FACILE AND SHORT-STEP SYNTHESIS OF 5-SUBSTITUTED 2,3,4,5-TETRAHYDROBENZO[f][1,4]OXAZEPINES USING A MODIFIED PICTET-SPENGLER REACTION

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Abstract — 5-Substituted 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepines (6) were synthesized using a modified Pictet-Spengler reaction of formyliminium ion (4) as the key step. Cyclization of 4 proceeded readily by using trifluoroacetic acid as a catalyst, giving 5-substituted N-formyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepines (5) in 26–78% yield. The imination of 2-phenoxyethanamine (1) with aldehydes, formylation of the resulting imines (3), and the acid-catalyzed cyclization steps could be carried out in a one-pot procedure. Hydrolysis of 5 with hydrochloric acid gave the 5-substituted 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepines (6) in high yields.

The Pictet-Spengler reaction is one of the key reactions for synthesizing tetrahydroisoquinoline and heteroaryl homologs, which constitute an important class of naturally occurring bioactive substances.1 The reaction involves acid-catalyzed cyclization of the intermediate imine formed by condensation of the arylethylamine with an aldehyde. We recently improved this key cyclization reaction by substituting N-formyliminium ion for the imine. This modified Pictet-Spengler reaction provides a highly efficient and convenient method for synthesizing 1-substituted and 1,1-disubstituted 1,2,3,4-tetrahydroisoquinolines,2,3 1,2,3,4-tetrahydro-β-carbolines,4,5 1-substituted-2,3-dihydro-1H-isoindoles (isoindolines),6 and 4-substituted and 4,4-disubstituted 4,5,6,7-tetrahydrothieno[3,2-c]pyridines.7 In the synthesis of these compounds, the N-formyliminium ion, as anticipated, exhibits stronger electrophilic properties than the
imine. Thus, the modified Pictet-Spengler reaction proceeds under mild acidic conditions, even with substrates in which the aromatic ring lacks electron-donating groups and sterically congested substrates derived from ketones. Furthermore, this method has the added advantage that the overall reactions can be carried out in a one-pot procedure.

In this report, we describe the synthesis of 5-substituted-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepins using the modified Pictet-Spengler reaction. Benzoxazepines with 7-membered ring systems are known to play crucial roles in a number of biological processes. Benzoxazepines have been synthesized from amides using the Bischler-Napieralski reaction or from ketones using an intramolecular imination reaction. However, synthesis of benzoxazepines using the Pictet-Spengler reaction has not been reported. The development of new methods for synthesizing benzoxazepines should contribute not only to heterocyclic chemistry but also to pharmacology.

The modified Pictet-Spengler reaction was carried out in a one-pot procedure, as follows (Scheme 1). The condensation reaction of 2-phenoxyethanamine (1) (1.0 mol equiv) and aldehyde (2) (1.3 mol equiv) to yield imine (3) was carried out in titanium(IV) tetraisopropoxide (1.2 mol equiv) at 70 °C for 2 h without the use of any solvent. Heating the imine (3) thus formed in situ in a solution containing a large amount of acetic-formic anhydride (50 mol equiv) at 70 °C for 2 h yielded N-formyliminium ion (4). The reaction mixture of 4 was used as the substrate for the acid-catalyzed cyclization reaction after removal of the excess acetic-formic anhydride by evaporation in vacuo.

When N-formyliminium ion (4a), which has a phenyl group at the C=N position, was treated with a large excess of trifluoroacetic acid (TFA) (100 mol equiv) at 70 °C for 16 h, the expected cyclization reaction
occurred to give N-formyl-5-phenylbenzoxazepine (5a) in 78% yield. Similarly, TFA treatment of N-formyliminium ions (4b-h) with alkyl substituents also induced the cyclization to give benzoxazepines (5b-h), respectively, in moderate to low yields. The yield depended on the size of the alkyl substituent; thus, N-formyliminium ions with a relatively large alkane, such as cyclohexyl (4b), cyclopentyl (4c), n-hexyl (4d), or n-pentyl (4e), gave products (5b-e) in moderate yields (50–70%). By contrast, substrates (4f-h), which have small alkyl groups, yielded products (5f-g) in low yields (26–36%). The lower yields obtained in the latter cases could be attributed to loss of volatile aldehydes as well as side reactions such as aldol self-condensation, probably in the imination step. The structures of the products were determined using MS, IR, 1H-NMR, and 13C-NMR spectroscopy.12

Acidic hydrolysis of N-formyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (5) afforded 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (6) in excellent yield. The results are summarized in Table 1.13

Thus, the modified Pictet-Spengler reaction represents a convenient and highly efficient method for synthesizing various 5-substituted 2,3,4,5-tetrahydrobenzo[f][1,4]oxazepines, as shown in Table 1. Finally, we wish to note that this is the first reported example of the construction of a 7-membered benzoxazepine ring system using the Pictet-Spengler reaction.

<table>
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<th>Run</th>
<th>N-Formyliminium ion (4)</th>
<th>TFA (mol eq.)</th>
<th>Conditions</th>
<th>Products</th>
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<td>100</td>
<td>70</td>
<td>16</td>
<td>5a 78</td>
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<tr>
<td>2</td>
<td>4b c-hexyl</td>
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<td>70</td>
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<td>100</td>
<td>70</td>
<td>2</td>
<td>5h 26</td>
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</table>

| Products | 6a 93 | 6b 95 | 6c 76 | 6d 91 | 6e 78 | 6f 90 | 6g 98 | 6h 89 |

**EXPERIMENTAL**

Unless otherwise noted, the following procedures were adopted. Melting points were determined using a
Yanagimoto SP-M1 hot-stage melting point apparatus and are uncorrected. IR spectra were acquired as KBr disks using a HORIBA FT-710 spectrophotometer, and the values are given in cm\(^{-1}\). NMR spectra were acquired using a JEOL JNM-AL 300 (\(^1\)H-NMR, 300 MHz; \(^13\)C-NMR, 75 MHz) NMR spectrometer in CDCl\(_3\) with tetramethylsilane as an internal standard, and the chemical shifts are given as \(\delta\) values. HRFAB-MS spectra were recorded using a JEOL-MS700 spectrometer with glycerol as the matrix. TLC was performed on Merck precoated Silica gel 60 F\(_{254}\) plates. Column chromatography was carried out with silica gel (Wakogel C-200). The organic extract from each reaction mixture was washed with brine, dried over anhydrous Na\(_2\)SO\(_4\), and concentrated \textit{in vacuo} to dryness.

Modified Pictet-Spengler reaction of 2-phenoxyethanamine (1) and aldehyde (2). General procedure: A mixture of 1 (0.5 g, 3.65 mmol), aldehyde (2) (1.2 mol equiv), and Ti(O-iPr)\(_4\) (1.2 mol equiv) was heated at 70 °C for 2 h under an argon atmosphere. A solution of acetic-formic anhydride (50 mol equiv) (prepared from HCO\(_2\)H [50 mol equiv] and Ac\(_2\)O [50 mol equiv]) was added to the reaction mixture at 0 °C, then the mixture was heated at 70 °C for 2 h. After removal of excess acetic-formic anhydride by heating \textit{in vacuo}, CF\(_3\)CO\(_2\)H (100 mol equiv) was added to the reaction mixture and heated at 70 °C for 2-16 h (as shown in Table 1). The reaction mixture was diluted with MeOH (100 mL) and passed through a short SiO\(_2\) column (CHCl\(_3\)-MeOH) to remove TiO\(_2\). The eluent was concentrated \textit{in vacuo} to ca. 50 mL, and the resulting residue was extracted with CHCl\(_3\). After removal of the extraction solvent \textit{in vacuo}, the residue was purified by chromatography over SiO\(_2\) and elution with AcOEt-hexane (1:1-1:3) to give (5).

\textbf{N-Formyl-5-phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (5a):} Colorless plates recrystallized from Et\(_2\)O, mp 113-115 °C. IR: 1664, 1598, 1577. \(^1\)H-NMR: [3.06 (ddd, \(J=15, 10, 3\) Hz), 3.53-3.56 (m), 3.77 (ddd, \(J=12, 10, 2\) Hz), 4.22-4.30 (m), 4.40-4.45 (m)] (total 4H, C2-H and C3-H), 5.83, 6.91 (total 1H, each s, C5-H), 7.03-7.36 (9H, m, Ar-H), 8.27, 8.52 (total 1H, each s, -CHO). HR-FABMS \textit{m/z} (MH\(^+\)): Calcd for C\(_{16}\)H\(_{16}\)NO\(_2\): 254.1181. Found: 254.1197.

\textbf{N-Formyl-5-cyclohexyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (5b):} Colorless plates from Et\(_2\)O. mp 82-84 °C. IR: 1677, 1658, 1644, 1602, 1581. \(^1\)H-NMR: 0.83-0.98, 1.10-1.20, 1.65-1.76 (total 10H, each m, cyclohexyl-CH\(_2\)), 2.17-2.30 (1H, each m, C1’-H) 3.26-3.35, 3.50-3.73, 3.84-3.95, 4.39-4.46 (total 4H, each m, C2-H and C3-H), 4.56, 5.09 (total 1H, each d, \(J=15, 11\), C5-H), 7.00-7.36 (total 4H, m, Ar-H), 8.13, 8.19 (total 1H, each s, CHO). HR-FABMS \textit{m/z} (MH\(^+\)): Calcd for C\(_{16}\)H\(_{22}\)NO\(_2\): 260.1651 Found: 260.1662.

\textbf{N-Formyl-5-cyclopentyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (5c):} Yellow gum. IR: 1691, 1666, 1639, 1602, 1579. \(^1\)H-NMR: 1.12-1.28, 1.49-1.78 (total 8H, each m, cyclopentyl-CH\(_2\)), 2.81-2.91 (1H, m, C1’-H), 3.35-3.45, 3.53-3.72, 3.92-4.02, 4.33-4.77 (total 4H, each m, C2-H and C3-H), 4.56, 5.12 (total 1H, each d, \(J=15, 11\), C5-H), 6.99-7.25 (4H, m, Ar-H), 8.10, 8.23 (total 1H, each s, CHO). HR-FABMS
m/z (MH⁺): Calcd for C₁₅H₂₀NO₂: 246.1494. Found: 246.1490.

N-Formyl-5-hexyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (5d): Yellow oil. IR: 1722, 1693, 1660, 1629, 1604, 1579. ¹H-NMR: 0.83-0.87 (3H, m, C₆'-H), 1.18-1.28 (8H, m, n-hexyl-CH₂), 1.82-1.88 (2H, m, C₁'-H), 3.13-3.40, 3.52-3.75, 3.86-3.95, 4.09-4.16, 4.36-4.56, 5.41-5.46 (total 5H, each m, C₂-H and C₃-H and C₅-H), 6.99-7.28 (4H, m, Ar-H), 8.11, 8.23 (total 1H, each s, CHO). HRMS m/z (MH⁺): Calcd for C₁₆H₂₄NO₂: 262.1807. Found: 262.1814.

N-Formyl-5-pentyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (5e): Yellow oil. IR: 1677, 1602, 1577. ¹H-NMR: 0.86-0.89 (3H, m, C₅'-H), 1.18-1.28 (6H, m, n-pentyl), 1.81-1.89, 2.11-2.22 (total 2H, each m, C₁'-H), 3.31-3.40, 3.52-3.75, 3.87-3.95, 4.36-4.56, 5.41-5.47 (total 5H, each m, C₂-H and C₃-H and C₅-H), 6.99-7.28 (4H, m, Ar-H), 8.11, 8.23 (total 1H, each s, CHO). HR-FABMS m/z (MH⁺): Calcd for C₁₅H₂₂NO₂: 248.1650. Found: 248.1639.

N-Formyl-5-butyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (5f): Yellow oil. IR: 1687, 1644, 1602, 1577. ¹H-NMR: 0.85-0.92 (3H, m, C₄'-H), 1.14-1.36 (4H, m, butyl-CH₂), 1.80-1.90, 2.13-2.21 (2H, each m, C₁'-H), 3.32-3.40, 3.52-3.75, 3.87-3.95, 4.36-4.56, 5.41-5.47 (total 5H, each m, C₂-H and C₃-H and C₅-H), 6.99-7.28 (4H, m, Ar-H), 8.11-8.23 (total 1H, each s, CHO). HR-FABMS m/z (MH⁺): Calcd for C₁₄H₂₀NO₂: 234.1494. Found: 234.1488.

N-Formyl-5-propyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (5g): Yellow oil. IR: 1687, 1656, 1602, 1577. ¹H-NMR: 0.90-0.96 (3H, m, C₃'-H), 1.19-1.32 (2H, m, propyl-CH₂), 1.79-1.89, 2.02-2.21 (total 2H, each m, C₁'-H), 3.32-3.40, 3.52-3.75, 3.86-3.95, 4.38-4.56, 5.44-5.49 (total 5H, each m, C₂-H and C₃-H and C₅-H), 6.99-7.28 (4H, m, Ar-H), 8.11-8.23 (total 1H, each s, CHO). HR-FABMS m/z (MH⁺): Calcd for C₁₃H₁₈NO₂: 220.1339. Found: 220.1352.

5-Phenyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (6a): Reaction time 3 h. Colorless oil. IR: 1602, 1573. ¹H-NMR: 3.22-3.25 (2H, m, C₃'-H), 3.91-3.99, 4.13-4.20 (total 2H, each m, C₂-H), 5.22 (1H, s, C₅-H), 6.69-6.71, 6.89-6.94, 7.07-7.09, 7.15-7.20, 7.24-7.39 (total 9H, each m, Ar-H). ¹³C-NMR: 49.2 (C₃), 64.5 (C₅), 74.1 (C₂), 121.4 (Ar or Ph-CH), 123.3 (Ar or Ph-CH), 127.1 (Ar or Ph-CH), 128.0 (Ar or
Ph-CHx2), 128.2 (Ar or Ph-CH), 128.4 (Ar or Ph-CHx2), 129.3 (Ar or Ph-CH), 137.0 (C5a), 141.5 (C1’), 159.5 (C9a). HR-FABMS m/z (MH⁺): Caled for C15H16NO: 226.1232. Found: 226.1228.

5-Cyclohexyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (6b): Reaction time 3 h. Colorless needles. mp 47-51 °C. IR: 1664, 1581. 1H-NMR: 0.70-1.23, 1.71-1.82, 2.00-2.10 (total 11H, each m, C1'-H and cyclohexyl-CH2), 2.83 (1H, d, J=15 Hz, C3-H), 3.34 (1H, d, J=10 Hz, C3-H), 3.33-3.39 (1H, m, C2-H), 3.63 (1H, t, J=12 Hz, C2-H), 4.22 (1H, d, J=12 Hz, C5-H), 6.86-7.08 (4H, m, Ar-H). 13C-NMR: 26.0 (cyclohexyl-CH2), 26.1 (cyclohexyl-CH2), 26.4 (cyclohexyl-CH2), 30.1 (cyclohexyl-CH2), 31.5 (cyclohexyl-CH2), 36.0 (C1’), 45.3 (C3), 67.8 (C5), 74.9 (C2), 121.7 (Ar-CH), 123.0 (Ar-CH), 127.8 (Ar-CH), 130.3 (Ar-CH), 137.1 (C5a), 158.6 (C9a). HR-FABMS m/z (MH⁺): Caled for C15H22NO: 232.1702. Found: 232.1712.

5-Cyclopentyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (6c): Reaction time 16 h. Yellow oil. IR: 1675, 1600, 1577. 1H-NMR: 1.25-2.00 (8H, m, cyclopentyl-CH2), 2.62-2.76 (1H, m, C1'-H), 2.99 (1H, ddd, J=2, 10, 12 Hz, C2-H), 3.47 (1H, ddd, J=2, 10, 12 Hz, C2-H), 4.22 (1H, ddd, J=3, 4, 12 Hz, C5-H), 6.95-7.17 (4H, m, Ar-H). 13C-NMR: 25.2 (cyclopentyl-CH2), 25.3 (cyclopentyl-CH2), 30.1 (cyclopentyl-CH2), 31.5 (cyclopentyl-CH2), 40.1 (C’1), 46.3 (C3), 67.3 (C5), 74.8 (C2), 121.5 (Ar-CH), 123.1 (Ar-CH), 127.7 (Ar-CH), 129.1 (Ar-CH), 138.0 (C5a), 158.7 (C9a). HR-FABMS m/z (MH⁺): Caled for C14H20NO: 218.1545. Found: 218.1553.

5-Hexyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (6d): Reaction time 16 h. Yellow oil. IR: 1677, 1639, 1600, 1577. 1H-NMR: 0.85-0.89 (3H, m, CH3), 1.28-1.33 (8H, m, hexyl-CH2), 1.83-1.92 (2H, m, C1’-H), 3.05 (1H, ddd, J=2, 5, 7 Hz, C3-H), 3.39 (1H, ddd, J=2, 8, 11 Hz, C3-H), 3.85 (1H, t , J=8 Hz, C2-H), 3.86 (1H, ddd, J=2, 8, 12 Hz, C2-H), 4.13 (1H, ddd, J=3, 5, 8 Hz, C5-H), 6.97-7.18 (4H, m, Ar-H). 13C-NMR: 14.0 (CH3), 22.6 (hexyl-CH2), 26.8 (hexyl-CH2), 29.2 (hexyl-CH2), 31.7 (hexyl-CH2), 32.3 (hexyl-CH2), 46.9 (C3), 61.1 (C5), 75.0 (C2), 121.6 (Ar-CH), 123.3 (Ar-CH), 127.8 (Ar-CH), 128.1 (Ar-CH), 138.4 (C5a), 159.0 (C9a). HR-FABMS m/z (MH⁺): Caled for C15H24NO: 234.1858. Found: 234.1850.

5-Pentyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (6e): Reaction time 16 h. Yellow oil. IR: 1639, 1600, 1577. 1H-NMR: 0.85-0.90 (3H, m, CH3), 1.30-1.43 (6H, m, pentyl-CH2), 1.82-1.92 (2H, m, C1’-H), 3.06 (1H, ddd, J=2, 5, 8 Hz, C3-H), 3.39 (1H, ddd, J=3, 8, 11 Hz, C3-H), 3.84-3.91 (2H, m, C2-H), 4.12 (1H, ddd, J=3, 6, 8 Hz, C5-H), 6.97-7.18 (4H, m, Ar-H). 13C-NMR: 13.9 (CH3), 22.5 (pentyl-CH2), 26.5 (pentyl-CH2), 31.7 (pentyl-CH2), 32.3 (pentyl-CH2), 46.9 (C3), 61.1 (C5), 75.0 (C2), 121.5 (Ar-CH), 123.3 (Ar-CH), 127.7 (Ar-CH), 128.1 (Ar-CH), 138.4 (C5a), 159.0 (C9a). HR-FABMS m/z (MH⁺): Caled for C14H22NO: 220.1702. Found: 220.1705.

5-Butyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (6f): Reaction time 48 h. Yellow oil. IR: 1675, 1600, 1577. 1H-NMR: 0.88-0.93 (3H, m, CH3), 1.24-1.44 (4H, m, butyl-CH2), 1.84-1.90 (2H, m, C1’-H), 3.06
(1H, ddd, J = 2, 5, 7 Hz, C3-H), 3.40 (1H, ddd, J = 2, 5, 7 Hz, C3-H), 3.84-3.91 (2H, m, C2-H), 4.13 (1H, ddd, J = 2, 5, 7 Hz, C5-H), 6.98-7.18 (4H, m, Ar-H). $^{13}$C-NMR: 14.0 (CH$_3$), 22.6 (butyl-CH$_2$), 29.1 (butyl-CH$_2$), 32.1 (butyl-CH$_2$), 47.0 (C3), 61.2 (C5), 75.1 (C2), 121.6 (Ar-CH), 123.4 (Ar-CH), 127.8 (Ar-CH), 128.2 (Ar-CH), 138.4 (C5a), 159.1 (C9a). HR-FABMS $m/z$ (MH$^+$): Calcd for C$_{13}$H$_{20}$NO: 206.1545. Found: 206.1551.

5-Propyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (6g): Reaction time 3 h. Yellow oil. IR: 1675, 1600, 1579. $^1$H-NMR: 0.92-0.97 (3H, m, CH$_3$), 1.26-1.31 (1H, m, propyl-CH$_2$), 1.41-1.48 (1H, m, propyl-CH$_2$), 1.83-1.90 (2H, m, C1'-H), 3.03-3.09 (1H, m, C3-H) 3.37-3.43 (1H, m, C3-H), 3.84-3.91 (2H, m, C2-H), 4.06-4.16 (1H, m, C5-H), 6.93-7.17 (4H, m, Ar-H). $^{13}$C-NMR: 13.9 (CH$_3$), 20.0 (propyl-CH$_2$), 34.5 (propyl-CH$_2$), 46.9 (C3), 60.8 (C5), 75.0 (C2), 121.6 (Ar-CH), 123.3 (Ar-CH), 127.8 (Ar-CH), 128.2 (Ar-CH), 138.3 (C5a), 159.0 (C9a). HR-FABMS: Calcd for C$_{12}$H$_{18}$NO: 192.1388. Found: 192.1395.

5-Ethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (6h): Reaction time 48 h. Yellow oil. IR: 1602, 1577. $^1$H-NMR: 0.95 (3H, t, J = 7 Hz, CH$_3$), 1.92 (2H, quint, J = 7 Hz, CH$_2$), 3.06 (1H, ddd, J = 2, 5, 7 Hz, C3-H), 3.39 (1H, ddd, J = 2, 8, 11 Hz, C3-H), 3.77 (1H, t, J = 7 Hz, C5-H), 3.87 (1H, ddd, J = 2, 8, 11 Hz, C2-H), 4.13 (1H, ddd, J = 3, 5, 8 Hz, C2-H), 6.92-7.24 (4H, m, Ar-H). $^{13}$C-NMR: 11.4 (CH$_3$), 25.3 (CH$_2$), 46.8 (C3), 62.8 (C5), 74.9 (C2), 121.6 (Ar-CH), 123.3 (Ar-CH), 127.8 (Ar-CH), 128.3 (Ar-CH), 138.0 (C5a), 159.0 (C9a). HR-FABMS: Calcd for C$_{11}$H$_{16}$NO: 178.1232. Found: 178.1229.

REFERENCES AND NOTES


12. The $^1$H- and $^{13}$C-NMR spectra of $N$-formyl compounds (5) exhibited complex signals attributable to rotational isomerism of the N-CO bond. Therefore, $^{13}$C-NMR spectra of cyclized products were assigned based on measurements of $N$-deformyl derivatives (6).

13. In this modified Pictet-Spengler reaction, unstable intermediate imine (3) and $N$-formylimimium ion (4) were not isolated. The yield of cyclization products (5) was calculated from starting material amine (1).