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Synthesis of Dihydrobenzoheterocycles through Al(OTf)$_3$-Mediated Cascade Cyclization and Ionic Hydrogenation

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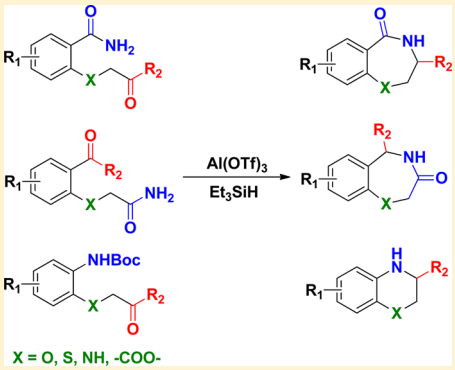
Supporting Information

ABSTRACT: A facile and versatile synthesis of dihydrobenzoheterocycles via Al(OTf)$_3$-mediated cascade cyclization and ionic hydrogenation has been developed. The reaction is applicable to a wide range of substrates with various functional groups to afford the corresponding products in good yields.



INTRODUCTION

Six- and seven-membered dihydrobenzoheterocycles are privileged scaffolds that have been found in a wide variety of natural products and bioactive important molecules.[1] Among them, heterocycles with two heteroatoms in 1,4-distance such as dihydro-1,4-benzoxazepinones and dihydro-1,4-benzoxazines are known to possess high biological activity (Figure 1).[2] In the past few decades, the development of methods for the preparation of such types of compounds has attracted remarkable attention in the synthetic community.[3]

Ionic hydrogenation has been considered to be an efficient method for the reduction of ketones, alcohols, and imines.[4] Recently, our group has developed a cascade cyclization and ionic hydrogenation strategy to synthesize a vast array of lactams from ketoamides using the Et$_3$SiH/Lewis acid system.[5] This method provided an important way to form the intramolecular N−C bond, especially the amide N−C bond in *N*-heterocycles. Based on this cascade reaction, structural diverse *N*-substituted lactams such as pyrrolidinones, piperidones, isoindolinones, and oxazolidinone were readily assembled from different kinds of building blocks in good yields. To continue our efforts on this project, we applied this strategy to the construction of dihydrobenzoheterocycles, such as dihydro-1,4-benzoxazepinones, dihydro-1,4-benzoxazines and other related heterocycles (Scheme 1).

RESULTS AND DISCUSSION

Initially, 2-(2-oxopropoxy)benzamide (**1a**) was chosen as a model substrate to investigate the reaction conditions for construction of 3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one (**2a**). To our delight, in the presence of Al(OTf)$_3$ (0.5 equiv) and Et$_3$SiH (2.0 equiv) in CH$_3$CN at room temperature, the desired product was observed and isolated in 55% yield after 12 h (Table 1, entry 1). Encouraged by this result, we examined optimal conditions to obtain more satisfactory results (Table 1). Changing CH$_3$CN to other solvents such as CH$_2$Cl$_2$, CH$_3$NO$_2$, DMF, and THF led to lower yields (Table 1, entries 2−5). When the temperature was raised to 80 °C, the yield of **2a** was increased to 85% and the reaction time for complete conversion was shortened to 30 min (Table 1, entry 6). Screening of Lewis and Brønsted acids indicated that Al(OTf)$_3$ displayed the highest reaction activity toward the formation of **2a** (Table 1, entries 6−14).

With the optimal conditions in hand, we examined the scope and limitation of this cascade reaction to assemble 3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one (Table 2). Both methyl (**2a**−**c**) and aryl groups (**2d**−**k**) were introduced into the 3-position of the dihydrobenzoxazepin-5(2*H*)-one scaffold successfully. The formation of 3-aryl-substituted products took longer time than for 3-methyl-substituted products, perhaps because of steric hindrance from the aryl groups. The reaction was found to be tolerant to electron-donating groups (**2b**,**e**−**f**), electron-withdrawing groups (**2j**), and halides (**2c**,**g**−**i**) as well as a heterocyclic group (**2k**) and generated the target products in good to excellent yields. Interestingly, a tricyclic compound, 6,7,8,9,9a,10-hexahydro-1,4-dibenzoxazepin-11(5a*H*)-one (**2l**), could be efficiently synthesized using this cascade reaction and is the important motif found in various natural products and pharmaceutical compounds.[6]

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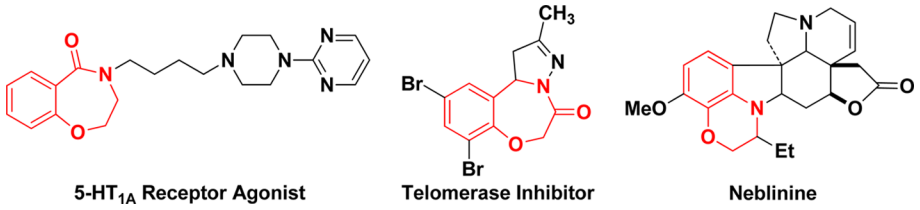


Figure 1. Representative examples of dihydrobenzoheterocycles.

Scheme 1. Strategies for the Construction of *N*-Heterocycles

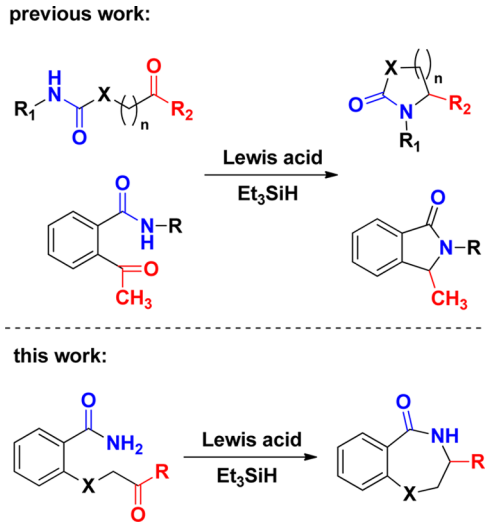
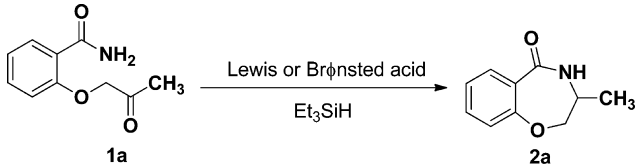


Table 1. Optimization of Reaction Conditions[a,b]



entry	acid	solvent	*T* (°C)	time (h)	yield (%)
1	$Al(OTf)_3$	CH_3CN	rt	12	55
2	$Al(OTf)_3$	CH_2Cl_2	rt	12	0
3	$Al(OTf)_3$	CH_3NO_2	rt	12	38
4	$Al(OTf)_3$	DMF	rt	12	trace
5	$Al(OTf)_3$	THF	rt	12	trace
6	$Al(OTf)_3$	CH_3CN	80	0.5	85
7	$AlCl_3$	CH_3CN	80	1	68
8	$SnCl_4$	CH_3CN	80	4	23
9	$TiCl_4$	CH_3CN	80	4	12
10	$ZnCl_2$	CH_3CN	80	4	0
11	$FeCl_3$	CH_3CN	80	4	trace
12	$SnCl_2$	CH_3CN	80	4	0
13	$BF_3{\cdot}Et_2O$	CH_3CN	80	1	64
14	CF_3COOH	CH_3CN	80	4	22

[a]The reaction was performed using **1a** (1.0 equiv), Lewis or Brønsted acid (0.5 equiv), and Et_3SiH (2.0 equiv) in solvent. [b]Isolated yield.

Furthermore, it was found that the benzodiazepin-5-one scaffold can also be constructed based on this method, as 3-phenyl-3,4-dihydro-1*H*-1,4-benzodiazepin-5(2*H*)-one (**2m**) was readily achieved from 2-((2-oxo-2-phenylethyl)amino)-benzamide in moderate yield.

Next, we extended our work to construct another seven-membered dihydrobenzoheterocycle, 4,5-dihydro-1,4-benzoxazepin-3(2*H*)-one (**4**), from 2-(2-acetylphenoxy)acetamide (**3**) (Scheme 2) in a manner similar to that observed with the preparation of **2**. Two target molecules were successfully obtained in moderate yields, indicating that the method is noteworthy for its utility in preparing versatile seven-membered dihydrobenzoheterocycles with high efficiency.

Encouraged by the above results, we turned our attention to the preparation of 3,4-dihydro-1,4-benzoxazine (Table 3), a six-membered dihydrobenzoheterocycle which is a common structure in bioactive molecules.[7] The most common method to synthesize this compound is the reduction of the C═N double bond in 2*H*-1,4-benzoxazine,[8] or the tandem reductive cyclization of nitro compounds (Scheme 3).[9] In our study, when *N*-Boc-2-(2-oxo-2-substituted ethoxy)aniline (e.g., **5a**) was used as the substrate in the $Al(OTf)_3/Et_3SiH$ system, the Boc group was removed and the reaction proceeded very quickly (10 min) to afford the 3,4-dihydro-2*H*-1,4-benzoxazine (e.g., **6a**). The result indicated that a one-pot reaction including removal of Boc group, intramolecular cyclization, and ionic hydrogenation had taken place. We found that a variety of functional groups including electron-donating groups (**6b,c**) and electron-withdrawing groups (**6g,k**) were well tolerated. Of note, compounds with halogen substitutions (**6d−f,i,j**), especially chloro and bromo, could be synthesized successfully in good yields but were difficult to prepare under catalytic hydrogenation conditions. The thienyl ring can also be easily introduced to the 3-position of the dihydro-1,4-benzoxazine scaffold (**6l**). Moreover, three other dihydrobenzoheterocycles with different scaffolds, 3-methyl-3,4-dihydro-2*H*-1,4-benzothiazine (**6m**), 2-methyl-1,2,3,4-tetrahydroquinoxaline (**6n**), and 2-methyl-2,3-dihydro-1,4-benzoxazepin-5(1*H*)-one (**6o**), were easily achieved using the corresponding substrates under standard conditions.

For the formation of dihydro-1,4-benzoxazepinones, two reaction pathways are possible. One way is ketone reduction to the alcohol initially and then direct amination with assistance from a Lewis acid to form 3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one. The other way is ketone cyclization with assistance from a Lewis acid and then reduction of the imine intermediate by ionic hydrogenation. In our study, the alcohol product was not observed during the reaction process. Furthermore, when 2-(2-hydroxy-2-phenylethoxy)benzamide (**7d**) was treated with $Al(OTf)_3$ (0.5 equiv) in CH_3CN at 80 °C, no target product was observed, which did not support the reduction−direct amination procedure. On the other hand, when 2-(2-oxo-2-phenylethoxy)benzamide (**1d**) was treated first with $Al(OTf)_3$ (0.5 equiv), the imine intermediate 3-phenyl-1,4-benzoxazepin-5(2*H*)-one (**8d**) was isolated, which can be reduced by $Al(OTf)_3/Et_3SiH$ to give target product **2d** (Scheme 4). On the basis of the above results, the formation of 3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one deriva-

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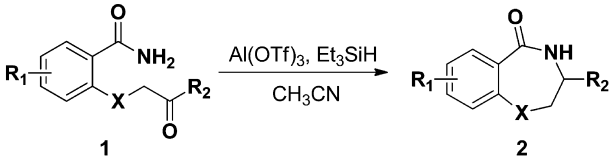
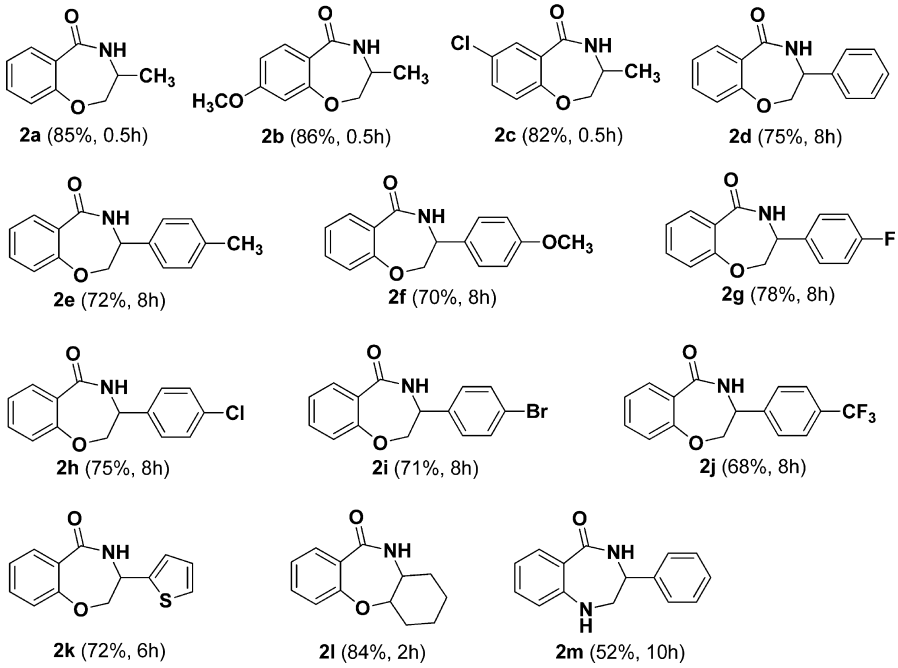
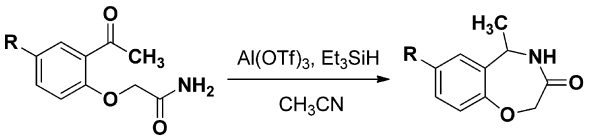
Table 2. Synthesis of 3,4-Dihydrobenzoxazepin-5(2*H*)-ones[a,b]





[a]All reactions were performed using **1** (1.0 equiv), Al(OTf)$_3$ (0.5 equiv), and Et$_3$SiH (2.0 equiv) in CH$_3$CN at reflux for the corresponding time. [b]Isolated yield.

Scheme 2. Synthesis of 4,5-Dihydro-1,4-benzoxazepin-3(2*H*)-ones[a,b]



4a R = H 60%
4b R = CH$_3$O 68%

[a]All reactions were performed using **3** (1.0 equiv), Al(OTf)$_3$ (0.5 equiv), and Et$_3$SiH (2.0 equiv) in CH$_3$CN at reflux for 8 h. [b]Isolated yield.

tives may proceed through a cascade cyclization and reduction pathway (Scheme 5).

Meanwhile, controlled reactions were conducted to explore possible pathways to understand the mechanism of assembling dihydro-1,4-benzoxazines. When *N*-Boc-2-(2-oxo-2-phenylethoxy)aniline (**5h**) was treated with Al(OTf)$_3$ (0.5 equiv) in CH$_3$CN at 80 °C, 3-phenyl-2*H*-1,4-benzoxazine (**9h**) was rapidly formed, which can be easily reduced by Al(OTf)$_3$/Et$_3$SiH to afford target product **6h** (Scheme 4). The results indicated that a sequential Boc removal, condensation, and reduction process occurred to furnish 3,4-dihydro-2*H*-1,4-benzoxazine derivatives (Scheme 5).

CONCLUSIONS

In summary, we have developed a facile and versatile Al(OTf)$_3$-mediated cascade cyclization and ionic hydrogenation reaction which allows access to a variety of dihydrobenzoheterocycles including 3,4-dihydro-1,4-benzoxazepin-5(2*H*)-one (**2a**–**l**), 3,4-dihydro-1*H*-1,4-benzodiazepin-5(2*H*)-one (**2m**), 4,5-dihydro-1,4-benzoxazepin-3(2*H*)-one (**4a**,**b**), 3,4-dihydro-2*H*-1,4-benzoxazine (**6a**–**l**), 3,4-dihydro-2*H*-1,4-benzothiazine (**6m**), 1,2,3,4-tetrahydroquinoxaline (**6n**), and 2,3-dihydro-1,4-benzoxazepin-5(1*H*)-one (**6o**). The relevant reaction mechanism was explored to verify a cascade cyclization and reduction pathway. This method is attractive for its tolerance of a wide range of functional groups, ease of preparation of nitrogen-containing precursors, mild reaction conditions, and high efficiency and has immense potential application in organic synthesis.

EXPERIMENTAL SECTION

General Information. Melting points were determined on a microscope melting point apparatus. NMR spectra were recorded on a 400 MHz NMR spectrometer. Chemical shifts are referenced to the residual solvent peak and reported in ppm (δ scale), and all coupling constant (J) values are given in hertz. ESI-HRMS data were measured on an orbitrap mass spectrometer. Flash column chromatography was performed with 230–400 silica. All the solvents and reagents were obtained from commercial sources and used without further purification.

General Procedure for Synthesis of Dihydrobenzoheterocycles (2a–m, 4a,b, 6a–o). To a solution of **1** or **3** or **5** (1.0 mmol) in CH$_3$CN (5 mL) were added Et$_3$SiH (2.0 mmol) and

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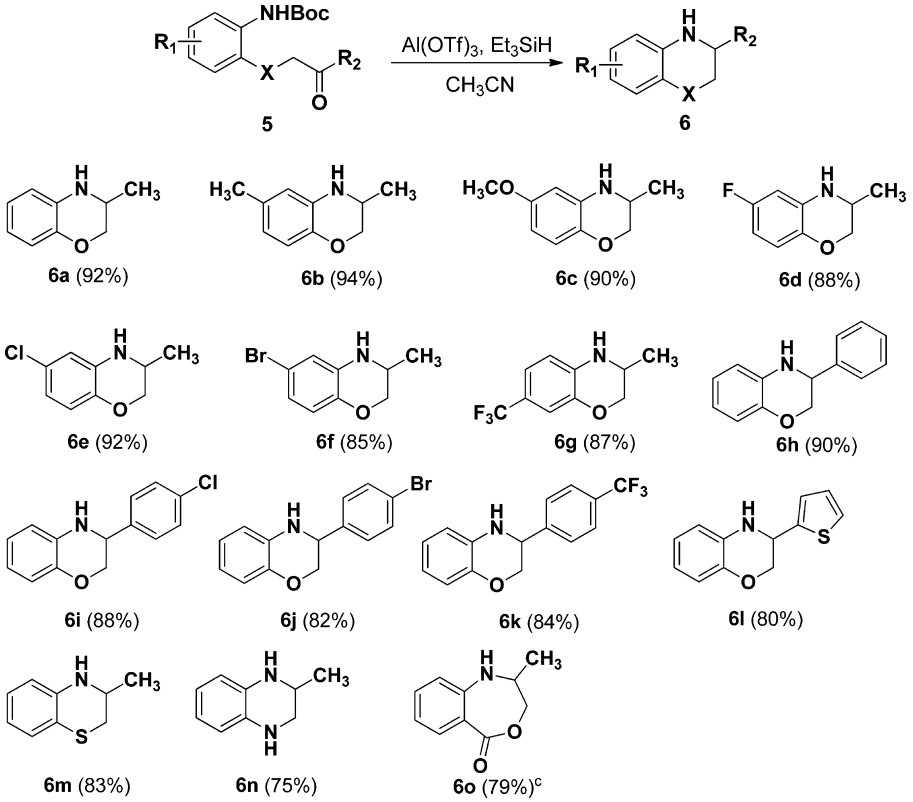
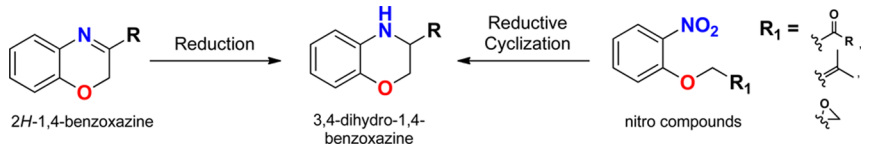
Table 3. Synthesis of 3,4-Dihydrobenzoxazines[a,b]

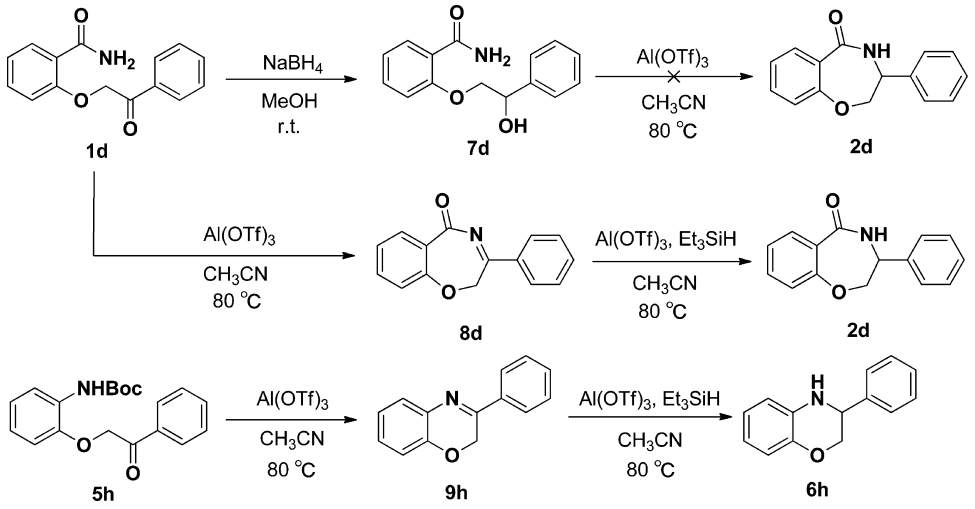


[a]All reactions were performed using **5** (1.0 equiv), $Al(OTf)_3$ (0.5 equiv), and Et_3SiH (2.0 equiv) in CH_3CN at reflux for 10 min. [b]Isolated yield. [c]The reaction was stirred for 1 h.

Scheme 3. Most Common Methods To Synthesize 3,4-Dihydro-1,4-benzoxazines



Scheme 4. Investigation of the Reaction Mechanism



$Al(OTf)_3$ (0.5 mmol) at room temperature. The reaction mixture was heated at reflux for the corresponding time and then concentrated under vacuum. The residue was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel flash column chromatography to afford the desired product.

3-Methyl-3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one (***2a***). Yield: 85% (150 mg); (CH_2Cl_2/EtOAc = 4:1, R_f = 0.40); white

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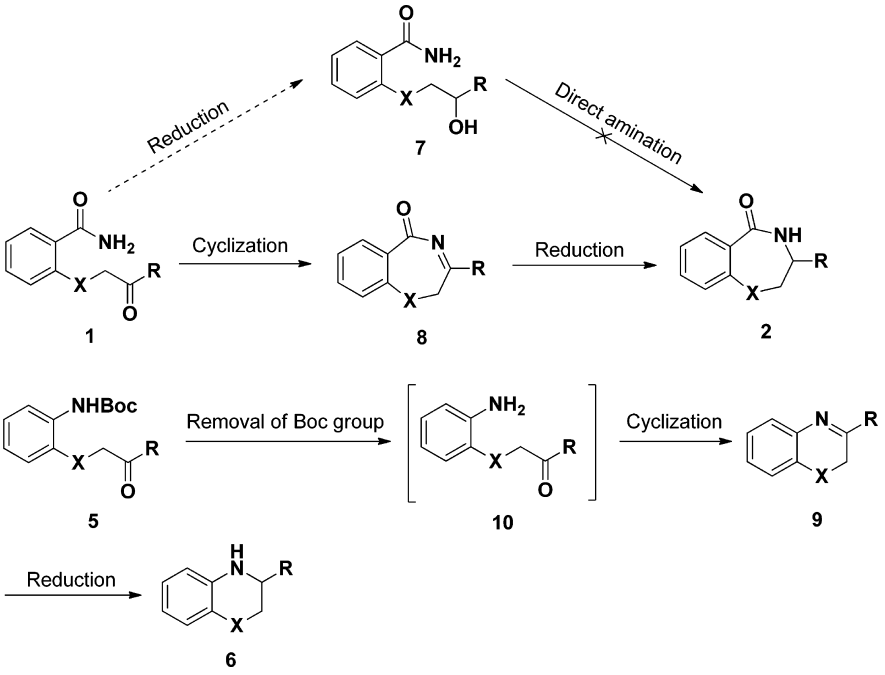
Scheme 5. Proposed Pathway for the Synthesis of Dihydrobenzoheterocycles



solid; mp: 142−144 °C; ^{1}H NMR (400 MHz, acetone) δ 7.92 (d, J = 7.8 Hz, 1H), 7.46−7.39 (m, 2H), 7.12 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 4.26 (dd, J = 11.3, 2.5 Hz, 1H), 4.22−4.09 (m, 1H), 3.78−3.73 (m, 1H), 1.27 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, acetone) δ 167.4, 156.2, 132.7, 131.7, 124.9, 122.4, 120.8, 77.7, 47.3, 15.5; ESI-HRMS m/z calcd for $C_{10}H_{12}NO_2$ [M + H]$^+$ 178.0863, found 178.0861.

8-Methoxy-3-methyl-3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one (***2b***). Yield: 86% (178 mg); (CH_2Cl_2/EtOAc = 4:1, R_f = 0.38); light yellow solid; mp: 87−89 °C; ^{1}H NMR (400 MHz, acetone) δ 7.98 (d, J = 8.9 Hz, 1H), 7.49 (s, 1H), 6.67 (d, J = 8.9 Hz, 1H), 6.50 (s, 1H), 4.27 (dd, J = 11.6, 1.8 Hz, 1H), 4.15 (dd, J = 11.6, 7.9 Hz, 1H), 3.83 (s, 3H), 3.77−3.74 (m, 1H), 1.26 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, acetone) δ 166.7, 163.5, 158.2, 134.0, 115.7, 109.1, 104.0, 76.8, 55.0, 47.8, 16.2; ESI-HRMS m/z calcd for $C_{11}H_{14}NO_3$ [M + H]$^+$ 208.0968, found 208.0967.

7-Chloro-3-methyl-3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one (***2c***). Yield: 82% (173 mg); (CH_2Cl_2/EtOAc = 4:1, R_f = 0.43); white solid; mp: 143−145 °C; ^{1}H NMR (400 MHz, acetone) δ 7.92 (s, 1H), 7.57 (s, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.04 (d, J = 8.7 Hz, 1H), 4.30 (dd, J = 11.5, 2.3 Hz, 1H), 4.19 (dd, J = 11.3, 8.5 Hz, 1H), 3.88−3.73 (m, 1H), 1.28 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, acetone) δ 165.7, 155.1, 132.5, 131.2, 126.9, 125.7, 122.7, 77.5, 47.5, 15.7; ESI-HRMS m/z calcd for $C_{10}H_{11}NO_2Cl$ [M + H]$^+$ 212.0473, found 212.0473.

3-Phenyl-3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one (***2d***). Yield: 75% (179 mg); (CH_2Cl_2/EtOAc = 4:1, R_f = 0.55); white solid; mp: 89−91 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.61 (d, J = 5.3 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.37−7.22 (m, 5H), 7.12 (t, J = 7.6 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 4.79 (t, J = 5.1 Hz, 1H), 4.64 (dd, J = 12.1, 6.4 Hz, 1H), 4.32 (dd, J = 12.1, 1.9 Hz, 1H); ^{13}C NMR (100 MHz, acetone) δ 166.7, 157.2, 138.4, 132.92, 132.82, 128.6, 127.8, 127.1, 123.0, 122.1, 120.4, 75.8, 57.1; ESI-HRMS m/z calcd for $C_{15}H_{14}NO_2$ [M + H]$^+$ 240.1019, found 240.1015.

3-(p-Tolyl)-3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one (***2e***). Yield: 72% (182 mg); (CH_2Cl_2/EtOAc = 4:1, R_f = 0.55); yellow syrup; ^{1}H NMR (400 MHz, acetone) δ 8.13 (d, J = 8.0 Hz, 1H), 7.61 (s, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.20−7.09 (m, 3H), 6.96 (d, J = 8.1 Hz, 1H), 4.85−4.83 (m, 1H), 4.58 (dd, J = 11.9, 7.6 Hz, 1H), 4.37 (dd, J = 11.9, 2.2 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, acetone) δ 166.8, 157.1, 137.5, 135.2, 132.9, 132.7, 129.2, 127.0, 123.3, 122.2, 120.4, 76.1, 56.8, 20.2; ESI-HRMS m/z calcd for $C_{16}H_{16}NO_2$ [M + H]$^+$ 254.1176, found 254.1172.

3-(4-Methoxyphenyl)-3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one (***2f***). Yield: 70% (188 mg); (CH_2Cl_2/EtOAc = 4:1, R_f = 0.50); yellow solid; mp: 95−97 °C; ^{1}H NMR (400 MHz, acetone) δ 8.11 (d, J = 7.9 Hz, 1H), 7.49 (s, 1H), 7.44 (t, J = 7.7 Hz, 1H), 7.33 (d, J = 8.6 Hz, 2H), 7.14 (t, J = 7.6 Hz, 1H), 6.98 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 8.7 Hz, 2H), 4.86−4.78 (m, 1H), 4.56 (dd, J = 11.8, 7.9 Hz, 1H), 4.36 (dd, J = 11.8, 2.4 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, acetone) δ 166.8, 159.6, 157.0, 132.9, 132.6, 129.9, 128.4, 123.5, 122.3, 120.5, 114.0, 76.3, 56.4, 54.7; ESI-HRMS m/z calcd for $C_{16}H_{16}NO_3$ [M + H]$^+$ 270.1125, found 270.1120.

3-(4-Fluorophenyl)-3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one (***2g***). Yield: 78% (200 mg); (CH_2Cl_2/EtOAc = 4:1, R_f = 0.52); yellow solid; mp: 135−137 °C; ^{1}H NMR (400 MHz, acetone) δ 8.17 (d, J = 8.0 Hz, 1H), 7.64 (s, 1H), 7.48−7.41 (m, 3H), 7.15−7.11 (m, 3H), 6.96 (d, J = 8.2 Hz, 1H), 4.95−4.92 (m, 1H), 4.64 (dd, J = 12.0, 7.1 Hz, 1H), 4.41 (dd, J = 12.1, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, acetone) δ 166.7, 163.5, 161.1, 157.2, 133.00, 132.86, 129.2, 122.2, 120.3, 115.3, 115.1, 75.6, 56.5; ESI-HRMS m/z calcd for $C_{15}H_{13}NO_2F$ [M + H]$^+$ 258.0925, found 258.0923.

3-(4-Chlorophenyl)-3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one (***2h***). Yield: 75% (204 mg); (CH_2Cl_2/EtOAc = 4:1, R_f = 0.52); yellow solid; mp: 94−96 °C; ^{1}H NMR (400 MHz, acetone) δ 8.20 (d, J = 8.0 Hz, 1H), 7.67 (s, 1H), 7.46−7.37 (m, 5H), 7.13 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 8.2 Hz, 1H), 4.96−4.94 (m, 1H), 4.67 (dd, J = 12.2, 6.8 Hz, 1H), 4.43 (dd, J = 12.2, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, acetone) δ 166.4, 157.3, 137.7, 133.04, 133.01, 128.8, 128.5, 122.46, 122.36, 122.1, 120.2, 75.1, 56.5; ESI-HRMS m/z calcd for $C_{15}H_{13}NO_2Cl$ [M + H]$^+$ 274.0629, found 274.0625.

3-(4-Bromophenyl)-3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one (***2i***). Yield: 71% (225 mg); (CH_2Cl_2/EtOAc = 4:1, R_f = 0.58); yellow solid; mp: 97−99 °C; ^{1}H NMR (400 MHz, acetone) δ 8.19 (d, J = 8.0 Hz, 1H), 7.71 (s, 1H), 7.54 (d, J = 8.4 Hz, 2H), 7.43 (t, J = 6.8 Hz, 1H), 7.37 (d, J = 8.3 Hz, 2H), 7.13 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 8.1 Hz, 1H), 4.94−4.92 (m, 1H), 4.67 (dd, J = 12.2, 6.7 Hz, 1H), 4.42 (dd, J = 12.2, 1.9 Hz, 1H); ^{13}C NMR (100 MHz, acetone) δ 166.5, 157.2, 138.1, 133.06, 133.02, 131.5, 129.2, 122.4, 122.1, 121.2, 120.2, 75.1, 56.6; ESI-HRMS m/z calcd for $C_{15}H_{13}NO_2Br$ [M + H]$^+$ 318.0124, found 318.0124.

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*3-(4-(Trifluoromethyl)phenyl)-3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one (**2j**).* Yield: 68% (208 mg); (CH_2Cl_2/EtOAc = 4:1, R_f = 0.57); light yellow solid; mp: 141−143 °C; ^{1}H NMR (400 MHz, acetone) δ 8.24 (d, J = 6.8 Hz, 1H), 7.82 (s, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 8.1 Hz, 2H), 7.43 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 5.08 (m, 1H), 4.77 (dd, J = 12.3, 6.2 Hz, 1H), 4.48 (d, J = 12.3 Hz, 1H); ^{13}C NMR (100 MHz, acetone) δ 166.5, 157.4, 143.6, 133.24, 133.22, 133.09, 129.3 (q, J = 31.9 Hz), 127.8, 125.3 (q, J = 3.8 Hz), 124.4 (q, J = 269.6 Hz), 122.0, 120.2, 74.8, 56.9; ESI-HRMS m/z calcd for $C_{16}H_{13}NO_2F_3$ $[M + H]^+$ 308.0893, found 308.0889.

*3-(Thiophene-2-yl)-3,4-dihydrobenzo[f][1,4]oxazepin-5(2H)-one (**2k**).* Yield: 72% (176 mg); (CH_2Cl_2/EtOAc = 4:1, R_f = 0.58); yellow solid; mp: 83−85 °C; ^{1}H NMR (400 MHz, acetone) δ 8.11 (d, J = 8.0 Hz, 1H), 7.83 (s, 1H), 7.44 (t, J = 7.7 Hz, 1H), 7.38 (d, J = 5.1 Hz, 1H), 7.12 (t, J = 7.6 Hz, 2H), 7.03−6.96 (m, 2H), 5.25−5.08 (m, 1H), 4.67 (dd, J = 11.9, 7.0 Hz, 1H), 4.52−4.39 (m, 1H); ^{13}C NMR (100 MHz, acetone) δ 166.3, 156.9, 141.3, 133.0, 132.7, 126.9, 125.6, 125.4, 123.0, 122.3, 120.5, 75.5, 52.7; ESI-HRMS m/z calcd for $C_{13}H_{12}NO_2S$ $[M + H]^+$ 246.0583, found 246.0580.

*6,7,8,9,9a,10-Hexahydrodibenzo[b,f][1,4]oxazepin-11(5aH)-one (**2l**).* Yield: 84% (182 mg); (CH_2Cl_2/EtOAc = 4:1, R_f = 0.55); white solid; mp: 231−233 °C; ^{1}H NMR (400 MHz, DMSO) δ 8.27 (s, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.44 (t, J = 6.9 Hz, 1H), 7.16 (t, J = 7.2 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 4.05 (td, J = 10.7, 4.1 Hz, 1H), 3.08−3.00 (m, 1H), 2.01−1.92 (m, 2H), 1.69−1.59 (m, 2H), 1.44−1.22 (m, 3H), 1.16−1.06 (m, 1H); ^{13}C NMR (100 MHz, DMSO) δ 168.8, 153.8, 133.0, 130.4, 128.7, 123.8, 122.8, 88.4, 54.4, 31.3, 30.0, 24.1, 23.9; ESI-HRMS m/z calcd for $C_{13}H_{16}NO_2$ $[M + H]^+$ 218.1176, found 218.1173.

*3-Phenyl-3,4-dihydro-1H-benzo[e][1,4]diazepin-5(2H)-one (**2m**).* Yield: 52% (123 mg); (CH_2Cl_2/EtOAc = 4:1, R_f = 0.50); light yellow solid; mp: 162−164 °C; ^{1}H NMR (400 MHz, acetone) δ 8.17 (d, J = 8.0 Hz, 1H), 7.35−7.23 (m, 6H), 7.15 (t, J = 7.3 Hz, 1H), 6.69−6.85 (m, 2H), 5.98 (s, 1H), 4.80 (t, J = 5.2 Hz, 1H), 3.85−3.72 (m, 1H), 3.60 (dd, J = 13.6, 3.3 Hz, 1H); ^{13}C NMR (100 MHz, acetone) δ 168.4, 148.3, 141.3, 133.8, 131.8, 128.3, 127.2, 126.6, 117.6, 116.5, 116.3, 58.2, 52.1; ESI-HRMS m/z calcd for $C_{15}H_{15}N_2O$ $[M + H]^+$ 239.1179, found 239.1176.

*5-Methyl-4,5-dihydrobenzo[f][1,4]oxazepin-3(2H)-one (**4a**).* Yield: 60% (106 mg); (CH_2Cl_2/EtOAc = 4:1, R_f = 0.46); white solid; mp: 152−154 °C; ^{1}H NMR (400 MHz, acetone) δ 7.39−7.23 (m, 3H), 7.17 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 8.3 Hz, 1H), 4.79−4.74 (m, 1H), 4.54−4.36 (m, 2H), 1.64 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, acetone) δ 157.7, 136.8, 129.4, 126.47, 126.45, 124.7, 121.0, 72.5, 48.2, 20.2; ESI-HRMS m/z calcd for $C_{10}H_{12}NO_2$ $[M + H]^+$ 178.0863, found 178.0860.

*7-Methoxy-5-methyl-4,5-dihydrobenzo[f][1,4]oxazepin-3(2H)-one (**4b**).* Yield: 68% (140 mg); (CH_2Cl_2/EtOAc = 4:1, R_f = 0.45); white solid; mp: 148−150 °C; ^{1}H NMR (400 MHz, acetone) δ 7.32 (s, 1H), 7.05 (d, J = 8.2 Hz, 1H), 6.91−6.82 (m, 2H), 4.80−4.65 (m, 1H), 4.45−4.33 (m, 2H), 3.79 (s, 3H), 1.62 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, acetone) δ 170.5, 156.6, 151.2, 137.9, 121.7, 113.6, 112.1, 72.7, 55.0, 48.3, 20.0; ESI-HRMS m/z calcd for $C_{11}H_{14}NO_3$ $[M + H]^+$ 208.0968, found 208.0965.

*3-Methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (**6a**).* Yield: 92% (137 mg); (PE/EtOAc = 15:1, R_f = 0.35); brown oil; ^{1}H NMR (400 MHz, acetone) δ 6.66−6.63 (m, 2H), 6.58 (d, J = 7.9 Hz, 1H), 6.50 (t, J = 7.5 Hz, 1H), 4.94 (s, 1H), 4.22−4.06 (m, 1H), 3.70−3.63 (m, 1H), 3.51−3.40 (m, 1H), 1.13 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, acetone) δ 143.5, 134.6, 120.9, 117.3, 115.9, 114.9, 70.4, 44.9, 16.9; ESI-HRMS m/z calcd for $C_9H_{12}NO$ $[M + H]^+$ 150.0913, found 150.0912.

*3,6-Dimethyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (**6b**).* Yield: 94% (153 mg); (PE/EtOAc = 15:1, R_f = 0.35); brown oil; ^{1}H NMR (400 MHz, acetone) δ 6.53 (d, J = 8.0 Hz, 1H), 6.39 (s, 1H), 6.31 (d, J = 8.0 Hz, 1H), 4.82 (s, 1H), 4.13−4.06 (m, 1H), 3.67−3.59 (m, 1H), 3.45−3.41 (m, 1H), 2.12 (s, 3H), 1.11 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, acetone) δ 141.4, 134.2, 129.9, 117.9, 115.60, 115.48, 70.4, 44.9, 20.0, 17.0; ESI-HRMS m/z calcd for $C_{10}H_{14}NO$ $[M + H]^+$ 164.1070, found 164.1067.

*6-Methoxy-3-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (**6c**).* Yield: 90% (161 mg); (PE/EtOAc = 15:1, R_f = 0.21); brown solid; mp: 47−49 °C; ^{1}H NMR (400 MHz, acetone) δ 6.56 (d, J = 8.6 Hz, 1H), 6.19 (s, 1H), 6.09 (d, J = 9.5 Hz, 1H), 5.00 (s, 1H), 4.14−4.03 (m, 1H), 3.64 (s, 3H), 3.62−3.58 (m, 1H), 3.47−3.44 (m, 1H), 1.12 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, acetone) δ 154.6, 137.6, 135.0, 116.0, 102.1, 100.5, 70.3, 54.6, 45.0, 17.0; ESI-HRMS m/z calcd for $C_{10}H_{14}NO_2$ $[M + H]^+$ 180.1019, found 180.1016.

*6-Fluoro-3-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (**6d**).* Yield: 88% (146 mg); (PE/EtOAc = 15:1, R_f = 0.30); brown solid; mp: 30−32 °C; ^{1}H NMR (400 MHz, acetone) δ 6.66−6.57 (m, 1H), 6.35 (d, J = 10.4 Hz, 1H), 6.22 (t, J = 8.6 Hz, 1H), 5.32 (s, 1H), 4.18−4.09 (m, 1H), 3.70−3.59 (m, 1H), 3.54−3.42 (m, 1H), 1.14 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, acetone) δ 158.9, 156.6, 139.4, 135.7, 116.1, 102.4, 102.2, 100.9, 100.6, 70.1, 44.7, 16.8; ESI-HRMS m/z calcd for $C_9H_{11}NOF$ $[M + H]^+$ 168.0819, found 168.0817.

*6-Chloro-3-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (**6e**).* Yield: 92% (168 mg); (PE/EtOAc = 15:1, R_f = 0.32); yellow solid; mp: 60−62 °C; ^{1}H NMR (400 MHz, acetone) δ 6.64 (d, J = 8.4 Hz, 1H), 6.61 (s, 1H), 6.48 (d, J = 8.5 Hz, 1H), 5.31 (s, 1H), 4.22−4.11 (m, 1H), 3.73−3.61 (m, 1H), 3.56−3.42 (m, 1H), 1.15 (dd, J = 6.4, 0.9 Hz, 3H); ^{13}C NMR (100 MHz, acetone) δ 142.1, 135.9, 125.2, 116.9, 116.4, 113.9, 70.2, 44.6, 16.8; ESI-HRMS m/z calcd for $C_9H_{11}NOCl$ $[M + H]^+$ 184.0524, found 184.0525.

*6-Bromo-3-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (**6f**).* Yield: 85% (193 mg); (PE/EtOAc = 15:1, R_f = 0.32); yellow solid; mp: 73−75 °C; ^{1}H NMR (400 MHz, acetone) δ 6.75 (s, 1H), 6.63−6.58 (m, 2H), 5.30 (s, 1H), 4.22−4.10 (m, 1H), 3.73−3.61 (m, 1H), 3.55−3.41 (m, 1H), 1.14 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, acetone) δ 142.6, 136.4, 119.4, 117.4, 116.8, 112.6, 70.2, 44.6, 16.8; ESI-HRMS m/z calcd for $C_9H_{11}NOBr$ $[M + H]^+$ 228.0019, found 228.0020.

*3-Methyl-7-(trifluoromethyl)-3,4-dihydro-2H-benzo[b][1,4]-oxazine (**6g**).* Yield: 87% (188 mg); (PE/EtOAc = 15:1, R_f = 0.30); yellow solid; mp: 63−65 °C; ^{1}H NMR (400 MHz, acetone) δ 6.99 (d, J = 8.3 Hz, 1H), 6.93 (s, 1H), 6.71 (d, J = 8.3 Hz, 1H), 5.72 (s, 1H), 4.29−4.18 (m, 1H), 3.80−3.67 (m, 1H), 3.58−3.56 (m, 1H), 1.18 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, acetone) δ 142.6, 138.1, 125.1 (q, J = 267.8 Hz), 118.3 (q, J = 4.1 Hz), 117.8 (q, J = 32.2 Hz), 113.9, 112.7 (q, J = 3.8 Hz), 70.1, 44.7, 16.7; ESI-HRMS m/z calcd for $C_{10}H_{11}NOF_3$ $[M + H]^+$ 218.0787, found 218.0785.

*3-Phenyl-3,4-dihydro-2H-benzo[b][1,4]oxazine (**6h**).* Yield: 90% (190 mg); (PE/EtOAc = 15:1, R_f = 0.50); yellow oil; ^{1}H NMR (400 MHz, acetone) δ 7.44 (d, J = 7.9 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.34−7.27 (m, 1H), 6.81−6.68 (m, 3H), 6.57 (t, J = 7.5 Hz, 1H), 5.37 (s, 1H), 4.49 (d, J = 7.8 Hz, 1H), 4.29−4.17 (m, 1H), 4.02−3.83 (m, 1H); ^{13}C NMR (100 MHz, acetone) δ 143.4, 140.2, 134.9, 128.5, 127.8, 127.1, 121.2, 117.7, 116.0, 115.3, 70.5, 53.7; ESI-HRMS m/z calcd for $C_{14}H_{14}NO$ $[M + H]^+$ 212.1070, found 212.1076.

*3-(4-Chlorophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine (**6i**).* Yield: 88% (215 mg); (PE/EtOAc = 15:1, R_f = 0.49); brown oil; ^{1}H NMR (400 MHz, acetone) δ 7.46 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 7.5 Hz, 2H), 6.78−6.72 (m, 3H), 6.58 (t, J = 7.4 Hz, 1H), 5.44 (s, 1H), 4.53 (d, J = 6.5 Hz, 1H), 4.23 (dd, J = 10.5, 1.4 Hz, 1H), 3.93 (dd, J = 9.9, 8.3 Hz, 1H); ^{13}C NMR (100 MHz, acetone) δ 143.4, 139.3, 134.6, 132.9, 128.9, 128.5, 121.3, 117.8, 116.0, 115.3, 70.2, 53.1; ESI-HRMS m/z calcd for $C_{14}H_{13}NOCl$ $[M + H]^+$ 246.0680, found 246.0677.

*3-(4-Bromophenyl)-3,4-dihydro-2H-benzo[b][1,4]oxazine (**6j**).* Yield: 82% (237 mg); (PE/EtOAc = 15:1, R_f = 0.49); yellow solid; mp: 57−59 °C; ^{1}H NMR (400 MHz, acetone) δ 7.55 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 7.8 Hz, 2H), 6.78−6.72 (m, 3H), 6.58 (t, J = 7.4 Hz, 1H), 5.45 (s, 1H), 4.52 (d, J = 7.3 Hz, 1H), 4.24 (dd, J = 10.6, 2.4 Hz, 1H), 3.93 (dd, J = 10.0, 8.2 Hz, 1H); ^{13}C NMR (100 MHz, acetone) δ 143.4, 139.8, 134.5, 131.5, 129.2, 121.3, 121.0,

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117.8, 116.0, 115.3, 70.1, 53.1; ESI-HRMS m/z calcd for $C_{14}H_{13}NOBr$ $[M + H]^+$ 290.0175, found 290.0176.

*3-(4-(Trifluoromethyl)phenyl)-3,4-dihydro-2H-benzo[b][1,4]-oxazine (**6k**).* Yield: 84% (234 mg); (PE/EtOAc = 15:1, R_f = 0.45); yellow solid; mp: 62−64 °C; ^{1}H NMR (400 MHz, acetone) δ 7.69 (dd, J = 18.2, 8.3 Hz, 4H), 6.80−6.73 (m, 3H), 6.60 (t, J = 7.4 Hz, 1H), 5.53 (s, 1H), 4.66 (d, J = 6.7 Hz, 1H), 4.34−4.22 (m, 1H), 4.07−3.92 (m, 1H); ^{13}C NMR (100 MHz, acetone) δ 145.2, 143.4, 134.4, 129.3 (q, J = 31.8 Hz), 127.9, 125.3 (q, J = 3.8 Hz), 124.5 (q, J = 269.5 Hz), 121.4, 117.9, 116.1, 115.3, 70.0, 53.4; ESI-HRMS m/z calcd for $C_{15}H_{13}NOF_3$ $[M + H]^+$ 280.0944, found 280.0941.

*3-(Thiophene-2-yl)-3,4-dihydro-2H-benzo[b][1,4]oxazine (**6l**).* Yield: 80% (173 mg); (PE/EtOAc = 15:1, R_f = 0.49); yellow solid; mp: 55−57 °C; ^{1}H NMR (400 MHz, acetone) δ 7.38 (d, J = 5.1 Hz, 1H), 7.14 (d, J = 2.7 Hz, 1H), 7.01 (t, J = 4.3 Hz, 1H), 6.74−6.72 (m, 3H), 6.59 (t, J = 8.9 Hz, 1H), 5.54 (s, 1H), 4.85 (d, J = 7.2 Hz, 1H), 4.33−4.22 (m, 1H), 4.04−3.99 (m, 1H); ^{13}C NMR (100 MHz, acetone) δ 143.9, 143.5, 134.0, 126.7, 125.0, 124.7, 121.4, 118.2, 116.1, 115.5, 70.7, 49.8; ESI-HRMS m/z calcd for $C_{12}H_{12}NOS$ $[M + H]^+$ 218.0634, found 218.0633.

*3-Methyl-3,4-dihydro-2H-benzo[b][1,4]thiazine (**6m**).* Yield: 83% (136 mg); (PE/EtOAc = 15:1, R_f = 0.52); brown oil; ^{1}H NMR (400 MHz, acetone) δ 6.88 (d, J = 7.7 Hz, 1H), 6.81 (t, J = 7.6 Hz, 1H), 6.56−6.45 (m, 2H), 5.17 (s, 1H), 3.73−3.58 (m, 1H), 2.95−2.87 (m, 1H), 2.80−2.71 (m, 1H), 1.27 (d, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, acetone) δ 142.7, 126.8, 125.2, 116.8, 115.0, 114.6, 46.8, 31.7, 21.5; ESI-HRMS m/z calcd for $C_9H_{12}NS$ $[M + H]^+$ 166.0685, found 166.0683.

*2-Methyl-1,2,3,4-tetrahydroquinoxaline (**6n**).* Yield: 75% (111 mg); (PE/EtOAc = 4:1, R_f = 0.30); yellow solid; mp: 48−50 °C; ^{1}H NMR (400 MHz, acetone) δ 6.46−6.34 (m, 4H), 4.60 (s, 2H), 3.40 (s, 1H), 3.28 (d, J = 10.7 Hz, 1H), 2.97−2.88 (m, 1H), 1.12 (d, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, acetone) δ 134.1, 133.8, 117.5, 117.3, 113.63, 113.47, 48.0, 45.2, 19.2; ESI-HRMS m/z calcd for $C_9H_{13}N_2$ $[M + H]^+$ 149.1073, found 149.1071.

*2-Methyl-2,3-dihydrobenzo[e][1,4]oxazepin-5(1H)-one (**6o**).* Yield: 79% (139 mg); (PE/EtOAc = 2:1, R_f = 0.33); yellow solid; mp: 64−66 °C; ^{1}H NMR (400 MHz, acetone) δ 7.67 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 7.7 Hz, 1H), 6.78 (d, J = 8.3 Hz, 1H), 6.69 (t, J = 7.5 Hz, 1H), 5.74 (s, 1H), 4.35 (d, J = 12.7 Hz, 1H), 4.27 (dd, J = 12.7, 6.0 Hz, 1H), 3.93−3.84 (m, 1H), 1.26 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, acetone) δ 170.2, 146.6, 133.8, 133.6, 118.5, 117.0, 114.2, 69.7, 52.5, 18.2; ESI-HRMS m/z calcd for $C_{10}H_{12}NO_2$ $[M + H]^+$ 178.0863, found 178.0861.

General Procedure for Synthesis of 2-(2-Hydroxy-2-phenylethoxy)benzamide (7d). To a solution of **1d** (255 mg, 1.0 mmol) in MeOH was added $NaBH_4$ (75 mg, 2.0 mmol) portionwise. The reaction mixture was stirred at room temperature for 2 h and then concentrated. The residue was diluted with EtOAc, washed with 1 N HCl, saturated aq $NaHCO_3$, and brine, and then dried over Na_2SO_4. After filtration and concentration, the residue was purified by silica gel flash column chromatography (CH_2Cl_2/MeOH = 25:1, R_f = 0.42) to afford the desired product (215 mg, 84% yield) as a yellow oil. ^{1}H NMR (400 MHz, acetone) δ 8.04 (d, J = 7.7 Hz, 1H), 7.94 (s, 1H), 7.55 (d, J = 7.7 Hz, 2H), 7.46 (t, J = 7.8 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 6.8 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.78 (s, 1H), 5.23−5.19 (m, 1H), 5.14 (d, J = 4.1 Hz, 1H), 4.40 (dd, J = 9.7, 3.4 Hz, 1H), 4.28−4.15 (m, 1H); ^{13}C NMR (100 MHz, acetone) δ 166.2, 157.3, 141.6, 132.7, 131.7, 128.3, 127.6, 126.3, 122.5, 120.9, 113.5, 74.3, 71.6; ESI-HRMS m/z calcd for $C_{15}H_{16}NO_3$ $[M + H]^+$ 258.1125, found 258.1120.

General Procedure for Synthesis of 3-Phenylbenzo[*f*][1,4]-oxazepin-5(2*H*)-one (8d). To a solution of **1d** (255 mg, 1.0 mmol) in CH_3CN was added $Al(OTf)_3$ (237 mg, 0.5 mmol) at room temperature. The reaction mixture was heated to reflux for 8 h and then concentrated. The residue was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (CH_2Cl_2/EtOAc = 10:1, R_f = 0.58) to afford the desired product (80 mg, 34% yield) as a yellow solid. mp: 135−137 °C; ^{1}H NMR (400 MHz, acetone) δ 8.07 (d, J = 8.0 Hz, 2H), 7.70 (d, J = 6.9 Hz, 2H), 7.59 (t, J = 7.5 Hz, 3H), 7.21−7.06 (m, 2H), 5.80 (s, 2H); ^{13}C NMR (100 MHz, acetone) δ 193.0, 160.1, 134.6, 134.3, 133.8, 133.7, 128.8, 127.9, 121.3, 116.0, 113.1, 101.8, 70.6; ESI-HRMS m/z calcd for $C_{15}H_{12}NO_2$ $[M + H]^+$ 238.0863, found 238.0860.

General Procedure for Synthesis of 3-Phenyl-2*H*-benzo[*b*]-[1,4]oxazine (9h). To a solution of **5h** (327 mg, 1.0 mmol) in CH_3CN was added $Al(OTf)_3$ (237 mg, 0.5 mmol) at room temperature. The reaction mixture was heated to reflux for 10 min and then concentrated. The residue was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel flash column chromatography (PE/EtOAc = 15:1, R_f = 0.65) to afford the desired product (186 mg, 89% yield) as a white solid. mp: 100−102 °C; ^{1}H NMR (400 MHz, acetone) δ 8.05 (d, J = 8.0 Hz, 2H), 7.54−7.52 (m, 3H), 7.38 (d, J = 7.7 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 5.19 (s, 2H); ^{13}C NMR (100 MHz, acetone) δ 158.9, 146.7, 135.4, 134.0, 131.1, 128.6, 128.5, 127.6, 126.5, 122.1, 115.4, 62.5; ESI-HRMS m/z calcd for $C_{11}H_{13}NO_2F$ $[M + H]^+$ 210.0925, found 210.0927.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR, ^{13}C NMR, and HRMS spectra of compounds **2a−m**, **4a,b**, **6a−o**, **7d**, **8d**, and **9h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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