A Convenient Synthesis of 4-(Phenylsulfonylthio)-2-azetidinones[1)]

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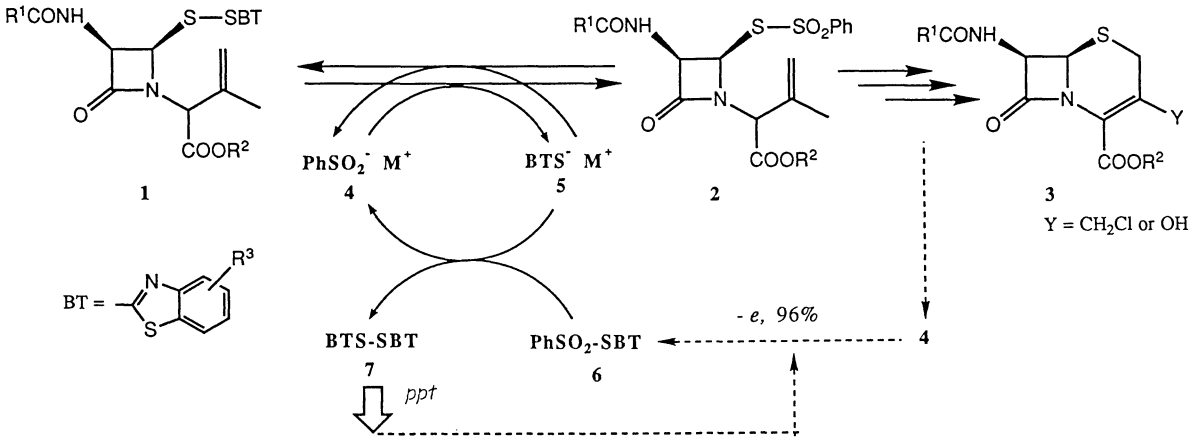
Synopsis. 4-(Phenylsulfonylthio)-2-azetidinones have been prepared conveniently by the reaction of 4-(2-benzothiazolyldithio)-2-azetidinones with 2-benzothiazolyl benzenethiosulfonates. A combination of this reaction with the electrolytic cross-coupling of bis(benzothiazolyl) disulfide and ammonium benzenesulfinate can establish a recycling system, in which *S*-(2-benzothiazolyl) benzenethiosulfonate is regenerated to play a critical role in penicillin-cephalosporin conversions.

4-(Phenylsulfonylthio)-2-azetidinones **2** are versatile intermediates for the synthesis of useful β-lactam antibiotics.[2)] For example the ene-type chlorination and/or C=C bond fission of **2** followed by intramolecular cyclization can provide C(3)-substituted cephems, such as 3-chloromethyl-[3)] and 3-hydroxycephems **3** (Y=CH_2Cl or OH),[4)] wherein the phenylsulfonyl group works not only as a protecting group of the 4-thiol moiety but also as a leaving group in the cephem-ring forming process. (Scheme 1). In spite of a strong interest of **2** in cephem synthesis, only a few reports for the preparation of **2** have appeared so far.[4,5)] Woodward and Gosteli prepared **2** by the replacement of the 2-benzothiazolylthio moiety of Kamiya's disulfides **1** derived from penicillins[6)] with arylsulfonyl groups.[4)] However, the method has disadvantages that it inevitably requires a stoichiometric or excessive amount of heavy metal salts or silver salt of arenesulfinates. Thermolysis of penicillin sulfoxides in the presence of arenesulfinic acids was also attempted by Allan et al.,[5)] but they failed in obtaining **2** owing to a terminal/internal olefin migration of the *N*-alkenyl substituent of **2** (R^2=CH_2CCl_3) under the conditions. Thus, the lack of an acceptable method for the large scale production of **2** enabled us to develop an alternative access to **2**.

Incidentally, the reaction of **1** with arenesulfinates **4** produced **2** together with 2-benzothiazolethiolate **5** but the reaction reached rapidly a state of equilibrium and only 30—45% yields of **1** were obtained. Hence, one can expect that removal of **5** from the equilibrium mixture may shift the equilibrium to the right so as to complete the reaction leading to **2**. Herein, we disclose a new device for this purpose, in which 2-benzothiazolyl benzenethiosulfonate **6** works as an efficient trapping agents of **5** and at the same time liberates benzenesulfinate **4** to complete the transformation of **1** to **2** as illustrated in Scheme 1.

A representative procedure is as follows (Entry 1 in Table 1): A mixture of 4-(2-benzothiazolyldithio)-2-azetidinone **1a** (R^1=$PhOCH_2$; R^2=CH_2Ph) and *S*-(2-benzothiazolyl) benzenethiosulfonate **6** (1 : 1.1) in aqueous acetone containing a catalytic amount of sodium benzenesulfinate **4** was stirred at an ambient temperature for 3.5 h. During the course of the reaction, pale yellow precipitates were formed. The solids were collected by filtration and air-dried to afford disulfide **7** (96%) and the filtrates afforded the 4-(phenylsulfonylthio)-2-azetidinone **2** in 91% yield. The presence of a catalytic amount of **4** is influential to effect the reaction smoothly. Indeed, the reaction hardly started without **4** and did not complete even after the prolonged reaction time (Entry 2).[7)] In place of **4**, sodium 2-benzothiazolethiolate **5** can be used without any disadvantages (Entry 3) presumably because **5** reacts with **6** liberating **4** together with disulfide **7**.

The elimination of the disulfide **7** as precipitates from the equilibrium mixture (vide supra) is also essential to shift the equilibrium to the desired direction. The disulfide **7** is virtually insoluble in various



Scheme 1.

Table 1. Reaction of Kamiya's Disulfides with *S*-(2-Benzothiazolyl)benzenethiosulfonates

Entry	1	R^1	R^2	R^3	Additive	Time/h	Yield[a]/%
1	**1a**	$PhOCH_2$	$PhCH_2$	H	$PhSO_2Na$	3.5	91
2	**1a**	$PhOCH_2$	$PhCH_2$	H	—	7	77
3	**1a**	$PhOCH_2$	$PhCH_2$	H	BTSNa	3.5	89
4	**1b**	$PhCH_2$	PMB[b]	H	$PhSO_2Na$	5	91
5	**1b**	$PhCH_2$	PMB[b]	H	BTSNa	1.5	92
6	**1c**	$PhOCH_2$	$PhCH_2$	5-CH_3O	BTSNa	3.5	91
7	**1d**	$PhOCH_2$	$PhCH_2$	4-CH_3	$PhSO_2Na$	3.5	90

a) Isolated yields based on disulfides **1**. b) *p*-Methoxybenzyl.

solvents and, thus, chloroform, acetonitrile, benzene, nitromethane, and isopropyl alcohol were successfully used in place of aqueous acetone without any appreciable change of the products.

The reaction of azetidinones **1b**, **1c**, and **1d** with **6** was performed in a similar manner, affording the corresponding 4-(phenylsulfonylthio)-2-azetidinones **2** in good yields (Entries 4—7 in Table 1).

It has already been described that azetidinones **2** were able to be converted to 3-substituted cephems **3**[3,4] and ammonium benzenesulfinate **4** was liberated in the course of the thiazolidine ring formation. On the other hand, we have recently reported a facile electrolytic cross-coupling of benzenesulfinates **4** and disulfide **7** affording **6** in good yields.[8] These two interesting results provided a clue that **6** could be supplied from **4** given in the course of **2**→**3** transformation for the **1**→**2** conversion as indicated by dotted arrows in Scheme 1.

Experimental

Melting points were determined on a Yamato melting point apparatus Model MP-21 and were uncorrected. IR spectra were obtained on a JASCO IRA-1 grating spectrometer or a JEOL RFX-3002 FTIR spectrophotometer. ^1H NMR spectra were mesured at 60 MHz with a Hitachi R-24 spectrometer or at 300 MHz with a Varian VXR-300S spectrometer. Chemical shifts are expressed in parts per million downfield from Me_4Si as an internal reference. Mass spectra were obtained on a Hitachi M-80 spectrometer. Elemental analyses were performed in our laboratory on a Yanaco CHN corder MT-3. 4-(2-Benzothiazolyldithio)-2-azetidinones **1**[6] and *S*-(2-benzothiazolyl) benzenethiosulfonates **6**[8,9] were prepared by the reported procedures.

4-Phenylsulfonylthio-3-phenoxyacetamido-1-(1-benzyloxycarbonyl-2-methyl-2-propenyl)-2-azetidinone (2a): Procedure A (Table 1, Entry 1). 4-(2-benzothiazolyldithio)-2-azetidinone **1a** (R^1=$PhOCH_2$, R^2=$PhCH_2$, R^3=H, 1.68 g, 2.8 mmol), 2-benzothiazolyl benzenethiosulfonate **6** (0.89 g, 2.9 mmol), and sodium benzenesulfinate hydrate (26 mg, 0.13 mmol) in acetone (35 mL) and water (5 mL) was stirred at room temperature for 3.5 h. The mixture was filtered and the solids were washed with acetone (5 mL) and air-dried to give bis(benzothiazolyl) disulfide (0.88 g, 96%). The filtrate and washings were combined and concentrated in vacuo. The residue was taken up with benzene (30 mL), washed with water (20 mL), and dried (Na_2SO_4). After evaporation of the solvents, the residue was chromatographed (SiO_2, benzene/EtOAc: 5/1) to afford **2a**[10] (1.46 g, 91%) as colorless solids: IR(KBr) 1794, 1756, 1692, 1615, 1537 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=1.79 (s, 3H), 4.38 (d, J=15 Hz, 1H), 4.15 (s, 1H), 4.51 (d, J=15 Hz, 1H), 4.83 (s, 1H), 4.85 (s, 1H), 5.14 (d, 12 Hz, 1H), 5.21 (d, J=12 Hz, 1H), 5.30 (dd, J=5 and 8 Hz, 1H), 5.92 (d, 5 Hz, 1H), 6.90—7.90 (m, 16H); MS (FD) *m/z* 780 (M^+).

Anal. Calcd for $C_{29}H_{28}N_2O_7S_2$: C, 59.98; H, 4.86; N, 4.82%. Found: C, 59.80; H, 4.84; N, 4.76%.

Procedure B (Table 1, Entry 3). A mixture of 4-(2-benzothiazolyldithio)-2-azetidinone **1a** (R^1=$PhOCH_2$, R^2=$PhCH_2$, R^2=H, 200 mg, 0.33 mmol), S-(2-benzothiazolyl) benzenethiosulfonate **6** (112 mg, 0.36 mmol), and sodium 2-benzothiazolethiolate (1 mg, 0.005 mmol) in acetone (5 mL) and water (1.5 mL) was stirred at room temperature for 3.5 h. Workup in the same manner as described above afforded **2a** (171 mg, 89%).

The reactions of 4-(2-benzothiazolyldithio)-2-azetidinone **1b** (R^1=$PhCH_2$, R^2=*p*-$CH_3OC_6H_4CH_2$, R^3=H), **1c** (R^1=$PhOCH_2$, R^2=$PhCH_2$, R^3=5-CH_3O), and **1d** (R^1=$PhOCH_2$, R^2=$PhCH_2$, R^3=4-CH_3O) with *S*-(2-benzothiazolyl) benzenethiosulfonates **6** were carried out according to Procedure A and/or B. Reaction conditions and results are summarized in Table 1.

4-Phenylsulfonylthio-3-phenylacetamido-1-[1-(*p*-methoxybenzyloxycarbonyl)-2-methyl-2-propenyl]-2-azetidinone (2b): Mp 115—116 °C from $CHCl_3/C_2H_5OH$ (1/10); IR (KBr) 1794, 1749, 1653, 1627, 1557, 1531 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ=1.73 (s, 3H), 3.56 (d, J=16 Hz, 1H), 3.62 (d, J=16 Hz, 1H), 3.82 (s, 3H), 4.43 (s, 1H), 4.75 (s, 1H), 4.76 (s, 1H), 5.04 (d, J=12 Hz, 1H), 5.10 (d, J=12 Hz, 1H), 5.11 (dd, J=5 and 8 Hz, 1H), 5.78 (d, J=5 Hz, 1H), 5.87 (d, J=8 Hz, 1H), 6.90—7.90 (m, 14H); MS (FD) *m/z* 594 (M^+).

Anal. Calcd for $C_{30}H_{30}N_2O_7S_2$: C, 60.59; H, 5.09; N, 4.71%. Found: C, 60.45; H, 5.07; N, 4.58%.

Refereces

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7) Some unknown contaminants seemed to act as a nucleophile to react with **1** or **6** to generate **5** or **4**. However, it is likely that the concentration of **5** and **4** is too low to efficiently promote the reaction.

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