Stereoselective Synthesis of Bridged Azepine Derivatives via Polyfunctionalized Spiroannulated Thiophene. Novel Rearrangement of Oxime Esters

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Introduction

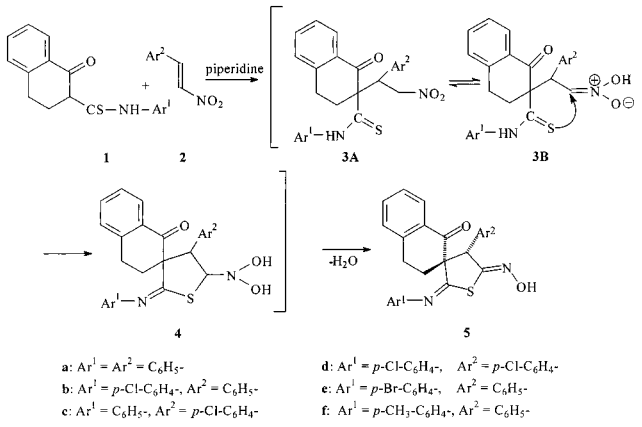
Various azepine derivatives have been the subject of considerable interest owing to their application in medicinal chemistry. For instance, some azepines and benzazepines are structural elements of numerous natural compounds[1] of biological activity and form important pharmacological and biological agents.[2−5]

We report herein the highly convenient synthesis of polyfunctionalized bridged benzazepines by transformation of some spiroannulated thiophenes containing oxime and arylimine functions. Recently, we have published an efficient method for the preparation of oximes of 2-arylimino-5-oxothiophenes and their transformation to pyrroles.[6] In this study, our interest was directed to the synthesis of oximes of 2-arylimino-5-oxothiophenes spiroannulated to a 1-tetralone system as well as their conversion to nitrogen heterocycles.

Results and Discussion

The starting materials were 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carbothioic acid arylamides, **1**,[7,8] and (*E*)-*β*-nitrostyrenes, **2**. The reaction of **1** with **2** catalyzed by piperidine (Scheme 1) afforded spirothiophenes **5a**−**f** in good yields (57%−72%). The key step of the above reaction is the Michael addition of **1** to **2** yielding the saturated nitroalkane **3**, which may exist in tautomeric forms **3A** or **3B**. In the next step, the nucleophilic attack of the sulfur atom on the α-carbon atom attached to a nitro group involves cyclization to **4**. Elimination of a water molecule from **4** yields spirothiophene **5**.[6] Because

Scheme 1



a: $Ar^1 = Ar^2 = C_6H_5$-
b: $Ar^1 = p$-Cl-C_6H_4-, $Ar^2 = C_6H_5$-
c: $Ar^1 = C_6H_5$-, $Ar^2 = p$-Cl-C_6H_4-
d: $Ar^1 = p$-Cl-C_6H_4-, $Ar^2 = p$-Cl-C_6H_4-
e: $Ar^1 = p$-Br-C_6H_4-, $Ar^2 = C_6H_5$-
f: $Ar^1 = p$-CH_3-C_6H_4-, $Ar^2 = C_6H_5$-

5 was formed as a single diastereoisomer, it means that the coupling of two reagents at prostereogenic centers with formation of two new stereogenic centers proceeded in diastereoselective way.

The presence of two exocyclic C═N− bonds, in oxime and arylimine groups in **5,** suggested the possibility of ring enlargement or ring transformation either by Beckman rearrangement or by Dimroth reaction. Because both processes are catalyzed by acidic reagents, **5a**−**f** were refluxed in a mixture of acetic acid and acetic anhydride (3:1) providing compounds **10a**−**f** in good yields (55%−89%) (Scheme 2). The spectral features of **10** showed that formation of these products proceeds neither via Beckman nor via Dimroth reactions. Analytical data and molecular weight determination of **10a** indicated the elimination of a water molecule from **5a**. The IR spectrum of **10a** revealed the band of CO (1697 cm^{-1}) and the weak band of CN (2229 cm^{-1}) groups. On the other hand, no absorption characteristic of the oxime OH group was observed. The presence of an AMX spin system of aliphatic protons in the ^1H NMR spectrum of **10a** indicated that one of the hydrogen atoms of the 1-tetralone moiety was involved in the elimination reaction. The bicyclic structure of **10** was established by heteronuclear multiple-quantum coherence (HMQC), heteronuclear multiple-bond correlation (HMBC), and NOESY experiments. The NMR measurements, however, did not allow us to determine the relative configuration at the stereogenic centers. To this end, X-ray structure analysis was performed.[9] The three stereogenic centers, C1′, C2, and C5′, possess the relative configurations of *R*, *S*, and *R*, respectively.

To explain the course of transformation of **5** into **10**, we carried out reactions of **5a** with acetic anhydride and separately with glacial acetic acid. The reaction of **5** with boiling acetic anhydride led to a mixture of two products, **10** and the ester **6**. Compounds **6**, as colorless prisms, were the major products (45%−64%) and were separated from **10** (11%−17%). The formation of **10** and **6** in the above reaction suggested that compound **6** was the

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(9) The structure was solved and refined using the SHELX-97 system. Sheldrick, G. M. *SHELX-97, A program for structure solution and refinement*; Göttingen University: Göttingen, Germany, 1997. The atomic coordinates and the details of the crystal structure investigation have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, United Kingdom.

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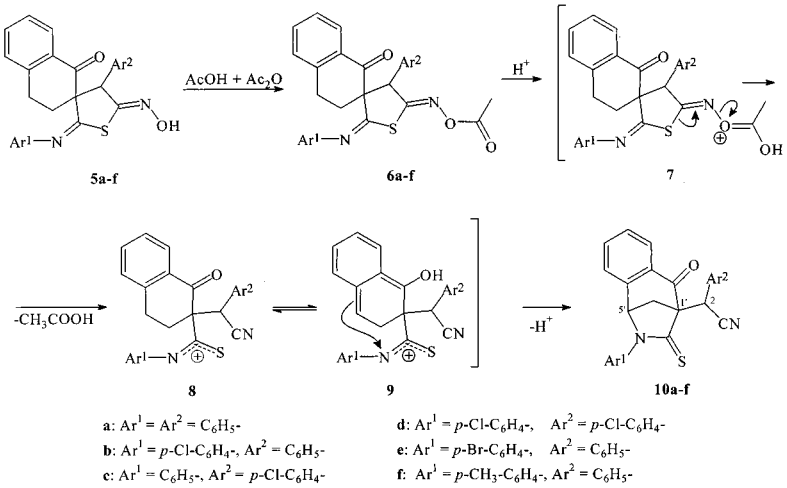
Scheme 2



intermediate in the rearrangement of **5** into **10**. This assumption was confirmed by the following experiments. When **6a** was refluxed in acetic acid (99.5%), compound **10a** was obtained in excellent yield (84%), whereas **5a** under the same condition did not undergo change. Thus, the formation of the oxime ester is necessary for rearrangement of **5** into **10**.

To our knowledge, the rearrangement of oximes or their esters into nitriles under the influence of acetic acid and acetic anhydride[10] occurs in the case of molecules that are prone to eject positive ions.[11,12] The rearrangement of **5** into **10** is outlined in Scheme 2. The formation of a nitrile group is accomplished by the following sequence of reactions. The acylation of the oxime hydroxyl group gives ester **6**, which, after protonation (**7**), splits acetic acid and then, after cleavage of the carbon−sulfur bond, gives rise to CN function in **8**. The intermediate **8**, existing in the tautomeric form **9**,[13] undergoes intramolecular cyclization by nucleophilic attack of the π electrons of the double bond at C-4 (**9**) on the electron-deficient nitrogen atom of the thiocarbamoyl moiety, which results in the formation of the bridged azepine **10**.

The configuration of the new stereogenic center at the carbon atom C5′ in **10** is determined by the configuration of the spiro-carbon atom in compound **5**, as the attack on the nitrogen atom can occur from the same side of the six-membered ring that is occupied by the phenylimine moiety. During the rearrangement reaction of **5** into **10**, the configuration on the existing stereogenic centers does not change. This allowed us to state that the diastereoselective conjugated addition of achiral **1** to achiral nitrostyrene **2** proceeds, in a relative sense, between the *si* face of **1** and the *re* face of β-nitrostyrene **2**. A balance of several factors may determine the stereochemical outcome of the reaction discussed. The steric interference with electrophile trajectories and the requirement to maintain orbital overlap in the structure of the transition state may play the most important role. The stereochemical outcome of this reaction might be rationalized by assuming the perpendicular approach of the electron-deficient sp^2 carbon atom to the enolate anion of the 1-tetralone moiety.[14] The unlike (*re* to *si*) fashion of that approach allows the avoidance of steric interaction, in the transition state, between the phenyl or nitro group and the β-axial hydrogen atom.

In conclusion, a facile and efficient diastereoselective synthesis of polyfunctionalized spirothiophenes from cyclic β-keto acid thioanilides and nitroalkenes has been shown, and the transformation of spiroaryliminothiophenes into bridged azepines has been established. In our laboratory, further aspects of the reactions of nitroalkenes and β-keto acid thioanilides are under continued investigation.

Experimental Section

General Procedure for Synthesis of (2*R,4′*S**)-4′-Aryl-2′-arylimino-5′-hydroxyimino-1-oxo-1,2,3,4,2′,3′,4′,5′-octahydrospiro[naphthalene-2,3′-thiophene] (5a−f).** A solution of thioanilide **1** (5 mmol) and the appropriate (*E*)-β-nitrostyrene **2** (5 mmol) in 80 mL of absolute ethanol was refluxed with a few drops of piperidine for 2.5 h. After the solution was cooled, the precipitate was filtered off, washed with 10 mL of cold ethanol, and crystallized from ethanol or a mixture of methanol and methylene chloride (1:3) affording **5a**−**f** as colorless prisms.[8]

5a: yield 61%; mp 254−256 °C; IR (KBr) ν_{max} 3397, 1659, 1617, 948 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.08 (dd, ^3J = 7.9 Hz, ^4J = 1.2 Hz, 1H), 7.58 (s, 1H), 7.43−7.14 (m, 11H), 6.86 (dd, ^3J = 8.4 Hz, ^4J = 2.0 Hz, 2H), 5.42 (s, 1H), 3.34 (ddd, ^2J = 16.8 Hz, ^3J = 11.9 Hz, ^3J = 4.2 Hz, 1H), 2.88 (dt, ^2J = 16.8 Hz, ^3J = 4.2 Hz, 1H), 2.47 (dt, ^2J = 13.7 Hz, ^3J = 4.2 Hz, 1H), 2.11 (ddd, ^2J = 13.7 Hz, ^3J = 12.0 Hz, ^3J = 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 193.8, 167.0, 156.7, 150.5, 143.7, 134.3, 133.8, 132.1, 130.5, 129.2, 128.6, 128.3, 128.1, 126.8, 125.4, 119.7, 64.8, 54.3, 29.3, 25.5. MS (EI) *m*/*z* (%) 411.8 (100) M$^+$. Anal. Calcd for $C_{25}H_{20}N_2O_2S$ (412.50): C, 72.79; H, 4.89; N, 6.79. Found: C, 72.51; H, 4.81; N, 7.01.

5b: yield 69%; mp 234−236 °C; IR (KBr) ν_{max} 3397, 1659, 1620, 948 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.08 (d, ^3J = 7.9 Hz, 1H), 7.51 (s, 1H), 7.44−7.31 (m, 10H), 6.82 (dd, ^3J = 8.4 Hz, ^4J = 2.1 Hz, 2H), 5.41 (s, 1H), 3.27 (ddd, ^2J = 17.1 Hz, ^3J = 11.8 Hz, ^3J = 4.2 Hz, 1H), 2.86 (dt, ^2J = 16.6 Hz, ^3J = 4.2 Hz, 1H), 2.46 (dt, ^2J = 13.5 Hz, ^3J = 4.2 Hz, 1H), 2.12 (ddd, ^2J = 13.7 Hz, ^3J = 12.1 Hz, ^3J = 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 193.7, 168.3, 156.2, 148.9, 143.6, 134.6, 134.1, 133.9, 133.8, 132.0, 130.8, 130.4, 129.3, 129.2, 128.6, 128.3, 128.1, 127.5, 127.3, 126.6, 121.2, 64.7, 54.0, 29.3, 25.5; MS (EI) *m*/*z* (%) 446 (100) M$^+$. Anal. Calcd for $C_{25}H_{19}ClN_2O_2S$ (446.95): C, 67.18; H, 4.28; N, 6.27. Found: C, 67.32; H, 4.16; N, 6.18.

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5c: yield 57%; mp 233−235 °C; IR (KBr) ν_{max} 3406, 1662, 1596, 952 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, ^3J = 8.0 Hz, 1H), 7.96 (s, 1H), 7.43−7.31 (m, 10H), 6.85 (d, ^2J = 8.3 Hz, 2H), 5.44 (s, 1H), 3.35 (dd, ^2J = 16.6 Hz, ^3J = 11.5 Hz, 1H), 2.86 (dt, ^2J = 16.6 Hz, ^3J = 4.1 Hz, 1H), 2.42 (dt, ^2J = 13.7 Hz, ^3J = 4.1 Hz, 1H), 2.04 (ddd, ^2J = 13.5 Hz, ^3J = 12.0 Hz, ^3J = 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 193.7, 166.3, 156.0, 150.2, 143.6, 134.0, 133.8, 132.2, 132.0, 131.9, 129.8, 129.2, 129.1, 128.5, 128.2, 127.4, 126.9, 126.8, 125.5, 119.6, 119.0, 64.9, 53.4, 29.2, 25.5; MS (EI) *m*/*z* (%) 446 (100) M$^+$. Anal. Calcd for $C_{25}H_{19}ClN_2O_2S$ (446.95): C, 67.18; H, 4.28; N, 6.27. Found: C, 67.21; H, 4.26; N, 6.24.

5d: yield 72%; mp 260−263 °C; IR (KBr) ν_{max} 3390, 1660, 1626, 940 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, ^3J = 7.7 Hz, 1H), 7.45 (s, 1H), 7.39−7.17 (m, 9H), 6.8 (dd, ^3J = 8.2 Hz, ^4J = 2.0 Hz, 2H), 5.46 (s, 1H), 3.31 (dd, ^2J = 16.7 Hz, ^3J = 12.1 Hz, 1H), 2.89 (dt, ^2J = 16.8 Hz, ^3J = 4.2 Hz, 1H), 2.43 (dt, ^2J = 13.7 Hz, ^3J = 4.2 Hz, 1H), 2.07 (ddd, ^2J = 13.7 Hz, ^3J = 12.0 Hz, ^3J = 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 193.4, 148.7, 134.2, 133.9, 132.0, 131.9, 129.3, 128.6, 128.5, 128.3, 126.9, 121.2, 64.9, 53.5, 29.3, 25.5; MS (EI) *m*/*z* (%) 480 (100) M$^+$. Anal. Calcd for $C_{25}H_{18}Cl_2N_2O_2S$ (481.39): C, 62.38; H, 3.77; N, 5.82. Found: C, 62.61; H, 3.83; N, 6.01.

5e: yield 64%; mp 231−232 °C; IR (KBr) ν_{max} 3375, 1664, 1622, 944 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.08 (d, ^3J = 8.0 Hz, 1H), 7.49 (s, 1H), 7.45−7.16 (m, 10H), 6.76 (d, ^3J = 8.4 Hz, 2H), 3.28 (dd, ^2J = 16.8 Hz, ^3J = 11.7 Hz, 1H), 2.86 (dt, ^2J = 16.5 Hz, ^3J = 4.0 Hz, 1H), 2.46 (dt, ^2J = 13.7 Hz, ^3J = 4.0 Hz, 1H), 2.12 (ddd, ^2J = 13.7 Hz, ^3J = 12.0 Hz, ^3J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 193.7, 149.4, 143.5, 142.3, 134.1, 133.8, 132.3, 132.0, 130.4, 128.6, 128.3, 128.1, 126.8, 121.6, 64.9, 54.3, 29.3, 25.5; MS (EI) *m*/*z* (%) 492 (100), 490 (90) M$^+$. Anal. Calcd for $C_{25}H_{19}BrN_2O_2S$ (491.40): C, 61.11; H, 3.90; N, 5.70. Found: C, 61.38; H, 4.11; N, 5.92.

5f: yield 58%; mp 235−237 °C; IR (KBr) ν_{max} 3376, 1655, 1606, 948 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.09 (d, ^3J = 7.9 Hz, 1H), 7.39 (s, 1H), 7.29−7.14 (m, 10H), 6.78 (d, ^3J = 8.2 Hz, 2H), 5.40 (s, 1H), 3.32 (ddd, ^2J = 16.7 Hz, ^3J = 11.7 Hz, ^3J = 4.1 Hz, 1H), 2.86 (dt, ^2J = 16.3 Hz, ^3J = 4.0 Hz, 1H), 2.47 (dt, ^2J = 13.5 Hz, ^3J = 4.0 Hz, 1H), 2.32 (s, 3H), 2.10 (ddd, ^2J = 13.7 Hz, ^3J = 12.0 Hz, ^3J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 193.9, 166.3, 156.8, 148.0, 143.7, 135.1, 134.3, 133.6, 132.1, 130.5, 129.7, 128.3, 128.0, 126.7, 119.7, 64.8, 54.1, 29.3, 25.5, 20.9; MS (EI) *m*/*z* (%) 426 (100) M$^+$. Anal. Calcd for $C_{26}H_{22}N_2O_2S$ (426.53): C, 73.21; H, 5.20; N, 6.57. Found: C, 72.98; H, 511; N, 6.44.

General Procedure for Synthesis of (2*R,4′*S**)-5′-Acetoxyimino-4′-aryl-2′-arylimino-1,2,3,4,2′,3′,4′,5′-octahydro-1-oxospiro[naphthalene-2,3′-thiophene] (6a−f).** A solution of **5** (2 mmol) in 15 mL of acetic anhydride was refluxed for 2 h. The yellowish solution was poured into ice water. The product was filtered off and washed with water. The crude product was a mixture of **6** and **10**. The compounds were separated by column chromatography on silica gel using chloroform as the eluent and crystallized from methanol (colorless prisms).

6a: yield 49%; mp 142−143 °C; IR (KBr) ν_{max} 1597, 1665, 1781, 2916, 3062 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.08 (d, ^3J = 7.8 Hz, 1H), 7.50−7.19 (m, 11H), 6.92 (d, ^3J = 7.7 Hz, 2H), 5.22 (s, 1H), 3.25 (ddd, ^2J = 17.2 Hz, ^3J = 8.4 Hz, ^3J = 5.0 Hz, 1H), 2.86 (dt, ^2J = 17.2 Hz, ^3J = 5.0 Hz, 1H), 2.52 (dt, ^2J = 14.2 Hz, ^3J = 5.0 Hz, 1H), 2.11 (ddd, ^2J = 14.2 Hz, ^3J = 8.4 Hz, ^3J = 5.0 Hz, 1H and s, 3H); ^{13}C NMR ($CDCl_3$) δ 193.8, 167.1, 166.6, 165.4, 150.4, 143.5, 134.4, 131.2, 134.0, 129.6, 129.5, 129.4, 128.7, 128.6, 128.3, 126.9, 125.7, 119.6, 64.7, 54.8, 29.0, 25.4, 19.1; MS (EI) *m*/*z* (%) 454.2 (30) M$^+$, 246.1 (100). Anal. Calcd for $C_{27}H_{22}N_2O_3S$ (454.54): C, 71.35; H, 4.88; N, 6.16. Found: C, 71.43; H, 4.80; N, 5.85.

6b: yield 45%; mp 192−194 °C; IR (KBr) ν_{max} 1561, 1661, 1774, 2929, 3002 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.08 (d, ^3J = 7.8 Hz, 1H), 7.34−7.17 (m, 10H), 6.87 (d, ^3J = 7.8 Hz, 2H), 5.20 (s, 1H), 3.20 (ddd, ^2J = 17.2 Hz, ^3J = 8.4 Hz, ^3J = 5.0 Hz, 1H), 2.86 (dt, ^2J = 17.2 Hz, ^3J = 5.0 Hz, 1H), 2.50 (dt, ^2J = 14.2 Hz, ^3J = 5.0 Hz, 1H), 2.10 (ddd, ^2J = 14.2 Hz, ^3J = 8.4 Hz, ^3J = 5.0 Hz, 1H and s, 3H); ^{13}C NMR ($CDCl_3$) δ 193.7, 191.4, 167.8, 167.0, 164.9, 148.8, 134.3, 134.1, 131.2, 131.0, 130.4, 129.5, 128.7, 128.7, 128.6, 128.4, 127.0, 121.1, 64.8, 54.8, 28.9, 25.3, 19.1; MS (EI) *m*/*z* (%) 488 (18) M$^+$, 259 (100). Anal. Calcd for $C_{27}H_{21}ClN_2O_3S$ (488.98): C, 66.32; H, 4.33; N, 5.73. Found: C, 66.45; H, 4.52; N, 5.61.

6c: yield 64%; mp 197−198 °C; IR (KBr) ν_{max} 1567, 1680, 1781, 2937, 3010 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.08 (d, ^3J = 7.9 Hz, 1H), 7.46−7,19 (m, 10H), 6.87 (d, ^3J = 7.8 Hz, 2H), 5.36 (s, 1H), 3.31 (ddd, ^2J = 17.3 Hz, ^3J = 8.4 Hz, ^3J = 5.1 Hz, 1H), 2.86 (dt, ^2J = 17.2 Hz, ^3J = 5.1 Hz, 1H), 2.46 (dt, ^2J = 14.2 Hz, ^3J = 5.1 Hz, 1H), 2.10 (ddd, ^2J = 14.2 Hz, ^3J = 8.4 Hz, ^3J = 5.1 Hz, 1H and s, 3H); ^{13}C NMR ($CDCl_3$) δ 193.3, 166.9, 165.6, 165.0, 150.1, 143.4, 134.3, 134.1, 132.3, 131.4, 131.3, 129.4, 128.7, 128.6, 128.5, 126.9, 125.8, 119.5, 64.7, 54.0, 29.1, 25.3, 19.1; MS (EI) *m*/*z* (%) 488(34) M$^+$, 246(100). Anal. Calcd for $C_{27}H_{21}ClN_2O_3S$ (488.98): C, 66.32; H, 4.33; N, 5.73. Found: C, 66.36; H, 4.57; N, 5.81.

6d: yield 56%; mp 195−196 °C; IR (KBr) ν_{max} 1567, 1693, 1776, 2937, 3062 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, ^3J = 7.8 Hz, 1H), 7.47−7.17 (m, 9H), 6.83 (d, ^3J = 7.8 Hz, 2H), 5.35 (s, 1H), 3.26 (ddd, ^2J = 17.2 Hz, ^3J = 8.4 Hz, ^3J = 5.2 Hz, 1H), 2.86 (dt, ^2J = 17.2 Hz, ^3J = 5.2 Hz, 1H), 2.45 (dt, ^2J = 14.2 Hz, ^3J = 5.2 Hz, 1H), 2.07 (ddd, ^2J = 14.2 Hz, ^3J = 8.4 Hz, ^3J = 5.2 Hz, 1H and s, 3H); ^{13}C NMR ($CDCl_3$) δ 193.2, 166.8, 166.8, 164.5, 148.5, 143.3, 134.4, 134.2, 132.2, 131.3, 131.2, 129.5, 129.3, 128.8, 128.6, 128.5, 121.2, 121.0, 64.8, 54.0, 29.0, 25.3, 19.0; MS (EI) *m*/*z* (%) 522 (41) M$^+$, 293 (100). Anal. Calcd for $C_{27}H_{20}Cl_2N_2O_3S$ (523.43): C, 61.96; H, 3.85; N, 5.35. Found: C, 62.16; H, 3.85; N, 5.49.

6e: yield 65%; mp 196−198 °C, IR (KBr) ν_{max} 1591, 1664, 1781, 2379, 3062 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, ^3J = 7.9 Hz, 1H), 7.47−7.17 (m, 10H), 6.81 (d, ^3J = 7.9 Hz, 2H), 5.20 (s, 1H), 3.23 (ddd, ^2J = 17.3 Hz, ^3J = 8.2 Hz, ^3J = 5.2 Hz, 1H), 2.86 (dt, ^2J = 17.2 Hz, ^3J = 5.2 Hz, 1H), 2.51 (dt, ^2J = 14.2 Hz, ^3J = 5.2 Hz, 1H), 2.11 (ddd, ^2J = 14.2 Hz, ^3J = 8.4 Hz, ^3J = 5.2 Hz, 1H and s, 3H); ^{13}C NMR ($CDCl_3$) δ 193.7, 167.9, 167.0, 164.9, 149.2, 143.5, 143.3, 134.3, 133.8, 132.5, 131.0, 130.4, 129.5, 128.7, 127.0, 126.8, 121.5, 121.4, 118.9, 64.8, 54.8, 28.9, 25.3, 19.1; MS (EI) *m*/*z* (%) 532 (5), 534 (5) M$^+$, 475 (100). Anal. Calcd for $C_{27}H_{21}BrN_2O_3S$ (533.43): C, 60.79; H, 3.97; N, 5.25. Found: C, 61.03; H, 4.11; N, 5.32.

6f: yield 63%; mp 172−173 °C; IR (KBr) ν_{max} 1567, 1655, 1776, 2916 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.08 (d, ^3J = 7.8 Hz, 1H), 7.45−7.15 (m, 10H), 6.83 (d, ^3J = 7.7 Hz, 2H), 5.31 (s, 1H), 3.25 (ddd, ^2J = 17.1 Hz, ^3J = 8.2 Hz, ^3J = 5.0 Hz, 1H), 2.86 (dt, ^2J = 17.2 Hz, ^3J = 5.0 Hz, 1H), 2.51 (dt, ^2J = 14.2 Hz, ^3J = 5.0 Hz, 1H), 2.35 (s, 3H), 2.11 (ddd, ^2J = 14.2 Hz, ^3J = 8.4 Hz, ^3J = 5.0 Hz, 1H and s, 3H); ^{13}C NMR ($CDCl_3$) δ 193.9, 167.1, 165.8, 165.6, 147.8, 143.6, 143.4, 135.5, 134.4, 133.9, 133.6, 131.2, 130.5, 129.9, 129.7, 129.6, 128.6, 128.3, 126.9, 126.7, 119.7, 64.6, 54.7, 29.0, 25.4, 20.9, 19.1; MS (EI) *m*/*z* (%) 468 (15) M$^+$, 259 (100). Anal. Calcd for $C_{28}H_{24}N_2O_3S$ (468.57): C, 71.77; H, 5.16; N, 5.98. Found: C, 71.39; H, 5.03; N 6.12.

General Procedure for Synthesis of (1′*R,2*S**,5′*R**)-2-Aryl-2-(6′-aryl-3′,4′-benzo-2′-oxo-7′-thioxo)-6′-azabicyclo-[3.2.1]octan-1-yl Acetonitrile (10a−f).** A solution of **5** (2 mmol) in 50 mL of glacial acetic acid and 15 mL of acetic anhydride was refluxed for 3 h. The yellow solution was poured into ice water. The product was filtered off, purified by column chromatography on silica gel using chloroform as the eluent, and crystallized from methanol or ethanol (yellow prisms).

10a: yield 61%; mp 222−223 °C; IR (KBr) ν_{max} 1697, 2229, 2958 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.0 (d, ^3J = 7.3 Hz, 1H), 7.6−7.1 (m, 13H), 5.58 (s, 1H), 5.15 (d, ^3J = 5.5 Hz, 1H), 3.48 (dd, ^2J = 11.1 Hz, ^3J = 5.5 Hz, 1H), 2.82 (d, ^2J = 11.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 195.8, 186.0, 141.8, 139.7, 134.3, 132.7, 130.2, 129.9, 129.5, 129.4, 129.1, 128.6, 128.5, 126.0, 125.3, 119.7, 74.0, 67.8, 40.9, 40.6; MS (EI) *m*/*z* (%) 394.1 (48) M$^+$, 259.1 (100). Anal. Calcd for $C_{25}H_{18}N_2OS$ (394.49): C, 76.12; H, 4.60; N, 7.10. Found: C, 75.84; H, 4.54; N, 6.85.

10b: yield 58%; mp 231−233 °C; IR (KBr) ν_{max} 1693, 2245, 2960 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.0 (d, ^3J = 7.3 Hz, 1H), 7.6−7.1 (m, 12H), 5.56 (s, 1H), 5.13 (d, ^3J = 5.7 Hz, 1H), 3.47 (dd, ^2J = 11.4 Hz, ^3J = 5.8 Hz, 1H), 2.82 (d, ^2J = 11.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 196.1, 185.7, 141.5, 139.2, 134.3, 132.7, 130.0, 129.7, 129.3, 128.4, 128.1, 124.9, 119.6, 74.1, 67.8, 41.8, 40.6; MS (EI) *m*/*z* (%) 428 (36) M$^+$, 259 (100). Anal. Calcd for $C_{25}H_{17}ClN_2OS$ (428.93): C, 70.00; H, 3.99; N, 6.53. Found: C, 70.03; H, 3.80; N, 6.60.

10c: yield 66%; mp 212−213 °C; IR (KBr) ν_{max} 1699, 2239, 2973 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.0 (d, ^3J = 7.0 Hz, 1H), 7.6−7.16 (m, 12H), 5.56 (s, 1H), 5.16 (d, ^3J = 5.7 Hz, 1H), 3.45 (dd, ^2J = 11.4 Hz, ^3J = 6.0 Hz, 1H), 2.82 (d, ^2J = 11.4 Hz, 1H); ^{13}C

NMR ($CDCl_3$) δ 195.4, 185.9, 141.7, 139.6, 134.8, 134.5, 131.6, 130.6, 130.0, 129.4, 128.8, 126.0, 125.9, 125.3, 119.3, 73.9, 67.8, 41.8, 40.1; MS (EI) *m*/*z* (%) 428 (40) M^+, 293 (100). Anal. Calcd for $C_{25}H_{17}ClN_2OS$ (428.93): C, 70.00; H, 3.99; N, 6.53. Found: C, 70.12; H, 4.17; N, 6.72.

10d: yield 89%; mp 200−203 °C; IR (KBr) ν_{max} 1688, 2200, 2916 cm^{-1}; ^1H NMR ($CDCl_3$), δ 8.0 (d, ^3J = 7.0 Hz, 1H), 7.5−6.82 (m, 11H), 5.53 (s, 1H), 5.13 (d, ^3J = 5.7 Hz, 1H), 3.42 (dd, J = 11.4 Hz, ^3J = 6.0 Hz, 1H), 2.79 (d, ^2J = 11.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 195.7, 185.7, 141.4, 137.9, 134.9, 134.6, 134.3, 131.5, 130.5, 130.1, 129.8, 129.5, 128.9, 128.8, 126.7, 125.9, 119.2, 73.9, 67.8, 41.6, 40.1; MS (EI) *m*/*z* (%) 462 (30) M^+, 293 (100). Anal. Calcd for $C_{25}H_{16}Cl_2N_2OS$ (463.38): C, 64.80; H, 3.48; N, 6.05. Found: C, 64.93; H, 3.49; N, 6.27.

10e: yield 55%; mp 250−252 °C; IR (KBr) ν_{max} 1699, 2245, 2936 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.0 (d, ^3J = 7.2 Hz, 1H), 7.6−7.0 (m, 12H), 5.55 (s, 1H), 5.12 (d, ^3J = 5.7 Hz, 1H), 3.46 (dd, ^2J = 11.2 Hz, ^3J = 6.0 Hz, 1H), 2.75 (d, ^2J = 11.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 196.0, 185.7, 141.5, 138.6, 134.4, 132.7, 130.2, 132.0, 130.1, 129.5, 129.1, 128.7, 128.6, 127.0, 125.9, 122.2, 119.6, 74.1, 67.7, 41.8, 40.6; MS (EI) *m*/*z* (%) 474 (20), 472 (20) M^+, 259 (100). Anal. Calcd for $C_{25}H_{17}BrN_2OS$ (473.38): C, 63.43; H, 3.62; N, 5.92. Found: C, 63.27; H, 3.60; N, 5.72.

10f: yield 55%; mp 231−233 °C; IR (KBr) ν_{max} 1687, 2245, 2937 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98 (d, ^3J = 7.0 Hz, 1H), 7.5−7.0 (m, 12H), 5.56 (s, 1H), 5.11 (d, ^3J = 5.7 Hz, 1H), 3.47 (dd, ^2J = 11.2 Hz, ^3J = 6.1 Hz, 1H), 2.81 (d, ^2J = 11.2 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 196.0, 186.0, 141.8, 138.6, 137.0, 134.8, 132.1, 130.2, 130.0, 129.8, 129.3, 129.0, 128.6, 128.5, 125.9, 125.1, 119.7, 73.9, 67.9, 41.9, 40.6, 21.2; MS (EI) *m*/*z* (%) 408 (58) M^+, 259 (100). Anal. Calcd for $C_{26}H_{20}N_2OS$ (408.51): C, 76.44; H, 4.93; N, 6.86. Found: C, 76.60; H, 4.97; N, 6.60.

Supporting Information Available: Tables of X-ray results and crystal packing views for **10f** and NMR spectra (^1H, ^{13}C, COSY, HMBC, HMQC, and NOESY) of **10a.** This material is available free of charge via the Internet at http://pubs.acs.org.

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