Synthesis and Chemical Modification of 3,3-Dimethyl-1*H*,3*H*-furo[4,3-*b*][1,5]benzothiazepin-1-one

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Heating of 3-(2-aminophenylthio)-2-methoxycarbonyl-4-methyl-2-penten-4-olide with triethylamine hydrochloride gave 3,3-dimethyl-1*H*,3*H*-furo[4,3-*b*][1,5]benzothiazepin-1-one. Some chemical modifications of the product including [2+2]cycloaddition and 1,3-dipolar cycloaddition to the imino group in the product were performed.

Key words 1*H*,3*H*-furobenzothiazepin-1-one; [2+2]cycloaddition; 1,3-dipolar cycloaddition; β-lactam; [1,2,4]oxadiazolo-fused heterocycle

In the course of our synthetic studies on biologically active heterocyclic compounds using tetronic acids and tetramic acids,[1] we reported the syntheses of 10-aryl-3,3-dimethyl-2,3,4,10-tetrahydro-1*H*-pyrrolo[3,4-*c*][1,5]-benzothiazepin-1-ones (**1**)[2] and 10-aryl-3a,9-dihydro-1*H*,3*H*-furo[4,3-*b*][1,5]benzothiazepin-1-ones (**2**).[3] Some of them showed antimicrobial or analgesic activities.[2]

As a continuation of our work on this line, 3-(2-aminophenylthio)-2-methoxycarbonyl-4-methylpentan-4-olide (**5**), which was obtained by a Michael-type addition of 2-aminothiophenol (**4**) to 2-methoxycarbonyl-4-methyl-2-penten-4-olide (**3**),[4] was heated with 1.5 eq of triethylamine hydrochloride (Et_3N–HCl) at 160—170 °C (bath temperature) for 2 h, with removal of methanol and water formed during the reaction. The product (obtained in 50.9% yield) was not the expected lactam (**8**), but the cyclic imino compound, 3,3-dimethyl-1*H*,3*H*-furo[4,3-*b*][1,5]-benzothiazepin-1-one (**6**),[5] which is possibly formed through isomerization of the enol form of **8** followed by dehydration, as shown in Chart 2. In its ^{1}H-NMR spectrum, the imine proton appeared at δ 8.23 as a singlet peak. When the above cyclization reaction was carried out at around 140 °C (bath temperature) without removal of methanol and water, the major product was the methanol adduct **7** (31.4%), and **6** was obtained in only 8.9% yield.

It would be interesting to examine the reactivity of the imino group as an approach for chemical modifications of **6**. Thus, the following cycloaddition reactions and the conversion to the amino group were conducted. First, [2+2]cycloaddition of ketenes[6] to the imino group of **6** was tried. When **6** was treated with dichloroketene, generated *in situ* from dichloroacetyl chloride in the presence of Et_3N in benzene at refluxing temperature, the α,β-unsaturated β-lactam (**10**) was unexpectedly obtained in 82.4% yield and no saturated β-lactam (**9**) was detected.[6] On the other hand, the starting imine (**6**) was recovered when **6** was treated with chloroacetyl chloride and Et_3N under similar reaction conditions.

Next, 1,3-dipolar cycloaddition of arylnitrile oxides to the imino group of **6** was performed.[7] Arylaldehydes (**11a—e**) were converted to their oximes (**12a—e**) in the usual way in good yields, and these products were subsequently chlorinated with *N*-chlorosuccinimide (NCS) in *N*,*N*-dimethylformamide (DMF)[8] to give the arylhydroximidoyl chlorides (**13a—e**) (Table 1). Treatment of **6** with **13a** in the presence of Et_3N in tetrahydrofuran (THF) at 0 °C—room temperature furnished a [1,2,4]-oxadiazolo-fused adduct (**14a**) in 58.3% yield as an oil. In the ^{1}H-NMR spectrum, the methine proton appeared at δ 5.43 as a singlet peak, which means that 1,3-dipolar cycloaddition occurred in a regioselective manner, as shown in Chart 4. Other arylhydroximidoyl chlorides (**13b—e**) were also reacted with **6** under the same conditions, and the results are shown in Table 2. It is interesting to note that the nature of the substituents on the phenyl ring of **13** influenced the yields. Namely, an electron-withdrawing group (Cl or NO_2) greately lowered

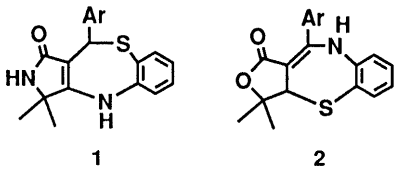

Chart 1

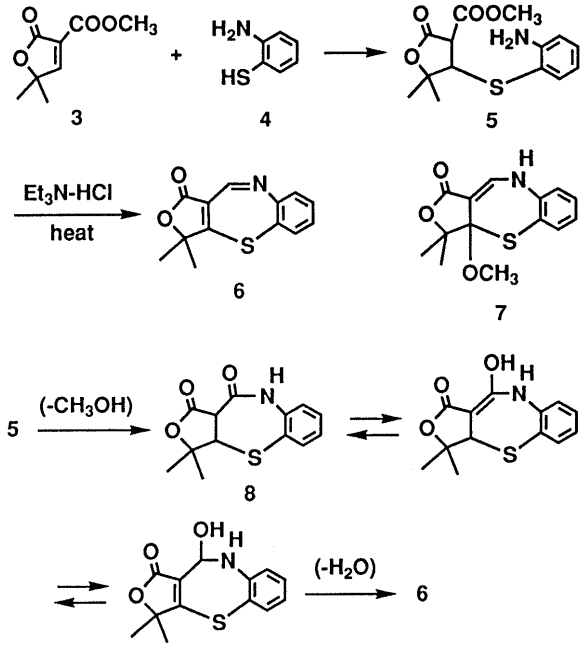

Chart 2

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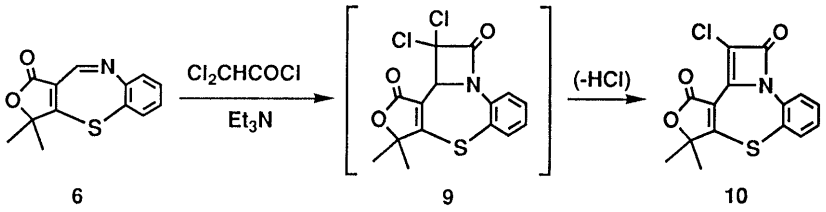
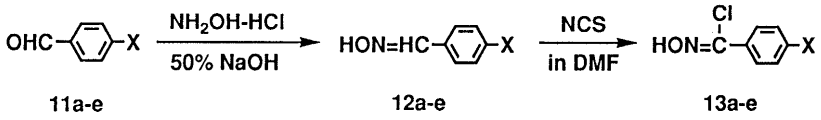


Chart 3



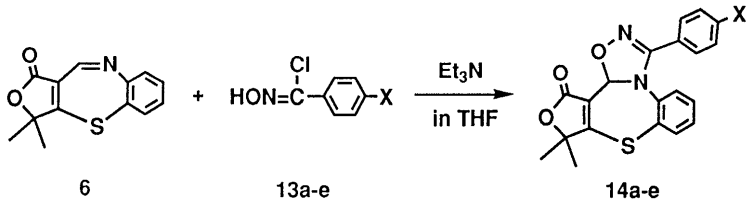


Chart 4

Table 1. Melting Points and Yields of **12** and **13**

	X	mp (°C)	Yield (%)		X	mp (°C)	Yield (%)
12a	H[a]	(Oil)	91.1	**13a**	H[9]	(Oil)	92.2
12b	Cl[8]	104—106	81.4	**13b**	Cl[8]	88—89	74.4
12c	NO_2[9]	130—134	83.3	**13c**	NO_2[10]	126—128	84.5
12d	OCH_3[9]	56—61	87.2	**13d**	OCH_3[11]	85—89	85.5
12e	CH_3[10]	70—75	82.6	**13e**	CH_3[11]	69—71	66.2

a) Commercially available.

Table 2. Melting Points, Yields and ^{1}H-NMR Data of **14**

	X	mp (°C)	Yield (%)	^{1}H-NMR ($CDCl_3$) δ: (CH-N)
14a	H	(Oil)	58.3	5.43[a]
14b	Cl	118—120	5.2	5.07
14c	NO_2	222—223	1.2	5.18
14d	OCH_3	(Oil)	68.4	5.04
14e	CH_3	(Oil)	51.0	5.06

a) DMSO-d_6 was used as a solvent.

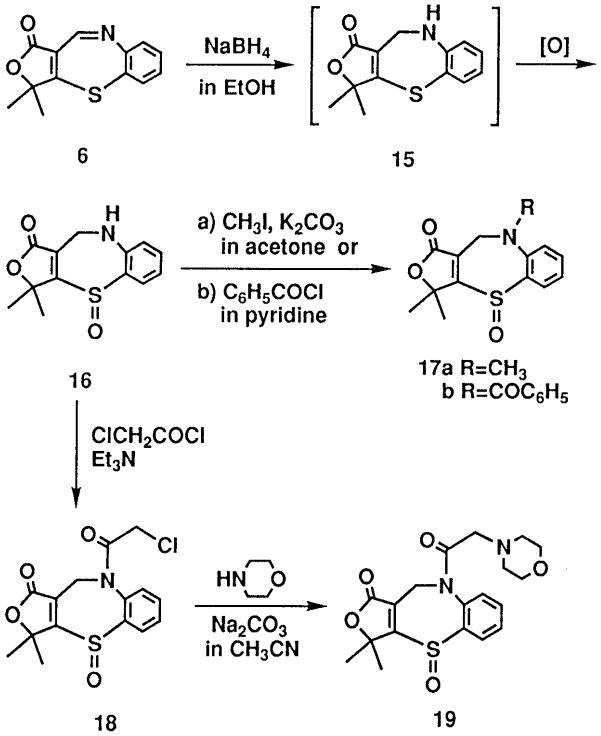


Chart 5

the yield of the cycloadducts (**14b, c**).

We next tried to reduce the 9,10-double bond in **6** and to introduce some substituents at the 9-position. Thus, **6** was treated with sodium borohydride in ethanol in an attempt to obtain **15**, but the isolated product was the sulfoxide (**16**) (64.8%). This result indicates that **15**, the initial reduction product, was air-sensitive and oxidized spontaneously to the sulfoxide (**16**) during the isolation procedures. As the reduction product of the 9,10-double bond in **6** was in our hands, we examined methylation and benzoylation at the 9-position of **16**. When **16** was treated with iodomethane in the presence of potassium carbonate in acetone at refluxing temperature, the *N*-methylated compound (**17a**) was obtained in 59.0% yield. Similarly, benzoylation of **16** was performed with benzoyl chloride in pyridine to give **17b** in 77.1% yield. Finally, we attempted to introduce a 1-morpholinylacetyl group at the 9-position of **16**, expecting to get a biologically interesting compound.[12] Treatment of **16** with chloroacetyl chloride in the presence of Et_3N in dioxane gave **18** in 54.3% yield. Reaction of **18** with morpholine in the presence of sodium carbonate in acetonitrile furnished the desired substitution product (**19**) in 42.2% yield along with **16** (31.7%). On the other hand, reaction of **18** with *N*-methylpiperazine in the presence of sodium carbonate and sodium iodide in acetonitrile resulted in the formation of **16**. Pharmacological testing of the synthesized compounds is under way.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus, model MP-S3, and are uncorrected. IR spectra were measured with a Hitachi 260-30 IR spectrometer, and ^{1}H-NMR spectra were recorded on a JEOL JNM-FX270 (270 MHz) spectrometer using tetramethylsilane as an internal standard. MS were taken with a JEOL LMS-HX100 instrument.

3,3-Dimethyl-1*H*,3*H*-furo[4,3-*b*][1,5]benzothiazepin-1-one (6) 2-Aminothiophenol (**4**) (3.63 g, 29 mmol) was added to a solution of **3** (5.0 g, 29 mmol) in ethanol (100 ml) and the mixture was refluxed for 1 h, then concentrated under reduced pressure to give **5** (6.1 g, 70.3%) as an oil, which was used directly for the next reaction. A mixture of **5** (6.1 g, 20.6 mmol) and Et_3N–HCl (4.25 g, 30.9 mmol) was heated at 160—170 °C (bath temperature) for 2 h, during which time methanol and water formed were removed through a Liebig condenser. After having been cooled to room temperature, the mixture was partitioned between $CHCl_3$ (110 ml) and water (50 ml). The separated $CHCl_3$ layer was washed with 100 ml each of 3% HCl, water and brine, successively. The organic layer was dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give an oil, which crystallized on standing. Recrystallization from a mixture of 2-propanol and hexane gave **6** (2.14 g) as colorless needles. The filtrate was concentrated and the product was crystallized again from the same solvent system to furnish more **6** (0.43 g, total 2.57 g, 50.9%), mp 115.5—116.5 °C. IR (Nujol): 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.64 (6H, s, 2 × CH_3), 7.45 and 7.54 (each 1H, dt, J=8.0, 1.0 Hz, ArH), 7.98 and 8.07 (each 1H, dd, J=8.0, 1.0 Hz, ArH), 8.23 (1H, s, CH=N). MS *m/z*: Calcd for $C_{13}H_{11}NO_2S$: 245.0510. Found: 245.0485. *Anal.* Calcd for $C_{13}H_{11}NO_2S$: C, 63.66; H, 4.52; N, 5.71. Found: C, 63.70; H, 4.59; N, 5.75. When a mixture of the crude **5** (17.74 g, 60 mmol) and Et_3N–HCl (12.82 g, 93 mmol) was heated at around 140 °C (bath temperature) for 4 h using a Dimroth condenser instead of a Liebig condenser and worked up as above, **5** (1.28 g, 8.9%) and **7** (5.11 g, 31.4%) were obtained after separation by SiO_2 column chromatography ($CHCl_3$) and crystallization (2-propanol–hexane) of the crude products. **7**: mp 93—95 °C (colorless plates). IR (Nujol): 3200, 1720, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.60 (6H, s, 2 × CH_3), 2.44 (3H, s, OCH_3), 7.13 and 7.31 (each 1H, dt, J=8.0, 1.0 Hz, ArH), 7.51 and 8.39 (each 1H, dd, J=8.0, 1.0 Hz, ArH), 8.28 (1H, s, =CHNH), 10.53 (1H, br s, NH). *Anal.* Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.56; H, 5.44; N, 4.94.

β-Lactam Derivative (10) A solution of dichloroacetyl chloride (0.39 ml, 4.1 mmol) in dry benzene (8 ml) was added to a mixture of **6** (0.50 g, 2.0 mmol) and Et_3N (0.56 ml, 4.0 mmol) in dry benzene (8 ml) and the whole was refluxed. The reaction mixture was concentrated under reduced pressure, and the residue was partitioned between $CHCl_3$ and water. The separated organic layer was washed with saturated aqueous $NaHCO_3$, water and brine, successively, and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave a residue, which was crystallized from a mixture of 2-propanol and hexane to give **10** (0.48 g, 82.4%) as colorless needles, mp >300 °C. IR (Nujol): 1740, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.86 (6H, s, 2 × CH_3), 7.57—7.69 (2H, m, ArH), 7.82—7.87 (1H, m, ArH), 9.31—9.37 (1H, m, ArH). *Anal.* Calcd for $C_{15}H_{10}ClNO_3S$: C, 56.34; H, 3.15; N, 4.38. Found: C, 56.26; H, 3.24; N, 4.34.

Arylhydroximidoyl Chlorides (13a—e) Hydroxylamine hydrochloride (1.04 g, 14.5 mmol) was added to a mixture of 4-nitrobenzaldehyde (**11c**) (2.0 g, 13.2 mmol) in water (3.3 ml), ethanol (3.3 ml) and ice (5.7 g). Then, 50% NaOH (2.8 ml) was added with stirring; the temperature was maintained at 25—30 °C by adding ice. The mixture was stirred for 1 h, extracted with ether to remove neutral impurities, acidified to pH 6 with concentrated HCl, and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give yellow crystals, which were recrystallized from a mixture of ether and hexane to furnish **12c** (1.83 g, 83.3%), mp 130—134 °C. IR (Nujol): 3300, 1600, 1350, 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.75 (2H, dt, J=9.0, 2.0 Hz, ArH), 8.20 (1H, s, CHN), 8.25 (2H, dt, J=9.0, 2.0 Hz, ArH), 8.52 (1H, s, NOH). Other oximes (**12a, b, d, e**) were prepared similarly, and their melting points and yields are listed in Table 1.

NCS (0.28 g, 2.1 mmol) was added to a solution of **12c** (1.72 g, 10.3 mmol) in dry DMF (8.6 ml). The temperature of the mixture went down initially and then rose. More NCS (1.11 g, 8.28 mmol) was added portionwise to the reaction mixture under cooling with ice-water to keep the temperature below 35 °C. After the exothermic reaction ceased, the mixture was stirred for 30 min. Cold water (35 ml) was added under cooling, and the whole was extracted with ether. The combined extracts were washed with water and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave yellow crystals, which were recrystallized from a mixture of ether and hexane to give **13c** (1.75 g, 84.5%) as yellow crystals, mp 126—128 °C. IR (Nujol): 3280, 1600, 1520, 1355, 1005, 950 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.05 (2H, dt, J=9.0, 2.0 Hz, ArH), 8.27 (2H, dt, J=9.0, 2.0 Hz, ArH), 8.41 (1H, s, NOH). *Anal.* Calcd for $C_7H_5ClN_2O_3$: C, 41.92; H, 2.51; N, 13.97. Found: C, 41.79; H, 2.59; N, 13.67. Other hydroximidoyl chlorides (**13a, b, d, e**) were prepared similarly and their melting points, yields, and ^{1}H-NMR spectral data are listed in Table 1.

General Procedure for the Preparation of [1,2,4]Oxadiazolo-Fused Heterocycles (14a—e) To a stirred solution of **6** (0.20 g, 0.82 mmol) and Et_3N (0.23 ml, 1.64 mmol) in dry THF (6.4 ml), a solution of **13d** (0.303 g, 1.63 mmol) in dry THF (3.2 ml) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and at room temperature overnight, then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, and the solution was washed with water and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave an oil, which was purified by SiO_2 column chromatography (benzene : ethyl acetate = 20 : 1) to give **14d** (0.22 g, 68.4%) as a colorless oil. IR (neat): 1780, 1610, 1260, 1180, 1020, 940 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33 and 1.88 (each 3H, s, 2 × CH_3), 3.85 (3H, s, OCH_3), 5.04 (1H, s, CHN), 6.95 (2H, dt, J=9.0, 2.0 Hz, ArH), 7.39—7.53 (2H, m, ArH), 7.64 (2H, dt, J=9.0, 2.0 Hz, ArH), 7.90—7.96 (1H, m, ArH), 8.0—8.5 (1H, m, ArH). MS *m/z*: Calcd for $C_{21}H_{18}N_2O_4S$: 394.0987. Found: 394.0962. In a similar manner, other [1,2,4]oxadiazolo fused compounds (**14a—c, e**) were prepared. **14a**: The imine (**6**) (0.3 g, 1.22 mmol) afforded **14a** (0.26 g, 58.3%) as a yellow oil after purification by SiO_2 column chromatography (benzene). IR (neat): 1770, 1590, 1260, 1015, 940 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.22 and 1.83 (each 3H, s, 2 × CH_3), 5.43 (1H, s, CHN), 7.48—7.64 (5H, m, ArH), 7.79—7.85 (2H, m, ArH), 8.08—8.13 (1H, s, ArH), 8.18—8.22 (1H, m, ArH). MS *m/z*: Calcd for $C_{20}H_{16}N_2O_3S$: 364.0881. Found: 364.0904. **14b**: The imine (**6**) (0.2 g, 0.82 mmol) afforded **14b** (0.017 g, 5.2%) as colorless crystals after purification by SiO_2 preparative thin layer chromatography ($CHCl_3$), mp 118—120 °C (2-propanol). IR (Nujol): 1770, 1590, 1250, 1090, 935 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 and 1.88 (each 3H, s, 2 × CH_3), 5.07 (1H, s, CHN), 7.38—7.52 (4H, m, ArH), 7.62—7.68 (2H, m, ArH), 7.92—7.97 (1H, m, ArH), 8.02—8.05 (1H, m, ArH). MS *m/z*: Calcd for $C_{20}H_{15}ClN_2O_3S$: 398.0492. Found: 398.0464. **14c**: The imine (**6**) (0.2 g, 0.82 mmol) afforded **14c** (0.004 g, 1.2%) as colorless crystals after purification by SiO_2 column chromatography (benzene : ethyl acetate = 20 : 1) and recrystallization from a mixture of $CHCl_3$ and hexane, mp 222—223 °C. IR (Nujol): 1780, 1600, 1350, 1250, 950 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.315 and 1.91 (each 3H, s, 2 × CH_3), 5.175 (1H, s, CHN), 7.42—7.56 (2H, m, ArH), 7.87—7.98 (3H, m, ArH), 8.01—8.06 (1H, m, ArH), 8.29—8.36 (2H, m, ArH). MS *m/z*: Calcd for $C_{20}H_{15}N_3O_5S$: 409.0733. Found: 409.0759. **14e**: The imine (**6**) (0.2 g, 0.82 mmol) afforded **14e** (0.16 g, 51.0%) as a colorless oil after purification by SiO_2 column chromatography (benzene : ethyl acetate = 20 : 1). IR (neat): 1780, 1610, 1345, 1250, 1095, 1010, 930 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 and 1.87 (each 3H, s, 2 × CH_3), 2.38 (3H, s, Ar-CH_3), 5.06 (1H, s, CHN), 7.20—7.27 (2H, m, ArH), 7.38—7.52 (2H, m, ArH), 7.55—7.61 (2H, m, ArH), 7.89—7.94 (1H, m, ArH), 8.0—8.3 (1H, m, ArH). MS *m/z*: Calcd for $C_{21}H_{18}N_2O_3S$: 378.1038. Found: 378.1068.

9,10-Dihydro-3,3-dimethyl-1*H*,3*H*-furo[4,3-*b*][1,5]benzothiazepin-1-one 4-Oxide (16) The imine (**6**) (1.695 g, 6.91 mmol) was dissolved in warm ethanol (50.6 ml) and the solution was allowed to cool to room temperature. $NaBH_4$ (0.065 g, 1.72 mmol) was added to the solution with stirring at room temperature, and the whole was stirred for 4 h. The reaction mixture was concentrated under reduced pressure to give a residue, to which ice-water was added. After saturation with solid NaCl, the mixture was extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was crystallized from a mixture of 2-propanol and hexane to give **16** (1.175 g, 64.8%) as colorless crystals, mp 126—128 °C. IR (Nujol): 3320, 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.61 and 1.64 (each 3H, s, 2 × CH_3), 2.64 and 2.94 (each 1H, d, J=14 Hz, CH_2), 4.34 (1H, br s, NH), 7.41 and 7.50 (each 1H, dt, J=8.0, 1.0 Hz, ArH), 7.88 and 8.03 (each 1H, dd, J=8.0, 1.0 Hz, ArH). *Anal.* Calcd for $C_{13}H_{13}NO_3S$: C, 59.30; H, 4.98; N, 5.32. Found: C, 59.26; H, 5.04; N, 5.18.

9,10-Dihydro-3,3,9-trimethyl-1*H*,3*H*-furo[4,3-*b*][1,5]benzothiazepin-1-one 4-Oxide (17a) Anhydrous K_2CO_3 (0.24 g, 1.7 mmol) and iodomethane (0.32 g, 2.3 mmol) were added to a solution of **16** (0.40 g, 1.5 mmol) in dry acetone (18.4 ml) and the whole was refluxed for 3 h. After addition of iodomethane (1.56 g, 11.0 mmol), reflux was continued for a further 3 h. The cooled reaction mixture was concentrated under reduced pressure, and the residue was diluted with cold water. The mixture was extracted with $CHCl_3$, and the combined extracts were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a pale yellow oil, which was purified by SiO_2 column chromatography (benzene : ethyl acetate = 8 : 1) and crystallization from a mixture of 2-propanol and hexane to afford **17a** (0.20 g, 59.0%), mp 102—103 °C. IR (Nujol): 1760, 1280, 1140, 960 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.52 and 1.62 (each 3H, s, 2 × CH_3), 2.62 and 3.09 (each 1H, d, J = 14 Hz, CH_2), 3.44 (3H, s, NCH_3), 7.43 and 7.50 (each 1H, dt, J = 8.0, 1.0 Hz, ArH), 7.93 and 8.05 (each 1H, dd, J = 8.0, 1.0 Hz, ArH). *Anal.* Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.60; H, 5.51; N, 4.94.

9-Benzoyl-9,10-dihydro-3,3-dimethyl-1*H*,3*H*-furo[4,3-*b*][1,5]benzothiazepin-1-one 4-Oxide (17b) Benzoyl chloride (0.10 ml, 0.86 mmol) was added dropwise to a solution of **16** (0.20 g, 0.81 mmol) in dry pyridine (1.2 ml) with stirring under ice-water cooling. The whole was stirred at room temperature overnight. After addition of water, the mixture was extracted with $CHCl_3$, and the combined extracts were washed with 2 N HCl, water and brine, successively. After drying over anhydrous Na_2SO_4, the extract was concentrated under reduced pressure to give a pale yellow oil, which was crystallized from a mixture of 2-propanol and hexane to afford **17b** (0.22 g, 77.1%) as colorless needles, mp 134—136 °C. IR (Nujol): 1760, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.77 and 1.78 (each 3H, s, 2 × CH_3), 2.92 and 3.56 (each 1H, d, J = 14 Hz, CH_2), 7.40—8.20 (9H, m, ArH). MS *m/z*: Calcd for $C_{20}H_{17}NO_4S$: 367.0879. Found: 367.0870.

9,10-Dihydro-3,3-dimethyl-9-(1-morpholinylacetyl)-1*H*,3*H*-furo[4,3-*b*][1,5]benzothiazepin-1-one 4-Oxide (19) Chloroacetyl chloride (0.68 ml, 8.54 mmol) and Et_3N (1.59 ml, 11.4 mmol) were added successively to a solution of **16** (1.00 g, 3.81 mmol) in dry dioxane (20 ml) at room temperature. The mixture was stirred at room temperature overnight, then diluted with water under ice cooling and extracted with ethyl acetate. The combined extract was washed with water and brine, successively. After drying over anhydrous Na_2SO_4, removal of the solvent under reduced pressure gave an oil, which was purified by SiO_2 column chromatography (benzene : ethyl acetate = 10 : 1) to give **18** (0.70 g, 54.3%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.68 and 1.71 (each 3H, s, 2 × CH_3), 2.79 and 3.50 (each 1H, d, J = 14 Hz, CH_2N), 4.21 and 4.27 (each 1H, d, J = 15 Hz, $COCH_2Cl$), 7.45 and 7.52 (each 1H, td, J = 8.0, 1.0 Hz, ArH), 7.89—7.96 (1H, m, ArH), 8.025—8.09 (1H, m, ArH). Morpholine (0.22 ml, 2.42 mmol) and anhydrous Na_2CO_3 (0.26 g, 2.40 mmol) were added successively to a solution of **18** (0.40 g, 1.18 mmol) in dry CH_3CN (8.9 ml), and the solution was heated under reflux for 3 h. The reaction mixture was cooled, diluted with water, and extracted with ethyl acetate. The combined extracts were washed with water and brine, respectively, and dried over anhydrous Na_2SO_4. Removal of the solvent gave an oil, which was purified by SiO_2 column chromatography (benzene : ethyl acetate = 5 : 3) and then SiO_2 preparative thin layer chromatography (benzene : ethyl acetate = 5 : 3) to afford **19** (0.19 g, 42.2%) as colorless crystals and **16** (0.10 g, 31.7%). **19**: mp 123—126 °C (2-propanol–hexane). IR (Nujol): 1760, 1740, 1595, 1270, 1240, 1115, 1030, 965, 920 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.68 and 1.70 (each, 3H, 2 × CH_3), 2.61 and 2.69 (each 2H, dt, J = 10, 4.5 Hz, 2 × NCH_2CH_2O), 2.80 and 3.49 (each 1H, d, J = 14 Hz, CH_2N), 3.40 (2H, s, $COCH_2N$), 3.77 (4H, t, J = 4.5 Hz, 2 × NCH_2CH_2O), 7.44 and 7.51 (each 1H, dt, J = 7.5. 1.5 Hz, ArH), 7.87—7.94 (1H, m, ArH), 8.0—8.08 (1H, m, ArH). *Anal.* Calcd for $C_{19}H_{22}N_2O_5S$: C, 58.45; H, 5.68; N, 7.17. Found: C, 58.17; H, 5.66; N, 7.18.

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