Synthesis of 1H-1,5-Benzodiazepine Derivatives and Pyridinylquinoxalines with Heterocyclic Ketones

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Benzodiazepines are interesting compound cops because of their pharmacological properties.1 Many members of this family are, in fact, nowadays widely used as tranquilizing and anticonvulsant agents. Although the first benzodiazepine was introduced as a drug nearly 30 years ago,2 the research in this area is still very active and is directed towards the synthesis of compounds of enhanced pharmacological activity. Some benzodiazepine derivatives are also used in industry, such as in photography (as dyes for acryl fibers),3 and also as anti-inflammatory agents.4 1H-1,5-Benzodiazepines are used as starting materials for the preparation of some fused ring benzodiazepine derivatives, such as triazol5 and oxadiazol.5 Despite their wide range of pharmacological activity, industrial and synthetic application, the synthesis of 1H-1,5-benzodiazepines has received little attention.7 As a part of research program related to the synthetic study of pharmacologically interesting benzodiazepine compounds, herein we now report the synthesis of 1H-1,5-benzodiazepine derivatives with heteroaromatic ketones (2-acetylfuran 2a, 2-acetyltiophene 2b, 2-acetyl-pyridine 2c, 3-acetylpyridine 2d, and 4-acetylpyridine 2e) by using conc-HCl, SiO2, or polyphosphoric acid (PPA) (Scheme 1). Specially we report synthesis of quinoxaline derivatives with phenylenediamine 1a and acetylpyridines 2c, 2e in aqueous 10% conc-HCl solution (Scheme 2).

Moreover we describe the structural analysis of 7-chloro-2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine 3f and 8-chloro-2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine 3g synthesized by 4-chloro-1,2-phenylenediamine 1b with acetone.

Earlier we reported the synthesis of 2,4,4-trimethyl-3H-5-hydro-1,5-benzodiazepine and 2,4-diphenyl-4-methyl-3H-5-hydro-1,5-benzodiazepine by using various reagents instead of PPA8.

When 1a was treated with 2a in the presence of PPA at 40-45 °C for 5 h, a yellow crystalline solid, 3a was isolated.

Scheme 1

Scheme 2
Table 1. Yields of synthesized 1H,1,5-benzodiazepines 3a–e with heterocyclic ketones 2a–e

<table>
<thead>
<tr>
<th>Amine</th>
<th>Heterocyclic ketone</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>2a</td>
<td>PPA (or SiO₂)</td>
<td>5</td>
<td>3a</td>
<td>48 (52)</td>
</tr>
<tr>
<td>2b</td>
<td>PPA</td>
<td></td>
<td>5</td>
<td>3b</td>
<td>49</td>
</tr>
<tr>
<td>2c</td>
<td>cone-HCl</td>
<td></td>
<td>5</td>
<td>3c</td>
<td>62</td>
</tr>
<tr>
<td>2d</td>
<td>cone-HCl</td>
<td></td>
<td>5</td>
<td>3d</td>
<td>74</td>
</tr>
<tr>
<td>2e</td>
<td>cone-HCl</td>
<td></td>
<td>5</td>
<td>3e</td>
<td>54</td>
</tr>
</tbody>
</table>

*Isolated yield

Table 2. Yields of synthesized quinoxalines 4c, 4e with phenylenediamine 1a and acetylpuridines 2c, 2e

<table>
<thead>
<tr>
<th>Amine</th>
<th>Acetylpuridine</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>2c</td>
<td>cone-HCl, SiO₂</td>
<td>5</td>
<td>4c</td>
<td>92</td>
</tr>
<tr>
<td>2e</td>
<td>cone-HCl, SiO₂</td>
<td></td>
<td>8</td>
<td>4e</td>
<td>39</td>
</tr>
</tbody>
</table>

*Isolated yield

(48%). Its structure was assigned on the basis of ¹H NMR, ¹³C NMR, and GC/MS spectra. Similar result was obtained when SiO₂ (isolated yield 52%) was added to the reaction mixture. Treatment of 1a with 2b at 40–45 °C in the presence of PPA offered 3b in 49% yield (Table 1).

A possible mechanism for the formation of 1H,1,5-benzodiazepine was shown in the preceding communication. In the case of 2c according to reaction conditions, 2-methyl-2,4-dipyridin-2-yl-2,3-dihydro-1H,1,5-benzodiazepine 3c and 2-pyridin-2-yl-quinoline 4c were obtained. But treatment of 1a with 2c in the presence of cone-HCl at room temperature afforded only benzodiazepine derivative 3c in 62% yield. On the other hand, when 1a with 2c in the presence of cone-HCl and SiO₂ was refluxed, a yellow crystalline solid, 2-pyridin-2-yl-quinoline 4c was isolated in 92% yield. And also, in case of 2e, 2-pyridin-4-yl-quinoline 4e as a yellowish brown crystalline solid obtained in 39% yield (Table 2).

This result indicates that not 2 equiv of 2c but 1 equiv of 2c is reacted. A possible mechanism for the formation of 4c is shown in Figure 1.

Seeing the plausible formation mechanism of quinoxaline (Figure 1), first of all, amino group of 1a attacks carbonyl group of ketone to give the imine. Then a 1,3 shift of the hydrogen attached methyl group then occurs to afford an isomeric enamine О. Enamine О changed into intermediate P by the movement of lone-paired electron of nitrogen. Then, proton transfer, ring formation, and proton elimination occur to afford six-membered ring intermediate Q. In order to form quinoxaline, the aromatization subsequent to the formation of the intermediate Q occurred. But the reaction of 1a with 2d in the same manner did not occur. In case of 2d in the presence of cone-HCl at room temperature, 2-methyl-2,4-dipyridin-3-yl-2,3-dihydro-1H,1,5-benzodiazepine 3d was only isolated. Besides, Julia Stephanidou-Stephanatou et al.² showed a facile synthesis of 2,3-dihydro-1H,1,5-benzodiazepines by condensation of ketones with 1a by application of microwave irradiation without solvent. But, they did not separate 2,3-dihydro-1H,1,5-benzodiazepines structural isomers. In the case of the reaction of 4-chloro-1,2-phenylenediamine 1b with acetone, we separated and analyzed (experimental section) precisely 7-chloro-2,2,4-trimethyl-2,3-dihydro-1H,1,5-benzodiazepine 3f and 8-chloro-2,2,4-trimethyl-2,3-dihydro-1H,1,5-benzodiazepine 3g as structural isomers. In the ¹H NMR spectrum of 3f, a doublet (J = 1.2 Hz) due to one proton of C-6 is appeared at δ 7.11. One proton of C-8 is seen at δ 6.93 (dd, J = 1.2, 4.2 Hz, 1H). A doublet (J = 4.4 Hz) due to one proton of C-9 is appeared at δ 6.65. In case of ¹H NMR spectrum of 3g as a structural isomer, a doublet (J = 4.2 Hz) due to one proton of C-7 is appeared at δ 7.04. One proton of C-6 is seen at δ 6.92 (dd, J = 1.1, 4.2 Hz, 1H). A doublet (J = 1.2 Hz) due to the C-9 proton is seen at δ 6.71. From these observations to the ¹H NMR spectrum of 3f and 3g, we analyzed precisely the structures of 3f and 3g as structural isomers (Figure 2).

**Experimental Section**

Melting point was determined on an electrothermal capillary melting point apparatus and uncorrected. TLC was

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![Figure 1](image1.png)

**Figure 1.** Plausible formation mechanism of quinoxaline.

![Figure 2](image2.png)

**Figure 2.** 7-Chloro-2,2,4-trimethyl-2,3-dihydro-1H,1,5-benzodiazepine 3f and 8-chloro-2,2,4-trimethyl-2,3-dihydro-1H,1,5-benzodiazepine 3g.
2-Methyl-2,4-dipyridin-3-yl-2,3-dihydro-1H-1,5-benzodiazepine (3d). ^1H NMR (200 MHz, CDCl₃) δ 8.82 (d, J = 1.9 Hz, 1H, pyridinyl H), 8.71 (d, J = 1.7 Hz, 1H, pyridinyl H), 8.5 (dd, J = 1.7, 1.6 Hz, 1H, pyridinyl H), 8.4 (dd, J = 1.5, 1.5 Hz, 1H, pyridinyl H), 7.90 (t, J = 1.1, 1.5 Hz, 2H, phenyl H), 7.31 (d, J = 2.5 Hz, 1H, pyridinyl H), 7.14 (m, 2H, phenyl H and 2H, phenyl H), 6.90 (d, J = 2.2 Hz, 1H, pyridinyl H), 3.52 (s, 1H, NH), 3.48 (d, J = 13.2 Hz, 1H, methylene H), 2.98 (d, J = 13.2 Hz, 1H, methylene H), 1.83 (s, 3H, CH₃). ^13C NMR (50 MHz, CDCl₃) δ 164.58, 150.44, 148.39, 148.10, 147.33, 142.17, 139.40, 127.26, 134.12, 133.95, 133.47, 133.30, 128.80, 126.98, 122.93, 122.050, 121.45, 72.50, 42.70, 29.70. GC/M: M⁺ = 314.

2-Methyl-2,4-dipyridin-3-yl-2,3-dihydro-1H-1,5-benzodiazepine (3e). ^1H NMR (200 MHz, CDCl₃) δ 8.82 (d, J = 2.16 Hz, 1H, pyridinyl H), 8.71 (d, J = 1.74 Hz, 1H, pyridinyl H), 8.50 (dd, J = 1.6, 1.4 Hz, 1H, pyridinyl H), 8.38 (d, J = 1.4 Hz, 1H, pyridinyl H), 7.88 (t, J = 1.6 Hz, 2H, phenyl H), 7.30 (d, J = 2.4 Hz, 1H, pyridinyl H), 7.13 (m, 1H, phenyl H and 2H, pyridinyl H), 6.89 (d, J = 2.12 Hz, 1H, pyridinyl H), 3.81 (s, 1H, NH), 3.17 (d, J = 13.4 Hz, 1H, methylene H), 2.89 (d, J = 13.4 Hz, 1H, methylene H), 1.74 (s, 3H, CH₃). ^13C NMR (50 MHz, CDCl₃) δ 164.6, 150.4, 148.3, 148.4, 148.1, 147.3, 139.43, 137.25, 134.14, 133.50, 128.8, 127.02, 122.96, 122.12, 121.47, 72.59, 42.81, 29.75. GC/M: M⁺ = 314.

General procedure for quinoline (4c, 4e). In a methanol (20 mL) solution of 1,2-phenylenediamine 1a (2.7 g, 2.5 × 10⁻² mol) and acetylpyridine 2c, 2e (2.5 × 10⁻³ mol) catalytic amount of SiO₂ (0.08 g) and 10% HCl (2 mL) were added and stirred. The reaction mixture was refluxed for 5 h. After refluxing for 5h, the reaction mixture was diluted with water and neutralized with 5% NaOH (50 mL). It was extracted with chloroform (3 × 100 mL). The extract was washed with water and dried (MgSO₄). The chloroform was removed under aspirator pressure and the remaining sticky oil was separated by flash column chromatography on silica gel (n-hexane/EtOAc).

2-Pyridin-2-yl-quinoline (4c). mp 87-88 °C; ^1H NMR (300 MHz, CDCl₃) δ 9.95 (s, 1H, quinoline H), 8.78 (d, J = 1 Hz, 1H, pyridinyl H), 8.60 (d, J = 1.5 Hz, 1H, pyridinyl H), 7.90 (d, J = 1.8 Hz, 1H, pyridinyl H), 7.80 (m, 2H, phenyl H), 7.41 (m, 1H, pyridinyl H). ^13C NMR (75 MHz, CDCl₃) δ 154.9, 151.0, 149.8, 144.5, 142.9, 142.2, 137.5, 130.6, 130.5, 131.9, 127.5, 125.0, 122.5. GC/M: M⁺ = 207.

2-Pyridin-4-yl-quinoline (4e). mp 119-120 °C; ^1H NMR (300 MHz, CDCl₃) δ 9.36 (s, 1H, quinoline H), 8.84 (d, J = 4.8 Hz, 2H, pyridinyl H), 8.17 (m, 2H, pyridinyl H), 7.47 (m, 2H, phenyl H), 7.33 (m, 1H, pyridinyl H), 7.21 (t, J = 4.9, 7.1 Hz, 1H, pyridinyl H), 6.96 (m, 2H, pyridinyl H and 2H, phenyl H), 5.27 (s, 1H, NH), 4.01 (d, J = 12.4 Hz, 1H, methylene H), 2.17 (d, J = 12.4 Hz, 1H, methylene H), 1.57 (s, 3H, CH₃). ^13C NMR (50 MHz, CDCl₃) δ 167.18, 165.13, 156.29, 148.28, 147.80, 139.12, 138.86, 136.08, 135.91, 128.81, 128.54, 124.56, 124.05, 123.95, 123.12, 120.67, 119.61, 73.24, 37.03, 31.16. GC/M: M⁺ = 207.
H3, 8.10 (d, J = 6.0 Hz, 2H, pyridinyl H3), 7.83 (m, 2H, phenyl H), 1H NMR (75 MHz, CDCl3) δ 150.8, 149.1, 143.8, 142.4, 130.7, 130.0, 121.4; GC/MS: M+ = 207.

Synthesis of 7-chloro-2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine (3f) and 8-chloro-2,2,4-trimethyl-2,3-dihydro-1H-1,5-benzodiazepine (3g). In a solution of 4-chloro-1,2-phenylenediamine 1b (2.85 g, 2 × 10−3 mol) and acetone (30 mL), catalytic amount of PPA (0.5 g) was added and refluxed at 40–45 °C for 3 h. After stirring for 3 h, the reaction mixture was diluted with water and neutralized with 5% NaHCO3 (50 mL). The aqueous solution was extracted with chloroform (3 × 100 mL). The chloroform extract was washed with water, dried (MgSO4), and the solvent was evaporated to give the crude products. The remaining sticky oil was separated by flash column chromatography on silica gel (n-hexane:EtOAc = 10:1, v/v) to yield 3f (2.03 g, 55%) and 3g (1.66 g, 45%) as yellow solids. 3f: mp 151-152 °C; IR (KBr, cm−1) ν 3270, 3055, 2930, 1660; 1H NMR (200 MHz, CDCl3) δ 7.11 (d, J = 1.2 Hz, 1H, phenyl H), 6.93 (dd, J = 1, 4.2 Hz, 1H, phenyl H), 6.65 (d, J = 4.42 Hz, 1H, phenyl H), 3.05 (s, 1H, NH), 2.34 (s, 3H, CH3), 2.25 (s, 2H, CH2), 1.53 (s, 6H, CH3); 13C NMR (50 MHz, CDCl3) δ 172.6, 141.8, 139.2, 126.3, 124.7, 122.3, 120.3, 69.8, 45.2, 30.5, 29.7; GC/MS: M+ = 222. 3g: 1H NMR (200 MHz, CDCl3) δ 7.04 (d, J = 4.2 Hz, 1H, phenyl H), 6.92 (dd, J = 1.1, 4.2 Hz, 1H, phenyl H), 3.05 (s, 1H, NH), 2.36 (s, 3H, CH3), 1.22 (s, 2H, CH2), 1.34 (s, 6H, CH3); GC/MS: M+ = 222.

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References