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

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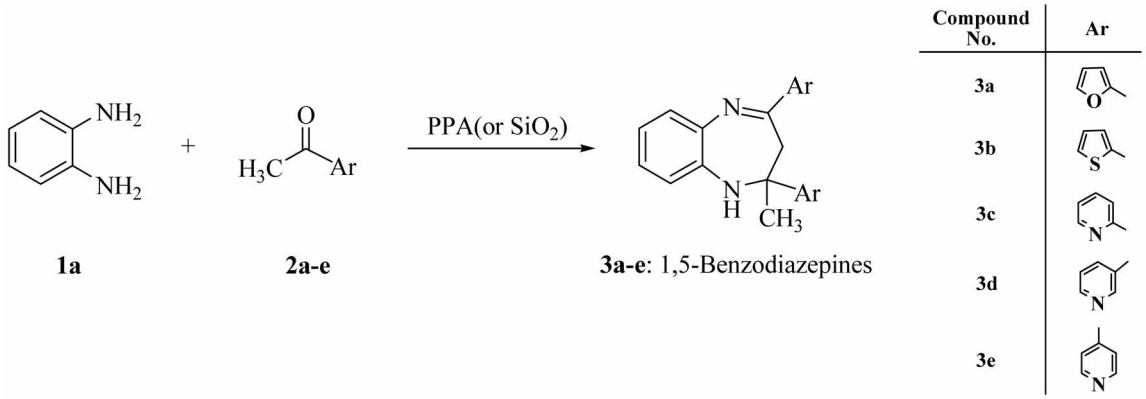
Benzodiazepines are interesting compounds because of their pharmacological properties.[1] Many members of this family are, in fact, nowadays widely used as tranquilizing and anticonvulsant agents. Although the first benzodiazepine was introduced as a drug nearly 30 years ago,[2] the research in this 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 acrylic fibers),[3] and also as anti-inflammatory agents.[4] 1*H*-1,5-Benzodiazepines are used as starting materials for the preparation of some fused ring benzodiazepine derivatives, such as triaxol[5] and oxadiazol.[6] Despite their wide range of pharmacological activity, industrial and synthetic application, the synthesis of 1*H*-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 1*H*-1,5-benzodiazepine derivatives with heteroaromatic ketones (2-acetylfuran **2a**, 2-acetylthiophene **2b**, 2-acetylpyridine **2c**, 3-acetylpyridine **2d**, and 4-acetylpyridine **2e**) by using *conc*-HCl, SiO_2, 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).

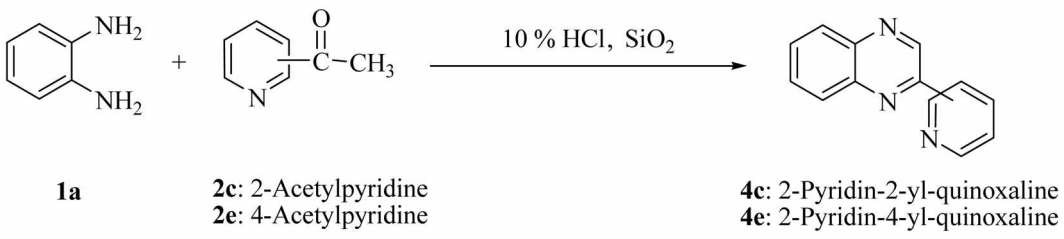
Moreover we describe the structural analysis of 7-chloro-2,2,4-trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine **3f** and 8-chloro-2,2,4-trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine **3g** synthesized by 4-chloro-1,2-phenylenediamine **1b** with acetone.

Earlier we reported the synthesis of 2,4,4,-trimethyl-3*H*-5-hydro-1,5-benzodiazepine and 2,4-diphenyl-4-methyl-3*H*-5-hydro-1,5-benzodiazepine by using various reagents instead of PPA[8].

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 synthezied 1*H*-1,5-benzodiazepines **3a-e** with heterocyclic ketones **2a-e**

Amine	Heterocyclic ketone	Catalyst	Time (h)	Product	Yield (%)[a]
1a	**2a**	PPA (or SiO_2)	5	**3a**	48 (52)
	2b	PPA	5	**3b**	49
	2c	*conc*-HCl	5	**3c**	62
	2d	*conc*-HCl	5	**3d**	74
	2e	*conc*-HCl	5	**3e**	54

[a]Isolated yield

Table 2. Yields of synthezied quinoxalines **4c**, **4e** with phenylenediamine **1a** and acetylpyridines **2c**, **2e**

Amine	Acetylpyridine	Catalyst	Time (h)	Product	Yield (%)[a]
1a	**2c**	*conc*-HCl, SiO_2	5	**4c**	92
	2e	*conc*-HCl, SiO_2	8	**4e**	39

[a]Isolated yield

(48%). It's structure was assigned on the basis of ^{1}H NMR, ^{13}C NMR, and GC/MS spectra. Similar result was obtained when SiO_2 (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 1*H*-1,5-benzodiazepine was shown in the preceding communication.[8] In the case of **2c** according to reaction conditions, 2-methyl-2,4-dipyridin-2-yl-2,3-dihydro-1*H*-1,5-benzodiazepine **3c** and 2-pyridin-2-yl-quinoxaline **4c** were obtained. But treatment of **1a** with **2c** in the presence of *conc*-HCl at room temperature afforded only benzodiazepine derivative **3c** in 62% yield. On the other hand, when **1a** with **2c** in the presence of *conc*-HCl and SiO_2 was refluxed, a yellow crystalline solid, 2-pyridin-2-yl-quinoxaline **4c** was isolated in 92% yield. And also, in case of **2e**, 2-pyridin-4-yl-quinoxaline **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** attaches 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 **O**. Enamine **O** 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 *conc*-HCl at room temperature, 2-methyl-2,4-dipyridin-3-yl-2,3-dihydro-1*H*-1,5-benzodiazepine **3d** was only isolated. Besides, Julia Stephanidou-Stephanatou *et al.*[9] showed a facile synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines by condensation of ketones with **1a** by application of microwave irradiation without solvent. But, they did not separate 2,3-dihydro-1*H*-1,5-benzodiazepines structural isomers. In 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-1*H*-1,5-benzodiazepine **3f** and 8-chloro-2,2,4-trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine **3g** as structural isomers. In the ^{1}H 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 ^{1}H 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 ^{1}H 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

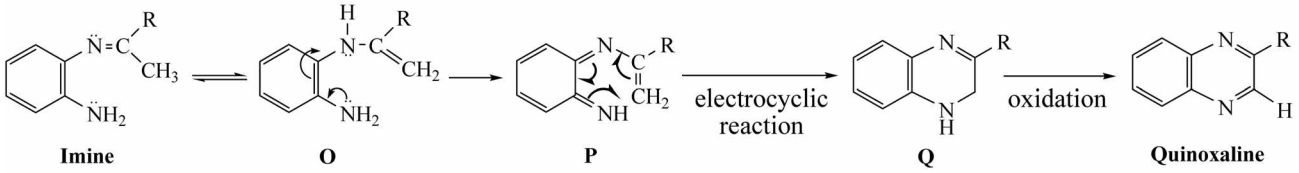


Figure 1. Plausible formation mechanism of quinoxaline.

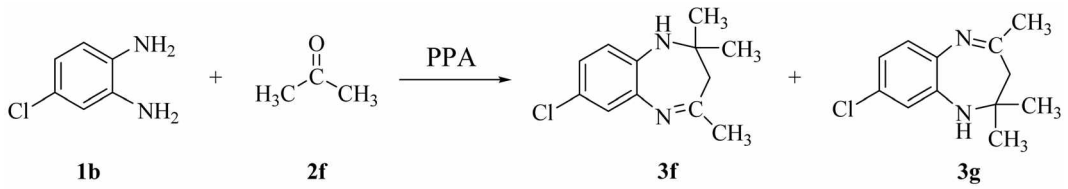


Figure 2. 7-Chloro-2,2,4-trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine **3f** and 8-chloro-2,2,4-trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine **3g**.

performed on glass plates coated with silicon oxide (silica gel $60F_{254}$) and compounds were visualized using a UV lamp. ^1H and ^{13}C NMR spectra were obtained with Bruker AC200 (200 MHz) and Varian Gemini (200 or 300 MHz) spectrometers. Mass spectra were measured with HP 5890 GC/Mass (70 eV, EI). The organic solvents and chemicals were obtained from commercial products and purified by the appropriate methods before use.

General procedure for 1*H*-1,5-benzodiazepines using PPA (3a, 3b). PPA(0.16 g) was added to a solution of 1,2-phenylenediamine **1a** (2.70 g, 2.5×10^{-2} mol), heteroaromatic ketones **2a**, **2b** (5×10^{-2} mol) in chloroform (15 mL) and it was stirred at 40-45 °C for 5 h. After stirring for 5 h the reaction mixture was diluted with water and neutralized with 5% $NaHCO_3$ (50 mL). It was extracted with chloroform (3×100 mL), the extract was washed with water and dried ($MgSO_4$). The chloroform was removed under reduced pressure to give sticky oil was separated by flash column chromatography on silica gel (*n*-hexane:EtOAc).

2,4-Difuran-2-yl-2-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3a). mp 151-152 °C; IR (KBr, cm^{-1}) υ 3320, 3040, 2970, 1640; ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (s, 1H, furanyl Hα), 7.51 (s, 2H, phenyl H), 7.03 (m, 2H, phenyl H), 6.79 (s, 1H, furanyl Hβ), 6.76 (d, J = 6 Hz, 1H, furanyl Hβ), 6.46 (d, J = 2.2 Hz, 1H), 3.41 (s, 1H, NH), 3.05 (d, J = 13.2 Hz, 1H, methylene H), 2.91 (d, J = 13.2 Hz, 1H, methylene H), 1.68 (s, 3H, methyl H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 158.4, 154.0, 145.6, 142.0, 137.7, 128.4, 126.6, 123.1, 122.4, 113.7, 112.4, 110.6, 105.1, 71.4, 39.6, 28.8; GC/MS: M^+ = 292.

2-Methyl-2,4-dithiophen-2-yl-dihydro-1*H*-1,5-benzodiazepine (3b). mp 103-105 °C; IR (KBr, cm^{-1}) υ 3320, 3040, 2970, 1640; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, J = 3.2 Hz, 1H, thiophenyl Hα), 7.29 (d, J = 1.2 Hz, 1H, thiophenyl Há), 7.05 (m, 5H, phenyl H and thiophenyl Hβ), 6.92 (s, 1H, thiophenyl Hβ), 3.59 (s, 1H, NH), 3.04 (d, J = 13.8 Hz, 1H, methylene H), 2.96 (d, J = 13.8 Hz, 1H, methylene H), 1.82 (s, 3H, methyl H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 153.7, 147.0, 141.3, 137.5, 130.5, 128.5, 128.3, 127.9, 127.3, 126.6, 124.5, 123.2, 122.9, 122.5, 73, 44.7, 31.0; GC/MS: M^+ = 324.

General procedure for 1*H*-1,5-benzodiazepines using *conc*-HCl (3c-e). In a methanol (100 mL) solution of 1,2-phenylenediamine **1a** (0.54 g, 5×10^{-3} mol) and heteroaromatic ketones **2c-e** (1.2×10^{-2} mol) catalytic amount of *conc*-HCl (0.5 mL) was added and stirred. The reaction mixture was stirred at room temperature for 5 h diluted with water, and neutralized with 5% $NaHCO_3$ (50 mL). It was extracted with chloroform (5×100 mL). The extract was washed with water and dried ($MgSO_4$). 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-Methyl-2,4-dipyridin-2-yl-2,3-dihydro-1*H*-1,5-benzodiazepine (3c). ^1H NMR (200 MHz, $CDCl_3$) δ 8.56 (d, J = 4.5 Hz, 1H, pyridinyl H), 8.51 (d, J = 4.5 Hz, 1H, pyridinyl H), 8.31 (d, J = 7.8 Hz, 1H, pyridinyl H), 7.65 (t, J = 7.6, 0.7 Hz, 1H, 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), 3.17 (d, J = 12.4 Hz, 1H, methylene H), 1.57 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.18, 165.13, 156.29, 148.28, 147.80, 139.12, 138.86, 136.08, 135.91, 128.81, 128.54, 126.56, 124.05, 123.95, 121.32, 120.67, 119.61, 73.24, 37.03, 31.16; GC/MS: M^+ = 314.

2-Methyl-2,4-dipyridin-3-yl-2,3-dihydro-1*H*-1,5-benzodiazepine (3d). ^1H NMR (200 MHz, $CDCl_3$) 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, pyridinyl 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, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.58, 150.44, 148.39, 148.10, 147.33, 142.17, 139.40, 137.26, 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/MS: M^+ = 314.

2-Methyl-2,4-dipyridin-4-yl-2,3-dihydro-1*H*-1,5-benzodiazepine (3e). ^1H NMR (200 MHz, $CDCl_3$) 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 1H), 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, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) 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/MS: M^+ = 314.

General procedure for quinoxaline (4c, 4e). In a methanol (20 mL) solution of 1,2-phenylenediamine **1a** (2.70 g, 2.5×10^{-2} mol) and acetylpyridine **2c**, **2e** (2.5×10^{-2} mol) catalytic amount of SiO_2 (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% $NaHCO_3$ (50 mL). It was extracted with chloroform (3×100 mL). The extract was washed with water and dried ($MgSO_4$). 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-quinoxaline (4c). mp 87-88 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 9.95 (s, 1H, quinoxalinyl 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). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 151.0, 149.8, 144.5, 142.9, 142.2, 137.5, 130.6, 130.5, 130.1, 129.7, 125.0, 122.5; GC/MS:M^+ = 207.

2-Pyridin-4-yl-quinoxaline (4e). mp 119-120 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 9.36 (s, 1H, quinoxalinyl H), 8.84 (d, J = 4.8 Hz, 2H, pyridinyl H), 8.17 (m, 2H, pyridinyl

H), 8.10 (d, J = 6.0 Hz, 2H, pyridinyl H), 7.83 (m, 2H, phenyl H); ^{13}C NMR (75 MHz, $CDCl_3$) 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-1*H*-1,5-benzodiazepine (3f) and 8-chloro-2,2,4-trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3g). In a solution of 4-chloro-1,2-phenylenediamine **1b** (2.85 g, 2 × 10^{-2} 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% $NaHCO_3$ (50 mL). The aqueous solution was extracted with chloroform (3 × 100 mL). The chloroform extract was washed with water, dried ($MgSO_4$), 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}) υ 3270, 3055, 2930, 1660; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.11 (d, J = 1.2 Hz, 1H, phenyl H), 6.93 (dd, J = 1.2, 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, CH_3), 2.25 (s, 2H, CH_2), 1.33 (s, 6H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.6, 141.8, 139.2, 126.3, 124.7, 122.9, 120.3, 69.8, 45.2, 30.5, 29.7; GC/MS: M^+ = 222. **3g**: ^{1}H NMR (200 MHz, $CDCl_3$) 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), 2.35 (s, 3H, CH_3), 2.22 (s, 2H, CH_2), 1.34 (s, 6H, CH_3); GC/MS: M^+ = 222.

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