3a: reported;[12] oil; IR 2230 cm^{-1} (CN); MS 159 (M^+, 13.6%), 117 [$(M - CH_2{=}C{=}O)^+$, 100%]; ^1H NMR δ 7.66 (d, 7.6 Hz, 1 H, arom), 7.51 (d, 7.7 Hz, 1 H, arom), 3.99 (s, 2 H, CH_2), 2.30 (s, 3 H, CH_3); ^{13}C NMR δ 203.31 (CO), 138.07 (q), 132.78, 132.62, 130.78, 127.56, 117.66 (CN), 113.25 (q), 48.49 (CH_2), 29.92 (CH_3).

4a: white solid: mp 63-64 °C; MW calcd 193.2018 for $C_{10}H_{11}NO_3$; IR 1720 (CO), 1520 and 1345 cm^{-1} (NO_2); MS 193 (M^+, 0.1%), 151 [$(M - CH_2{=}C{=}O)^+$, 10.73%]; ^1H NMR δ 8.04 (d, 8.1 Hz, 1 H, arom), 7.26 (d, 8.1 Hz, 1 H, arom), 7.06 (s, 1 H, arom), 4.08 (s, 2 H, CH_2), 2.42 (s, 3 H, CH_3Ph), 2.32 (s, 3 H, CH_3CO); ^{13}C NMR δ 203.64 (CO), 146.19 (q), 144.83 (q), 134.08, 130.42 (q), 128.85, 125.27, 48.56 (CH_2), 29.84 (CH_3CO), 21.19 (CH_3Ph). Anal. Calcd: C, 62.17; H, 5.71; N, 7.25. Found: C, 62.01; H, 5.89; N, 7.13.

5a: white solid; mp 51-53 °C; MW calcd 243.3159 for $C_{16}H_9D_5O_2$; IR 1720 (CO aliph), 1670 cm^{-1} (CO arom); MS 243 (M^+, 0.1%), 197 [$(M - CD_3CO)^+$, 85.3%]; ^1H NMR δ 7.79 (m, 2 H, arom), 7.58 (t, 7.3 Hz, 1 H, arom), 7.45 (m, 4 H, arom); 7.30 (m, 2 H, arom); ^{13}C NMR δ 205.42 (CO aliph), 198.10 (CO arom), 137.92 (q), 137.88 (q), 134.52 (q), 132.80, 131.67, 130.97, 130.25 (3 C), 128.25 (2 C), 126.29, 47.74 (CD_2, m, 19.2 Hz), 29.77 (CD_3, m, 19.2 Hz). Anal. Calcd C, 79.00; H, 7.84. Found: C, 78.89; H, 7.89.

6a: reported;[13] mp 116 °C (lit.[13] mp 118 °C); ^1H NMR;[14] ^{13}C NMR δ 146.80 (q), 135.57, 134.26, 133.68, 125.52, 114.85 (CN), 108.07 (q).

7a: reported;[15] mp 84 °C (lit.[15] mp 84.5-85.5 °C); ^1H NMR δ 7.83 (m, 3 H, arom), 7.66 (m, 4 H, arom), 7.51 (t, 7.5 Hz, 2 H, arom); ^{13}C NMR δ 193.71 (CO), 141.60 (q), 136.02 (q), 134.17, 133.84, 132.36, 132.03, 131.26, 130.30 (2 C), 129.96, 128.66 (2 C), 116.96 (CN), 111.99 (q).

8a: yellowish microcystals; mp 140 °C dec; MW calcd 264.2800 for $C_{17}H_{12}O_3$; IR 1710 (CO aliph), 1660 cm^{-1} (CO arom); MS 264 (M^+, 18.65%), 222 [$(M - CH_2{=}CO)^+$, 100%]; ^1H NMR (acetone-d_6) δ 8.23 (m, 3 H, arom), 7.45 (m, 3 H, arom), 7.67 (d, 8.4 Hz, 1 H, arom), 4.39 (s, 2 H, CH_2), 2.35 (s, 3 H, CH_3); ^{13}C NMR (DMSO-d_6) δ 205.90 (CO aliph), 185.34 and 183.83 (CO arom), 139.59, 138.84 (q), 135.52 (q), 134.96 (q), 134.92, 134.55, 134.10, 133.39 (q), 131.83 (q), 127.20, 126.92, 50.21 (CH_2), 29.53 (CH_3). Anal. Calcd C, 77.26; H, 4.58. Found: C, 7.12; H, 4.53.

9a: yellow crystals; mp 160-161 °C; MW calcd 268.3336 for $C_{15}H_{12}O_2S$; IR 1720 (CO aliph), 1660 cm^{-1} (CO arom); MS 268 (M^+, 10%), 240 [$(M - CO)^+$, 100%]; ^1H NMR δ 8.43 (d, 8.0 Hz, d, 1.0 Hz, 1 H, arom), 7.55 (m, 5 H, arom), 7.16 (d, 5.7 Hz, d, 3.0 Hz, 1 H, arom), 4.27 (s, 2 H, CH_2), 2.43 (s, 3 H, CH_3); ^{13}C NMR δ 205.31 (CO aliph), 181.72 (CO arom), 139.57 (q), 139.12 (q), 136.07 (q), 131.94, 131.37 (2 C), 129.72, 129.57 (q), 127.52 (q), 126.21, 125.83, 125.23, 51.61 (CH_2), 30.07 (CH_3). Anal. Calcd C, 71.62; H, 4.51. Found: C, 71.58, H, 4.25.

10a: reported;[16] mp 194 °C (lit.[16] mp 196-198 °C); MW calcd 221.2148; MS 221 (M^+, 100%), 193 [$(M - CO)^+$; 68.48%]; ^1H NMR δ 8.33 (d, 7.7 Hz, 1 H, arom), 7.76 (m, 4 H arom), 7.50 (d, 7.7 Hz, 1 H arom), 7.43 (t, 7.7 Hz, 1 H arom); ^{13}C NMR δ 174.59 (CO), 156.20 (q), 155.40 (q), 135.59, 134.00, 131.64, 126.88, 124.86, 123.85 (q), 123.05, 121.47 (q), 117.81, 117.45 (CN), 110.85 (q).

11a: white powder; mp >200 °C; MW calcd 269.2782 for $C_{14}H_7NO_3S$; IR 2240 (CN), 1680 cm^{-1} (CO); MS 269 (M^+, 3.6%), 241 [$(M - CO)^+$, 100%]; ^1H NMR (DMSO-d_6) δ 8.52 (d, 8.0 Hz, 1 H, arom), 8.38 (d, 7.8 Hz, 1 H, arom), 8.34 (d, 7.7 Hz, 1 H, arom), 8.24 (d, 7.8 Hz, 1 H, arom), 8.20 (t, 7.9 Hz, 1 H, arom), 8.08 (t, 7.6 Hz, 1 H, arom), 8.00 (t, 7.6 Hz, 1 H, arom); ^{13}C NMR (DMSO-d_6) δ 177.07 (CO), 141.71 (q), 140.14, 139.19 (q), 135.57, 135.24, 134.25, 132.37 (q), 130.43 (q), 129.40, 127.46, 123.22, 116.99 (CN), 112.11 (q). Anal. Calcd C, 62.45; H, 2.62; N, 5.20. Found: C, 62.20; H, 2.43; N, 5.00.

12a: reported;[17] light yellow oil; MS 148 (M^+, 1.3%), 106 [$(M - CH_2{=}C{=}O)^+$, 100%]; ^1H NMR δ 6.65 (t, 3.0 Hz, 2 H), 6.19 (d, 9.4 Hz; t, 2.4 Hz; 2 H), 5.15 (d, 9.4 Hz; d, 5.8 Hz; 2 H), 2.79 (d, 7.5 Hz, 2 H, CH_2), 2.29 (d, 5.8 Hz, 1 H), 2.14 (s, 3 H, CH_3); ^{13}C NMR δ 207.28 (CO), 130.88 (2 C), 125.10 (2 C), 124.88 (2 C), 46.67 (CH_2), 34.43 (CH), 29.90 (CH_3).

12b: reported;[18] colorless oil; MS 117 (M^+, 8.2%), 91 [$(M - CN)^+$, 100%]; ^1H NMR[19] δ 6.74 (t, 3.3 Hz, 2 H), 6.34 (d, 8.9 Hz; t, 2.7 Hz; d, 0.7 Hz; 2 H), 5.40 (d, 8.9 Hz d, 6.1 Hz; 2 H), 3.00 (t, 6.1 Hz, 1 H).

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Reaction of 2-(Alkylsulfinyl)-, 2-(Arylsulfinyl)-, and 2-(Aralkylsulfinyl)benzimidazoles with Thiols: A Convenient Synthesis of Unsymmetrical Disulfides

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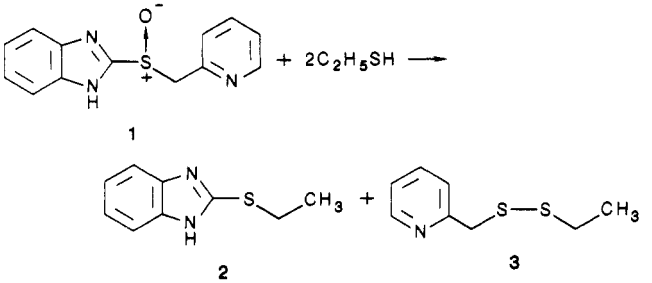
In the course of some studies dealing with proton-pump inhibitors, we had occasion to investigate the displacement of the (pyridinylmethyl)sulfinyl side chain of **1** with various mercaptans. Treatment of **1** in 95% ethanol with ethanethiol gave not only thioether **2**, as one may have predicted, but unexpectedly yielded disulfide **3** in 63% yield.



1

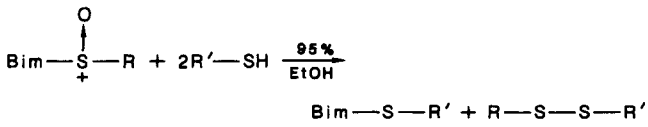
2 3

We were attracted to this reaction by the convenience and the mild reaction conditions under which disulfide **3** was formed, i.e., 2.5 equiv of ethanethiol, room temperature, and 15 h reaction time. To define the scope of this reaction, we carried out a systematic study employing 2-(alkylsulfinyl)-, 2-(phenylsulfinyl)- and 2-(aralkylsulfinyl)benzimidazoles. These 2-sulfinyl-substituted benzimidazoles[1] [Bim-$S^+(\rightarrow O^-)$-R] were allowed to react

(1) The sulfoxide starting materials were prepared by oxidation of the corresponding thioethers with *m*-chloroperbenzoic acid (1 equiv, 0-5 °C) in chloroform. See the Experimental Section for details. The 2-(alkylthio)- and 2-(aralkylthio)benzimidazoles were prepared by alkylation of 2-mercaptobenzimidazole with the appropriate alkyl or aralkyl halide in 95% ethanol in the presence of aqueous sodium hydroxide. 2-(Phenylthio)benzimidazole was prepared by reaction of 2-chlorobenzimidazole in ethanol with excess thiophenol at 90-100 °C. See: Harrison, D., Ralph, R. T. *J. Chem. Soc.* **1965**, 3132.

0022-3263/87/1952-4620$01.50/0

Table I. Preparation of Unsymmetrical Disulfides



entry[a]	R	R′	product[b]	yield,[c] %
1	2-$C_5H_4NCH_2$	C_2H_5	2-$C_5H_4NCH_2SSC_2H_5$	63
2	2-$C_5H_4NCH_2$	$PhCH_2$	2-$C_5H_4NCH_2SSCH_2Ph$	60
3	$PhCH_2$	Ph	$PhCH_2SSPh$	52[e]
4	$PhCH_2$	$CH_2CO_2C_2H_5$	$PhCH_2SSCH_2CO_2C_2H_5$	75
5	CH_3	$PhCH_2$	CH_3SSCH_2Ph	67[f]
6	$PhO(CH_2)_4$	Ph	$PhO(CH_2)_4SSPh$	82
7[d]	$PhO(CH_2)_4$	n-C_4H_9	$PhO(CH_2)_4SS$-n-C_4H_9	88
8	Ph	Ph	$PhSSPh$	90[g]
9	Ph	$PhCH_2$	$PhSSCH_2Ph$	65[e]
10[d]	Ph	n-C_4H_9	$PhSS$-n-C_4H_9	78

[a] Unless otherwise noted, the reactions were carried out for 18–24 h at 25 °C. [b] All products gave satisfactory combustion analyses (±0.4%) and/or correct molecular ion by high-resolution mass spectroscopy. [c] Isolated yield of pure product after chromatography; except for entry 8, all other disulfides were obtained as low-melting waxy solids or oils. [d] Heated for 15 h in a 75 °C oil bath. [e] Lit.[15] bp 125–128 °C (0.05 mm). [f] Lit.[16] bp 66 °C (0.2 mm). [g] Mp 59–61 °C; Aldrich Chemical Co., mp 58–60 °C.

with primary alkyl mercaptans, thiophenol, and aralkyl mercaptans (benzyl, picolyl). The results are summarized in Table I.

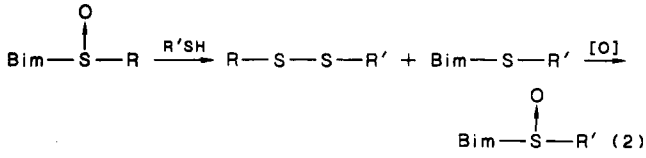
The reaction provided unsymmetrical disulfides in yields ranging, in general, from 60% to 80%. On those occasions where we isolated the benzimidazole thioether side product, the yield of thioether was very similar to that of disulfide. Early in the study, we routinely used 5 equiv of mercaptan reagent. We soon discovered excess reagent was detrimental since the unsymmetrical disulfide product was being destroyed to produce the unwanted symmetrical disulfide[2] (R–S–S–R′ + excess R′–SH → R′–S–S–R′). When the amount of mercaptan reagent was limited to 2.5–3.0 molar equiv, the yield of mixed disulfide increased, and the formation of symmetrical disulfides was virtually eliminated. All the reactions were performed at 25 °C for 18–24 h[3] in 95% ethanol solvent. Occasionally, the presence of some unreacted benzimidazole starting material was observed after 24 h reaction time (Table I, entries 7 and 10). When these reactions were carried out in a 75 °C oil bath, no starting materials remained, and the desired disulfides were obtained in good yields. The mild reaction conditions make the present method attractive for the preparation of disulfides possessing the ester functionality. For example, the carbethoxy group of ethyl 2-mercaptoacetate remained intact during the reaction (entry 4).

The literature abounds with reports for the synthesis of unsymmetrical disulfides. A major method for the preparation of mixed disulfides comprises a series of nucleophilic displacement reactions of sulfenyl derivatives with thiols (eq 1).

$$RS\text{–}X + R'\text{–}SH \rightarrow R\text{–}S\text{–}S\text{–}R' + X^- \quad (1)$$

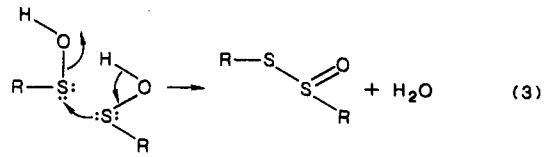
The most notable sulfenyl reagents presently available for constructing mixed disulfides are sulfenyl halides,[4] thiosulfates,[5] sulfenyl thioureas,[6] thiolsulfonates,[7] sulfenimides,[8] and sulfenyl thiocarbonates.[9] Unfortunately, the synthetic maneuvers created by the instability and unreactivity of the sulfenyl moiety have substantially reduced the scope and utility of some of these known procedures. Most seriously, disulfide interchange is especially prevalent in basic media and constitutes a major obstacle to the design of homogeneous unsymmetrical disulfides via these electrophilic substrates.

We believe that the present method offers some advantages over known S_N2 pathways to mixed disulfides. Briefly, the key synthetic merits are the facile preparation of the sulfinyl benzimidazole reagents;[1] their high reactivity; the neutral, nonbasic reaction conditions; and the ease of isolation of the mixed disulfides.[10] A salient feature of this method is that the side product formed in the reaction (Bim–S–R′) can be reoxidized and reused in the synthesis of a new unsymmetrical disulfide (eq 2). In



principle, this allows one to prepare any mixed disulfide from a single Bim–S(→O)–R starting material. The only limitation in this process would then be the availability of the thiol.

We believe the mechanism of disulfide formation involves the intermediacy of a sulfenic acid generated during displacement of the benzimidazole sulfinyl side chain by mercaptan. Relatively little is known about the chemistry of sulfenic acids. Recent reports suggest that sulfenic acids may be involved in disulfide formation.[11] The reaction considered to be the most characteristic of sulfenic acids is dehydration to afford thiosulfinates (RS(O)SR), possibly via an intermediate such as 4 (eq 3).[12] Thiosulfinate



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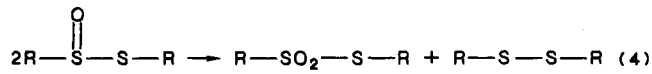
intermediates, which are thermally labile and disproportionate to thiosulfonate and disulfide (eq 4),[13] have often



(2) This cleavage reaction was particularly prone to occur during removal of excess reagent and ethanol solvent on the rotary evaporator (40–50 °C) during workup of the reaction.

(3) Most of the reactions were carried out overnight for convenience (15–24 h). When the progress of the reaction was monitored by TLC, the reactions were usually completed in 5 h or less.

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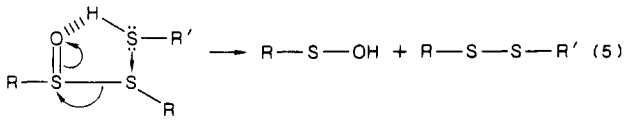
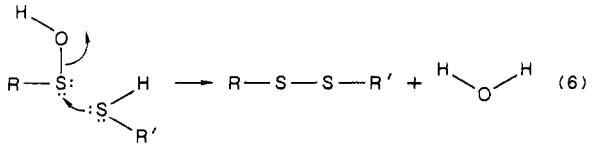
been evoked in reactions believed to involve sulfenic acids. On the basis of the greater than 50% isolated yield of disulfide and the absence of any thiosulfonate or thiolsulfonate-derived products, we do not believe that a thermal disproportionation mechanism can account for the formation of disulfide. Therefore, we favor a nucleophilic displacement at sulfur of thiosulfinate by thiol aided by a "push-pull" weakening of the S-S bond (eq 5).[14] Of



course, one cannot rule out the formation of disulfides by direct nucleophilic attack of thiol on the sulfur of sulfenic acid (eq 6).[11]



Experimental Section

General Procedure for the Preparation of Starting Materials. The specific example given for the preparation of 2-[(2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole (entry 1, Table I) is representative of a general procedure used for the synthesis of the starting materials.

a. To a solution of sodium hydroxide (8.0 g, 0.2 mol) in water (20 mL) was added ethanol (200 mL) followed by 2-mercaptobenzimidazole (16.4 g, 0.1 mol). The yellow solution was treated with 2-picolyl chloride hydrochloride (16.4 g, 0.1 mol) and heated under reflux with stirring for 2.5 h. The chilled reaction mixture was filtered, the solid was washed with absolute ethanol (50 mL), and the filtrate was concentrated under reduced pressure, azeotroped with toluene (150 mL), treated with acetone (250 mL), and filtered. The filtrate was removed under reduced pressure to give a beige solid. Recrystallization from ethanol–water (1:1) afforded 22.3 g of 2-[(2-pyridinylmethyl)thio]-1*H*-benzimidazole: mp 100–102 °C; NMR ($CDCl_3$) δ 4.4 (s, 2, CH_2), 6.98–7.72 (m, 7, Ar H), 8.53 (d, 1, Ar H), 9.3–11.3 (br s, 1, NH). Anal. Calcd for $C_{13}H_{11}N_3S$: C, 64.70; H, 4.59; N, 17.41; S, 13.28. Found: C, 64.41; H, 4.63; N, 18.35; S, 13.23.

b. A vigorously stirred solution of 2-[(2-pyridinylmethyl)-thio]-1*H*-benzimidazole (7.24 g, 0.03 mol) in chloroform (40 mL) was cooled to 0–5 °C (internal temperature) and treated during 10 min with solid *m*-chloroperbenzoic acid (6.1 g, 0.0353 mol) in small portions. The reaction mixture was further stirred for 10 min, the precipitated benzoic acid was filtered off, methylene chloride (30 mL) was added, and the organic layer was washed with a saturated solution of sodium bicarbonate (3 × 25 mL), water (2 × 25 mL) and saturated brine, and the organic solvent was dried through anhydrous Na_2SO_4. Removal of the solvent in vacuo gave the crude product, which was recrystallized from acetonitrile to yield 5.94 g of 2-[(2-pyridinylmethyl)sulfinyl]-1*H*-benzimidazole: mp 154–156 °C; IR ($CHCl_3$, cm^{-1}) 3063, 2970, 2890, 2810, 1600, 1500, 1480, 1471, 1438, 1270, 1136, 1110, 1091, 1009; NMR ($CDCl_3$) δ 4.37 (s, 2, SCH_2), 6.98–7.72 (m, 7, Ar H), 8.53 (dd, 1 Ar H). Anal. Calcd for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33; S, 12.46. Found: C, 60.28; H, 4.32; N, 16.46; S, 12.49.

General Procedure for the Preparation of Unsymmetrical Sulfides (Table I). To a magnetically stirred solution of Bim-$S^+(\rightarrow O)$-R (1.0 mmol) in 20 mL of 95% ethanol was added 3.0 mmol of R′-SH. Stirring was then continued at 25 °C or at elevated temperatures. (See Table I for reaction times and reaction temperatures.) The ethanol solvent was then removed in vacuo, pentane or pentane–ether solvent mixture was added to precipitate the insoluble thioether side product, and the resulting solid was removed by suction filtration. Concentration of the filtrate in vacuo afforded the crude disulfide product. The crude product was then purified by LPLC or flash chromatography with 0–50% ethyl acetate in hexane as the eluent.

The homogeneity of the purified disulfides was established by ^1H and ^{13}C NMR, TLC analyses, and high-resolution mass spectroscopy. The latter technique was especially diagnostic for detecting the absence of any symmetrical disulfides in the final unsymmetrical disulfide products. In the reactions studied, the symmetrical disulfides were readily distinguishable by TLC from the desired unsymmetrical products. The absence of any undesired symmetrical disulfides in the final product was further ruled out by HRMS exact mass measurement.

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Aglycon Modifications of Erythromycin A: Regiospecific and Stereospecific Elaboration of the C-12 Position

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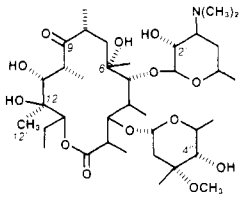
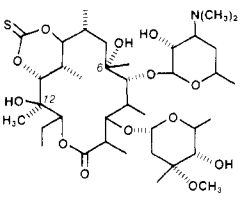
We have previously reported the incorporation of carbon nucleophiles at the C-9 position of erythromycin A (1) via the intermediacy of the readily available thionocarbonate **2**.[1] As a consequence of this research, we sought to prepare a synthetic intermediate that would allow incorporation of moieties at the relatively inaccessible C-12 position of **1**. The central consideration of the synthetic plan was the preparation of an intermediate that would ultimately permit the regiospecific and stereospecific functionalization of the C-12 position of erythromycin A (1). We now detail not only the synthesis of an intermediate (**5**), which fulfills these requirements, but also the stereospecific conversion of olefin **5** into the corresponding C-12, C-12′ modified diol **6**.



1



2

Regiospecific Olefin Formation. The blocked olefin **4** was selected as the synthetic target, since, in principle, it presents the opportunity to stereoselectively manipulate the C-12 through C-9 positions; however, the preparation of **4** presents the obvious difficulty of regioselectively dehydrating the C-12 position in such a fashion as to prepare the corresponding exocyclic double bond isomer. A suitable substrate to test the selectivity of olefin formation between the C-6 and C-12 positions is bisacetylated

(1) Hauske, J. R.; Guadliana, M.; Kostek, G. *J. Org. Chem.* **1983**, *48*, 5138.

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