A Ring Opening Reaction of Benzisothiazolones. A New Route to Unsymmetrical Disulfides

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A series of unsymmetrical disulfides has been prepared by employing a reaction involving a ring opening, nucleophilic attack of a thiol on a 1,2-benzisothiazol-3-one. The benzisothiazolones were in turn prepared by an intramolecular ring closure of an amide on a sulfenyl thiocarbonate. The sulfenyl esters were synthesized as intermediates for preparing mixed-disulfides, but the benzisothiazolone ring closure occurred spontaneously. It was initially thought that the mixed-disulfides were being formed from the sulfenyl ester, but the isolation and stepwise reaction of the benzisothiazolones provided proof for the reaction mechanism.

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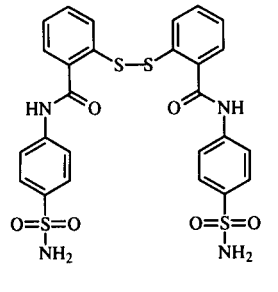
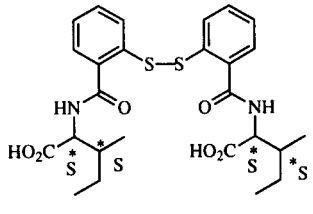
As part of our antiviral program [1], we wished to prepare a series of mixed-disulfides based on our two lead symmetrical disulfides, 2,2'-dithiobis[4'-sulfamoylbenzanilide] (**1**) and [*S*-(*R**,*R**)]-2-[[2-[[2-[(1-carboxy-2-methylbutyl)carbamoyl]phenyl]disulfanyl]benzoyl]-amino]-3-methylpentanoic acid (**2**), and compare their relative antiviral activities. The symmetrical disulfides **1** and **2** had been shown to have good activity against HIV-1, HIV-2, simian immunovirus (SIV) and AZT (3'-azido-2',3'-dideoxythymidine) resistant isolates [1]. The proposed mechanism of action for the disulfides, as well as the benzisothiazolones prepared from them, compounds **3** and **4**, involved an interaction with nucleocapsid protein (NCp7) which results in an extrusion of zinc from the zinc fingers of nucleocapsid protein. This zinc ejection prevents virion formation or causes the virions that do form to be non-infectious [1].

There are several procedures in the literature for preparing unsymmetrical disulfides including the use of diethyl azodicarboxylate [2], thioimides [3], thionitrites [4], *S*-alkyl- and *S*-arylthiosulfates ("Bunte Salts") [5], thioalkoxytrialkyl- and thioalkoxytriarylphosphonium salts [6], dithioperoxyesters [7], alkylthiodialkylsulfonium salts [8], tosyl thiolates [9] and sulfenyl thiocarbonates [10]. Since we had experience, as well as good results, with the tosyl thiolate procedure, we chose this route for our initial attempt. The reaction of the thiol **5**, prepared by the dithiothreitol reduction of **1**, with *p*-toluenesulfonyl chloride provided the tosyl thiolate **6** (Scheme 1). However, when **6** was reacted with *N*-acetylcysteine (**7**), none of the desired product was formed (even under forcing conditions) due to the unexpected stability of the thiotosylate.



1



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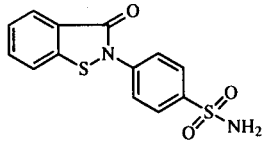

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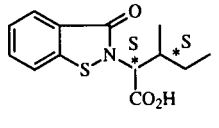

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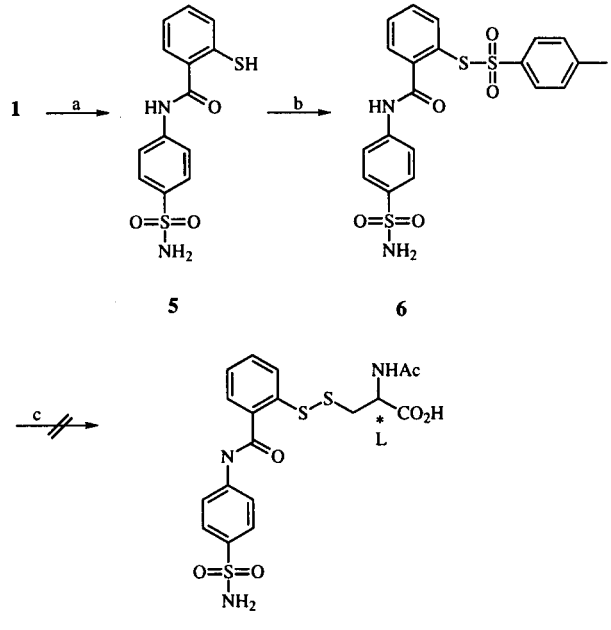
Scheme 1

Attempted Synthesis of a Mixed Disulfide *via* a Tosylthiolate



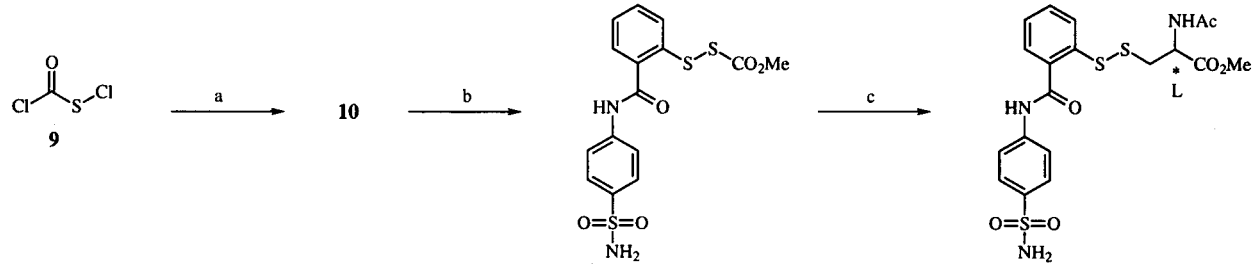
a. Dithiothreitol/0.1 *M* NaH_2PO_4/DMF; b. TosCl/pyridine/DMF; c. *N*-acetyl-L-cysteine/DMF/R.T.

It was felt that a sulfenyl thiocarbonate might be more readily displaced by the incoming thiol to give the desired mixed disulfide [10]. Therefore, chlorocarbonylsulfenyl chloride (**9**) was reacted with cold methanol to provide the chlorosulfenyl ester **10** (Scheme 2). The thiol **5** was then added to prepare the thiocarbonate **11** *in situ*. After conversion had been confirmed by thin-layer chromatography (tlc), *N*-acetyl-L-cysteine (**7**) was added and the desired mixed-disulfide was isolated as the methyl ester **12**. The esterification of the product is catalyzed by the two equivalents of hydrogen chloride produced by the formation of the chlorosulfenyl ester followed by the thiosulfinate ester in the first two steps of Scheme 2.

ing a suspension of **3** in tetrahydrofuran/methanol (1:1) with the appropriate thiol at 60° for 30 minutes. In most cases, the solvent could be removed and the residue triturated with a suitable solvent (Table 1). The reaction worked for a wide variety of thiols, as seen in Table 1 [12]. However, some of the mixed disulfides were unstable in basic medium and reverted back to the starting benzisothiazolone and thiol. For example, in an attempt to purify a second crop of **13**, the residue was dissolved in 5% sodium bicarbonate. A solution formed, followed by an immediate precipitate which was shown to be the starting benzisothiazolone **3**. The mixed disulfides were stable under neutral and acidic conditions and may serve as pro-

Scheme 2

The Formation of a Mixed Disulfides From an Activated Thiol Ester



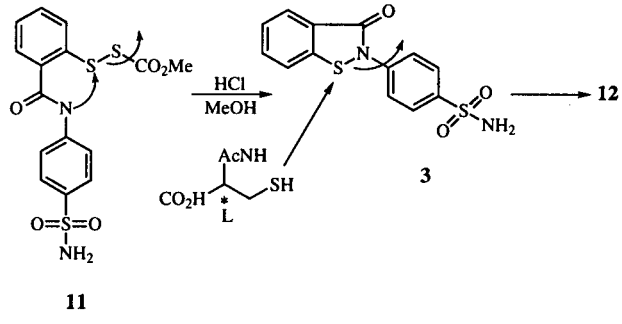
a. MeOH, 0°C; b. **5**/MeOH; c. *N*-acetyl-L-cysteine/MeOH

Since having the free carboxyl group in the final disulfide was desirable for both solubility and bioavailability, it was decided to rerun the reaction sequence and isolate **11** to free it from any acid contamination. The reaction was run as before and the intermediate previously identified by tlc was isolated. However, ^{1}H nmr spectroscopy failed to show the presence of either the methyl of the thiosulfinate ester or the hydrogen of the benzamide. Further spectral analysis (infrared and mass spectrometry) and analytical data as well as a previous unequivocal synthesis, showed this material to be the benzisothiazolone **3**.

This strongly suggested that the previously isolated mixed-disulfide **12** had resulted from ring opening of the benzisothiazolone **3** by the thiol of *N*-acetyl-L-cysteine (Scheme 3). Therefore, when acid-free **3** was allowed to react with **7** in methanol, the desired free acid of the mixed-disulfide **13** was isolated (Scheme 4). Since the only report of a ring opening reaction of a benzisothiazolone was with sulfite ion to produce a Bunte salt [11], it was decided to take advantage of this novel reaction in the preparation of the desired series of unsymmetrical disulfides.The reaction for the preparation of the benzisothiazolone **3** was scaled up and a general procedure for the ring opening reaction was developed. This involved react-

Scheme 3

The Conversion of an Activated Ester to a Mixed Disulfide *via* a Benzisothiazolone Intermediate



Scheme 4

Preparation of the Benzisothiazolone Free Acid Derivative

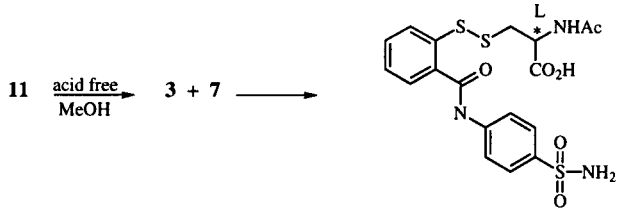
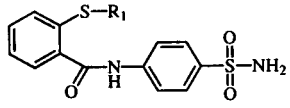
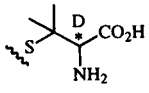
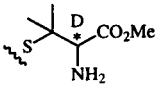
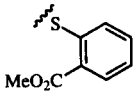
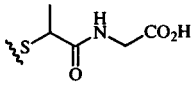
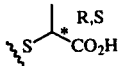
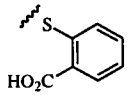
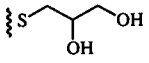
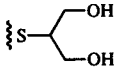
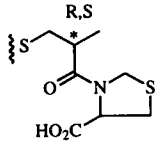
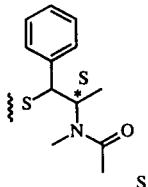
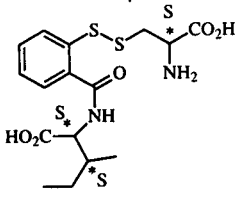


Table 1



No	Structure	mp, °C	Yield %	Method of Purification	Formula	Analysis (%) Calcd./(Found) C	H	N
14a		115-118	88	lyophilize	$C_{18}H_{21}N_3O_5S_3 \cdot 1.0HCl \cdot 2.75H_2O$	39.91 (39.82)	5.11 (4.77)	7.76 (7.36)
14b		140-142	92	lyophilize	$C_{19}H_{23}N_3O_5S_3 \cdot 1.0HCl \cdot 1.5H_2O$	42.80 (42.70)	4.92 (5.11)	7.88 (7.57)
14c		288-290	93	triturated with ether	$C_{21}H_{18}N_2O_5S_3$	53.15 (52.97)	3.82 (4.01)	5.90 (5.62)
14d		254-256	93	triturated with ether	$C_{18}H_{19}N_3O_6S_3 \cdot 0.5H_2O$	45.17 (45.06)	4.21 (4.21)	8.78 (8.73)
14e		268-270	94	triturated with ether	$C_{16}H_{16}N_2O_5S_3 \cdot 0.25H_2O$	46.08 (46.18)	3.99 (4.04)	6.72 (6.59)
14f		276-278	96	triturated with ether	$C_{20}H_{16}N_2O_5S_3 \cdot 0.25H_2O$	51.64 (51.62)	3.58 (3.62)	6.03 (5.79)
14g		>260	98	triturated with ether	$C_{16}H_{18}N_2O_5S_3 \cdot 0.25H_2O$	45.85 (45.86)	4.45 (4.50)	6.69 (6.46)
14h		272-274	32	recrystallized from methanol	$C_{16}H_{18}N_2O_5S_3$	46.36 (46.68)	4.38 (4.28)	6.76 (6.84)
14i		128-130	50	triturated with ether acetate	$C_{21}H_{23}N_3O_6S_4 \cdot 0.5H_2O$	45.96 (46.27)	4.34 (4.45)	7.65 (7.28)
14j		240-242	93	triturated with ether	$C_{25}H_{27}N_3O_4S_3 \cdot 0.25H_2O$	56.26 (56.32)	5.19 (5.16)	7.87 (7.81)
14k		85-90	87	triturated with water	$C_{18}H_{24}N_2O_6S_2$	50.45 (50.59)	5.65 (5.95)	6.54 (6.79)

drugs for the delivery of the benzisothiazolones in biological systems. Indeed, compounds **2** and **4** are currently undergoing extensive testing and a mixed disulfide approach may prove to be a valuable prodrug delivery system for **4**.

EXPERIMENTAL

Melting points were taken on a Hoover capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were determined in potassium bromide pellet on a Matson FT IR Cygnus 100 spectrophotometer. Proton magnetic resonance (nmr) spectra were recorded on a 300 or 400 MHz Varian Unity 300/400 spectrometer. Chemical shifts are reported in δ units relative to internal tetramethylsilane. Mass spectra were recorded on a VG TRIO 2 or VG TRIO 2000 spectrometer. Elemental analyses were performed on a Lehman Labs 440 elemental analyzer or at Robertson Microlit Laboratories, Madison, NJ. Solutions were dried over magnesium sulfate and concentrated on a rotary evaporator at 30-45° mm Hg. All moisture sensitive reactions were carried out under a dry argon atmosphere. All starting materials were commercially available unless otherwise noted.

2-Acetylamino-3-[2-(4-sulfamoylphenylcarbamoyl)phenyldisulfanyl]propionic Acid Methyl Ester (**12**).

A solution of 20 ml of methanol and 20 ml of tetrahydrofuran was cooled to 0° and treated dropwise with 1.3 g (0.84 ml, 10 mmoles) of chlorocarbonylsulfenyl chloride. The reaction mixture was stirred at 0° for 15 minutes and 3.0 g (9.7 mmoles) of 2-mercapto-*N*-(4-sulfamoylphenyl)benzamide (**5**) was added portionwise as a solid [13]. The reaction was stirred at 0° for 30 minutes and allowed to come to room temperature where it was stirred for 4 hours. Solid *N*-acetyl-L-cysteine, 1.63 g (10 mmoles), was added all at once and the reaction was heated to 60° for 30 minutes. The solvent was evaporated *in vacuo* and the residue was triturated with water (50 ml) and the solid was removed by filtration. After washing with water (2 x 20 ml) and ether (2 x 20 ml), the precipitate was dried *in vacuo* to give 4.3 g (91%) of **12**, mp 138-140°; ^{1}H nmr (DMSO-d_6): δ 1.85 (s, 3H, NHCOCH_3), 3.05 (m, 1H), 3.12 (m, 1H), 3.59 (s, 3H, CO_2CH_3), 4.47 (m, 1H), 7.30 (s, 2H, SO_2NH_2), 7.42 (t, 1H), 7.63 (t, 1H), 7.76 (d, 1H), 7.82 (d, 2H), 7.90 (d, 2H), 8.52 (d, 1H NHCOCH$_3$), 8.01 (d, 1H), 10.78 (s, 1H, benzamide NH).

Anal. Calcd. for $C_{19}H_{21}N_3O_6S_3$•0.25H_2O: C, 46.75; H, 4.44; N, 8.61. Found: C, 46.56; H, 4.23; N, 8.47.

4-(3-Oxo-3*H*-benzo[*d*]isothiazol-2-yl)benzenesulfonamide (**3**).

A solution of 60 ml of methanol and 60 ml of tetrahydrofuran was cooled to 0° and treated dropwise with 3.94 g (2.52 ml, 30 mmoles) of chlorocarbonylsulfenyl chloride. The reaction was stirred at 0° for 20 minutes and 9.0 g (29.2 mmoles) of **1** was added portionwise as a solid [13]. The reaction was stirred at 0° for 30 minutes and then stirred at room temperature for 18 hours. The reaction mixture was diluted with 200 ml of ether, stirred one hour and the solid removed by filtration. After washing with ether (2 x 20 ml), the solid was dried to give 7.8 g of **3**, mp 283-285°. A second crop of comparable purity (2.2 g) was isolated by concentrating the mother liquors. The total yield was 9.0 g (98%); ^{1}H nmr (DMSO-d_6): δ 7.48 (s, 2H), 7.53 (d, 1H), 7.80 (t, 1H), 7.97 (s, 4H), 8.01 (d, 1H), 8.10 (d, 1H).

Anal. Calcd. for $C_{13}H_{10}N_2O_3S_2$: C, 50.96; H, 3.29; N, 9.15. Found: C, 51.04; H, 3.34; N, 8.95.

2-Acetylamino-3-[2-(4-sulfamoylphenylcarbamoyl)phenyldisulfanyl]propionic Acid (**13**).

A suspension of 0.8 g (2.4 mmoles) of **3** in a mixture of 10 ml of methanol and 10 ml of tetrahydrofuran was treated with 0.44 g (2.7 mmoles) of *N*-acetyl-L-cysteine. The reaction mixture was heated to 60° for 30 minutes and the solvent was removed *in vacuo*. The residue was triturated with water (50 ml) until a fine precipitate developed (approx. 30 minutes). The solid was removed by filtration, washed with water (2 x 20 ml) and dried *in vacuo* to give 0.92 g (93%) of **4**, mp 218-220°; ^{1}H nmr (DMSO-d_6): δ 1.85 (s, 3H, NHCOCH_3), 3.03 (m, 1H), 3.12 (m, 1H), 4.42 (m, 1H), 7.30 (s, 2H, SO_2NH_2), 7.42 (t, 1H), 7.62 (t, 1H), 7.76 (d, 1H), 7.81 (d, 2H), 7.89 (d, 2H), 8.01 (d, 1H), 8.39 (d, 1H, NHCOCH$_3$), 10.83 (s, 1H, benzamide NH).

Anal. Calcd. for $C_{18}H_{19}N_3O_6S_3$•1.75H_2O: C, 43.14; H, 4.52; N, 8.38. Found: C, 43.10; H, 4.34; N, 8.19.

General Procedure for Preparing Mixed Disulfides From Benzisothiazolones 2-Amino-3-methyl-3-[2-(4-sulfamoylphenylcarbamoyl)phenyldisulfanyl]butyric Acid Methyl Ester (**14b**).

A suspension of 0.61 g (2.0 mmoles) of **3** in a mixture of 10 ml of methanol and 10 ml of tetrahydrofuran was treated with 0.44 g (2.2 mmoles) of D(-)-penicillinamine methyl ester hydrochloride. After heating to 60° for 30 minutes, the solvent was removed *in vacuo*. The residue was dissolved in 20 ml of 2-propanol and precipitated by the addition of 100 ml of ether. The precipitate was removed by filtration, dissolved in water (30 ml), filtered through a fiber glass pad to clarify and freeze dried to give 0.92 g (92%) of **14b**, mp 140-142°; ^{1}H nmr (DMSO-d_6): δ 1.30 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 3.70 (s, 3H, CO_2CH_3), 4.04 (s, 1H), 7.32 (s, 2H, SO_2NH_2), 7.43 (t, 1H), 7.62 (t, 1H), 7.75 (d, 1H), 7.83 (d, 2H), 7.92 (d, 2H), 8.03 (d, 1H), 8.58 (bs, 3H, NH_3+), 10.88 (s, 1H, benzamide NH). Analysis: See Table 1.

(*R*)-*N*-[2-[[2-(Acetylamino)-2-carbethoxyethyl]dithio]benzoyl]-L-isoleucine (**14k**).

A solution of 0.53 g (2.2 mmoles) of [*S*-(*R**,*R**)]-3-methyl-2-(3-oxo-3*H*-benzo[*d*]isothiazol-2-yl)pentanoic acid [1b] in 20 ml of methanol was treated with 0.33 g (2.0 mmoles) of *N*-acetyl-L-cysteine and the reaction was stirred at room temperature for 18 hours. The solvent was removed *in vacuo* and the residue was triturated with 100 ml of 60° water. The water was decanted and the solid was dissolved in 50 ml of ethyl acetate. The organic solution was dried (magnesium sulfate), filtered and evaporated *in vacuo* to give 0.72 g (84%) of **14k** as a white, solid foam, mp 85-90°; ^{1}H nmr (DMSO-d_6): δ 0.87 (t, 3H), 0.94 (d, 3H), 1.26 (m, 1H), 1.48 (m, 1H), 1.85 (s, 3H), 1.90 (m, 1H), 3.02 (m, 1H), 3.10 (m, 1H), 4.30 (t, 1H), 4.40 (m, 1H), 7.33 (t, 1H), 7.53 (t, 1H), 7.63 (d, 1H), 7.94 (d, 1H), 8.38 (d, 1H), 8.60 (d, 1H), 12.77 (bs, 2H). Analysis: See Table 1.

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