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1,4-Thiazepines, 1,4-Benzothiazepin-5-ones, and 1,4-Benzothioxepin Orthoamides via Multicomponent Reactions of Isocyanides

Stefano Marcaccini,*,† Daniel Miguel,‡ Tomás Torroba,*,§ and María García-Valverde§

Dipartimento di Chimica Organica "Ugo Schiff", Università di Firenze, 50019-Sesto Fiorentino, Firenze, Italy, Departamento de Química Inorgánica, Facultad de Ciencias, Universidad de Valladolid, 47005 Valladolid, Spain, and Departamento de Química, Facultad de Ciencias, Universidad de Burgos, 09001 Burgos, Spain

ttorroba@ubu.es

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Abstract: The intramolecular Ugi four-component condensation between 6-oxo-4-thiacarboxylic acids, benzylamines, and cyclohexyl isocyanide gave hexahydro-1,4-thiazepin-5-ones and 1,4-benzothiazepin-5-ones, in some cases with high stereoselectivity, and the intramolecular Passerini three-component reaction, in the presence of catalytic amine, gave tetracyclic 1,4-benzothioxepin orthoamides.

Hexahydro-1,4-thiazepin-5-one derivatives have been the subject of intense chemical and pharmacological research after the early discovery that some members of the group were angiotensin-converting enzyme inhibitors.[1] This led to the development of temocapril,[2] a drug used for the treatment of hypertension. Very recently some thiazepinones have shown nanomolar affinity for a specific domain of a tyrosine kinase enzyme, the Src SH2, after structure-based rational drug design.[3] 5-Oxo-1,4-thiazepin-2-carboxylic acids have been studied by several groups as ring-constrained dipeptide mimetics[4] with potential angiotensin-converting enzyme and neutral endopeptidase dual inhibitor characteristics. On the other hand, 1,5-benzothiazepin-2-ones can act as calcium channel blockers and this fact, and the readily available synthetic methods for this heterocycle, has led to new cardiovascular drugs[5] as well as to the antihypertensive agent diltiazem,[6] and its inclusion into peptidic chains has led to new bradykinin agonists[7] and growth hormone secretagogues.[8] These pharmacological achievements were accompanied by extensive synthetic research.[9] In contrast, 1,4-benzothiazepin-5-ones have been much less studied due to their lower biological activity and because their traditional synthetic approaches by the Schmidt reaction[10] or the Beckmann rearrangement[11] usually gave mixtures of isomers. Nevertheless, tricyclic 1,4-benzothiazepin-5-one derivatives have been tested as inhibitors of HIV-1 integrase[12] and antitumor antibiotics.[13] Very few selective syntheses are available for these heterocycles.[14] The usefulness of 1,4-thiazepine and 1,4-benzothiazepine derivatives as pharmaceutical tools calls for rapid and atom-economical[15] methods that give access to molecular diversity in parallel to modern protein structure-based design of new medicinal leads. Multicomponent reactions[16] are best suited to achieve this goal and oxocarboxylic acids constitute useful starting materials for this purpose.[17] In continuation of our studies on the synthesis of heterocyclic compounds from isocyanides[18] we wish to report on a novel synthetic route to hexahydro-1,4-thi-

* Corresponding author.
† Università di Firenze.
‡ Universidad de Valladolid.
§ Universidad de Burgos.

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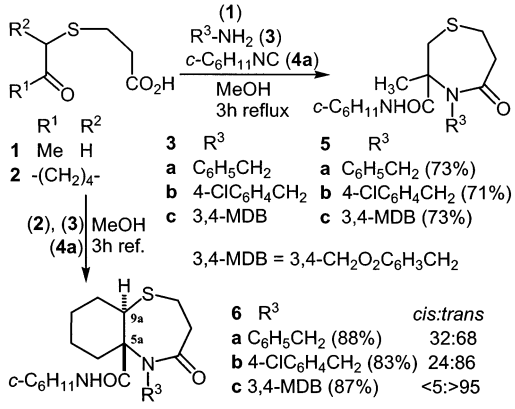
SCHEME 1



azepin-5-ones and 1,4-benzothiazepin-5-ones via intramolecular Ugi condensations.

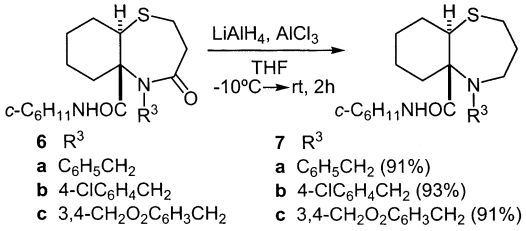
The Ugi four-component condensation between bifunctional 6-oxo-4-thiacarboxylic acids **1** and **2**, obtained following known methods,[19] commercial benzylamines **3a**−**c**, and the commercial cyclohexylisocyanide **4a** took place smoothly in boiling methanol to give monocyclic and bicyclic 5-oxohexahydro-1,4-thiazepin-3-carboxamides **5a**−**c** and **6a**−**c**, respectively, in good yields (71−88%) (Scheme 1). In a typical experiment, a solution of cyclohexyl isocyanide **4a** (4 mmol) in methanol (4 mL) was added to a solution of **1** or **2** (4 mmol) and **3a**−**c** (4 mmol) in methanol (4 mL). The resulting mixture was refluxed for 3 h and then evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate (30 mL) and washed with 0.5% NaOH in water. The organic layer was separated, washed with water, and dried (Na_2SO_4). Removal of the solvent left a residue, which was recrystallized from $^{i}PrOH/^{i}Pr_2O$ to give the products.

The structure of compounds **5a**−**c** and **6a**−**c** was confirmed by their analytical and spectral data. The bicyclic hexahydro-1,4-thiazepin-5-ones **6a**−**c** were obtained stereoselectively, probably due to 1,2-stereoinduction by the steric strain of the cyclohexane ring. The relative configuration of bicyclic compounds **6a**−**c** was established by their ^{1}HNMR spectra and NOESY experiments on the major diastereomer. These showed that the proton at the C-9a was trans with respect to the proton NH of the amide at C-5a. The reduction of compounds **6a**−**c** with $LiAlH_4/AlCl_3$ took place chemoselectively. The cyclic carbonyl group was reduced, whereas the *N*-cyclohexylcarboxamide group remained unchanged, giving bicyclic 1,4-thiazepine-3-carboxamides **7a**−**c**.

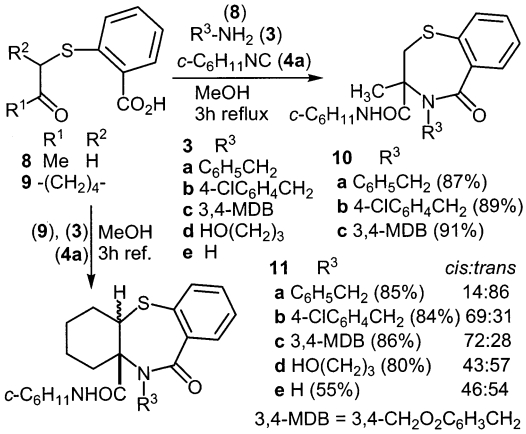
In the same way, the synthesis of 1,4-benzothiazepine-5-ones was achieved by the intramolecular Ugi condensation beetween bifunctional oxoacids **8** and **9**, obtained following known methods,[20] amines **3a**−**e**, and cyclohexyl isocyanide **4a** (Scheme 3).

As in previous examples, the reaction took place easily in refluxing methanol for 3 h, giving the expected products **10a**−**c** and **11a**−**e** in excellent yield. The stereoselectivity of the reaction that gave tricyclic systems **11a**−**d** depended on the benzyl substitution for

SCHEME 2



SCHEME 3



amines **3a**−**c**, resulting in the trans-diastereomer being favored when **3a** was employed and the cis-diastereomer when **3b**−**c** were used, probably mediated by $\pi-\pi$ interactions. Stereoselectivity was irrelevant for other amines. Diastereomeric excesses were determined by integration of the ^{1}HNMR signals on reaction mixtures.

When we used ammonia as amine we obtained **11d** in low yield, in addition to a new compound **12a** (40%) whose HRMS and microanalysis (as a 1:1 adduct with methanol) apparently corresponded to the product from a three-component Passerini reaction.[16b] But the ^{13}C NMR spectrum of **12a** showed a single carbonyl group (δ 172) and two quaternary carbon atoms at δ 108 and δ 83 instead of two carbonyl groups and one quaternary carbon, although the total number of carbon signals corresponded to the sum of those for **9** plus **4a**. The ^{1}H NMR of **12a** showed a broad signal at δ 4, confirmed by a strong signal at 3427 cm^{-1} in the IR, indicating the presence of an OH group instead of the expected NH group (the methanol present in the sample was also detected by characteristic signals in IR and ^{1}H NMR). Single-crystal X-ray diffraction of **12a** showed a tetracyclic structure (Figure 1) that included the expected 1,4-benzothioxepin group and a unexpected oxazolidinone ring, probably formed by a nucleophilic attack of the amide nitrogen to the lactone carbonyl group of the Passerini intermediate **13**, catalyzed by ammonia, with formation of a rare orthoamide group (Scheme 4). **12a** was obtained as the only product (91%) by performing the reaction in the absence of ammonia, but in the presence of a catalytic amount of tributylamine (product **12a** was also obtained at room temperature in the absence of base in 88% yield). Analogously, **12b**,**c** were prepared (87 and 73%) from isocyanides **4b**,**c** (Scheme 4). The same reaction conditions starting from acid **2** and

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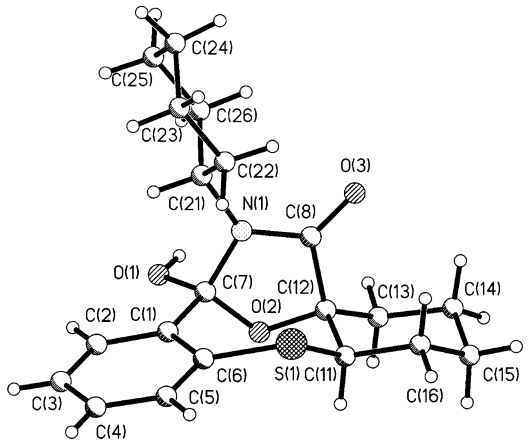
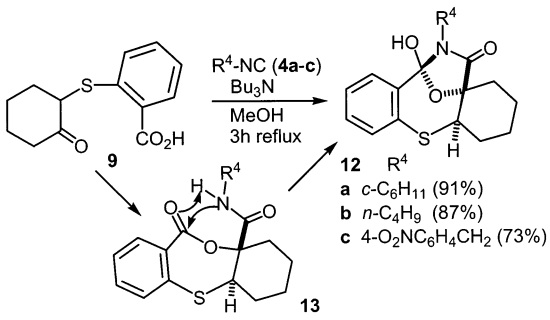
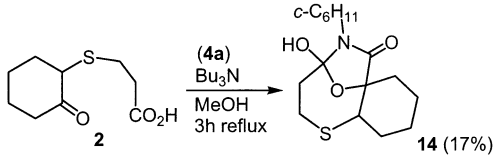


FIGURE 1. The molecular structure of **12a**.

SCHEME 4



SCHEME 5



isocyanide **4a** gave the corresponding orthoamide **14**, but in very low yield (Scheme 5).

The *N*-amidoalkoxycarbinol moiety (orthoamide) was considered as an unstable intermediate in the reaction of ester with amide anion or imide with alkoxy anion, and the only known stable compounds having this structural feature were peptide ergot alkaloids (ergopeptines)[21] and very few synthetic compounds.[22] The reported reaction constitutes a new and highly stereoselective path to stable polycyclic orthoamides.

In conclusion, the reported reactions constitute fast and useful methods for the one-pot syntheses of hexahydro-1,4-thiazepines, 1,4-benzothiazepines, and 1,4-benzothioxepin orthoamides from commercial or easily available starting materials. The method gives a fair cis:trans diastereoselectivity when cyclohexyl ketoacids are employed and permits a large structural diversity in the final products from simple structural changes in the starting materials.

Experimental Section

General Procedure for the Synthesis of Hexahydro-1,4-thiazepin-5-ones 5a−c. A solution of cyclohexyl isocyanide **4a** (0.44 g, 4 mmol) in methanol (4 mL) was added to a solution of **1**,**2** or **8**,**9** (4 mmol) and **3a**−**d** (4 mmol) in methanol (4 mL). The resulting mixture was heated under reflux for 3 h and then the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (30 mL) and washed with an aqueous solution of NaOH (0.5% w/v, 10 mL). The organic layer was separated, washed with water, and dried (Na_2SO_4). Removal of the solvent gave a residue that was recrystallized from ^{i}PrOH/$^{i}Pr_2O$. CH_3, CH_2, and CH assignments were performed from DEPT experiments on representative examples.

4-Benzyl-3-methyl-5-oxo-2,3,4,5,6,7-hexahydro-1,4-thiazepin-3-(*N*-cyclohexylcarboxamide), 5a: White solid, 1.05 g (73%), mp 150−151 °C; IR (KBr, cm^{-1}) ν 3337 (NH), 1667 (CO), 1632 (CO). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.98−1.97 (m, 13 H), 2.66−2.86 (m, 5 H), 3.36 (d, J = 15.6 Hz, 1 H), 3.41−3.60 (m, 1 H), 4.36 (d, J = 15.8 Hz, 1 H), 4.94 (d, J = 15.8 Hz, 1 H), 5.98 (d, J = 7.0 Hz, 1 H, NH), 7.04−7.48 (m, 5 H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0, 24.5 and 25.3 (3 × CH_2, DEPT), 26.7 (CH_3, DEPT), 31.9, 32.6, 35.8 and 38.0 (4 × CH_2, DEPT), 48.6 (CH, DEPT), 48.8 (CH_2, DEPT), 67.3 (Cq), 127.2, 127.4 and 128.8 (3 × CH_{Ar}, DEPT), 139.1 (C_{Ar}), 172.2 and 173.8 (2 × CO); MS (EI, *m*/*z*, %) 361 (M + 1, 46), 136 (100); HRMS (EI) $(M + 1)_{found}$ 361.1957, $C_{20}H_{29}N_2O_2S$ requires 361.1950. Anal. Calcd for $C_{20}H_{28}N_2O_2S$: C, 66.63; H, 7.83; N, 7.77. Found: C, 66.52; H, 8.00; N, 7.64.

4-(4-Chlorobenzyl)-3-methyl-5-oxo-2,3,4,5,6,7-hexahydro-1,4-thiazepin-3-(*N*-cyclohexylcarboxamide), 5b: White solid, 1.12 g (71%), mp 165−167 °C; IR (KBr, cm^{-1}) ν 3352 (NH), 1651 (CO); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98−1.98 (m, 13 H), 2.63−2.90 (m, 5 H), 3.26 (d, J = 16.0 Hz, 1 H), 3.41−3.60 (m, 1 H), 4.43 (d, J = 16.0 Hz, 1 H), 4.70 (d, J = 16.0 Hz, 1 H), 5.98 (d, J = 7.6 Hz, 1 H, NH), 7.19−7.51 (m, 4 H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.9, 24.7 and 25.3 (3 × CH_2), 26.2 (CH_3), 32.0, 32.5, 35.7 and 37.9 (4 × CH_2), 48.5 (CH), 48.6 (CH_2), 67.3 (Cq), 128.8 (CH_{Ar}), 132.9 and 137.4 (2 × C_{Ar}), 171.8 and 173.7 (2 × CO). Anal. Calcd for $C_{20}H_{27}ClN_2O_2S$: C, 60.82; H, 6.89; N, 7.09. Found: C, 60.71; H, 6.97; N, 7.00.

5-Benzyl-4-oxo-2,3,4,5,5a,6,7,8,8a,9-decahydrobenzo[1,5]-thiazepin-5a-(*N*-cyclohexylcarboxamide), 6a: White solid, 1.41 g (88%), mp 202−204 °C; IR (KBr, cm^{-1}) ν 3345 (NH), 1669 (CO), 1629 (CO); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98−1.98 (m, 17 H), 2.35−2.41 (m, 1 H), 2.80−3.10 (m, 4 H), 3.41 (dd, J = 11.7, 3.6 Hz, 1 H), 3.57−3.61 (m, 1 H), 4.58 (d, J = 15.8 Hz, 1 H), 4.68 (d, J = 15.8 Hz, 1 H), 7.04 (d, J = 7.6 Hz, 1 H, NH), 7.10−7.32 (m, 5 H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5, 24.5, 25.5, 26.5, 31.4, 32.1, 32.8, 37.4 and 37.6 (9 × CH_2, DEPT), 46.4 and 48.3 (2 × CH, DEPT), 48.6 (CH_2, DEPT), 70.6 (Cq), 126.7, 126.9 and 128.4 (3 × CH_{Ar}, DEPT), 139.2 (C_{Ar}), 169.3 and 173.7 (2 × CO); MS (EI, *m*/*z*, %) δ 400 (M^+, 1), 274 (39), 91 (100); HRMS (EI) M^+_{found} 400.2200, $C_{23}H_{32}N_2O_2S$ requires 400.2184. Anal. Calcd for $C_{23}H_{32}N_2O_2S$: C, 68.96; H, 8.05; N, 6.99. Found: C, 69.01; H, 8.12; N, 6.91.

5-(4-Chlorobenzyl)-4-oxo-2,3,4,5,5a,6,7,8,8a,9-decahydrobenzo[1,5]thiazepin-5a-(*N*-cyclohexylcarboxamide), 6b: White solid, 1.44 g (83%), mp 207−209 °C; IR (KBr, cm^{-1}) ν 3326 (NH), 1668 (CO), 1624 (CO); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94−2.00 (m, 17 H), 2.42−2.48 (m, 1 H), 2.80−3.10 (m, 4 H), 3.47 (dd, J = 12.0, 2.9 Hz, 1H), 3.57−3.61 (m, 1 H), 4.50 (d, J = 15.6 Hz, 1 H), 4.61 (d, J = 15.6 Hz, 1H), 7.09−7.26 (m, 4H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.6, 24.7, 25.5, 26.7, 31.5, 32.1, 32.6, 37.1 and 37.2 (9 × CH_2, DEPT), 46.4 (CH, DEPT), 48.2 (CH_2, DEPT), 48.4 (CH, DEPT), 70.8 (Cq), 128.4 (CH_{Ar}, DEPT), 132.3 and 137.7 (2 × C_{Ar}), 168.9 and 173.2 (2 × CO); MS (EI, *m*/*z*, %) δ 434 (M^+, 1), 308 (29), 125 (100); HRMS (EI) M^+_{found} 434.1808, $C_{23}H_{31}ClN_2O_2S$ requires 434.1795. Anal. Calcd for

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$C_{23}H_{31}ClN_2O_2S$: C, 63.50; H, 7.18; N, 6.44. Found: C, 63.57; H, 7.27; N, 6.42.

4-Benzyl-3-methyl-5-oxo-2,3,4,5-tetrahydro[1,4]benzothiazepine-3-(*N*-cyclohexylcarboxamide), 10a: White solid, 1.42 g (87%), mp 127−129 °C; IR (KBr, cm^{-1}) ν 3389 (NH), 1668 (CO), 1621 (CO); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.75−1.61 (m, 13 H), 2.60 (d, J = 12.8 Hz, 1 H), 3.00−3.04 (m, 1 H), 4.32 (d, J = 12.8 Hz, 1 H), 5.02 (d, J = 15.8 Hz, 1 H), 5.13 (d, J = 15.8 Hz, 1 H), 5.49 (d, J = 7.3 Hz, 1 H, NH), 7.25−7.54 (m, 9 H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.5, 24.8 and 25.6 (3 × CH_2, DEPT), 28.2 (CH_3, DEPT), 32.2, 32.7, 43.0 and 47.8 (4 × CH_2, DEPT), 49.0 (CH, DEPT), 66.6 (Cq), 127.7, 127.8, 128.7, 129.2, 131.0, 131.6 and 133.1 (7 × CH_{Ar}, DEPT), 139.6 and 141.1 (2 × C_{Ar}), 171.2 and 172.6 (2 × CO); MS (EI, *m*/*z*, %) 408 (M^+, 1), 282 (39), 91 (100); HRMS (EI), M^+_{found} 408.1852, $C_{24}H_{28}N_2O_2S$ requires 408.1871. Anal. Calcd for $C_{24}H_{28}N_2O_2S$: C, 70.55; H, 6.91; N, 6.86. Found: C, 70.23; H, 6.97; N, 6.62.

4-(4-Chlorobenzyl)-3-methyl-5-oxo-2,3,4,5-tetrahydro-[1,4]benzothiazepine-3-(*N*-cyclohexylcarboxamide), 10b: White solid, 1.58 g (89%), mp 217−218 °C; IR (KBr, cm^{-1}) ν 3340 (NH), 1651 (CO), 1618 (CO); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.76−1.61 (m, 13 H), 2.55 (d, J = 12.7 Hz, 1 H), 2.99−3.06 (m, 1 H), 4.30 (d, J = 12.7 Hz, 1 H), 4.91 (d, J = 15.8 Hz, 1 H), 5.16 (d, J = 15.8 Hz, 1 H), 5.38 (d, J = 7.3 Hz, 1 H, NH), 7.14−7.50 (m, 8 H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.5, 24.8 and 25.6 (3 × CH_2, DEPT), 28.2 (CH_3, DEPT), 32.3, 32.7, 43.0 and 47.1 (4 × CH_2, DEPT), 49.1 (CH, DEPT), 66.6 (Cq), 128.7, 129.2 and 129.3 (3 × CH_{Ar}, DEPT), 130.0 (C_{Ar}), 131.0, 131.7 and 133.1 (3 × CH_{Ar}, DEPT), 133.6, 137.9 and 140.9 (3 × C_{Ar}), 171.0 and 172.6 (2 × CO); MS (EI, *m*/*z*, %) 442 (M^+, 2), 316 (100), 125 (62); HRMS (EI), M^+_{found} 442.1495, $C_{24}H_{27}ClN_2O_2S$ requires 442.1482. Anal. Calcd for $C_{24}H_{27}ClN_2O_2S$: C, 65.07; H, 6.14; N, 6.32. Found: C, 64.97; H, 5.96; N, 6.29.

10-Benzyl-11-oxo-5a,6,7,8,9,9a,10,11-octahydrodibenzo-[*b*,*f*][1,4]thiazepin-9a-(*N*-cyclohexylcarboxamide), 11a: White solid, 1.52 g (85%), mp 214−215 °C; IR (KBr, cm^{-1}) ν 3367 (NH), 1661 (CO), 1630 (CO); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.61−2.13 (m, 18 H), 2.82−2.97 (m, 1 H), 4.59 (dd, J = 12.7, 3.9 Hz, 1 H), 4.76 (d, J = 16.1 Hz, 1 H), 5.36 (d, J = 7.0 Hz, 1 H, NH), 5.73 (d, J = 16.1 Hz, 1 H), 7.24−7.53 (m, 9 H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.8, 24.2, 24.4, 25.0, 25.6, 28.3, 32.2, 32.5, 35.9 and 48.6 (10 × CH_2, DEPT), 48.9 and 53.1 (2 × CH, DEPT), 68.7 (Cq), 127.1, 127.8, 128.4, 129.5, 131.1, 131.6 and 132.5 (7 × CH_{Ar}, DEPT), 140.3 and 141.4 (2 × C_{Ar}), 172.5 and 173.4 (2 × CO); MS (EI, *m*/*z*, %) 448 (M^+, 5), 322 (100), 91 (51). HRMS (EI), M^+_{found} 448.2179, $C_{27}H_{32}N_2O_2S$ requires 448.2184. Anal. Calcd for $C_{27}H_{32}N_2O_2S$: C, 72.29; H, 7.19; N, 6.24. Found: C, 72.19; H, 7.35; N, 6.27.

10-(4-Chlorobenzyl)-11-oxo-5a,6,7,8,9,9a,10,11-octahydrodibenzo[*b*,*f*][1,4]thiazepin-9a-(*N*-cyclohexylcarboxamide), 11b: White solid, 1.62 g (84%), mp 221−222 °C; IR (KBr, cm^{-1}) ν 3414 (NH), 1651 (CO), 1633 (CO); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.75−1.98 (m, 17 H), 2.89−3.02 (m, 2 H), 3.33 (dd, J = 12.8, 4.4 Hz, 1 H), 4.86−5.17 (m, 2 H), 5.30 (d, J = 7.0 Hz, 1 H), 7.24−7.49 (m, 8 H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.8, 24.4, 24.8, 25.6, 25.9, 32.0, 32.8, 33.8, 40.2 and 46.3 (10 × CH_2), 48.6 and 57.3 (2 × CH), 68.3 (Cq), 127.6, 128.6, 128.9, 129.3, 131.2, 131.5 and 132.3 (7 × CH_{Ar}), 133.5, 138.4 and 139.3 (3 × C_{Ar}), 169.8 and 172.9 (2 × CO); MS (EI, *m*/*z*, %) 482 (M^+, 3), 356 (85), 125 (100); HRMS (EI), M^+_{found} 482.1807, $C_{27}H_{31}ClN_2O_2S$ requires 482.1795. Anal. Calcd for $C_{27}H_{31}ClN_2O_2S$: C, 67.13; H, 6.47; N, 5.80. Found: C, 66.99; H, 6.62; N, 5.74.

11-Oxo-5a,6,7,8,9,9a,10,11-octahydrodibenzo[*b*,*f*][1,4]thiazepin-9a-(*N*-cyclohexylcarboxamide), 11e: White solid, 0.79 g (55%), mp 199−200 °C; IR (KBr, cm^{-1}) ν 3387 (NH), 3271 (NH), 1645 (CO); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.63−1.97 (m, 17 H), 2.18−2.22 (m, 1H), 3.09−3.23 (m, 2 H), 4.47 (dd, J = 11.8, 4.8 Hz, 1 H), 5.86 (d, J = 7.8 Hz, 1 H, NH), 7.18−7.41 (m, 4 H, H_{Ar}), 7.56−7.60 (m, 1 H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.2, 25.0, 30.2, 32.6, 32.8 and 38.6 (6 × CH_2, DEPT), 48.9 and 52.3 (2 × CH, DEPT), 63.3 (Cq), 128.1, 130.8, 132.0 and 133.0 (4 × CH_{Ar}, DEPT), 135.8 and 139.2 (2 × C_{Ar}), 171.4 and 172.4 (2 × CO); MS (EI, *m*/*z*, %) 358 (M^+, 28), 232 (100); HRMS (EI), M^+_{found} 358.1709, $C_{20}H_{26}N_2O_2S$ requires 358.1715. Anal. Calcd for $C_{20}H_{26}N_2O_2S$: C, 67.01; H, 7.31; N, 7.81. Found: C, 66.97; H, 7.23; N, 7.79.

General Procedure for the Synthesis of 12a−c. A solution of tributylamine in methanol (1:10 w/w, 0.25 mL) was added to a solution of isocyanide **4a**−**c** (1 mmol) and **9** (250 mg, 1 mmol) in methanol (4 mL). The resulting mixture was stirred at room temperature for 24 h and then filtered. The collected solid was washed with methanol to give **12a**−**c**. Removal of the solvent gave a residue that was recrystallized from methanol to give additional amounts of **12a**−**c**.

7-Aza-4,5-benzo-7-cyclohexyl-6-hydroxy-9-oxa-8-oxo-1,2-(tetramethylene)-3-thiabicyclo[4.2.1]nonane, 12a: White solid, 0.36 g (91%), mp 134−135 °C; IR (KBr, cm^{-1}) ν 3427 (OH), 1684 (CO); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.91−2.26 (m, 17 H), 3.16−3.27 (tt, J = 12.0, 4.0 Hz, 1 H), 3.32 (dd, J = 12.0, 4.0, 1 H), 3.5 (br s, 1 H, OH), 7.17−7.28 (m, 2 H, H_{Ar}), 7.40−7.49 (m, 1 H, H_{Ar}), 7.78−7.87 (m, 1 H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4, 25.2, 25.4, 26.1, 26.4, 28.5, 29.4, 30.9 and 34.4 (9 × CH_2, DEPT), 53.6 and 53.9 (2 × CH, DEPT), 82.9 and 107.9 (2 × Cq), 126.9, 127.7, 129.3 and 132.2 (4 × CH_{Ar}, DEPT), 133.5 and 141.0 (2 × C_{Ar}), 171.8 (CO); MS (EI, *m*/*z*, %) 359 (M^+, 72), 277 (20), 206 (60), 193 (80), 137 (100); HRMS (EI) M^+_{found} 359.1554, $C_{20}H_{25}NO_3S$ requires 359.1555. Anal. Calcd for $C_{20}H_{25}NO_3S{\cdot}CH_3OH$: C, 64.42; H, 7.47; N, 3.58. Found: C, 64.42; H, 7.80; N, 3.68.

Crystal Structure Determination for 12a·MeOH: This material is available from the Cambridge Crystallographic Data Centre, including atomic coordinates, thermal parameters, and a full list of bond lengths and angles (CCDC 202033).

7-Aza-4,5-benzo-7-butyl-6-hydroxy-9-oxa-8-oxo-1,2-(tetramethylene)-3-thiabicyclo[4.2.1]nonane 12b: White solid, 0.32 g (87%), mp 165−166 °C; IR (KBr, cm^{-1}) 3420−3060 (OH), 1688 (CO); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.78 (t, J = 7.3, 3 H), 1.16−1.32 (m, 4 H), 1.48−1.88 (m, 6 H), 2.16−2.22 (m, 2 H), 2.83−2.90 (m, 1 H), 3.21−3.29 (m, 1 H), 3.34 (dd, J = 6.5, 4.4 Hz, 1 H), 4.44 (br s, 1 H, NH), 7.18−7.25 (m, 2 H, H_{Ar}), 7.42−7.45 (m, 1 H, H_{Ar}), 7.82−7.84 (m, 1 H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8 (CH_3), 20.6, 22.4, 25.2, 28.5, 30.2, 34.2 and 40.1 (7 × CH_2), 53.7 (CH), 83.6 and 108.0 (2 × Cq), 127.0, 127.9, 129.4 and 132.3 (4 × CH_{Ar}), 133.2 and 141.2 (2 × C_{Ar}), 172.5 (CO); MS (EI, *m*/*z*, %) 333 (M^+, 71), 180 (100), 137 (69); HRMS, M^+_{found} 333.1401, $C_{21}H_{20}N_2O_5S$ requires 333.1399. Anal. Calcd for $C_{18}H_{23}NO_3S{\cdot}CH_3OH$: C, 62.44; H, 7.45; N, 3.83. Found: C, 62.90; H, 7.75; N, 3.65.

7-Aza-4,5-benzo-7-(4-nitrobenzyl)-6-hydroxy-9-oxa-8-oxo-1,2-(tetramethylene)-3-thiabicyclo[4.2.1]nonane, 12c: White solid, 0.30 g (73%), mp 241−242 °C; IR (KBr, cm^{-1}) ν 3290 (OH), 1687 (CO); ^1H NMR (DMSO, 400 MHz) δ 1.28−2.17 (m, 8 H), 3.39 (dd, J = 6.5, 4.0 Hz, 1 H), 4.21 (d, J = 15.6 Hz, 1 H), 4.29 (d, J = 15.6 Hz, 1 H), 7.10−7.25 (m, 3 H, H_{Ar}), 7.38−7.40 (m, 2 H, H_{Ar}), 7.61−7.64 (m, 1 H, H_{Ar}), 7.93−8.26 (m, 2 H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4, 24.9, 28.6, 34.0, and 42.9 (5 × CH_2, DEPT), 53.7 (CH, DEPT), 83.0 and 107.6 (2 × Cq), 123.3, 127.2, 128.3, 129.6, 130.1 and 132.0 (6 × CH_{Ar}, DEPT), 132.8, 141.6, 144.7 and 147.1 (4 × C_{Ar}), 172.1 (CO); MS (EI, *m*/*z*, %) 412 (M^+, 37), 259 (37), 136 (57), 109 (100); HRMS, M^+_{found} 412.1099, $C_{21}H_{20}N_2O_5S$ requires 412.1093. Anal. Calcd for $C_{21}H_{20}N_2O_5S$: C, 61.15; H, 4.89; N, 6.79. Found: C, 61.06; H, 4.76; N, 6.78.

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Supporting Information Available: Experimental procedure and characterization of **1**, **2**, **5c**, **6**, **7a**−**c**, **8**, **9**, **10c**, **11c,d**, and **14**; details of the crystal structure determination and crystallographic data (excluding structure factors) for **12a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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