Chinese Journal of Chemistry, **2004**, *22*, 1012—1018 **Article**

Reaction of 2,3-Dihydro-1,5-benzothiazepines and Phenylacetyl Chloride in the Presence of Triethylamine: A New Aspect on the Formation Mechanism of Dihydro-1,3-oxazin-4-one Derivatives†

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2a,4-Disubstituted 2,2a,3,4-tetrahydro-2-phenyl-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-ones, as well as 2-substituted 2,3-dihydro-3-phenylacetyl-2-styryl-benzothiazoles and 4a,6-disubstituted 3-benzyl-4a,5-dihydro-2-phenyl-1*H*,6*H*-[1,3]oxazino[2,3-*d*][1,5]benzothiazepin-1-ones, were obtained from the reaction of 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines with phenylacetyl chloride in the presence of triethylamine. The mechanism for the formation of 4a,5-dihydro-1*H*,6*H*-[1,3]oxazino[2,3-*d*][1,5]benzothiazepin-1-ones, 2,3-dihydro-1,3-oxazin-4-one derivatives, was suggested.

Keywords 1,5-benzothiazepine, 2,2a,3,4-tetrahydro-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-one, 2,3-dihydrobenzothiazole, 4a,5-dihydro-1*H*,6*H*-[1,3]oxazino[2,3-*d*][1,5]benzothiazepin-1-one, cycloaddition, mechanism

Introduction

The β-lactam (2-azetidinone) skeleton is a key structural element in the most widely employed family of antimicrobial agents. Most of the important antibiotics possess the representative structure of a β-lactam fused to a five- or six-membered heterocyclic ring containing nitrogen and sulfur atoms, for instance, the effective antibiotics, penicillin, penam, cephalosporin and cephem.[1,2] The syntheses of heterocycle-fused β-lactams became a growing interest research. Though there are some effective antimicrobial agents now, it seemed to be necessary to synthesize some novel compounds with a fused β-lactam-heterocyclic ring for bioassay of antibacterial activity because of the growing resistance of bacteria against penicillin and cephalosporin-like compounds. Till now, some β-lactam derivatives of thiazoline and dihydrothiazine have been synthesized by various methods.[1-3] In recent years, our group has synthesized numerous benzothiazepine tricyclic derivatives due to their potential biological and pharmaceutical importance.[4-7] The syntheses of a few examples of β-lactam derivatives of dihydrobenzothiazepines have been published by us and others.[8-15] To build up a structurally diverse dihydrobenzothiazepine-fused β-lactam library, we investigated the reactions of 2,3-dihydro-1,5-benzothiazepines with substituted acetyl chlorides in the presence of triethylamine, and found that phenylacetyl chloride gave a complex mixture of products. Herein, we report the studies on the reaction and the mechanism of the formation of 4a,5-dihydro-1*H*,6*H*-[1,3]oxazino[2,3-*d*][1,5]benzothiazepin-1-ones, 2,3-dihydro-1,3-oxazin-4-one derivatives, formed in the reaction.

Results and discussion

As a continuation of the preparation of dihydrobenzothiazepine-fused β-lactams, the reactions of 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines **1** with phenylacetyl chloride were conducted (Table 1). According to the literature procedure, a solution of triethylamine in benzene was added dropwise into a solution of phenylacetyl chloride and 1,5-benzothiazepines **1** in benzene (procedure A),[14] and azeto[2,1-*d*][1,5]benzothiazepin-1-ones **2** were obtained in low to moderate yields. In some cases, 2-substituted 2,3-dihydro-3-phenylacetyl-2-styrylbenzothiazoles **3**, the ring-contracted products of 2,4-diaryl-2,3-dihydro-*N*-phenylacetyl-1,5-benzothiazepines, were also obtained. The ring contraction of 2,4-diaryl-2,3-dihydro-1,5-benzothiazepine under acetylating conditions was reported previously.[16] Thus, the low yields of azeto[2,1-*d*][1,5]benzothiazepin-1-ones

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Scheme 1 Reaction of 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines **1** with phenylacetyl chloride in the presence of triethylamine

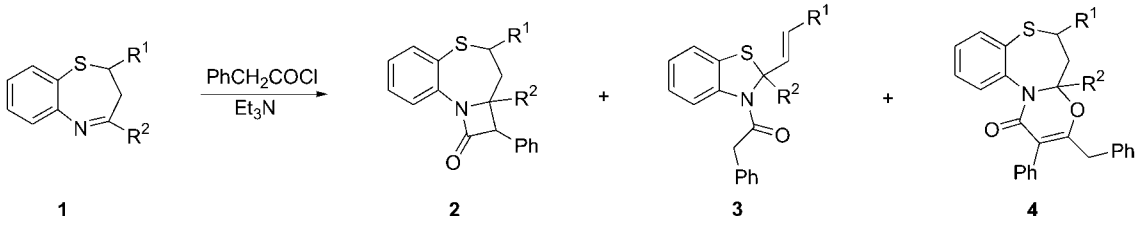


Table 1 Reactions of 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines and phenylacetyl chloride

Entry	R^1	R^2	Product **2**		Product **3**		Product **4**	
			m.p./℃	Yield/%	m.p./ ℃	Yield/%	m.p./ ℃	Yield/%
a	Me	Ph	203—204	54 (A)	—	—	—	—
				7 (B)		—	159—160	17 (B)
b	Me	4-MePh	169—170	50 (A)	—	—	—	—
				—		—	144—145	21 (B)
c	Ph	Ph	160—161	29 (A)	—	—	—	—
				14 (B)		—	176—177	15 (B)
d	2-ClPh	Ph	185—186	32 (A)	—	—	—	—
				—		—	166—167	12 (B)
e	4-ClPh	Ph	199—200	28 (A)	149—150	5 (A)		—
				—		—	175—176	8 (B)
				12 (B)*		—		3 (B)*
				—		—		7 (C)
f	4-BrPh	Ph	199—200	20 (A)	147—148	6 (A)		—
				15 (B)		—	173—173	12 (B)
g	Ph	4-ClPh	150—151	6 (A)	—	—		—
				—			174—175	7 (B)

A: Procedure A; B: Procedure B; C: Procedure C. * Phenylacetyl chloride 1.1 eq.

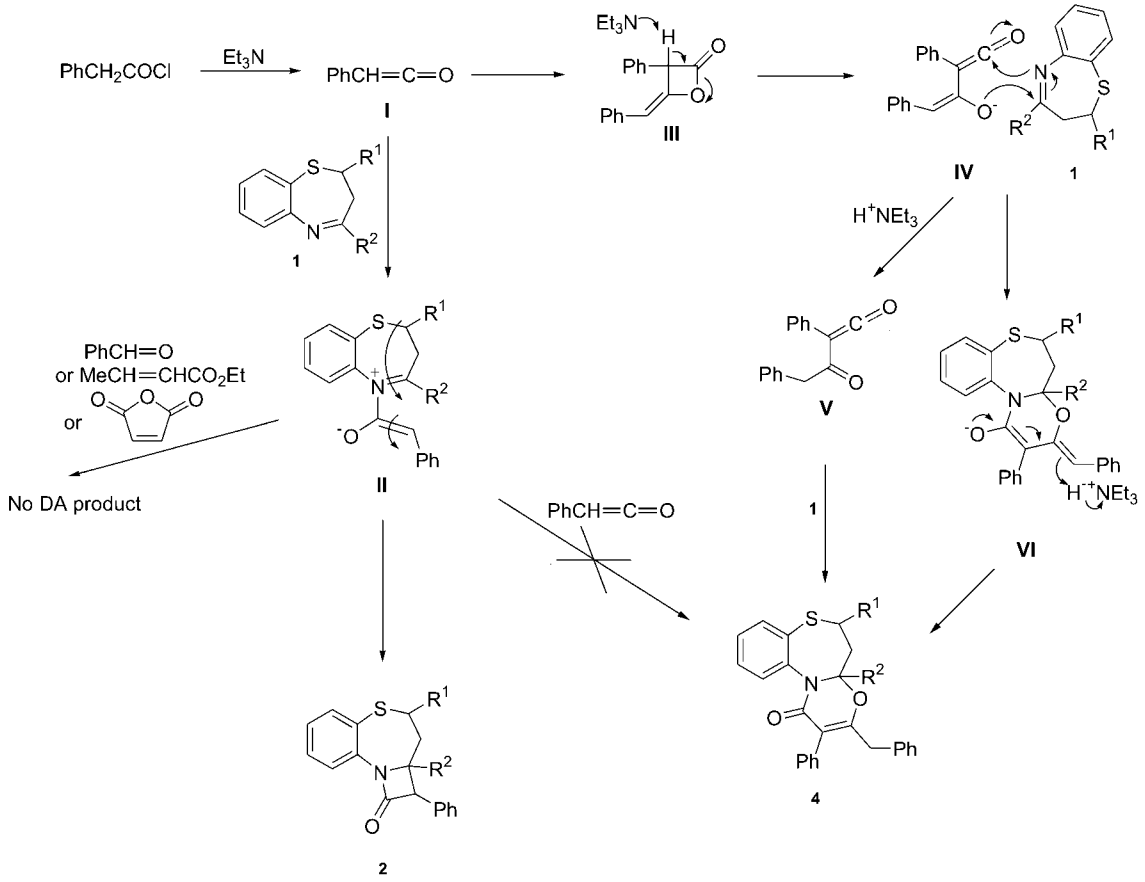
2 in the reactions could be rationalized that the ring contraction is a competitive reaction with the Staudinger reaction under the reaction conditions. *N*-Phenylacetylated 1,5-benzothiazepine intermediates formed in the reaction mixture and the ring contraction could occured before triethylamine was added. On the basis of literature mechanism,[16] the yields of azeto[2,1-*d*][1,5]benzothiazepin-1-ones **2** could be improved if a solution of phenylacetyl chloride in benzene was added dropwise into a solution of benzothiazepines **1** and triethylamine in benzene. The ring contraction could be inhibited under this addition mode. However, the yield of azeto[2,1-*d*][1,5]benzothiazepin-1-one **2** was still low when 1.1 equivalent of phenylacetyl chloride was used and a byproduct **4** was obtained in very low yield. When phenylacetyl chloride was increased to 2.2 equivalents to improve the yield of the desired product **2**, no desired azeto[2,1-*d*][1,5]benzothiazepin-1-one **2** was obtained (procedure B). The yield of the new byproduct **4** was improved slightly (for example, Entry e) (Scheme 1).

The new byproducts **4** are consisted of a tetrahydrobenzothiazepine ring and two phenylketene molecules, which was characterized by their ^{1}H NMR spectra and fast-atom bombardment mass spectra. In their ^{1}H NMR spectra, AMX systems of the tetrahydrobenzothiazepine rings still exist and an additional AB system appears. Fast-atom bombardment mass spectra (FAB-MS) show that compounds **4** could undergo a retro-Diels-Alder reaction to give the ions of protonated starting material benzothiazepines **1** at *m/z* ($[M+H]^+-2PhCH=C=O$) by loss of a dimer of phenylketene. DEPT spectrum of **4e** indicates that there is a CH and two CH_2 carbon atoms in aliphatic part. Thus, compound **4e** was assigned as 3-benzyl-6-(4-chlorophenyl)-4a,5-dihydro-2,4a-phenyl-1*H*,6*H*-[1,3]oxazino[2,3-*d*][1,5]benzothiazepin-1-one (Scheme 2). It was well known that oxazino[2,3-*d*][1,5]benzothiazepin-1-one derivatives could undergo a retro-Diels-Alder reaction under the mass spectrometric conditions.[17] FAB-MS results support the assigned structure. In their ^{1}H NMR spectra, AB system comes from magnetic nonequivalent protons in the CH_2 of benzyl group. After searching literature, it has been found that the formation of 2,3-dihydro-1,3-oxazin-4-one derivatives were found in the reactions of both

acetyl chloride and chloroacetyl chloride with imines in the presence of triethylamine.[18,19] The mechanism proposed in the literature[18] is as follows: ketene was formed from acetyl chloride, which dimerized to afford diketene. Subsequent triethylamine-catalyzed heterolytic cleavage of the diketene ring (*β*-lactone form) through attacking on the carbonyl by triethylamine yielded oxoketene, which was followed by stepwise or concerted 1,4-addition of the imine to the oxoketene to produce 2,3-dihydro-1,3-oxazin-4-one derivative. This was supported partly by the fact that the reaction of diketene and imines yielded 1,3-oxazin-4-one derivatives in the presence of triethylamine but did not in the absence of triethylamine. Recently, Arjona *et al.*[20] assumed a stepwise acylation mechanism for the formation of oxazinone from imines and acyl chlorides in the presence of triethylamine without any experimental supports.

Although the reaction of diketene with C=N double bond in some compounds has been investigated widely previously,[21-23] the reaction mechanism is still unclear. When we considered the above mechanism carefully and found that the step of triethylamine-catalyzed heterolytic cleavage of the diketene ring (*β*-lactone form) yielding oxoketene was unclear and seemed to be incorrect,[18] we tried to reinvestigate and analyze the formation mechanism of 1,3-oxazin-4-one derivative in the reaction of acyl chloride with an imine in the presence of triethylamine. At first, we doubted whether the zwitterionic intermediates **II**, which was generated through dehydrogenation of phenylacetylated benzothiazepines by triethylamine or attacking on phenylketene **I** by the imine,[24] underwent a conrotatory ring closure difficultly or they underwent a Diels-Alder reaction as dienes with phenylketene **I** as a dienophile to produce the 1,3-oxazin-4-one derivatives **4**. However, when we added some dienophiles, such as benzaldehyde, maleic anhydride, and ethyl crotonate, respectively, into the reaction mixture in the procedure **A** to capture the intermediates **II**, no correspondingly desired Diels-Alder adducts were found except for the 1,3-oxazin-4-one derivatives **4** (Scheme 2). Moreover, when we carried out the reaction of benzothiazepines and phenylacetyl chloride in the procedure **B**, the 1,3-oxazin-4-ones **4** almost became major products and in some cases almost no *β*-lactam product **2** was formed in the reaction mixture. When we prepared diketene **III** firstly through addition of triethylamine to a solution of phenylacetyl chloride in benzene[25] and then added 1,5-benzothiazepine **1e** into the resulting reaction mixture, only the 1,3-oxazin-4-one derivative **4e** was obtained (procedure C) (Entry e). All of the results support the formation of the 1,3-oxazin-4-one derivatives **4** from the reaction of 1,5-benzothia-

Scheme 2 Proposed mechanism for the formation of 4a,6-disubstituted 3-benzyl-4a,5-dihydro-2-phenyl-1*H*,6*H*-[1,3]oxazino[2,3-*d*][1,5]-benzothiazepin-1-ones 4 in the reaction of 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines **1** with phenylacetyl chloride



zepines with the diketene **III**. How does the reaction of a diketene with an imine occur to yield a 1,3-oxazin-4-one derivative? Farnum and his coworkers studied and found the base-catalyzed rearrangement of the β-lactone-formed dimer of arylketenes to its 3-hydroxycyclobutenone-formed dimer by enolization of the lactone.[26] Based on their results and our experiments, we propose the formation mechanism of 1,3-oxazin-4-one ring as follows (Scheme 2). When phenylacetyl chloride is added into the solution of 1,5-benzothiazepines **1** and triethylamine in anhydrous benzene, it converts to phenylketene **I** through triethylamine dehydrochlorination. The dimerization of phenylketene **I** yielding a β-lactone **III** is faster than the attack of phenylketene **I** by C=N double bond of 1,5-benzothiazepines **1**. The β-lactone-formed diketene **III** is then enolized through excess triethylamine dehydrogenation of α-hydrogen of the β-lactone to form an enolizated ketene intermediates **IV**, which undergoes a stepwise or concerted annulation with C=N double bond of 1,5-benzothiazepines **1** to form intermediate **VI**, which isomerizes and abstracts a proton from triethylamine hydrochloride to yield the 1,3-oxazin-4-one derivatives **4**. Of course, the enolized ketene intermediates **IV** could possibly abstract a proton from triethylamine hydrochloride and isomerize to produce an oxoketenes **V**, which undergoes a Diels-Alder cycloaddition with the C=N bond of 1,5-benzothiazepines **1** to yield the 1,3-oxazin-4-one derivatives **4**. Diels-Alder cycloadditions of 1,5-benzothiazepines **1** with oxoketenes have been investigated previously by us.[4,5] It is well known that an oxoketene can undergo Diels-Alder cycloaddition as a diene with C=N, C=O, and C=S double bonds.[4,5,27-31] It is really difficult to distinguish that the reaction undergoes an enolized ketene annulation, an oxokene Diels-Alder cycloaddition, or a dual pathway. In summary, 2a,4-disubstituted 2,2a,3,4-tetrahydro-2-phenyl-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-ones, 2-substituted 2,3-dihydro-3-phenylacetyl-2-styryl-benzothiazoles and 4a,6-disubstituted 3-benzyl-4a,5-dihydro-2-phenyl-1*H*,6*H*-[1,3]oxazino[2,3-*d*][1,5]benzothiazepin-1-ones were obtained from the reaction of 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines with phenyl-acetyl chloride in the presence of triethylamine in different reaction procedures. The mechanism for the formation of 4a,5-dihydro-1*H*,6*H*-[1,3]oxazino[2,3-*d*][1,5]-benzothiazepin-1-ones was discussed and suggested.

Experimental

Melting points were measured on a Yanaco MP-500 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Mercury 200 (200 MHz) or 300 (300 MHz) spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. ^{13}C NMR and DEPT spectra were recorded on the same equipment in $CDCl_3$. Mass spectra were obtained on a VG-ZAB-HS mass spectrometer. CHN analyses were conducted on an Elementar Vario EL analyzer. IR spectra were taken on a Brucker Vector 22 FT-IR spectrophotometer in KBr pellet. TLC separations were performed on silica gel G plates with petroleum ether (60—90 ℃) /ethyl acetate (8∶1, *V*/*V*), and the plates were visualized with UV light.

2,4-Disubstituted 2,3-dihydro-1,5-benzothiazepines were prepared according to literature method.[4] Benzene was refluxed over sodium and distilled prior to use. Triethylamine was refluxed over sodium hydroxide and distilled prior to use.

Although products **2c—2e** were reported previously,[14] their ^{1}H NMR data were presented in non-professional style and their melting points are obviously different from ours possibly due to different recrystallization solvents and purity. All data of these compounds are presented here again.

General procedure for the reactions of 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines 1 with phenylacetyl chloride (Procedure A)

A solution of triethylamine (152 mg, 1.5 mmol) in anhydrous benzene (4 mL) was added dropwise into a refluxing solution of 1,5-benzothiazepine **1** (1 mmol) and phenylacetyl chloride (310 mg, 2 mmol) in benzene (4 mL) under a nitrogen atmosphere for a period of 10—15 min. The resulting mixture was refluxed for 4 h. After removal of triethylamine hydrochloride through filtration, the filtrate was washed with saturated aqueous sodium bicarbonate solution (30 mL), water and saturated brine, respectively, and dried over $MgSO_4$. After removal of solvent, the residue was separated by chromatography on silica gel with a mixture of ethyl acetate and petroleum ether (60—90 ℃) (1∶15, *V*∶*V*) as the eluent to afford colorless crystals of dihydrobenzothiazole **3** (R_f approximates 0.42) and azeto[2,1-*d*][1,5]- benzothiazepin-1-one **2** (R_f approximates 0.33) after crystallization from a mixture of ethyl acetate and petroleum ether (60—90 ℃).

2,2a,3,4-Tetrahydro-4-methyl-2,2a-diphenyl-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-one (2a): Colorless crystals, yield 54%, m.p. 203—204 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.03—6.97 (m, 14H, ArH), 4.68 (s, 1H, COCH), 3.29 (d, J=13.8 Hz, 1H, C**H**H), 2.94 (dq, J=10.6, 7.2 Hz, 1H, SCH), 2.76 (dd, J=10.6, 13.8 Hz, 1H, CH**H**), 1.37 (d, J=7.2 Hz, 3H, CH_3); IR (KBr) *v*: 1751 (C=O) cm^{-1}; MS (EI) *m/z* (%): 371 (M^+, 7), 253 (M^+−PhCH=C=O, 86), 211 (100), 118 (9), 108 (22). Anal. calcd for $C_{24}H_{21}NOS$ (371.50): C 77.59, H 5.70, N 3.77; found C 77.45, H 5.52, N 3.71.

2,2a,3,4-Tetrahydro-4-methyl-2a-(4-methylphenyl)-2-phenyl-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-one (2b): Colorless crystals, yield 50%, m.p. 169—170 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.01—6.81 (m, 13H, ArH), 4.65 (s, 1H, COCH), 3.27 (d, J=13.6 Hz, 1H, C**H**H), 2.95 (dq, J=10.8, 6.8 Hz, 1H, SCH), 2.74 (dd, J=10.8, 14.0 Hz, 1H, CH**H**), 2.11 (s, 3H, Me), 1.37 (d, J=6.8 Hz, 3H, CH_3); IR (KBr) *v*: 1747 (C=O) cm^{-1}; MS (EI) *m/z* (%): 385 (M^+, 5), 267 (M^+−PhCH=C=O, 90), 225 (100), 118 (7), 108 (7), 91 (12). Anal. calcd for $C_{25}H_{23}NOS$

(385.52): C 77.89, H 6.01, N 3.63; found C 77.92, H 5.88, N 3.51.

2,2a,3,4-Tetrahydro-2,2a,4-triphenyl-1*H*-azeto-[2,1-*d*][1,5]benzothiazepin-1-one (2c): Colorless crystals, yield 29%, m.p. 160—161 ℃ (lit.[14]: 70—71 ℃); ^{1}H NMR ($CDCl_3$) δ: 8.04—6.88 (m, 19H, ArH), 4.71 (s, 1H, COCH), 3.93 (d, J=11.0 Hz, 1H, C**H**H), 3.56 (d, J=14.4 Hz, 1H, SCH), 3.27 (dd, J=11.0, 14.2 Hz, 1H, CH**H**); IR (KBr) ν: 1755 (C=O) cm^{-1}; MS (EI) *m/z* (%): 433 (M^+, 6.3), 315 (M^+−PhCH=C=O, 21), 211 (100), 118 (7), 108 (12), 91 (21). Anal. calcd for $C_{29}H_{23}NOS$ (433.57): C 80.34, H 5.35, N 3.23; found C 80.19, H 5.18, N 3.31.

4-(2-Chlorophenyl)-2,2a,3,4-tetrahydro-2,2a-diphenyl-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-one (2d): Colorless crystals, yield 32%, m.p. 185—186 ℃ (lit.[14]: 198—199 ℃); ^{1}H NMR ($CDCl_3$) δ: 8.10—6.98 (m, 18H, ArH), 4.78 (s, 1H, COCH), 4.51 (d, J=10.6 Hz, 1H, C**H**H), 3.53 (d, J=14.0 Hz, 1H, SCH), 3.32 (dd, J=10.8, 14.0 Hz, 1H, CH**H**); IR (KBr) ν: 1756 (C=O) cm^{-1}; MS (EI) *m/z* (%): 467 (M^+, 5.0), 349 (M^+−PhCH=C=O, 26), 211 (100), 118 (8), 108 (17), 91 (8). Anal. calcd for $C_{29}H_{22}ClNOS$ (468.01): C 74.42, H 4.74, N 2.99; found C 74.20, H 4.62, N 3.03.

4-(4-Chlorophenyl)-2,2a,3,4-tetrahydro-2,2a-diphenyl-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-one (2e): Colorless crystals, yield 28%, m.p. 199—200 ℃ (lit.[14]: 190—192 ℃); ^{1}H NMR ($CDCl_3$) δ: 8.10—6.94 (m, 18H, ArH), 4.77 (s, 1H, COCH), 3.96 (d, J=10.4 Hz, 1H, C**H**H), 3.58 (d, J=14.0 Hz, 1H, SCH), 3.30 (dd, J=10.8, 14.0 Hz, 1H, CH**H**); IR (KBr) ν: 1752 (C=O) cm^{-1}; MS (EI) *m/z* (%): 467 (M^+, 5.2), 349 (M^+−PhCH=C=O, 14), 211 (100), 118 (10), 108 (15), 91 (5.6). Anal. calcd for $C_{29}H_{22}ClNOS$ (468.01): C 74.42, H 4.74, N 2.99; found C 74.28, H 4.80, N 2.89.

4-(4-Bromophenyl)-2,2a,3,4-tetrahydro-2,2a-diphenyl-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-one (2f): Colorless crystals, yield 20%, m.p. 199—200 ℃; ^{1}H NMR ($CDCl_3$) δ: 8.10—6.94 (m, 18H, ArH), 4.77 (s, 1H, COCH), 3.94 (d, J=10.6 Hz, 1H, C**H**H), 3.58 (d, J=14.0 Hz, 1H, SCH), 3.29 (dd, J=11.0, 14.4 Hz, 1H, CH**H**); IR (KBr) ν: 1753 (C=O) cm^{-1}; MS (EI) *m/z* (%): 513 (M^++2, 3.0), 511 (M^+, 2.8), 393 (M^+−PhCH=C=O, 10), 211 (100), 118 (7), 108 (17). Anal. calcd for $C_{29}H_{22}BrNOS$ (512.46): C 67.97, H 4.33, N 2.73; found C 68.02, H 4.30, N 2.69.

2a-(4-Chlorophenyl)-2,2a,3,4-tetrahydro-2,4-diphenyl-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-one (2g): Colorless crystals, yield 6%, m.p. 150—151 ℃; ^{1}H NMR ($CDCl_3$) δ: 7.53—6.33 (m, 18H, ArH), 4.79 (s, 1H, COCH), 3.82 (d, J=2.8 Hz, 2H, CH_2), 3.68 (t, J=2.8 Hz, 1H, SCH); IR (KBr) ν: 1752 (C=O) cm^{-1}; MS (EI) *m/z* (%): 467 (M^+, 6), 376 (M^+−PhH, 6), 372 (2), 349 (M^+−PhCH=C=O, 19), 316 (10), 272 (3), 257 (8), 245 (100), 225 (14), 210 (11), 189 (4), 178 (4), 152 (7), 136 (8), 118 (31), 108 (35), 91 (43). Anal. calcd for $C_{29}H_{22}ClNOS$ (468.01): C 74.42, H 4.74, N 2.99; found C 74.31, H 4.78, N 3.05.

2-(4-Chlorostyryl)-2,3-dihydro-2-phenyl-3-phenylacetyl-benzothiazole (3e): Colorless crystals, yield 5%, m.p. 149—150 ℃; ^{1}H NMR ($CDCl_3$) δ: 7.78—7.07 (m, 18H, ArH), 6.92 (d, J=15.4 Hz, 1H, CH=), 6.53(d, J=15.8 Hz, 1H, CH=), 3.66 (d, J=15.0 Hz, 1H, C**H**H), 3.41 (d, J=15.0 Hz, 1H, CH**H**); IR (KBr) ν: 1678 (C=O) cm^{-1}; MS (EI) *m/z* (%): 467 (M^+, 23), 376 (22), 349 (47), 348 (35), 316 (24), 272 (50), 236 (15), 223 (60), 212 (74), 136 (22), 109 (23), 91 (100). Anal. calcd for $C_{29}H_{22}ClNOS$ (468.01): C 74.42, H 4.74, N 2.99; found C 74.28, H 4.59, N 3.11.

2-(4-Bromostyryl)-2,3-dihydro-2-phenyl-3-phenylacetyl-benzothiazole (3f): Colorless crystals, yield 6%, m.p. 147—148 ℃; ^{1}H NMR ($CDCl_3$) δ: 7.78—7.07 (m, 18H, ArH), 6.93 (d, J=15.8 Hz, 1H, CH=), 6.51 (d, J=15.8 Hz, 1H, CH=), 3.65 (d, J=15.0 Hz, 1H, C**H**H), 3.41 (d, J=15.4 Hz, 1H, CH**H**); IR (KBr) ν: 1680 (C=O) cm^{-1}; MS (EI) *m/z* (%): 513 (M^++2, 1), 511 (M^+, 1), 393 (5), 360 (17), 316 (3), 280 (8), 236 (3), 224 (11), 211 (100), 136 (4), 108 (21), 91 (34). Anal. calcd for $C_{29}H_{22}BrNOS$ (512.46): C 67.97, H 4.33, N 2.73; found C 68.02, H 4.09, N 2.88.

General procedure for the reaction of 2,4-disub- stituted 2,3-dihydro-1,5-benzothiazepines 1 with phenylacetyl chloride (Procedure B)

A solution of phenylacetyl chloride (340 mg, 2.2 mmol) in anhydrous benzene (4 mL) was added dropwise into a refluxing solution of 1,5-benzothiazepine **1** (1 mmol) and triethylamine (253 mg, 2.5 mmol) in benzene (4 mL) under a nitrogen atmosphere during 10—15 min. The resulting mixture was refluxed for 4 h. After the same workup as described in the procedure A, the residue was separated by chromatography on silica gel with a mixture of ethyl acetate and petroleum ether (60—90 ℃) (1∶20 to 1∶15, V∶V) as the eluent to afford colorless crystals of azeto[2,1-*d*][1,5]benzothiazepin-1-one **2** (R_f approximates 0.33) and [1,3]oxazino-[2,3-*d*]-[1,5]benzothiazepin-1-one **4** (R_f approximates 0.20) after crystallization from a mixture of ethyl acetate and petroleum ether (60—90 ℃).

3-Benzyl-4a,5-dihydro-6-methyl-2,4a-diphenyl-1*H*,6*H*-[1,3]oxazino[2,3-*d*][1,5]benzothiazepin-1-one (4a): Colorless crystals, yield 17%, m.p. 159—160 ℃; ^{1}H NMR ($CDCl_3$) δ: 7.83—6.98 (m, 19H, ArH), 3.61 (d, J=15.0 Hz, 1H, C**H**HPh), 3.50, (d, J=15.0 Hz, 1H, CH**H**Ph), 3.46 (ddq, J=4.4, 11.6, 6.8 Hz, 1H, SCH), 2.35 (dd, J=4.4, 15.6 Hz, 1H, C**H**H), 1.57 (dd, J=15.8, 11.6 Hz, 1H, CH**H**), 1.23 (d, J=6.8 Hz, 3H, CH_3); IR (KBr) ν: 1657 (C=O) cm^{-1}; MS (FAB) *m/z* (%): 490 ([M+H]$^+$, 30), 254 (25), 237 (6), 212 (11). Anal. calcd for $C_{32}H_{27}NO_2S$ (489.63): C 78.50, H 5.56, N 2.86; found C 78.30, H 5.49, N 2.90.

3-Benzyl-4a,5-dihydro-6-methyl-4a-(4-methylphenyl)-2-phenyl-1*H*,6*H*-[1,3]oxazino[2,3-*d*][1,5]benzothiazepin-1-one (4b): Colorless crystals, yield 21%, m.p. 144—145 ℃; ^{1}H NMR ($CDCl_3$) δ: 7.80—7.01 (m, 18H, ArH), 3.61 (d, J=14.8 Hz, 1H, C**H**HPh), 3.49, (d, J=14.8 Hz, 1H, CH**H**Ph), 3.45 (ddq, J=4.4, 11.2, 6.8 Hz, 1H, SCH), 2.34 (dd, J=16.2, 4.4 Hz, 1H, C**H**H),

1.54 (dd, J=15.8, 11.2 Hz, 1H, CH**H**), 2.33 (s, 3H, Me), 1.22 (d, J=6.8 Hz, 3H, CH_3); IR (KBr) ν: 1660 (C=O) cm^{-1}; MS (FAB) *m/z* (%): 504 ($[M+H]^+$, 2.5), 268 (9), 237 (3), 226 (5). Anal. calcd for $C_{33}H_{29}NO_2S$ (503.65): C 78.70, H 5.80, N 2.78; found C 78.75, H 5.69, N 2.59.

3-Benzyl-4a,5-dihydro-2,4a,6-triphenyl-1*H*,6*H*-[1,3]oxazino[2,3-*d*][1,5]benzothiazepin-1-one (4c): Colorless crystals, yield 15%, m.p. 176—177 ℃; ^{1}H NMR ($CDCl_3$) δ: 7.90—7.03 (m, 24H, ArH), 4.48 (dd, J=4.0, 11.8 Hz, 1H, SCH), 3.68 (d, J=15.0 Hz, 1H, C**H**HPh), 3.55 (d, J=15.0 Hz, 1H, CH**H**Ph), 2.56 (dd, J=15.8, 4.0 Hz, 1H, C**H**H), 2.19 (dd, J=12.4, 16.0 Hz, 1H, CH**H**); IR (KBr) ν: 1656 (C=O) cm^{-1}; MS (FAB) *m/z* (%): 552 ($[M+H]^+$, 13), 316 (4), 237 (2), 212 (13). Anal. calcd for $C_{37}H_{29}NO_2S$ (551.70): C 80.55, H 5.30, N 2.54; found C 80.33, H 5.49, N 2.43.

3-Benzyl-6-(2-chlorophenyl)-4a,5-dihydro-2,4a-diphenyl-1*H*,6*H*-[1,3]oxazino[2,3-*d*][1,5]benzothiazepin-1-one (4d): Colorless crystals, yield 12%, m.p. 166—167 ℃; ^{1}H NMR ($CDCl_3$) δ: 7.92—7.04 (m, 23H, ArH), 5.21 (dd, J=12.2, 4.0 Hz, 1H, SCH), 3.68 (d, J=14.8 Hz, 1H, C**H**HPh), 3.53 (d, J=15.0 Hz, 1H, CH**H**Ph), 2.56 (dd, J=15.8, 4.0 Hz, 1H, C**H**H), 2.06 (dd, J=12.0, 15.6 Hz, 1H, CH**H**); IR (KBr) ν: 1661 (C=O) cm^{-1}; MS (FAB) *m/z* (%): 586 ($[M+H]^+$, 9), 350 (3), 237 (3), 212 (9). Anal. calcd for $C_{37}H_{28}ClNO_2S$ (586.14): C 75.82, H 4.81, N 2.39; found C 75.60, H 4.90, N 2.21.

3-Benzyl-6-(4-chlorophenyl)-4a,5-dihydro-2,4a-diphenyl-1*H*,6*H*-[1,3]oxazino[2,3-*d*][1,5]benzothiazepin-1-one (4e): Colorless crystals, yield 7%, m.p. 175—176 ℃; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.91—6.99 (m, 23H, ArH), 4.43 (dd, J=4.2, 12.0 Hz, 1H, SCH), 3.67 (d, J=15.0 Hz, 1H, C**H**HPh), 3.55 (d, J=15.0 Hz, 1H, CH**H**Ph), 2.53 (dd, J=15.8, 4.2 Hz, 1H, C**H**H), 2.14 (dd, J=11.6, 15.8 Hz, 1H, CH**H**); ^{13}C NMR ($CDCl_3$) δ: 37.96, 41.59, 45.10, 91.91, 114.92, 125.68, 126.91, 127.62, 128.05, 128.34, 128.55, 128.59, 128.75, 128.81, 128.87, 129.33, 131.09, 132.98, 133.03, 135.25, 135.67, 141.16, 142.77, 143.40, 161.05, 161.98; DEPT (aliphatic part) δ: 45.03 (CH_2), 41.53 (CH), 37.90 (CH_2); IR (KBr) ν: 1657 (C=O) cm^{-1}; MS (FAB) *m/z* (%): 586 ($[M+H]^+$, 16), 350 (7), 237 (18), 212 (84). Anal. calcd for $C_{37}H_{28}ClNO_2S$ (586.14): C 75.82, H 4.81, N 2.39; found C 75.77, H 4.90, N 2.41.

3-Benzyl-6-(4-bromophenyl)-4a,5-dihydro-2,4a-diphenyl-1*H*,6*H*-[1,3]oxazino[2,3-*d*][1,5]benzothiazepin-1-one (4f): Colorless crystals, yield 12%, m.p. 172—173 ℃; ^{1}H NMR ($CDCl_3$) δ: 7.91—6.93 (m, 23H, ArH), 4.42 (dd, J=4.0, 12.0 Hz, 1H, SCH), 3.67 (d, J=15.0 Hz, 1H, C**H**HPh), 3.55 (d, J=15.0 Hz, 1H, CH**H**Ph), 2.53 (dd, J=4.2, 16.2 Hz, 1H, C**H**H), 2.14 (dd, J=12.0, 16.0 Hz, 1H, CH**H**); IR (KBr) ν: 1657 (C=O) cm^{-1}; MS (FAB) *m/z* (%): 632 (M^++2+H, 7), 630 ($[M+H]^+$, 6.5), 394 (4.5), 317 (6), 212 (58). Anal. calcd for $C_{37}H_{28}BrNO_2S$ (630.59): C 70.47, H 4.48, N 2.22; found C 70.59, H 4.29, N 2.38.

3-Benzyl-4a-(4-chlorophenyl)-4a,5-dihydro-2,6-diphenyl-1*H*,6*H*-[1,3]oxazino[2,3-*d*][1,5]benzothiazepin-1-one (4g): Colorless crystals, yield 8%, m.p. 174—175 ℃; ^{1}H NMR ($CDCl_3$) δ: 7.84—7.07 (m, 23H, ArH), 4.50 (dd, J=4.2, 12.0 Hz, 1H, SCH), 3.66 (d, J=15.4 Hz, 1H, C**H**HPh), 3.57 (d, J=15.0 Hz, 1H, CH**H**Ph), 2.50 (dd, J=4.2, 15.8 Hz, 1H, C**H**H), 2.17 (dd, J=12.0, 15.8 Hz, 1H, CH**H**); IR (KBr) ν: 1657 (C=O) cm^{-1}; MS (FAB) *m/z* (%): 586 ($[M+H]^+$, 8), 350 (2), 237 (5), 246 (9). Anal. calcd for $C_{37}H_{28}ClNO_2S$ (586.14): C 75.82, H 4.81, N 2.39; found C 75.58, H 4.66, N 2.47.

Reaction of 2-(4-chlorophenyl)-2,3-dihydro-4-phenyl-1,5-benzothiazepine 1e with dimeric phenylketene (Procedure C)

A solution of 1,5-benzothiazepine (1 mmol) in anhydrous benzene (4 mL) was added dropwise into a refluxing solution of phenylacetyl chloride (340 mg, 2.2 mmol) and triethylamine (253 mg, 2.5 mmol) in benzene (4 mL) under a nitrogen atmosphere for a period of 10—15 min. The resulting mixture was refluxed for 4 h. After the same workup as described in the procedure B, colorless crystals of [1,3]oxazino[2,3-*d*][1,5]benzothiazepin-1-one **4e** was obtained in the yield of 7%.

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