Novel green approaches for synthesis of quinoxaline derivatives

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ABSTRACT

The objective of present research work is to provide green technique for synthesis of quinoxaline derivative. Quinoxaline derivatives are well known in the pharmaceutical industry and have been shown to possess a broad spectrum of biological activities. Highly efficient and simple methods have been described for the synthesis with excellent yields (95-98%). Present synthesis complies with principle of Green chemistry. As part of current studies, we here in reports efficient practical techniques like- sonication (sonochemistry synthesis), UV radiations and simple mortal-pastel method (mechanochemistry). The overall progress of the reaction was monitored by TLC and characterized by IR and NMR. Compared with traditional methods, these methods are more convenient and reactions can be carried out in higher yield, shorter reaction time and milder conditions, without generation of pollution and safer to analyst. The synthesized 2, 3-diphenyle quinoxaline was confirmed by physical constant and spectroscopic studies. Low cost, simple to run, maximum efficiency are some advantages of these techniques. Compared with traditional methods, these methods are more convenient and reactions can be carried out in higher yield, shorter reaction time and milder conditions, without generation of pollution and safer to analyst. From these features present methods can be correlated for safer and efficient synthesis of other products.

Keywords: Synthesis by Sonication, Synthesis by Ultra-Violet Radiation, Synthesis by Morter Pastel, mechanochemistry, Green Approaches for Synthesis, Quinoxaline Derivatives

INTRODUCTION

Quinoxaline derivatives are well known in the pharmaceutical industry and have been shown to possess a broad spectrum of biological activities including antiviral, antibacterial, anti-inflammatory, as kinase inhibitors, anticancer and anthelmintic agents.[1] Quinoxaline ring is a part of a number of antibiotics such as echinomycin, levomycin, and actinomycin, which are
known to inhibit the growth of Gram-positive bacteria and are also active against various transplantable tumors.[2] Besides these, it has been reported for their application in dyes[3], efficient electroluminescent materials [4], organic semiconductors,[5] building blocks for the synthesis of anion receptor,[6] cavitands,[7] dehydroannulenes,[8] and DNA cleaving agents.[9] In light of these significances, a variety of synthetic strategies have been developed for the preparation of quinoxaline derivatives, despite the progress the synthesis of these compounds remains less than ideal. Thus, the development of environmentally friendly benign (Green Chemistry), high-yielding and clean approaches for the synthesis of quinoxaline derivatives is still remains a highly desired goal in organic synthesis. Here, we try to synthesize derivatives by different efficient techniques. Although many research have been came out in this field but effect of ultrasound waves in chemical reaction have not been fully understood yet.

Wang et al. noticed the effect of acoustic cavitations phenomenon that would be produce in solution because of ultrasonic sound. According to hot spot theory, explosion of bubbles in solution cause local and instant increase in temperature and pressure. Under such condition solvent molecules undergo homolytical bond breakage to generate radicals, H+ and OH- for example. Selection of solvent and ambient temperature both are essential for sonication reaction. Ultrasonic-assisted organic synthesis as a green synthetic approach is a powerful technique that is being used more and more to accelerate organic reactions.[10]

Mechanochemistry means mechanical breakage of intramolecular bonds by external force and must be differentiated from molecular solid-state chemistry. Grinding, milling, shearing, scratching and polishing provide the mechanical impact for mechanochemistry, while sonication and shock waving for intramolecular bond breaking are generally described as thermal processes. Here we used simple mortar and pastel for grinding purpose to complete the reaction.[11]

MATERIALS AND METHODS

Melting points were obtained using DBK programmed melting point apparatus and are uncorrected. The purification of synthesized compounds was performed by recrystallization with appropriate solvent system. The purity of the compounds was checked using TLC technique, spots were developed by exposure to iodine vapors and UV cabinet, ultraviolet spectra (λ max) were taken on UV 2401 (PC) S 220V double beam UV Spectrophotometer. Infrared spectra were recorded on FTIR spectrophotometer 8400S, Shimadzu corporation. Mass spectra were recorded in QP-2010 PLUS GC-MS system. Nuclear Magnetic Resonance spectra were recorded with AVANCE 300MHz, using CDCl3.

Materials

Methanol, Rectified Spirit benzyl and O-phenylene diamine, 2, 3, Diphenyl Quinoxaline, Pet. Ether, EtOAc and acetic acid were supplied from Rankem Chemical Co. and they were used as received.

General scheme for the synthesis

\[
\text{Benzil} + \text{O phenylene diamine} \xrightarrow{\text{U.V / Sonicator}} \text{2,3, diphenyl quinoxaline}
\]
Synthesis in presence of U. V. Rays

Equimole amount of benzyl and O-phenylene diamine are mixed well and placed in Ultra Violet Light source for 15 min. Formation of pale yellow colored product indicates completion of reaction. The synthesized product recrystallized by shock cooling method, using rectified spirit as a solvent to get fine crystals of 2, 3, Diphenyl Quinoxaline. The reaction monitored by TLC and confirmed by IR.

By using Sonicator [12]

a) Without catalyst : 0.1 Mole of benzyl dissolved in 5ml methanol and in another beaker 0.01 Mole of O-phenylene diamine dissolved in 5ml methanol. Both the contents are mixed in a beaker and place in sonicator at 45°C for 13-15 min. A pale yellow colored product is formed which indicated formation of product. The synthesized product recrystallized by shock cooling method, using rectified spirit as a solvent to get fine crystals of 2, 3, Diphenyl Quinoxaline. The reaction monitored by TLC and confirmed by IR.

b) With a catalyst : 0.1 Mole of benzyl dissolved in 5ml methanol and in another beaker 0.01 Mole of O-phenylene diamine dissolved in 5ml methanol. Both the contents are mixed in a beaker; a drop of acetic acid is added as a catalyst and beaker place in sonicator at 45°C for 9-10 min. A pale yellow colored product is formed which indicated formation of product. The synthesized product recrystallized by shock cooling method, using rectified spirit as a solvent to get fine crystals of 2, 3, Diphenyl Quinoxaline. The reaction monitored by TLC and confirmed by IR.

3. By using mortar and pastel

Equimole amount of benzyl and O-phenylene diamine triturated in mortar for 10-12 min. slight change in color is observed. Product placed in dark room, overnight standing yield the final product. A pale yellow colored product is formed which indicated formation of product. The synthesized product recrystallized by shock cooling method, using rectified spirit as a solvent to get fine crystals of 2, 3, Diphenyl Quinoxaline. The reaction monitored by TLC and confirmed by IR.

Thin layer chromatography: TLC was performed on silica gel G glass plates using suitable solvents systems to ascertain the purity of these compounds. Solvent system are mentioned in Table 1.

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Mobile Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pet. Ether: EtOAc (90:10)</td>
</tr>
</tbody>
</table>

Table 2: Synthesized conjugates with physical constants

<table>
<thead>
<tr>
<th>Method No</th>
<th>M.P. (°C)</th>
<th>YIELD (%)</th>
<th>R&lt;sub&gt;f&lt;/sub&gt; VALUE</th>
<th>Mol. Wt.</th>
<th>EXPERIMENTAL ANALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>122-124</td>
<td>96.90</td>
<td>0.71</td>
<td>282.34</td>
<td>C, 85.08; H, 5.00; N, 9.92</td>
</tr>
<tr>
<td>2a</td>
<td>122-124</td>
<td>97.00</td>
<td>0.70</td>
<td>282.34</td>
<td>C, 85.08; H, 5.00; N, 9.92</td>
</tr>
<tr>
<td>2b</td>
<td>122-124</td>
<td>98.30</td>
<td>0.70</td>
<td>282.34</td>
<td>C, 85.08; H, 5.00; N, 9.92</td>
</tr>
<tr>
<td>3</td>
<td>122-124</td>
<td>95.80</td>
<td>0.71</td>
<td>282.34</td>
<td>C, 85.08; H, 5.00; N, 9.92</td>
</tr>
</tbody>
</table>

The percentage yield, melting point and analytical data of the synthesized compounds are listed in Table 2.
RESULTS

Spectroscopical studies

\( \lambda_{\text{max}} \): 292 nm

**IR:** Characteristic IR (KBr) bands found at: 3065, 1441, 1395, 768, (\( \nu_{\text{max/cm}} \)).

**1H NMR:** (500 MHz, Chloroform) \( \delta \) 8.06, 8.06, 8.01, 8.01, 8.01, 8.01, 7.53, 7.53, 7.43, 7.43, 7.43, 7.43, 7.41, 7.41.

**MS (m/z):** 282.12 (100.0%), 283.12 (21.8%), 284.12 (2.4%)

<p>| Table 3: Comparison between traditional synthesis and green techniques |
|---------------------------------|----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Parameter</th>
<th>Traditional method</th>
<th>Traditional method</th>
<th>Green techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Time required</td>
<td>1-1.5 hrs</td>
<td>15 min</td>
<td>15 min</td>
</tr>
<tr>
<td>2</td>
<td>% yield</td>
<td>72-78%</td>
<td>96.90%</td>
<td>97.00%</td>
</tr>
</tbody>
</table>

DISCUSSION

Here we introduced techniques other than conventional route of synthesis for the synthesis of 2, 3-diphenyle quinoxaline. The synthesized compound complies the spectroscopical studies. Among the different methods used in synthesis, compound 2b shows maximum yield with short duration of reaction. Other compound yields more than traditional route of synthesis in lesser time span.

CONCLUSION

Compared with traditional methods, these methods are more convenient and reactions can be carried out in higher yield, shorter reaction time and milder conditions, without generation of pollution and safer to analyst.

REFERENCES

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