Palladium-Catalyzed One-Step Preparation of Novel Tricyclic Phenoxazine, Phenazine, and Dioxine Derivatives

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Phenoxazine and related systems are an important substructure for pharmaceuticals and biologically active natural products. For instance, the preparation of N-substituted phenoxazine 1 (Figure 1) and derivatives was directed toward reversing vinca alkaloid resistance in multidrug-resistant cancer cells.1 Natural phenoxazine, halxazine (2), produced by Streptomyces halstedii is known to be a neuronal cell-protecting substance.2 Although some traditional methods for the synthesis of phenoxazine derivatives are known, they require multisteps and also somewhat severe reaction conditions.1 Hence, development of a simple and flexible protocol is desired for the preparation of phenoxazine derivatives for the discovery of new drugs and the synthesis of biologically important natural products.

Sinou recently reported that the reaction of 2-aminophenol with (Z)-4-[(methoxycarbonyl)oxy]but-2-enyl methyl carbonate (3) catalyzed by a palladium complex gave 2-vinyl-3,4-dihydro-2H-1,4-benzoxazine (4) in moderate yield (Scheme 1).3 We assumed that reaction of 2-aminophenols with a cyclic symmetrical substrate such as meso allylic diacetates 5 and 6 under the same reaction conditions would produce novel tricyclic 1,4-benzoxazine derivatives, which would be an attractive building block for the synthesis of drug candidate and natural products.

For the synthesis, a mixture of various 2-aminophenols and diacacetate 5 and/or 6 was treated with Pd(dba)2 or π-allylpalladium chloride dimer and triphenylphospine or diphenyphosphinoferrocene in THF to give tricycles 7 in moderate to good yield. The results are summarized in Table 1. Electron-withdrawing group on benzene ring decreased the reactivity (entries 3, 4, 7 and 8). It should be assumed that the relative stereochemistry of the morpholine ring and cyclopentene and/or the cyclohexene ring of 7 should be cis based on well-known π-allylpalladium chemistry.5 Second nucleophilic substitution should occur from the opposite face of coordinated palladium (Scheme 2). This was also supported by NOESY experiment on NMR.

A plausible mechanism is presented in Scheme 2. First allylic substitution occurs at the less hindered site of allylic terminus7 in the π-allyl intermediate 8 generated from 5 to give the intermediate 9. At this point, N-alkylation is faster than O-alkylation because of the basicity on aniline nitrogen and phenol oxygen to produce 9, exclusively.3 Second π-allyl formation generates intermediate 10, which has coordinated palladium on the opposite face of aromatic substituent. Finally, O-alkylation occurs from the opposite face of palladium to give 7a possessing a cis juncture. No regioisomer or stereoisomer of 7a was detected.

Under the same conditions, the reaction of benzene-1,2-diamine and benzene-1,2-diol with diacetates 5 and 6 gave phenazine and dioxine derivatives 11 and 12, respectively, in good to excellent yields (Table 2).

On the other hand, reaction of 2-aminobenzenethiol with 5 and 6 under the same reaction conditions gave no desired product. Disappointingly, reaction of nonaromatic 2-amino alcohols such as phenyl alaninol, phenyl glycinol and valinol derived from corresponding α-amino acids...
In conclusion, we have developed a facile method for the synthesis of novel tricyclic phono/xazine, phenazine, and dioxine derivatives as a potential new scaffolds for drug discovery from 2-aminophenols, benzene-1,2-diamine and -diol and cyclic meso compounds in the presence of a palladium catalyst. By using this method, a variety of compound library would be obtained combinatorially by simply chosing the nucleophile and substrate in a single operation. Synthetic studies of halxazine 2 from 7 and asymmetric version of this process are now in progress.

Table 1  Reaction of 2-Aminophenols with meso-Diacetates 5 and 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aminophenol</th>
<th>Diacetate</th>
<th>7</th>
<th>Yield (%)a</th>
</tr>
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<tr>
<td>1</td>
<td><img src="image" alt="OH" /></td>
<td>5</td>
<td>7a</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="CH3" /></td>
<td>5</td>
<td>7b</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Cl" /></td>
<td>5</td>
<td>7c</td>
<td>48</td>
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<tr>
<td>4</td>
<td><img src="image" alt="O2N" /></td>
<td>5</td>
<td>7d</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="NH2" /></td>
<td>6</td>
<td>7e</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="CH3" /></td>
<td>6</td>
<td>7f</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Cl" /></td>
<td>6</td>
<td>7g</td>
<td>48</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="O2N" /></td>
<td>6</td>
<td>7h</td>
<td>26</td>
</tr>
</tbody>
</table>

*a Unoptimized yields of isolated products.

Scheme 2

with meso compounds 5 and/or 6 under the same reaction conditions gave no desired product. In this case, only the starting materials were recovered and/or a complex mixture was obtained.

In conclusion, we have developed a facile method for the synthesis of novel tricyclic phono/xazine, phenazine, and dioxine derivatives as a potential new scaffolds for drug discovery from 2-aminophenols, benzene-1,2-diamine and -diol and cyclic meso compounds in the presence of a palladium catalyst. By using this method, a variety of compound library would be obtained combinatorially by simply chosing the nucleophile and substrate in a single operation. Synthetic studies of halxazine 2 from 7 and asymmetric version of this process are now in progress.

**2,4a,10a-Tetrahydro-1H-pheno/xazine (7e): Typical Procedure**

A degassed solution of cis-cyclohex-2-enyl-1,4-diacetate (6; 1.98 g, 10.0 mmol, 1 equiv), o-aminophenol (1.64 g, 15.0 mmol, 1.5 equiv),
Table 2  Synthesis of Phenazines and Dioxines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Diacetate</th>
<th>11 and 12</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NH2</td>
<td>5</td>
<td>11a</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>NH2</td>
<td>6</td>
<td>11b</td>
<td>57</td>
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<tr>
<td>3</td>
<td>OH</td>
<td>5</td>
<td>12a</td>
<td>87</td>
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<tr>
<td>4</td>
<td>OH</td>
<td>6</td>
<td>12b</td>
<td>80</td>
</tr>
</tbody>
</table>

a Isolated yield.

Pd(dba)2 (14.4 mg, 0.025 mmol, 0.25 mol%), Ph3P (26.2 mg, 0.1 mmol, 1.00 mol%), and Cs2CO3 (0.1 g, 0.31 mmol) in THF (30 mL) was stirred at 60 °C for 15 h. The mixture was filtered through a pad of silica gel and the solvent evaporated in vacuo. After purification by silica gel chromatography (hexane–EtOAc, 3:1), 7e (1.40 g, 75%) was obtained as an orange oil; Rf = 0.46 (hexane–EtOAc, 4:1).

IR (neat): 3390 (NH), 3059, 2914 (C=C), 1607 (C=C), 1500, 1308, 1274, 1213, 1115, 1082 (Ar–Cl), 840, 808 cm–1.

EI-MS: \( m/z \) (%) = 187 (100, M+), 160 (12), 123 (31), 94 (34), 77 (37), 66 (63), 40 (47).

6-Nitro-1,3a,9,9a-tetrahydrobenzo[b]cyclopenta[e][1,4]oxazine (7b)

Colorless crystals; mp 108–110 °C; Rf = 0.68 (hexane–EtOAc, 4:1).

IR (neat): 3384 (NH), 2915 (C=C), 2860 (Ar–CH3), 1616, 1594, 1512 (C=C), 1588, 1215 (C–O–C), 930, 799 cm–1.

1H NMR (CDCl3): \( \delta = 6.71 \) (1 H, d, J = 8.0 Hz), 6.42 (1 H, d, J = 8.0 Hz), 6.40 (1 H, s), 6.08 (1 H, dt, J = 2.4, 6.0 Hz), 5.98 (1 H, ddd, J = 2.0, 4.0, 6.0 Hz), 4.67 (1 H, ddd, J = 1.6, 1.6, 5.2 Hz), 4.42 (1 H, s), 3.97 (1 H, ddt, J = 1.2), 6.0, 12.4 Hz), 2.63 (1 H, ddd, J = 0.8, 8.4, 16.0 Hz), 2.37 (1 H, dddd, J = 2.0, 4.0, 5.6, 16.0 Hz), 2.21 (1 H, s).

13C NMR (67.5 MHz, CDCl3): \( \delta = 135.8, 133.4, 131.2, 130.1, 118.4, 116.6, 114.6, 78.7, 53.9, 39.8, 20.9 \)

EI-MS: \( m/z \) (%) = 211 (100, M+, +1), 187 (100, M+), 162 (12), 121 (31), 94 (34), 77 (37), 66 (63), 40 (47).

6-Nitro-1,3a,9,9a-tetrahydrobenzo[b]cyclopenta[e][1,4]oxazine (7d)

Colorless crystals; mp 181–183 °C; Rf = 0.51 (hexane–EtOAc, 4:1).

IR (neat): 3381 (NH), 2915 (C=C), 2860 (Ar–CH3), 1616, 1594, 1512 (C=C), 1588, 1215 (C–O–C), 930, 799 cm–1.

1H NMR (CDCl3): \( \delta = 6.7, 1.1, 2.0, 2.4, 6.4 \) Hz), 6.42 (1 H, d, J = 8.0 Hz), 6.40 (1 H, s), 6.08 (1 H, dt, J = 2.4, 6.0 Hz), 5.98 (1 H, ddd, J = 2.0, 4.0, 6.0 Hz), 4.67 (1 H, ddd, J = 1.6, 1.6, 5.2 Hz), 4.42 (1 H, s), 3.97 (1 H, ddt, J = 1.2), 6.0, 12.4 Hz), 2.63 (1 H, ddd, J = 0.8, 8.4, 16.0 Hz), 2.37 (1 H, dddd, J = 2.0, 4.0, 5.6, 16.0 Hz), 2.21 (1 H, s).

13C NMR (67.5 MHz, CDCl3): \( \delta = 135.8, 133.4, 131.2, 130.1, 118.4, 116.6, 114.6, 78.7, 53.9, 39.8, 20.9 \)

EI-MS: \( m/z \) (%) = 218 (59, M+), 171 (19), 153 (8), 143 (9), 127 (5), 115 (13), 104 (5), 91 (8), 78 (33), 66 (100), 51 (70).

8-Chloro-2,4a,10a-tetrahydro-1H-phenoxazine (7g)

Colorless oil; Rf = 0.51 (hexane–EtOAc, 3:1).

IR (neat): 3399 (NH), 3062, 2921 (C=C), 1703, 1605, 1500 (C=C), 1273, 1213 (C–N), 1115, 1082 (Ar–Cl), 840, 800 cm–1.

1H NMR (CDCl₃): δ = 6.69 (1 H, d, J = 8.8 Hz), 6.53 (1 H, d, J = 2.0 Hz), 6.51 (1 H, s), 5.97 (1 H, dt, J = 3.2, 10.4 Hz), 2.19 (1 H, ddd, J = 2.0, 4.8, 18.0 Hz), 2.12–2.05 (1 H, m), 1.89–1.79 (1 H, m), 1.74–1.67 (1 H, m).

13C NMR (67.5 MHz, CDCl₃): δ = 140.4, 132.8, 129.5, 126.0, 124.6, 117.4, 115.2, 113.5, 68.8, 48.4, 25.8, 23.8.

EI-MS: m/z (%) = 221 (50, M+), 206 (6), 193 (5), 167 (47), 154 (8), 143 (34), 127 (3), 114 (5), 93 (5), 79 (100), 63 (11), 51 (31).

1H NMR (CDCl₃): δ = 7.13–7.04 (2 H, m), 6.91–6.82 (2 H, m), 6.79–6.67 (2 H, m), 5.79–5.68 (1 H, m), 2.19–2.10 (1 H, m), 2.06–1.97 (1 H, m), 1.80 (1 H, dddd, J = 1.8, 2.1, 5.2, 16.5 Hz), 1.65 (1 H, dddd, J = 1.8, 2.1, 5.3, 16.5 Hz).

13C NMR (67.5 MHz, CDCl₃): δ = 129.1, 126.9, 125.9, 124.6, 119.1, 118.9, 117.0, 116.8, 78.5, 74.3, 73.8, 36.9, 26.6, 23.5.

EI-MS: m/z (%) = 174 (36, M+), 157 (2), 146 (6), 131 (3), 109 (17), 93 (5), 80 (8), 66 (100), 52 (24).

References

(4) (a) cis-1,4-Diacetoxycyclopentene (5) was prepared from cyclopentadiene by the photosensitized oxygenation followed by acetylation in 41% yield, see: Kaneko, C.; Sugimoto, A.; Tanaka, S. Synthesis 1974, 876. (b) cis-1,4-Diacetoxyhexahexene (6) was prepared from cyclohexa-1,3-diene by the palladium-catalyzed 1,4-diacetoxylation in 80% yield, see: Bäckvall, J.-E.; Bystrom, S. E.; Nordberg, R. E. J. Org. Chem. 1984, 49, 4619. (c) The palladium-catalyzed 1,4-diacetoxylation of cyclopentadiene gave low yield of 5 (<20%).