3-Methyl-but-2-enyl)phenylsulfanyl]propionaldehyde (5a). To a solution of **4** (100 mg, 0.35 mmol) in dry, distilled acetone (5 mL) under nitrogen, methyl iodide (0.33 mL, 5.25 mmol) was added. This mixture was allowed to stir at 24 °C for 3 h. The excess methyl iodide was removed by blowing nitrogen over the flask (CAUTION! Methyl iodide is carcinogenic. This must be performed in a well-ventilated hood.) Fresh dry acetone (5 mL) was added to the resulting orange yellow solid, followed by acrolein (0.046 mL, 0.70 mmol). The mixture was allowed to stir for 5 min, and then, sodium acetate (58 mg, 0.71 mmol) in water (0.2 mL) was added to the rapidly stirred mixture. The resulting green solution was allowed to stir for 18 h at room temperature. The reaction mixture was quenched by addition of water (5 mL), and the crude mixture was extracted with ether (3 × 10 mL), water (2 × 5 mL), and brine (2 × 5 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated to give a brown oil. This product was purified by flash column chromatography on silica gel eluted with 12:1 hexane:ethyl acetate to give **5a** (46 mg, 56%, $R_f = 0.37$ in 9:1 hexane:ethyl acetate) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.77 (s, 1H), 7.34 (m, 2H), 7.17 (m, 2H), 5.24 (m, 1H), 3.45 (d, 2H, $J = 7.12$ Hz) 3.16 (t, 2H), 2.77 (t, 2H), 1.74 (d, 6H, $J = 4.51$ Hz) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 200.15, 142.12, 133.90, 133.04, 129.54, 129.26, 126.67, 126.56, 122.14, 43.05, 32.42, 26.17, 25.69, 17.91 ppm. HRMS (CI^+) calcd for $C_{14}H_{18}OS$ $[M]^+$, 234.1078; found, 234.1080.

3-[2-(3-Methyl-but-2-enyl)phenylsulfanyl]propionic Acid Ethyl Ester (5b). To a solution of **4** (100 mg, 0.35 mmol) in acetone (5 mL) under nitrogen, excess methyl iodide (0.33 mL, 5.25 mmol) was added. This mixture was allowed to stir at 24 °C for 3 h. The excess methyl iodide was removed by blowing nitrogen gas over the flask (CAUTION! Methyl iodide is carcinogenic. This must be performed in a well-ventilated hood.) Dry distilled THF (5 mL) was added to the yellow orange solid, and the mixture was cooled to −60 °C using an acetone−dry ice bath. To the cold solution, sodium methoxide in methanol (0.35 mL of a 1 M solution in methanol) was added, and the mixture was stirred for 20 min. Ethyl acrylate (0.118 mL, 1.05 mmol) was added, and the reaction mixture was stirred at −60 °C for an additional 45 min. [Care should be taken at this point because excess sodium methoxide will decompose the product **5b** to generate the thiophenolate. This product is stable at low temperatures (up to −30 °C) but undergoes Kwart cyclization (*49, 50*) with the adjacent alkene at higher temperatures.] The reaction was quenched with dilute HCl (5 mL, 0.5 M) and extracted with diethyl ether (3 × 10 mL). The organic layer was washed with water (2 × 5 mL) and brine (2 × 5 mL), followed by drying over anhydrous sodium sulfate. The organic solvent was evaporated under reduced pressure to give a red oil. The crude oil was purified by flash column chromatography on silica gel eluted with 9:1 hexane:ethyl acetate to give **5b** (45 mg, 44%, $R_f = 0.69$ in 4:1 hexane:ethylacetate) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.35 (m, 1H), 7.17 (m, 3H), 5.25 (m, 1H), 4.13 (q, 2H), 3.46 (d, 2H, $J = 7.13$ Hz), 2.61 (t, 2H), 1.73 (d, 6H), 1.25 (t, 3H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 171.73, 142.17, 134.09, 132.91, 129.74, 129.15, 126.57, 126.48, 122.24, 60.64, 34.30, 32.43, 28.85, 25.68, 17.89, 14.11 ppm. HRMS (EI) calcd for $C_{16}H_{22}O_2S$, 278.1341; found, 278.1345.

3-[2-(3-Methyl-but-2-enyl)benzenesulfinyl]propionaldehyde (6a). To a solution of **5a** (25 mg) in HPLC grade acetone (4 mL), freshly prepared DMD (2 mL, ∼0.09 M in acetone) was added slowly. Formation of a new, more polar spot was seen on TLC. The solvent was evaporated under reduced pressure to give **6a** (24 mg, 90%, $R_f = 0.19$ in 1:1 hexane:ethyl acetate) as a pale brown oil. This compound was approximately 90% pure as judged by NMR; however, it was highly unstable and was used immediatedly in subsequent reactions. ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.7 (s, 1H), 7.88 (m, 1H), 7.43 (m, 2H), 7.26 (m, 1H), 5.21 (m, 1H), 3.42 (d, 2H), 3.25 (m, 1H), 2.89 (m, 1H), 1.73 (d, 6H, $J = 8.95$ Hz) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 198.43, 140.89, 138.66, 134.19, 131.18, 129.74, 127.22, 123. 82, 121.40, 46.91, 35.42, 30.44, 25.61, 17.99 ppm. Because of the unstable nature of this compound, mass spectrometric analysis was not possible; however, the ^{1}H NMR spectra clearly show a vast increase in the complexity of the splitting patterns for the protons in the propionaldehyde chain. This is indicative of introduction of a single oxygen onto the sulfur residue to generate a chiral sulfoxide that, in turn, renders hydrogens in the propionaldehyde chain diastereotopic. In contrast, in the achiral sulfide and sulfone derivatives, these proton resonances appear as simple triplets.

3-[2-(3-Methyl-but-2-enyl)benzenesulfinyl]propionic Acid Ethyl Ester (6b). This compound was prepared using the method described above for compound **6a**. Evaporation of solvent gave **6b** in 94% yield ($R_f = 0.12$ in 4:1 hexane:ethylacetate) as a colorless oil. No further purification was necessary. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.90 (m, 1H), 7.43 (m, 2H), 7.23 (m, 1H), 5.22 (m, 1H), 4.13 (q, 2H), 3.40 (d, 2H, $J = 7.1$ Hz), 3.20 (m, 1H), 2.88 (m, 2H), 2.64 (m, 1H) 1.74 (d, 6H, $J = 5.3$ Hz), 1.23 (t, 3H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 171.18, 141.02, 138.69, 134.095, 131.067, 129.58, 127.19, 123.91, 121.42, 60.99, 49.80, 30.39, 26.43, 25.60, 17.97, 14.06 ppm. HRMS (EI) calcd for $C_{16}H_{22}O_3S$, 294.1290; found, 294.1295.

Reaction of 6a in Aqueous Neutral Aqueous Solution. To a rapidly stirred solution of **6a** (20 mg, 0.08 mmol) in acetonitrile (2.5 mL), sodium phosphate buffer (0.5 mL of a 500 mM, pH 7.4) and water (2 mL) were added. The reaction mixture was stirred for 10 h (final concentrations: **6a**, 16 mM; buffer, 50 mM, pH 7.4; and acetonitrile, 50% by volume). Water (5 mL) was added, and the resulting mixture was extracted with diethyl ether (3 × 5 mL). The ether extracts were combined and washed with water (1 × 5 mL) and brine (1 × 5 mL). The solution was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield a pale yellow oil. Flash column chromatography on silica gel eluted with 9:1 hexane:ethyl acetate provided **9a** as a colorless oil (3.9 mg, 25%, $R_f = 0.35$ in 4:1 hexane:ethyl acetate) and **10** as a pale yellow oil (9.9 mg, 35%, $R_f = 0.65$ in 4:1 hexane:ethylacetate). Compound **9a**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.14−7.09 (m, 3H), 6.98 (t, 1H), 4.07 (dd, 1H, $J = 3.85$ Hz, 4.40 Hz), 3.37 (dd, 1H, $J = 3.85$ Hz, 8.03 Hz), 3.30 (dd, 1H, $J = 4.42$ Hz, 8.01 Hz), 21.96 (s, 1H), 1.26 (d, 6H, $J = 11.81$) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 139.97, 139.88, 127.24, 124.32, 121.68, 71.68, 61.78, 37.17, 28.80, 25.97 ppm. HRMS (EI) calcd for $C_{11}H_{14}OS$, 194.0765; found, 194.0765. Compound **10**: ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.55 (M, 1H), 7.17−7.09 (m, 3H), 5.25 (m, 1H), 3.47 (d, 2H, $J = 5.98$ Hz), 1.73 (d, 6H, $J = 6.18$ Hz) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 140.87, 135.28, 133.29, 129.04, 128.89, 127.33, 126.72, 121.86, 65.78, 32.21, 25.68, 17.93, 15.20 ppm. HRMS (EI) calcd for $C_{22}H_{26}S_2$, 354.1476; found, 354.1472.

Trapping of the Sulfenic Acid Intermediate 7 by Methyl Iodide. To a stirred solution of **6a** (20 mg, 0.08 mmol) in acetonitrile (2.5 mL), sodium phosphate buffer (0.5 mL of a 500 mM, pH 7.4), excess methyl iodide (1 mL), and water (1 mL) were added. The reaction mixture was stirred for 10 h (final concentrations: **6a**, 16 mM; buffer, 50 mM, pH 7.4; and acetonitrile, 50% by volume). The methyl iodide was removed by blowing nitrogen over the reaction mixture (CAUTION! Methyl iodide is carcinogenic, and this procedure must be performed in a well-ventilated hood.) Water (5 mL) was added, and the resulting mixture was extracted with diethyl ether (3 × 5 mL). The ether extracts were combined and washed with water (1 × 5 mL) and brine (1 × 5 mL). The solution was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield a dark yellow oil. Flash column chromatography on silica gel eluted with 1:1 hexane:ethyl acetate gave **12** (3 mg, 18%, $R_f = 0.18$ in 1:1 hexane:ethylacetate) as a colorless oil. IR ($CHCl_3$): 1021 cm^{-1} (S═O). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.98 (d, 1H), 7.47−7.22 (m, 2H), 7.23 (m, 1H), 5.18 (m, 1H), 3.40 (m, 2H), 2.67 (s, 3H), 1.73 (d, 6H, $J = 2$ Hz) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 143.95, 138.19, 133.83, 130.95, 129.45, 127.61, 123.12, 121.71, 42.98, 30.65, 25.60, 17.96 ppm. HRMS (EI) calcd for $C_{12}H_{16}OS$, 208.0922; found, 208.0916. In addition, the alcohol **9a** (1 mg, 7%) and the disulfide **10** (8 mg, 28%) were obtained.

Reaction of 6a in 90% Methanol−10% Aqueous Buffer. To a rapidly stirred solution of **6a** (20 mg, 0.08 mmol) in methanol (4.5 mL), sodium phosphate buffer (0.5 mL of a 500 mM, pH 7.4) was added. The reaction mixture was stirred for 20 h (final concentrations: **6a**, 16 mM; buffer, 50 mM, pH 7.4; and methanol, 90% by volume). Water (5 mL) was added, and the resulting mixture was extracted with diethyl ether (3 × 5 mL). The ether extracts were combined and washed with water (1 × 5 mL) and brine (1 × 5 mL). The solution was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield a colorless oil. Flash column chromatography on silica gel eluted with 9:1 hexane:ethyl acetate yielded **9a** (4.4 mg, 28%, 3.9 mg, 25%, $R_f =$ 0.35 in 4:1 hexane:ethyl acetate) and **10** (8 mg, 28%). Reactions containing lithium perchlorate were conducted as described above except that $LiClO_4$ (26.5 mg) was added following addition of the sodium phosphate buffer. The reaction was worked up as described above. Flash column chromatography on silica gel eluted with 12:1 hexane:ethyl acetate yielded **9b** (mg, 25%, $R_f = 0.55$ in 4:1 hexane: ethyl acetate) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): 7.16−7.11 (3H, m), 7.00 (t, 1H), 4.13 (dd, 1H), 3.32 (m, 2H), 3.29 (s, 3H), 1.27 (s, 3H), 1.21 (s, 3H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 141.81, 140.47, 127.96, 124.98, 124.75, 122.40, 77.89, 58.91, 50.39, 37.91, 23.00, 22.22 ppm. HRMS (EI) calcd for $C_{12}H_{16}OS$, 208.0907; found, 208.0922. In addition, compounds **9a** (trace) and **10** (9 mg, 33%) were also formed. A control reaction shows that a solution of **9a** (16 mg, 0.08 mmol) stirred for 15 h in methanol (4.5 mL), sodium phosphate buffer (0.5 mL of a 500 mM, pH 7.4), and lithium perchlorate (26.5 mg, 0.25 mmol) and worked up as described above returns only starting material (lithium perchlorate does not catalyze exchange of methanol into the product).

Thermolysis of 6b in CCl_4. A solution of compound **6b** (20 mg, 0.08 mmol) in carbon tetrachloride (5 mL) was placed in a pressure tube with a Teflon screw cap (Ace Glass) equipped with a stir bar. The reaction mixture was heated at 100 °C for 3 h with rapid stirring. The solvent was then evaporated to give a pale yellow oil. Purification on silica gel eluted with 9:1 hexane ethyl acetate gave **9a** (8.5 mg, 55%) as a white waxy solid. In addition, **10** (3.4 mg, 12%) was also obtained as a pale yellow oil.

Thermolysis of 6b in CCl_4/MeOH. Compound **6b** (20 mg, 0.08 mmol) was placed in a sealed tube with a magnetic bar, carbon tetrachloride (4 mL), and methanol (1 mL). The mixture was heated at 80 °C for 10 h with rapid stirring. The reaction mixture was then transferred to a round-bottom flask, and the solvent was evaporated under reduced pressure. The crude products were purified by flash column chromatography on silica gel eluted with 9:1 hexane:ethyl acetate as an eluant, and **9b** (7.4 mg, 34%) in addition to a small amount of **9a** (1.5 mg, 9%) and **10** (5.6 mg, 16%) also formed.

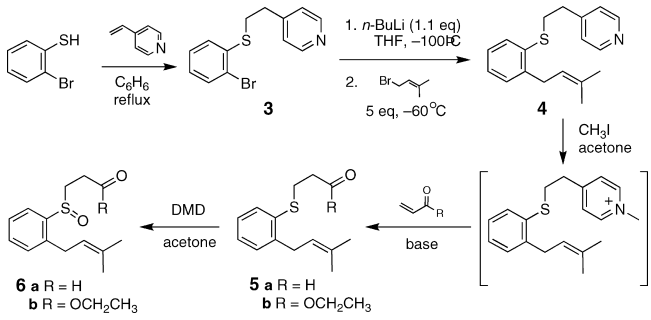
Trapping of Sulfenic Acid 7 by Methyl Propiolate in CCl_4. Compound **6b** (20 mg, 0.08 mmol) was placed in a sealed tube with a magnetic bar, carbon tetrachloride (4 mL), and methyl propiolate (1 mL). The mixture was heated at 100 °C for 3 h with rapid stirring. The reaction mixture was transferred to a round-bottom flask, and the solvent was evaporated under reduced pressure. Flash column chromatography eluted with 6:1 hexane: ethyl acetate afforded compound **13** (17 mg, 75%, $R_f = 0.37$ in 4:1 hexane:ethyl acetate) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.75 (m, 1H), 7.54 (d, 2H, $J = 7.1$ Hz), 7.41 (m, 2H), 7.28 (m, 1H), 6.72 (d, 1H, $J = 7.5$ Hz), 5.21 (m, 1H), 3.77 (s, 3H), 3.62−3.45 (m, 2H), 1.74 (d, 6H, $J = 6$ Hz) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 164.54, 150.90, 139.79, 139.56, 134.25, 131.72, 130.08, 127.97, 124.66, 123.31, 121.85 ppm. HRMS (EI) calcd for $C_{15}H_{18}O_3S$, 292.1133; found, 292.1130.

Results

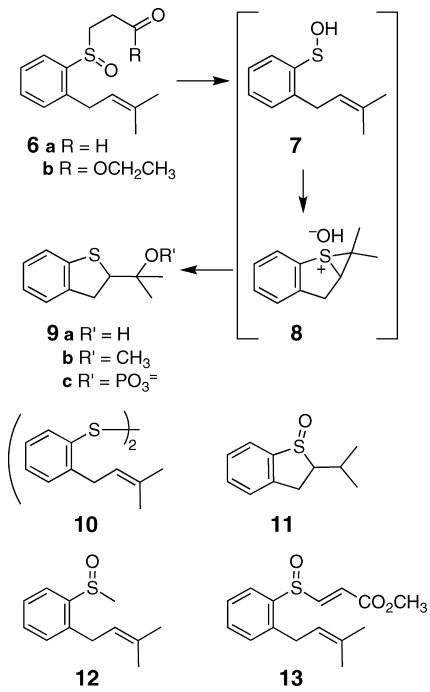
Design of Sulfenic Acid Precursors. To address the question of whether a sulfenic acid can undergo intramolecular reaction with an alkene under mild conditions to generate an alkylating intermediate, we set out to characterize the reactivity of [*ortho*-(3-methylbut-2-enyl)phenyl]sulfenic acid (**7**). Typically, it is not possible to isolate sulfenic acids due to their instability (*33, 51–54*); however, methods exist for the in situ generation of this functional group (*12, 22, 32, 48, 55–61*). In the present study, we employed a β-phenylsulfinyl aldehyde **6a** and a β-phenylsulfinyl ester derivative **6b** as phenylsulfenic acid precursors. β-Sulfinylketones such as these are known to release sulfenic acids under mild conditions via β-elimination reactions (*12, 22, 55, 56*).

Synthesis. We prepared the desired *ortho*-3-methylbut-2-enyl-substituted phenylsulfenic acid precursors **6a** and **6b** starting from commercially available 2-bromobenzenethiol (Scheme 2). The thiol substituent was masked with the ethylpyridine group by treatment with vinyl pyridine in refluxing benzene to give **3** in good yield (95%) (*48*). Protection of the thiol group is necessary prior to installation of the prenyl side chain because aromatic thiols have the potential to undergo intramolecular cyclization reactions with an adjacent alkene (*49, 50*). Lithium-halogen exchange at −100 °C, followed by treatment with prenyl bromide for 1 h at −60 °C, provided the alkene-

Scheme 2



Scheme 3

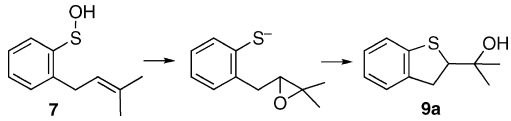


containing derivative **4** in reasonable yield (42%). The ethylpyridine group was replaced with the 3-oxopropyl side chain in a single pot by treatment of **4** with methyl iodide in acetone (*48*), followed by acrolein and sodium acetate in water to give **5a** in 56% yield. The resulting sulfide (**5a**) was oxidized with DMD in acetone (*47*) to generate the desired sulfenic acid precursor **6a**. This compound was rather unstable and was used immediately in the studies described below. We prepared an additional sulfenic acid precursor by treatment of **4** with methyl iodide in acetone, followed by sodium methoxide and ethyl acrylate in methanol at −60 °C to provide **5b** in 44% yield. Oxidation with DMD provided a 94% yield of the desired β-phenylsulfinyl ester **6b**.

Reactions of the Sulfenic Acid 7. Stirring the sulfenic acid precursor **6a** (16 mM) in a solvent mixture composed of 1:1 acetonitrile:sodium phosphate buffer (50 mM, pH 7.4) at room temperature led to the formation of the 2,3-dihydrobenzo[*b*-]thiophene derivative **9a** (25%) along with the disulfide **10** (30%). Compound **9a** is envisioned to arise via a Morin type cyclization reaction (Scheme 3), while the disulfide **10** is an expected byproduct of sulfenic acid dimerization (*51, 62*). It is possible that **9a** arises via hydrolysis of an initially formed product **9** resulting from reaction of phosphate with the episulfonium ion **8** (*63*). A related route to hydrolysis products, via a sulfate derivative, has been reported in the context of a sulfuric acid-catalyzed Morin rearrangement (see structure 56 in ref *43*). Polar material that could correspond to the phosphate-trapped episulfonium ion **9c** was observed by TLC analysis in the early stages of the reaction but was not isolated and characterized. Sulfenic acids have been observed to undergo sigmatropic addition reactions with alkenes (*15, 33, 46, 52, 64–67*); however, the product (**9a**) observed here is structurally (and spectroscopically) quite distinct from the compound (**11**) that would result from such a process in this molecular framework. The regiochemistry of this reaction (Scheme 3) can be rationalized as Markovnikov addition of the nucleophile to the more substituted carbon of the episulfonium ion, similar to the Morin process shown in Scheme 1. When the reaction was conducted in the presence of excess methyl iodide, the sulfoxide product (**12**) expected (*53, 68*) to arise from alkylation of the sulfenic acid intermediate **7** was generated in 20% yield alongside **9a** (7%) and **10** (28%). This result confirms the intermediacy of the sulfenic acid **7** in the reactions of **6a**.

Surprisingly, when **6a** was placed in a solvent mixture composed of 90:10 methanol−phosphate buffer (50 mM, pH 7), the alcohol **9a** was again obtained as the only isolable cyclized product. We had anticipated that under these reaction conditions, methanol would capture the episulfonium ion intermediate to yield **9b** (*31, 32*). The inability of methanol to trap the putative episulfonium ion **8** could indicate that this intermediate is generated as an ion pair that favors attack of hydroxide to yield the alcohol **9a**. Examples have been reported in which episulfonium ions are formed as ion pairs that evade reaction with bulk acetic acid (*69–72*); however, it should be noted that more polar solvents such as the methanol−water mixture employed here typically do not favor such ion pairing (*73*). Addition of salts such as lithium perchlorate can disrupt ion pairs, thus allowing reaction of the electrophilic intermediate with solvent (*71, 72, 74*). Indeed, addition of lithium perchlorate (50 mM) to our reaction led to the formation of the methanolysis product **9b** (25%), alongside **10** (33%) and a trace of **9a**. A control experiment confirmed that **9b** does not arise via exchange of methanol into **9a** under these reaction conditions. The origin of the lithium perchlorate salt effect, in this situtation, is not completely clear. As mentioned above, the addition of $LiClO_4$ may disrupt ion pairing via a special salt effect. Certainly, in the case of other episulfonium ions, the addition of lithium perchlorate (∼400 mM) can cause significant shifts away from reactions within an ion pair and toward reaction with the bulk solvent, but again, these examples were carried out in acetic acid, which is more supportive of ion pairing (*71*). Alternatively, the effect of added $LiClO_4$ on our reaction could arise through a kinetic salt effect (*75*). The term kinetic salt effect is used, for example, to describe the observation that reaction rates between two substrates of opposing charge decrease with increasing ionic strength of the reaction media. In our case, if the hydrolysis product **9a** arises via the reaction of oppositely charged phosphate and episulfonium ions to yield **9c**, the rate of this reaction is expected to decrease in the presence of added salt. Such a rate decrease in the pathway leading to the hydrolysis product **9a** could allow reaction of **8** with the neutral nucleophile methanol to become predominant. Finally, the inability to obtain a methanol adduct in the original reaction could reflect that the sulfenic acid **7** carries out a peroxide-like oxygenation of the alkene (this could be either intramolecular or intermolecular) followed by attack of the resulting thiol on the intermediate epoxide to yield **9a** (Scheme 4). Such peroxidic behavior of sulfenic acids is unprecedented to the best of our knowledge. Nonetheless, it is conceivable that **9a** arises via a peroxidic mechanism and that addition of $LiClO_4$ causes a shift in mechanism away from this route

Scheme 4



(Scheme 4) toward the Morin type reaction pathway that yields the episulfonium ion **8** (Scheme 3). While elucidation of the exact origin of the salt effect on this reaction awaits further study, the results, especially in light of those presented in the following paragraphs (which provide no evidence for peroxidic behavior of the sulfenic acid intermediate), are most consistent with the generation of an episulfonium ion **8** from the sulfenic acid **7**.

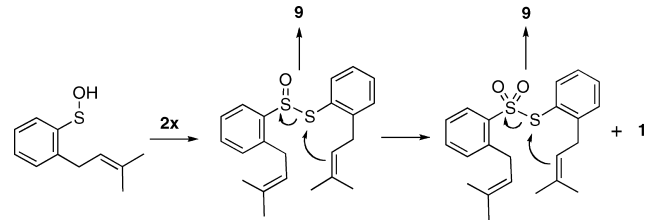
The sulfenic acid precursor **6b** is quite stable as compared to **6a**. For example, compound **6b** does not undergo decomposition even upon extended exposure (24 h) to the reaction conditions employed for the reactions of **6a**. The stability of **6b** against β-elimination is not surprising given the lower acidity of the proton α to the carbonyl in **6b** vs **6a** (pK_a ~30 vs ~22). A reaction was induced by heating a carbon tetrachloride solution of **6b** in a sealed tube at 100 °C for 3 h. This produced **9a** in 55% yield along with the disulfide **10** (12%). In this case, there was no difficulty in trapping the episulfonium intermediate with methanol. When the reaction was conducted in a 1:1 mixture of CCl_4/CH_3OH at 80 °C, the methanol-trapped product **9b** was isolated in 34% yield alongside the alcohol **9a** in 9% yield. The addition of methyl propiolate to the reaction led to the formation the vinyl sulfoxide **13** (75%) expected (*15, 33, 66, 67*) to arise from trapping of the sulfenic acid intermediate **7**. Again, this confirms the intermediacy of the sulfenic acid **7** in the reactions of **6b**.

Discussion

In the work reported here, a phenylsulfenic acid tethered to an alkene moiety (**7**) was generated from a β-phenylsulfinyl aldehyde precursor at room temperature in neutral aqueous solution. The resulting products can be explained by a mechanism involving intramolecular trapping of the sulfenic acid by the neighboring alkene to generate an episulfonium ion intermediate (**8**, Scheme 3) (*76, 77*).[1,2] Sulfenic acids readily undergo dehydrative dimerization to yield thiosulfinates (*51, 62*) that, in turn, disproportionate to the disulfide and thiosulfonate derivatives (*62*). In principle, generation of the electrophilic episulfonium ion **8** (or an equivalent carbocationic intermediate) could proceed via attack of the alkene on either thiosulfinate or thiosulfonate intermediates, with ejection of sulfinate or sulfonate leaving groups, respectively (Scheme 5). However, to the best of our knowledge, there is no precedent for such a reaction. On the contrary, in the context of molecules such as allicin (*78*) and pseudoallicin (*79*), thiosulfinate and thiosulfonate groups, respectively, coexist stably in the presence of an alkene moiety.

Episulfonium ions are of special relevance in the fields of medicinal chemistry and toxicology because these intermediates are highly reactive alkylating agents that often possess potent biological activities (*30, 80–83*). The general reaction characterized in this work might be applied to the development of biologically active episulfonium alkylating agents (*30, 80, 82, 83*).

Scheme 5. Alternatives to the Direct Cyclization of 8



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[1] In the course of thiol-triggered DNA alkylation by the natural product leinamycin, a sulfenate anion is generated proximal to an alkene unit (*29, 32*). In this case, however, the sulfenate does not react with the alkene moiety but instead undergoes facile intramolecular cyclization onto a neighboring dithioester group.

[2] For two reports in which an electrophilic intermediate was generated via intramolecular reaction of a sulfenic acid with an adjacent alkene in the absence of an acid catalyst or anhydride, see refs *76* and *77*.

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