Syntheses of 1,4-Benzothiazepines and 1,4-Benzoxazepines via Cyclizations of 1-[2-Arylthio(oxy)ethyl]-5-benzotriazolyl-2-pyrrolidinones and 3-Benzotriazolyl-2-[2-arylthio(oxy)ethyl]-1-isoindolinones

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1-[2-Arylthio(oxy)ethyl]-5-benzotriazolyl-2-pyrrolidinones **6a**−**e**, **12** and 3-benzotriazolyl-2-[2-arylthio(oxy)ethyl]-1-isoindolinones **9a**−**f**, **14** are readily available from reactions of benzotriazole (**4**), 2-(arylsulfanyl)ethylamines **3**, or 2-phenoxyethylamine (**11**) with 2,5-dimethoxy-2,5-dihydrofuran (**5**) or 2-formylbenzoic acid (**8**). Lewis acid mediated cyclizations of **6** and **9** produced novel 1,4-benzothiazepines **7a**−**e** and **10a**−**f**, respectively. Cyclizations of **12** and **14** gave 1,4-benzoxazepines **13** and **15**, respectively.

Introduction

Seven-membered ring systems containing two heteroatoms, e.g., benzothiazepines (N and S) and benzoxazepines (N and O), are of considerable interest. Benzothiazepines are active constituents of a series of new potent bradykinin agonists.[1] Some of these compounds have also shown activity as endogenous natriuretic factors,[2] enzyme inhibitors,[3] HIV-1 integrase inhibitors,[4] antitumor antibiotics,[5] muscle relaxants, anticonvulsants,[6] sedatives, hypnotics,[7] and antipsychotics.[8] Campiani and co-workers developed a series of novel and selective calcium entry blockers based on pyrrolobenzothiazepines.[9] Benzoxazepines also show some pharmacological properties, e.g., antipsychotic,[8b] and central nervous system activity.[10]

Known syntheses of benzoxazepines include (i) condensations of 2-aryloxyethylamines with 2-formylbenzoic acid to form aminophthalides, followed by cyclization to the corresponding 1,4-benzoxazepines in 18−70% yields;[11] (ii) rearrangement of methyl 2-(8-methoxy-2,3-dihydro-1,4-benzoxazepin-5-yl)benzoate using Bischler−Napieralski conditions;[12] and (iii) scandium or copper triflate catalyzed acylaminoalkylation of α-methoxyisoindolones with the formation of 1,4-benzoxazepines in moderate yields.[13]

Several methods have previously been reported for the preparation of benzothiazepines[14] and their condensed analogues.[9] However, the tricyclic ring system of compounds **7** is recorded in just a single paper: starting from the corresponding *N*-(bromoethyl)pyrrolidinone, 1,5,6,-11b-tetrahydropyrrolo[1,2-*d*][1,4]benzothiazepin-3(2*H*)-one (**7a**) and 10-methoxy-1,5,6,11b-tetrahydro-pyrrolo-[1,2-*d*][1,4]benzoxazepin-3(2*H*)-one were obtained in 44% and 10% overall yields, respectively.[15] There is no report of the synthesis of 6,7-dihydroisoindolo[2,1-*d*][1,4]benzothiazepin-9(13b*H*)-ones **10**. Versatile alternative routes to **7**, **10**, **13**, and **15** are desirable. We now report herein an efficient approach to the syntheses of related 1,4-benzothiazepines and 1,4-benzoxazepines using the benzotriazole methodology.

Results and Discussion

Syntheses of 1,5,6,11b-Tetrahydropyrrolo[1,2-*d*]-[1,4]benzothiazepin-3(2*H*)-ones 7a−**e.** Treatment of substituted thiophenols **1a**−**f** with 2-chloroethylamine hydrochloride (**2**) and excess potassium carbonate in

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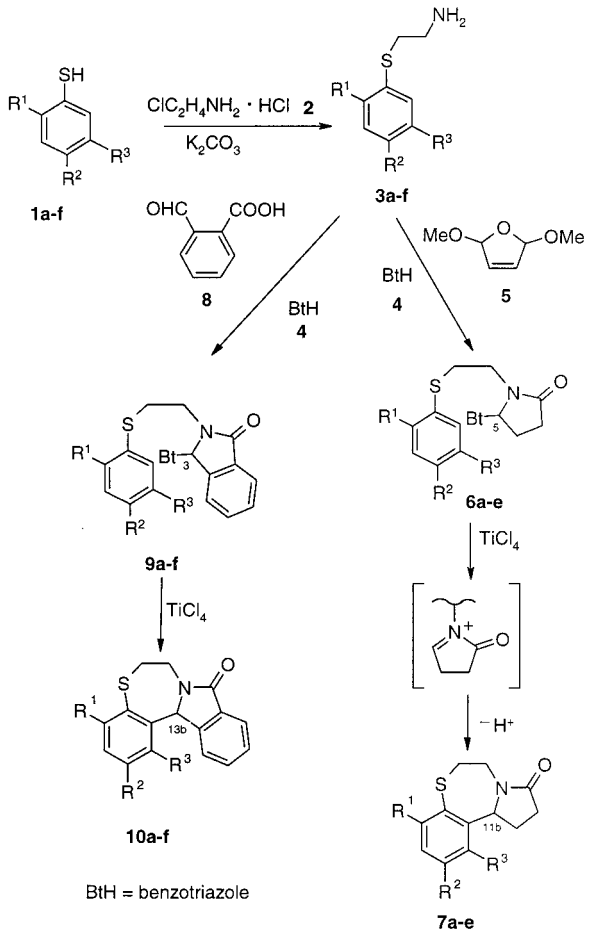
Scheme 1[a]



[a] For designation of substitutents R^1, R^2, and R^3 in series **a**−**f**, see Table 1.

Table 1. Preparation of Compounds 3, 6, 7, 9, and 10

	substitutents			isolated yields				
entry	R^1	R^2	R^3	**3**	**6**[a]	**7**[b]	**9**[a]	**10**[c]
a	H	H	H	68	58	81	84	86
b	CH_3	H	H	62	54	80	86	91
c	H	Cl	H	72	56	67	92	94
d	H	CH_3	H	63	47	84	81	96
e	2-naphthyl			71	61	96	84	78
f	CH_3	H	CH_3	74	*d*	*d*	82	81

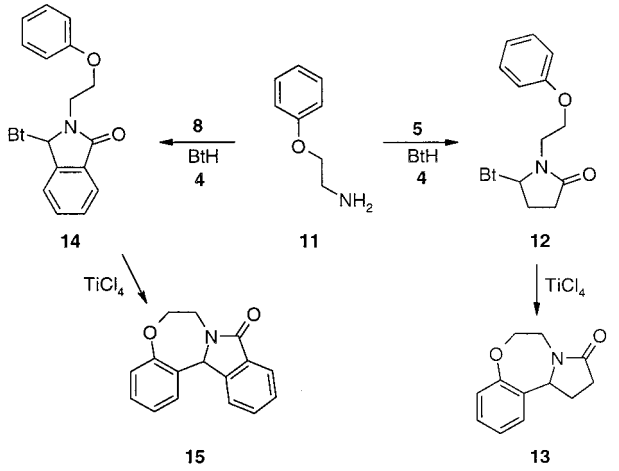
[a] Isolated yields based on **3**. [b] Isolated yields based on **6**. [c] Isolated yields based on **9**. [d] The reactions have not been done.

methylene chloride gave 2-(arylsulfanyl)ethylamines **3a**−**f** in 62−74% yields (Scheme 1, Table 1).

The crude amines **3a**−**e** were reacted with benzotriazole (**4**) and 2,5-dimethoxy-2,5-dihydrofuran (**5**) in acetic acid to afford the corresponding 5-benzotriazolyl-1-[2-(arylsulfanyl)ethyl]-2-pyrrolidinones **6a**−**e** in moderate yields. Crude **6a**−**e** were obtained as mixtures of Bt^1 (benzotriazol-1-yl) and Bt^2 (benzotriazol-2-yl) isomers in which the Bt^1 isomers predominated. We reported the ^1H and ^{13}C NMR data of the major Bt^1 isomers, and the ratio of Bt^1 and Bt^2 isomers as determined by ^1H NMR spectroscopy.

According to our previous work,[16] both Bt^1 and Bt^2 are good leaving groups in the presence of a Lewis acid. Also, removal of the benzotriazolyl groups from Bt^1 and Bt^2 isomers results in the same iminium cation. Therefore, compounds **6a**−**e** were used as mixtures of the two isomers for the subsequent reactions. Crude **6a**−**e** were stirred for 48 h at room temperature with 4 equiv of $TiCl_4$ to give 1,5,6,11b-tetrahydropyrrolo[1,2-*d*][1,4]benzothiazepin-3(2*H*)-ones **7a**−**e** in 67−96% yields (Scheme 1, Table 1). Compounds **6** and **7** were characterized by their ^1H and ^{13}C NMR spectra and by microanalysis. After cyclization, the H(5) signal in compounds **6** (shown as a doublet of doublets at 6.52−6.57 ppm) is shifted upfield to 5.19−5.77 ppm H(11b) in **7** (as a doublet of doublets or a multiplet). The correct numbers of quaternary carbons determined by APT spectra for **7a**−**e** further confirmed the cyclization of **6**.

Scheme 2



Syntheses of 6,7-Dihydroisoindolo[2,1-*d*][1,4]benzothiazepin-9(13b*H*)-ones 10a−f. Reactions of 2-(arylsulfanyl)ethylamines **3a**−**f**, benzotriazole (**4**), and 2-formylbenzoic acid (**8**) were carried out in refluxing toluene with *p*-toluenesulfonic acid as a catalyst, using a Dean−Stark apparatus to remove the water formed. After 24 h, the corresponding 3-(1*H*-1,2,3-benzotriazol-1-yl)-2-[2-(arylsulfanyl)ethyl]-1-isoindolinones **9a**−**f** were obtained in 81−92% yields. Compounds **9** were stirred for 48 h at room temperature with 2 equiv of $TiCl_4$ to give 6,7-dihydroisoindolo[2,1-*d*][1,4]benzothiazepin-9(13b*H*)-ones **10a**−**f** in 78−96% yields (Scheme 1, Table 1). For **10c** and **10f**, pure products were obtained after washing with 2 M NaOH without the need for column chromatography. The proton NMR spectra show that H(3) in **9a**−**f** always appears as a singlet at 7.46−7.52 ppm, overlapping with aromatic hydrogens. After $TiCl_4$-mediated cyclization, this proton is shifted upfield to 6.16−6.80 ppm as a well-defined singlet [H(13b) in **10a**−**f**].

Synthesis of 1,5,6,11b-Tetrahydropyrrolo[1,2-*d*][1,4]benzoxazepin-3(2*H*)-one (13) and 6,7-Dihydroisoindolo[2,1-*d*][1,4]benzoxazepin-9(13b*H*)-one (15). 1,5,6,11b-Tetrahydropyrrolo[1,2-*d*][1,4]benzoxazepin-3(2*H*)-one (**13**) and 6,7-dihydroisoindolo[2,1-*d*][1,4]benzoxazepin-9(13b*H*)-one (**15**) were synthesized in 72% and 89% yields, respectively, via a similar procedure to that described above using 2-phenoxyethylamine (**11**) instead of compounds **3** as the starting material (Scheme 2). In the case of **15**, the pure product was obtained directly after washing benzotriazole away with 2 M NaOH without additional purification by column chromatography.

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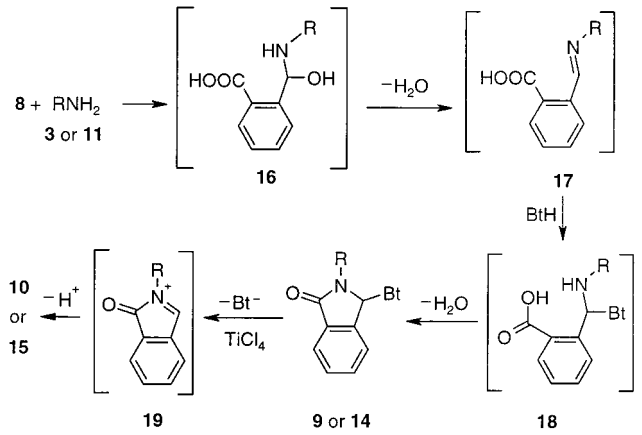
Scheme 3



The reaction mechanism proposed for the formation of **6a**−**e** and **12** is similar to that discussed in our previous report.[17] The formation of compounds **9a**−**f** and **14** may involve the nucleophilic attack of 2-(arylsulfanyl)ethylamines **3** or 2-phenoxyethylamine (**11**) at the aldehyde carbonyl group, which is the most electrophilic center in 2-formylbenzoic acid (**8**), to form α-carbinolamines **16**, which then eliminate 1 equiv of H_2O and are converted into 2-iminomethylbenzoic acids **17**.[11a,18] Next a benzotriazole molecule attacks the double bond of these imines **17** to afford the intermediates **18**, which undergo dehydrative cyclization to generate **9** or **14** in the presence of an acid (Scheme 3). With the help of a Lewis acid, compounds **9** or **14** formed eliminate the benzotriazole anion to give transient iminium cations **19**, which finally cyclize with the loss of one proton to furnish products **10a**−**f** or **15**.

In summary, we have developed efficient and versatile methods for the syntheses of 1,5,6,11b-tetrahydropyrrolo-[1,2-*d*][1,4]benzothiazepin-3(2*H*)-ones **7a**−**e**, 6,7-dihydroisoindolo[2,1-*d*][1,4]benzothiazepin-9(13b*H*)-ones **10a**−**f**, 1,5,6,11b-tetrahydropyrrolo[1,2-*d*][1,4]benzoxazepin-3(2*H*)-one (**13**), and 6,7-dihydroisoindolo[2,1-*d*][1,4]benzoxazepin-9(13b*H*)-one (**15**) from easily available starting materials.

Experimental Section

THF was distilled from sodium/benzophenone prior to use. Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra (300 and 75 MHz, respectively) were recorded on a Gemini 300 NMR spectrometer in $CDCl_3$ (with TMS for ^{1}H and chloroform-*d* for ^{13}C as the internal reference). Elemental analyses were performed on a Carlo Erba-1106 instrument. HRMS were measured on an AEI-30 mass spectrometer. Column chromatography was performed on silica gel. All of the reactions were carried out under N_2.

General Procedure for the Preparation of 2-(Arylsulfanyl)ethylamines 3a−f. A substituted thiophenol (**1**, 10 mmol), 2-chloroethylamine hydrochloride (**2**, 1.51 g, 13 mmol), and potassium carbonate (4.15 g, 30 mmol) were stirred in methylene chloride (40 mL) at room temperature for 48 h. Then the solution was washed with water and dried over Na_2SO_4. After removal of the solvent, crude 2-(arylsulfanyl)-ethylamines **3a**−**f** were obtained and used directly for the subsequent reactions (Scheme 1, Table 1).

General Procedure for the Preparation of 5-Benzotriazolyl-1-[2-(arylsulfanyl)ethyl]-2-pyrrolidinones 6a−e. 2,5-Dimethoxy-2,5-dihydrofuran (**5,** 0.57 g, 4.4 mmol), a crude 2-(arylsulfanyl)-1-ethanamine **3a**−**e** (4 mmol), and benzotriazole (0.96 g, 8 mmol) were dissolved in acetic acid (30 mL). The solution was stirred at 60−75 °C for 48 h. After the mixture cooled, 2 M NaOH was added. The mixture was then extracted three times with methylene chloride, and the organic fractions were dried over Na_2SO_4 and evaporated under reduced pressure. The black residue was purified by column chromatography (hexanes/EtOAc = 1/1) to give compounds **6a**−**e** as yellow to brown oils.

5-Benzotriazolyl-1-[2-(phenylthio)ethyl]-2-pyrrolidinone (6a): mixture of Bt^1 and Bt^2 isomers in 8/1 ratio; yellow oil; yield, 58%; ^{1}H NMR δ 8.10 (d, *J* = 7.9 Hz, 1H), 7.46−7.38 (m, 2H), 7.30−7.21 (m, 6H), 6.56 (dd, *J* = 7.6, 2.3 Hz, 1H), 3.79−3.70 (m, 1H), 3.24−3.14 (m, 1H), 2.97−2.81 (m, 3H), 2.64−2.50 (m, 2H), 2.45−2.36 (m, 1H); ^{13}C NMR δ 175.2, 146.8, 135.2, 131.9, 129.6, 129.4, 128.8, 126.9, 125.0, 121.0, 109.3, 73.6, 41.0, 31.2, 29.7, 25.9. Anal. Calcd for $C_{18}H_{18}N_4OS$: C, 63.88; H, 5.36; Found: C, 63.81; H, 5.65.

General Procedure for the Preparation of 1,5,6,11b-Tetrahydropyrrolo[1,2-*d*][1,4]benzothiazepin-3(2*H*)-ones 7a−e. To a solution of a 5-benzotriazolyl-1-[2-(arylsulfanyl)ethyl]-2-pyrrolidinones **6a**−**e** (2 mmol) in dry CH_2Cl_2 (20 mL) was added $TiCl_4$ (8 mmol, 4.7 mL, 1.71 M in CH_2Cl_2), and the mixture was stirred for 48 h. Then the solution was washed with 2 M NaOH and brine, the organic fractions were dried over Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by column chromatography (hexanes/EtOAc = 1/1−1/2) to give **7a**−**e**.

1,5,6,11b-Tetrahydropyrrolo[1,2-*d*][1,4]benzothiazepin-3(2*H*)-one (7a):[13] brown oil; yield, 81%; ^{1}H NMR δ 7.59 (d, *J* = 7.6 Hz, 1H), 7.37−7.32 (m, 2H), 7.27−7.21 (m, 1H), 5.15 (dd, *J* = 7.0, 2.9 Hz, 1H), 4.27 (dt, *J* = 14.0, 4.1 Hz, 1H), 3.35 (ddd, *J* = 13.7, 10.2, 3.5 Hz, 1H), 2.95 (dt, *J* = 13.7, 4.1 Hz, 1H), 2.79 (ddd, *J* = 14.0, 10.2, 4.1 Hz, 1H), 2.65−2.37 (m, 4H); ^{13}C NMR δ 174.3, 142.0, 135.0, 134.9, 128.6, 128.2, 126.5, 61.6, 42.5, 32.8, 30.5, 25.7.

8-Methyl-1,5,6,11b-tetrahydropyrrolo[1,2-*d*][1,4]-benzothiazepin-3(2*H*)-one (7b): pale yellow prisms (from CH_2Cl_2); mp 112−113 °C; yield, 80%; ^{1}H NMR δ 7.22−7.17 (m, 3H), 5.23−5.19 (m, 1H), 4.18−4.12 (m, 1H), 3.41−3.32 (m, 1H), 2.96−2.89 (m, 1H), 2.74−2.35 (m, 5H), 2.50 (s, 3H); ^{13}C NMR δ 174.2, 142.2, 141.8, 134.8, 129.8, 127.8, 124.1, 61.5, 42.0, 32.5, 30.6, 26.0, 22.0. Anal. Calcd for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00. Found: C, 66.89; H, 6.34; N, 6.17.

10-Chloro-1,5,6,11b-tetrahydropyrrolo[1,2-*d*][1,4]-benzothiazepin-3(2*H*)-one (7c): black oil; yield, 67%; ^{1}H NMR δ 7.51 (d, *J* = 8.2 Hz, 1H), 7.29 (s, 1H), 7.26−7.20 (m, 1H), 5.09 (dd, *J* = 7.0, 3.8 Hz, 1H), 4.27 (dt, *J* = 14.0, 4.1 Hz, 1H), 3.33 (ddd, *J* = 13.7, 10.2, 3.5 Hz, 1H), 2.93 (dt, *J* = 13.7, 3.8 Hz, 1H), 2.77 (ddd, *J* = 14.0, 10.2, 4.1 Hz, 1H), 2.63−2.38 (m, 4H); ^{13}C NMR δ 174.2, 143.7, 136.0, 134.5, 133.4, 128.1, 126.8, 61.3, 42.5, 32.8, 30.2, 25.6; HRMS calcd for $C_{12}H_{13}$-ClNOS 254.0406 (M + 1), found 254.0405; GC purity (after column) 95%.

10-Methyl-1,5,6,11b-tetrahydropyrrolo[1,2-*d*][1,4]-benzothiazepin-3(2*H*)-one (7d): brown oil; yield, 84%; ^{1}H NMR δ 7.46 (d, *J* = 7.6 Hz, 1H), 7.11 (s, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 5.12−5.09 (m, 1H), 4.24 (dt, *J* = 14.0, 4.4 Hz, 1H), 3.32 (ddd, *J* = 14.0, 9.2, 3.8 Hz, 1H), 2.91 (dt, *J* = 13.4, 4.0 Hz, 1H), 2.77 (ddd, *J* = 14.0, 9.9, 4.1 Hz, 1H), 2.64−2.40 (m, 4H), 2.37 (s, 3H); ^{13}C NMR δ 174.4, 141.8, 138.7, 134.9, 131.2, 128.9, 127.5, 61.9, 42.4, 32.9, 30.7, 25.9, 21.4; HRMS calcd for $C_{13}H_{16}NOS$ 234.0953 (M + 1), found 234.0952; GC purity (after column) 97%.

1,2,10,11-Tetrahydronaphtho[1,2-*f*]pyrrolo[1,2-*d*][1,4]-thiazepin-12(9c*H*)-one (7e): brown prisms (from CH_2Cl_2/Et_2O); mp 122−123 °C; yield, 96%; ^{1}H NMR δ 7.94 (d, *J* = 8.2 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.58−7.48 (m, 3H), 5.77 (t, *J* = 7.0 Hz, 1H), 4.37−4.28 (m, 1H), 3.28−3.04 (m, 3H), 2.75−2.66 (m, 1H), 2.60−2.55 (m, 2H), 2.29−2.22 (m, 1H); ^{13}C NMR δ 175.4, 137.3, 133.6, 133.0, 131.4, 130.0, 129.0, 128.0, 126.9, 126.0, 122.6, 62.1, 39.2, 33.8, 30.3,

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29.0. Anal. Calcd for $C_{16}H_{15}NOS$: C, 71.34; H, 5.61; N, 5.20. Found: C, 71.02; H, 5.79; N, 5.23.

General Procedure for the Preparation of 3-(1*H*-1,2,3-Benzotriazol-1-yl)-2-[2-(arylsulfanyl)ethyl]-1-isoindolinones 9a−f. 2-Formylbenzoic acid (**8**, 2.65 g, 18 mmol), a 2-(arylsulfanyl)-1-ethanamine **3a**−**f** (18 mmol), benzotriazole (**4**, 2.38 g, 20 mmol), and *p*-toluenesulfonic acid monohydrate (0.36 g, 2 mmol) were dissolved in toluene (50 mL) and heated under reflux using a Dean Stark apparatus. After 24 h, the reaction mixture was cooled. The solvent was evaporated, and CH_2Cl_2 was added to dissolve the residue. Then the solution was washed with 2 M NaOH three times. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. After removal of solvent in vacuo, the residue was purified by column chromatography (hexanes/EtOAc = 6/1−3/1) to give **9a**−**f**.

3-(1*H*-1,2,3-Benzotriazol-1-yl)-2-[2-(phenylsulfanyl)-ethyl]-1-isoindolinone (9a): yellow needles (from CH_2Cl_2/Et_2O); mp 100−101 °C; yield, 84%; ^{1}H NMR δ 8.06−8.01 (m, 2H), 7.65 (t, J = 7.3 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.52 (s, 1H), 7.37−7.16 (m, 7H), 7.08 (t, J = 7.0 Hz, 1H), 6.45 (d, J = 8.2 Hz, 1H), 3.95−3.86 (m, 1H), 3.23−3.10 (m, 2H), 2.94−2.85 (m, 1H); ^{13}C NMR δ 166.8, 146.6, 138.7, 134.2, 132.7, 131.2, 130.5, 130.2, 128.8, 128.6, 127.9, 126.0, 124.3, 123.7, 123.2, 120.0, 109.6, 72.6, 39.5, 30.9. Anal. Calcd for $C_{22}H_{18}N_4OS$: C, 68.37; H, 4.69; N, 14.50. Found: C, 68.05; H, 4.72; N, 14.49.

General Procedure for the Synthesis of 6,7-Dihydroisoindolo[2,1-*d*][1,4]benzothiazepin-9(13b*H*)-ones 10a−f. To a solution of **9a**−**f** (1.5 mmol) in CH_2Cl_2 (15 mL) was added $TiCl_4$ (3.0 mmol, 1.7 mL, 1.71 M in CH_2Cl_2), and the reaction mixture was stirred at room temperature for 48 h. The yellow solution was quenched with water and washed twice with 2 M NaOH and brine. The organic phase was dried over Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by column chromatography (hexanes/EtOAc = 3/1) to give the product **10a**,**b**,**e**. In case of **10c**,**d**,**f**, solids, formed after evaporation, were pure enough for NMR analysis. These substances were additionally recrystallized for microanalysis purposes.

6,7-Dihydroisoindolo[2,1-*d*][1,4]benzothiazepin-9(13b*H*)-one (10a): colorless plates (from CH_2Cl_2/hexanes); mp 147−148 °C; yield, 86%, ^{1}H NMR δ 7.93 (d, J = 7.2 Hz, 1H), 7.67−7.61 (m, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.30−7.17 (m, 2H), 6.92 (d, J = 7.5 Hz, 1H), 6.21 (s, 1H), 4.15−3.88 (m, 2H), 3.20−2.95 (m, 2H); ^{13}C NMR δ 168.7, 143.3, 139.1, 136.0, 134.0, 132.7, 131.4, 128.7, 128.6, 128.5, 127.4, 124.3, 124.1, 63.5, 42.6, 32.6. Anal. Calcd for $C_{16}H_{13}NOS$: C, 71.88; H, 4.90; N, 5.24. Found: C, 71.76; H, 4.89; N, 5.20.

4-Methyl-6,7-dihydroisoindolo[2,1-*d*][1,4]benzothiazepin-9(13b*H*)-one (10b): brown prisms (from CH_2Cl_2); mp 116−118 °C; yield, 91%; ^{1}H NMR δ 7.92 (d, J = 7.6 Hz, 1H), 7.61 (t, J = 7.3 Hz, 1H), 7.53 (t, J = 7.3 Hz, 1H), 7.43 (d, J = 7.3 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.06 (t, J = 8.6 Hz, 1H), 6.71 (d, J = 7.6 Hz, 1H), 6.30 (s, 1H), 3.95−3.93 (m, 2H), 3.19−3.11 (m, 1H), 3.01−2.95 (m, 1H), 2.53 (s, 3H); ^{13}C NMR δ 168.5, 143.8, 141.2, 139.5, 135.7, 132.6, 131.3, 130.3, 128.4, 127.7, 125.1, 124.2, 123.9, 63.6, 42.0, 32.4, 21.9. Anal. Calcd for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98. Found: C, 72.65; H, 5.44; N, 4.97.

2-Chloro-6,7-dihydroisoindolo[2,1-*d*][1,4]benzothiazepin-9(13b*H*)-one (10c): colorless needles (from CH_2Cl_2/Et_2O); mp 154−155 °C; yield, 94%, ^{1}H NMR δ 7.95 (d, J = 7.3 Hz, 1H), 7.68 (t, J = 7.3 Hz, 1H), 7.62−7.56 (m, 2H), 7.48 (d, J = 7.3 Hz, 1H), 7.25 (dd, J = 8.2, 2.3 Hz, 1H), 6.89 (d, J = 2.0 Hz, 1H), 6.16 (s, 1H), 4.12 (ddd, J = 14.3, 6.4, 2.9 Hz, 1H), 3.93 (ddd, J = 14.0, 8.7, 2.9 Hz, 1H), 3.16 (ddd, J = 13.4, 6.4, 2.9 Hz, 1H), 3.02 (ddd, J = 13.0, 8.7, 2.9 Hz, 1H); ^{13}C NMR δ 168.7, 142.6, 141.1, 135.2, 134.6, 134.5, 132.6, 131.9, 129.0, 128.8, 127.7, 124.3, 124.2, 63.2, 42.9, 32.7. Anal. Calcd for $C_{16}H_{12}ClNOS$: C, 63.68; H, 4.01; N, 4.64. Found: C, 63.60; H, 4.09; N, 4.88.

2-Methyl-6,7-dihydroisoindolo[2,1-*d*][1,4]benzothiazepin-9(13b*H*)-one (10d): colorless needles (from CH_2Cl_2/Et_2O); mp 162−163 °C; yield, 96%; ^{1}H NMR δ 7.95 (d, J = 7.3 Hz, 1H), 7.65 (t, J = 7.3 Hz, 1H), 7.57 (t, J = 7.3 Hz, 1H), 7.51 (d, J = 8.2 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 6.72 (s, 1H), 6.21 (s, 1H), 4.06−3.90 (m, 2H), 3.17−3.10 (m, 1H), 3.07−2.98 (m, 1H), 2.23 (s, 3H); ^{13}C NMR δ 168.7, 143.3, 138.9, 138.7, 134.0, 132.7, 132.3, 131.5, 129.5, 128.6, 128.2, 124.2, 124.1, 63.6, 42.5, 32.6, 21.2. Anal. Calcd for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98. Found: C, 72.19; H, 5.64; N, 4.90.

8,9-Dihydronaphtho[1′,2′:6,7][1,4]thiazepino[5,4-*a*]-isoindol-11(15b*H*)-one (10e): colorless plates (from CH_2Cl_2/hexanes); mp 230 °C (decomposed); yield, 78%; ^{1}H NMR δ 8.39 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.69 (d, J = 8.6 Hz, 1H), 7.60 (t, J = 7.3 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 7.3 Hz, 1H), 7.35 (t, J = 7.3 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 6.80 (s, 1H), 4.55−4.48 (m, 1H), 3.45−3.20 (m, 3H); ^{13}C NMR δ 169.6, 144.3, 134.3, 134.0, 132.3, 132.2, 131.7, 129.3, 128.9, 128.8, 128.5, 127.3, 126.4, 125.7, 123.7, 123.2, 122.5, 63.6, 39.1, 31.7. Anal. Calcd for $C_{20}H_{15}NOS$: C, 75.68; H, 4.76; N, 4.41. Found: C, 75.62; H, 4.80; N, 4.37.

1,4-Dimethyl-6,7-dihydroisoindolo[2,1-*d*][1,4]benzothiazepin-9(13b*H*)-one (10f): colorless plates (from CH_2Cl_2/hexanes); mp 179−180 °C; yield, 81%; ^{1}H NMR δ 7.94−7.91 (m, 1H), 7.49−7.43 (m, 2H), 7.21−7.12 (m, 3H), 6.16 (s, 1H), 4.46−4.39 (m, 1H), 3.36−3.10 (m, 2H), 2.98−2.92 (m, 1H), 2.64 (s, 3H), 2.38 (s, 3H); ^{13}C NMR δ 170.1, 144.4, 141.4, 137.0, 134.5, 132.6, 131.6, 131.6, 131.3, 130.2, 128.1, 123.5, 122.1, 64.1, 39.2, 31.2, 21.7, 21.3. Anal. Calcd for $C_{18}H_{17}NOS$: C, 73.19; H, 5.80; N, 4.74. Found: C, 73.14; H, 5.62; N, 4.74.

Procedure for the Preparation of 5-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(2-phenoxyethyl)-2-pyrrolidinone (12) and 1,5,6,11b-Tetrahydropyrrolo[1,2-*d*][1,4]benzoxazepin-3(2*H*)-one (13). 2,5-Dimethoxy-2,5-dihydrofuran (**5,** 0.72 g, 5.5 mmol), 2-phenoxyethylamine (**11**, 0.55 g, 4 mmol), and benzotriazole (**4**, 1.19 g, 10 mmol) were dissolved in acetic acid (30 mL). The mixture was kept at 60−75 °C for 72 h. The same workup procedure as for the preparation of **6** afforded **12** as brown oil.

To a solution of compound **12** (0.41 g, 2 mmol) in CH_2Cl_2 (20 mL) was added $TiCl_4$ (8 mmol, 4.7 mL, 1.71 M), and the reaction mixture was stirred for 72 h at room temperature. Then the mixture was washed with 2 M NaOH and brine. The organic fractions were dried over Na_2SO_4. The solvent was removed in vacuo. Then the residue obtained was purified by column chromatography (hexanes/EtOAc = 1/1−1/2) to give **13**.

5-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(2-phenoxyethyl)-2-pyrrolidinone (12): brown oil; yield, 50%; ^{1}H NMR δ 8.10 (d, J = 8.5 Hz, 1H), 7.57−7.49 (m, 2H), 7.41 (t, J = 7.9 Hz, 1H), 7.30−7.25 (m, 2H), 6.99−6.94 (t, J = 7.3 Hz, 1H), 6.83−6.78 (m, 3H), 4.16−4.07 (m, 1H), 4.00−3.90 (m, 2H), 3.08−2.96 (m, 2H), 2.87−2.74 (m, 1H), 2.69−2.60 (m, 1H), 2.54−2.46 (m, 1H); ^{13}C NMR δ 174.7, 157.9, 146.1, 131.9, 129.4, 128.1, 124.3, 121.2, 120.3, 114.1, 109.0, 73.0, 66.2, 40.0, 29.0, 25.7. Anal. Calcd for $C_{18}H_{18}N_4O_2$: C, 67.07; H, 5.63; N, 17.38. Found: C, 66.62; H, 5.57; N, 17.34.

1,5,6,11b-Tetrahydropyrrolo[1,2-*d*][1,4]benzoxazepin-3(2*H*)-one (13): brown oil; yield, 72%; ^{1}H NMR δ 7.27−7.23 (m, 2H), 7.13−7.05 (m, 2H), 4.94−4.88 (m, 1H), 4.35−4.27 (m, 2H), 3.85−3.76 (m, 1H), 3.40−3.37 (m, 1H), 2.57−2.38 (m, 4H); ^{13}C NMR δ 173.9, 159.0, 131.9, 129.2, 126.0, 124.0, 122.3, 70.9, 59.1, 43.4, 29.9, 24.0. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.68; H, 6.65; N, 6.87.

Procedure for the Preparation of 3-(1*H*-1,2,3-Benzotriazol-1-yl)-2-(2-phenoxyethyl)-1-isoindolinone (14) and 6,7-Dihydroisoindolo[2,1-*d*][1,4]benzoxazepin-9(13b*H*)-ones (15). 2-Formylbenzoic acid (**8**, 3.0 g, 20 mmol), 2-phenoxy-1-ethanamine (**11**, 2.74 g, 20 mmol), benzotriazole (**4**, 3.6 g, 30 mmol), and *p*-toluenesulfonic acid monohydrate (0.36 g, 2 mmol) were dissolved in toluene (60 mL) and heated under refluxing using a Dean Stark apparatus. After 24 h, the reaction mixture was cooled. The white solid was filtered off and washed with toluene three times to give crude **14**, which was used for the subsequent cyclization without further purification. The sample for microanalysis was purified by column chromatography (hexanes/EtOAc = 6/1−2/1).

To a solution of 3-(1*H*-1,2,3-benzotriazol-1-yl)-2-(2-phenoxyethyl)-1-isoindolinone (**14**, 0.37 g, 1.0 mmol) in CH_2Cl_2 (15 mL) was added $TiCl_4$ (2.0 mmol, 1.2 mL, 1.71 M in CH_2Cl_2), and the mixture was stirred at room temperature for 48 h. The solution was washed with 2 M NaOH twice and brine and dried over Na_2SO_4. After removal of solvents in vacuo, the residue was the pure product (^{1}H and ^{13}C NMR spectra). The sample for elemental analysis was additional purified by column chromatography (hexanes/EtOAc = 6/1−3/1).

3-(1*H*-1,2,3-Benzotriazol-1-yl)-2-(2-phenoxyethyl)-1-isoindolinone (14). Colorless plates (from CH_2Cl_2); mp 148−149 °C; yield, 76%; ^{1}H NMR δ 8.08 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 7.3 Hz, 1H), 7.70 (s, 1H), 7.66 (t, J = 7.3 Hz, 1H), 7.58 (t, J = 7.3 Hz, 1H), 7.34−7.18 (m, 5H), 6.91 (t, J = 7.3 Hz, 1H), 6.75 (d, J = 8.2 Hz, 2H), 6.53 (d, J = 8.5 Hz, 1H), 4.17−4.07 (m, 3H), 3.38−3.30 (m, 1H); ^{13}C NMR δ 167.4, 158.0, 147.0, 139.6, 133.0, 131.6, 130.8, 129.3 (2), 128.1, 124.5, 124.1, 123.5, 121.1, 120.4, 114.3, 109.9, 73.7, 65.7, 39.9. Anal. Calcd for $C_{22}H_{18}N_4O_2$: N, 15.13. Found: N, 14.85.

6,7-Dihydroisoindolo[2,1-*d*][1,4]benzoxazepin-9(13b*H*)-one (15): colorless needles (from EtOAc/hexanes); yield, 89%; mp 145−146 °C; ^{1}H NMR δ 7.94 (d, J = 7.6 Hz, 1H), 7.69−7.54 (m, 3H), 7.29 (t, J = 7.6 Hz, 1H), 7.16−7.10 (m, 2H), 7.02 (t, J = 7.6 Hz, 1H), 5.83 (s, 1H), 4.60−4.49 (m, 2H), 3.94−3.85 (m, 1H), 3.76−3.66 (m, 1H); ^{13}C NMR δ 168.1, 159.8, 142.2, 132.7, 131.1, 129.9, 129.8, 128.7, 127.0, 124.8, 124.5, 124.2, 122.1, 71.8, 61.6, 44.3. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.25; H, 5.20; N, 5.55.

Supporting Information Available: Characterization data for compounds **6b**−**e** and **9b**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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