A Facile and Efficient Synthesis of Quinoxalines from Phenacyl Bromides and Ortho Phenylenediamine Promoted by Zirconium Tungstate

Lingaiah Nagarapu*, Jyothsna Devi Palem, Rama Krishna Reddy Aruva and Rajashaker Bantu

Organic Chemistry Division II, CSIR-Indian Institute of Chemical Technology, Hyderabad, India

Abstract

Quinoxaline derivatives have been synthesized by a simple, efficient, one-pot, two-component condensation of α,β-unsaturated ketones, o-phenylenediamine in the presence of a catalytic amount of 5% WO₃/ZrO₂ in excellent yields. The effect of electron releasing and electron with drawing substituent on the aromatic ring of phenacyl bromides on the reaction was investigated. Electron releasing groups and electron withdrawing groups did not affect significantly on the yields and the reaction times. Using 1,2-diamines possessing electron-withdrawing substituent needed longer reaction times and the yields were lower. Environmental acceptability, low cost, high yields and recyclability of the 5%WO₃/ZrO₂ are the important features of this protocol.

Graphical Abstract

Quinoxalines have been synthesized in very good yield from various substituted phenacyl bromides in the presence of 5%WO₃/ZrO₂ as catalyst.

Keywords: Quinoxaline; o-phenylenediamine; Zirconium tungstate

Introduction

Quinoxaline derivatives are an important class of nitrogen-containing heterocycles in medicinal chemistry [1-5]. Quinoxaline synthesis and chemistry has attracted considerable attention in the past ten years [6,7]. For example, quinoxaline is a part of various antibiotics such as echinomycin, levomycin, and actinoleutin that are known to inhibit growth of gram positive bacteria, and are active against various transplantable tumors. Some of them exhibit biological activities including anti-viral, anti-bacterial, anti-inflammatory, anti-protozoal, anti-cancer (colon cancer therapies), anti-depressant, anti-HIV, and as kinase inhibitors [8-14]. They are also used in the agricultural field as fungicides, herbicides, and insecticides [1]. In addition, quinoxaline derivatives have also found applications in dyes, efficient electron luminescent materials, organic semiconductors, chemically controllable switches, building blocks for the synthesis of anion receptors, cavitands, and dehydroannulenes [15,16]. They also serve as useful rigid subunits in macrocyclic receptors in molecular recognition.

Several kinds of synthetic routes toward quinoxalines have been developed, which involve condensation of 1,2-diamines with α-diketones [17], Bi-catalyzed oxidative coupling of epoxides with ene-1,2-diamines [18], cyclization-oxidation of phenacyl bromides [19,20]. However, many of these processes suffer from one or more limitations such as drastic reaction conditions, low product yields, the use of toxic metal salts as catalysts, and relatively expensive reagents. Moreover, these reactions are often carried out in polar solvents such as DMSO leading to tedious work-up procedures. We were interested to examine the synthesis of quinoxalines by the condensation of α-phenylenediamine and substituted phenacyl bromides in the presence of a catalytic amount of 5%WO₃/ZrO₂ [21,22].

Experimental

Melting points were determined by using Fisher John’s melting point apparatus and are uncorrected [23,24]. IR spectra were recorded on a Thermo Nicolet Nexus 670 FT-IR spectrometer. Accurate mass measurement was performed on Q STAR mass spectrometer (Applied Biosystems USA). 1H NMR spectra and 13C NMR were recorded at 300 MHz on a Bruker Avance NMR spectrometer with TMS as an internal standard (chemical shifts in δ, ppm). For column chromatography, silica gel 60-120 mesh was used. For TLC, silica gel 60F254 (Merck) was used.

General procedure for synthesis of 3a-k

To a solution of o-phenylene diamine (1a, 1.1 mmol), phenacyl bromide (2a, 1.0 mmol) was added 5%WO₃/ZrO₂ (0.3 mmol). The mixture was refluxed for 0.5 h in 3.0 mL of CH₂CN (progress of the reaction was monitored by TLC). After completion, the reaction mass was cooled to room temperature and the solid catalyst was filtered through a Buchner funnel, washed with CH₂CN (2×5 mL). The filtrate was removed under reduced pressure, and the crude product was...
purified by column chromatograph. The recovered 5%WO3/ZrO2 dried and reused for a number of cycles without significant loss of activity.

2-Phenyl quinoxaline (3a): Solid; Yield 98%; mp 75-78°C; IR (KBr): v max 2923, 2855, 1916, 1711, 1623, 1521, 1401, 952, 821, 709 cm−1; 1H NMR (300 MHz, CDCl3): δ 7.52-7.61 (s, 3H,Ar-H); 7.73-7.83 (m, 2H, Ar-H); 8.13-8.22 (m, 4H, Ar-H); 9.33 (s, 1H); 13C NMR (75 MHz, CDCl3): δ 127.3, 129.0, 129.1, 129.5, 129.6, 130.1, 130.2, 136.7, 141.5, 142.2, 143.3; MS(ESI)+: m/z = 207 [M+H]+.

2-(4-Methoxyphenyl)quinoxaline (3b): Solid; Yield 97%; mp 75-78°C; IR (KBr): v max 2923, 2855, 1916, 1711, 1623, 1521, 1401, 952, 821, 709 cm−1; 1H NMR (300 MHz, CDCl3): δ 3.89 (s, 3H, OCH3); 7.01-7.07 (m, 2H, Ar-H); 7.70-7.77 (m, 2H, Ar-H); 8.09-8.12 (t, j = 6.34 Hz, 2H, Ar-H); 8.16-8.19 (d, j = 8.49 Hz, 2H, Ar-H); 9.29 (s, 1H, =CH); 13C NMR (75 MHz, CDCl3): δ 127.31, 129.45, 129.60, 130.41, 136.92, 162.59, 165.91.

2-Chloroquinoxaline (3c): Solid; Yield 95%; mp 75-78°C; IR (KBr): v max 2923, 2855, 1916, 1711, 1623, 1521, 1401, 952, 821, 709 cm−1; 1H NMR (300 MHz, CDCl3): δ 7.7-7.79 (m, 2H, Ar-H); 7.5-7.57 (m, 2H, Ar-H); 8.09-8.12 (t, j = 6.34 Hz, 2H, Ar-H); 8.16-8.19 (d, j = 8.49 Hz, 2H, Ar-H); 9.29 (s, 1H, =CH); 13C NMR (75 MHz, CDCl3): δ 128.76, 129.16, 129.40, 129.57, 129.78, 130.47, 142.84, 142.2, 150.55, 753; MS(ESI)+: m/z = 241 [M+H]+.

2-(Bromophenyl)-7-methylquinoxaline (3i): Solid; Yield 78%; mp 126-129°C; IR (KBr): v max 2923, 2855, 1937, 1727, 1676, 1541, 1426, 954, 825, 712 cm−1; 1H NMR (300 MHz, CDCl3): δ 7.29 (s, 3H, CH3); 6.69 (d, j = 8.68 Hz, 2H, Ar-H); 7.67-7.91 (m, 2H, Ar-H); 8.04-8.06 (m, 2H, Ar-H); 8.19-8.27 (m, 2H) 9.30 (s, 1H, =CH); 13C NMR (75 MHz, CDCl3): δ 21.32, 128.29, 128.32, 129.43, 129.91, 130.9, 131.27, 140.36, 141.64, 143.19. MS(ESI)+: m/z = 298 [M+H]+.

Results and Discussion

In order to optimize the reaction conditions, including solvents and temperature, and a suitable catalyst for the preparation of quinoxalines from o-phenylene diamine and α-halo-ketones, the condensation of o-phenylene diamine, with phenacyl bromide was chosen as a model reaction, and its behavior was studied in the presence of different catalysts and without catalyst in CH3CN at reflux temperature. The reaction, and its behavior was studied in the presence of different solvents and without catalyst in CH3CN at reflux temperature. The reaction was very slow and resulted in lower product yield. Similar results were obtained in coordinating solvents such as chloroform the reaction was very slow and resulted in lower product yield. However, by using 5%WO3/ZrO2, the product was produced in excellent yield. Similar results were obtained in coordinating solvents such as chloroform the reaction was very slow and resulted in lower product yield. However, by using 5%WO3/ZrO2, the product was produced in excellent yield.

Results and Discussion

In order to optimize the reaction conditions, including solvents and temperature, and a suitable catalyst for the preparation of quinoxalines from o-phenylene diamine and α-halo-ketones, the condensation of o-phenylene diamine, with phenacyl bromide was chosen as a model reaction, and its behavior was studied in the presence of different catalysts and without catalyst in CH3CN at reflux temperature. The results are listed in Table 1. As Table 1 indicates, pTSA, PMA solid, FeCl3 gave relatively good yields of the product in long reaction times: however by using 5%WO3/ZrO2, the product was produced in excellent yield in very short reaction time. Thus, 5%WO3/ZrO2 was the catalyst of choice for all the reactions (Scheme 1).

Subsequently, we investigated on the use of different solvents for the purpose. In chlorinated solvents such as dichloromethane and chloroform the reaction was very slow and resulted in lower product yield. Similar results were obtained in coordinating solvents such as

![Scheme 1: The condensation of o-phenylene diamine, with phenacyl bromide.](image)

Table 1: Effect of different reagents and solvents in the condensation of o-phenylene diamine, 1, phenacyl bromide 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Condition</th>
<th>Time (h)</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSCl</td>
<td>CH3CN</td>
<td>Reflux</td>
<td>14.0</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>PMA solid</td>
<td>CH3CN</td>
<td>Reflux</td>
<td>11.0</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>FeCl3</td>
<td>CH3CN</td>
<td>Reflux</td>
<td>10.0</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>PTA</td>
<td>CH3CN</td>
<td>Reflux</td>
<td>9.0</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>5%WO3/ZrO2</td>
<td>CH3CN</td>
<td>Reflux</td>
<td>4.6</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>5%WO3/ZrO2</td>
<td>CH3CN</td>
<td>Reflux</td>
<td>0.5</td>
<td>94</td>
</tr>
</tbody>
</table>

THF, diethyl and dimethyl ether. On the other hand, conducting the reaction in inert solvents such as CH$_3$CN improved the reaction rates as well as product yields. After screening different solvents, CH$_3$CN came out as the solvent of choice, which not only afforded the products in good yield, but also with higher reaction rates (90% yield in 0.5 hours) (Table 1). It is also noticed that the condensation using 5% WO$_3$/ZrO$_2$ proceeds rapidly and is superior to the different reagents with respect to reaction time, temperature and yield. This claim is justified through the representative examples, illustrated in Table 1, in which the efficiency of 5% WO$_3$/ZrO$_2$ has been compared with those of different Lewis/protic acid catalysts (Table 1). The formation of compound 3a was evident from the appearance of [M+H]$^+$ peak at m/z 221 in mass spectrum (ESI), C-H stretching at 2923 cm$^{-1}$, C=N stretching at 1727 cm$^{-1}$ in IR and the appearance of methyl protons as singlet at $\delta$ 2.45 and the characteristic proton of quinoxalines at $\delta$ 9.29 in $^1$H NMR.

To establish the generality and scope of our method, various phenacyl bromides have been reacted with o-phenylenediamine. The results are displayed in Figure 1. As seen, the reaction proceeds efficiently and the respective quinoxalines were obtained in good to excellent yields and shorter reaction times.

In continuation of our studies [25-30] towards the synthesis of

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diamine</th>
<th>Haloketone</th>
<th>Product (3a-3k)</th>
<th>Time h</th>
<th>Yield %a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NH$_2$</td>
<td>OBr</td>
<td></td>
<td>0.5</td>
<td>98.0</td>
</tr>
<tr>
<td>2</td>
<td>NH$_2$</td>
<td>OBr</td>
<td></td>
<td>0.5</td>
<td>96.0</td>
</tr>
<tr>
<td>3</td>
<td>NH$_2$</td>
<td>OBr</td>
<td></td>
<td>0.5</td>
<td>97.0</td>
</tr>
<tr>
<td>4</td>
<td>NH$_2$</td>
<td>OF</td>
<td></td>
<td>0.5</td>
<td>92.0</td>
</tr>
<tr>
<td>5</td>
<td>NH$_2$</td>
<td>OCl</td>
<td></td>
<td>0.5</td>
<td>95.0</td>
</tr>
<tr>
<td>6</td>
<td>NH$_2$</td>
<td>OBr</td>
<td></td>
<td>0.5</td>
<td>94.0</td>
</tr>
<tr>
<td>7</td>
<td>NH$_2$</td>
<td>OBr</td>
<td></td>
<td>0.5</td>
<td>96.0</td>
</tr>
<tr>
<td>8</td>
<td>NH$_2$</td>
<td>OBr</td>
<td></td>
<td>0.5</td>
<td>95.0</td>
</tr>
<tr>
<td>9</td>
<td>NH$_2$</td>
<td>OBr</td>
<td></td>
<td>0.5</td>
<td>95.0</td>
</tr>
<tr>
<td>10</td>
<td>NH$_2$</td>
<td>OBr</td>
<td></td>
<td>0.5</td>
<td>89.0</td>
</tr>
<tr>
<td>11</td>
<td>NH$_2$</td>
<td>OBr</td>
<td></td>
<td>0.5</td>
<td>95.0</td>
</tr>
</tbody>
</table>

*aisolated yields

Figure 1: Synthesis of quinoxaline derivatives using 5%WO$_3$/ZrO$_2$. 

Organic Chem Current Res Synthetic Organic Chemistry ISSN: 2161-0401 OCCR an open access journal
novel compounds as useful biologically active compounds, we report in this communication an efficient synthesis of quinoxalines derivatives. To the best of our knowledge, in the literature there appear no reports for the synthesis and screening of quinoxalines derivatives using ZrO\textsubscript{2}/WO\textsubscript{3}. This fact has prompted us to investigate in depth the utility of 5\% WO\textsubscript{3}/ZrO\textsubscript{2} for the synthesis of quinoxalines.

The effect of electron releasing and electron with drawing substituent on the aromatic ring of phenacyl bromides on the reaction was investigated. As Figure 1 demonstrates, electron releasing groups and electron withdrawing groups did not affect significantly on the yields and the reaction times (Figure 1, entries 2, 3 and 4, 5, 6). Using 1,2-diamines possessing electron-withdrawing substituent needed longer reaction times and the yields were lower (Table 2, entry 10).

Ease of recycling of the catalyst is one of the most advantages of our method. For the reaction of o-phenylenediamine with phenacyl bromide no significant loss of the product yield was observed when 5\%WO\textsubscript{3}/ZrO\textsubscript{2} was used after four times recycling (Table 2) (Scheme 2).

### Conclusion

In conclusion, we have successfully synthesized and characterized derivatives of substituted quinoxalines using a catalytic amount of 5\%WO\textsubscript{3}/ZrO\textsubscript{2}. This simple procedure is efficient and can be applied to a wide variety of phenacyl bromides. Shorter reaction times and excellent product yields make this catalytic system an alternative method for the synthesis of substituted quinoxaline derivatives. Further application to explore this simple catalytic system for construction of biological molecules is under progress. The remarkable catalytic activity of 5\%WO\textsubscript{3}/ZrO\textsubscript{2} exhibited is convincingly superior to the recently reported other catalytic methods with respect to reaction time, amount of catalyst used. Easy workup and ready availability of the catalyst makes the procedure superior over the existing methods. Environmental acceptability, low cost, high yields and recyclability of the 5\%WO\textsubscript{3}/ZrO\textsubscript{2} are the important features of this protocol. Furthermore the present protocol is readily amenable to parallel synthesis and generation of combinatorial substituted quinoxaline libraries.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cycle</th>
<th>Time(min)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>78</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2**: The results of the condensation of o-Phenylenediamine with phenacyl bromide in the presence of recycled 5\%WO\textsubscript{3}/ZrO\textsubscript{2}.

**Scheme 2**: Plausible mechanism for the formation of 2-phenylquinoxaline 3a.
Acknowledgment

The authors are gratefully acknowledged to the DST-SERB/EMEQ-078/2013 for the financial support.

References