Facile, One Pot Synthesis of Indoloquinoxaline and its Derivatives Using Aqueous Orange Peel Extract at Room Temperature

Nitin A. Sasane¹, Gangadhar A. Meshram², Kirti S. Bhise², Bhushan B. Popatkar²

Department of Chemistry, University of Mumbai, Vidyanagari, Kalina, Santacruz (E), Mumbai, India

Abstract: A current report expresses that Orange Peel Extract use as catalytic medium for the synthesis of Indoloquinoxaline derivatives from commercially available starting materials. Isatin and O-phenylenediamine in presence of fresh orange peel extract resulted into desired product at room temperature in a given reaction condition. Advantages of this method include greener and cleaner conditions, shorter reaction time, and good to moderate yield of products. A simple one-pot procedure has been developed for the synthesis of Indoloquinoxaline derivatives from readily available starting materials.

Keywords: Indoloquinoxaline, Quinoxaline, Orange Peel Extract, Cyclisation

I. INTRODUCTION

Conventional methods of organic synthesis normally needs longer reaction time, tedious apparatus setup, that results in higher cost of method and the excessive use of solvents reagents lead to environment pollution.

It is widely acknowledged that there is a growing need for more environmentally acceptable processes in the chemical industry and laboratory. This trend towards what has become known as “Green Chemistry” necessitates a paradigm shift from conventional concepts of process effectiveness, that focus largely on chemical yield, to one that assigns economic value for reduces waste at source and avoiding the use of toxic and/or hazardous substances. Sustainable chemistry reduces waste at source, i.e. it is main pollution prevention rather than waste remediation. Prevention is better than cure, the first principle of green chemistry.

An alternative term that is currently favoured by the chemical industry is sustainable technologies. Sustainable progress has been defined as “meeting the needs of the present generation without compromising the ability of future generations to meet their own needs. The first reports were published more than a century ago (Hinsberg 1884; Korner 1884) but even today chemist endeavour to create new and superior routes to these versatile compounds because of wide range of applications.

Quinoxalines are particularly one of the most important classes of nitrogen-containing heterocyclic compounds in synthetic organic chemistry. The fusion of two aromatic rings i.e. of benzene and pyrazine leads formation of quinoxalines and therefore it also named as benzopyrazine, and is described as a bioisoster of quinoline, naphthalene and benzothiophene. This structure is found in numerous biologically relevant molecules. For example, quinoxalines derivatives are found to have antibacterial, antimalarial and anticancer activities. Because of their wide areas of application functionalized quinoxaline are desirable species that can lead to new and/or improved drugs and well known for their luminescent properties. Molecular weight of quinoxaline is 130.15, having molecular formula C₈H₆N₂ and at standard conditions it is a white crystalline powder. Chemically, quinoxaline is a low melting solid, purified by distillation and a fraction of boiling point 108°-111°/12 mm has a melting point 29-30°C. Quinoxalines are water soluble and forms salt with acids. Some of the Indoloquinoxaline derivatives are synthesized using tedious reaction methodologies. Diversity-oriented synthesis indoloquinoxaline ring using poly (ethylene glycol) solvent, Pd-catalyzed and palladium catalyzed reaction system with very high temperature NaN₃, HAMP, CuI catalyzed reaction, Acid catalyzed reaction condition with high temperature required for the synthesis of Indoloquinoxaline
derivatives. Most of the quinoxaline derivatives are synthetic and natural quinoxaline derivatives are rare such as echinomycin\(^1\) and triostin A. The study of quinoxaline and its derivatives has become a subject of interest in recent years due to their wide variety of biological activities as well as therapeutic applications. Quinoxaline derivatives have been widely used in dyes\(^12\), pharmaceuticals\(^13, 14\) and as an electrical or photochemical\(^14\) materials.

Quinoxaline ring moiety constitute part of the chemical structures of various antibiotics such as Echinomycin, Levomycin and Actinoleutin that are known to inhibit the growth of gram positive bacteria and are active against various transplantable tumours\(^15, 16\). Interestingly, it also shows hypoglycemic and antiglaucoma activity. Modification in their structure has offered a high degree of diversity that has proven useful for development of new therapeutic agents having improved potency and lesser toxicity. Considering the extensive research on quinoxaline in the past, it was essential to review the wide spectrum of biological activity of quinoxalines. Quinoxalines are reported to possess a wide range of biological activities in literature such as anti-microbial, anti-tubercular, anti-fungal\(^17, 18\), anti-cancer, anti-inflammatory, anti-convulsant, anti-viral\(^19, 20\), anti-HIV\(^21, 22\), anti-parasitic, anti-bacterial\(^23, 24\), anti-amoebic activity.

The common procedure for their synthesis consists of condensing \(O\)-disubstituted benzene with two carbon synthon. Therefore, the condensation of \(O\)-phenylenediamine with \(\alpha\)-dicarbonyl compounds results in quinoxalining formation. Numerous methods are available for the synthesis of quinoxaline derivatives which involves the condensation of 1,2-diamines with \(\alpha\)-diketones. The 1,4-addition of 1,2-diamines to diazenylbutenes, cyclization-oxidation of phenyl bromides and oxidative coupling of epoxides with ene-1,2-diamines. Recently many research groups have reported the synthesis of different quinoxaline derivatives involving some green methodologies, which includes recyclable catalyst, microwave-assisted synthesis and reactions in aqueous medium. Quinoxalines and its derivatives could be converted in both mono and di-N-oxides by oxidation with peracids. Nitration occurs only under forcing conditions (Conc. HNO\(_3\), oleum, 90°C) to give 5-nitroquinoxaline\((1.5\%)\) and 5,7-dinitro-quinoxaline\((24\%)\).

Jain et al. have synthesized isatin embedded quinoxalines by reaction of isatin with \(O\)-phenylenediamine using tetrabutylammonium bromide (TBAB) as a surfactant in water at heating condition\(^25\). Therefore, there is stronger need to develop an attractive and demanding methodology which should have green reagents and greener routes for the synthesis of Indoloquinoxaline derivatives. To the best of our knowledge, there is no protocol available for the synthesis for Indoloquinoxaline derivatives using orange peel extract.

### II. GENERAL PROCEDURE

This work focuses on the synthesis of indoloquinoxaline by employing fresh orange peel aqueous extract as a solvent and catalyst which provided the eco-friendly condition. In this, an equimolar solution of isatin\((1)\) \((147\text{mg}, 1\text{mmol})\) and \(O\)-phenylenediamine\((2)\) \((108\text{mg}, 1\text{mmol})\) and fresh aqueous orange peel extract was added as catalyst \((20\text{ml})\) and the reaction mixture kept on magnetic stirrer after 30 minutes the clear reaction mixture turns to turbid solution and finally get precipitated. The completion of reaction was monitored by TLC using ethyl acetate-hexane system \((40:60)\). This gives good result for synthesis of Indoloquinoxaline\((3)\).

### III. RESULTS AND DISCUSSION

To explore generality of the reaction variety of substrates were reacted with optimized reaction condition. Various substituted isatin derivatives reacted with \(O\)-phenylenediamine using fresh orange peel extract as a natural catalyst which on subjected to stirring at room temperature. A variety of isatin derivatives like 5-nitroisatin, 5-chloroisatin, 5-idoisatin and 7-bromoisatin were well tolerated and provided good yield (Entries 1–4). As well as \(O\)-phenylenediaminederviative like 4-methylbenzene-1,2-diamine when react with isatin, 5-nitroisatin and 5-chloroisatin derivatives gives moderate to good yield of the desired product (Entries, 5–7). The 4-chlorobenzene-1,2-diamine and 4,5 dichlorobenzene-1,2-diamine react with isatin and its derivatives provide good yield (Entry, 8). 4-nitrobenzene-1,2-diamine in combination with plane isatin gives product with moderate yield of the product. All formed products were characterized by comparing spectral properties and comparing their physical properties with that of reported compounds in the literature.
Table 1: Synthesis of Indoloquinoxaline derivatives from isatin and o-phenylenediamine

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound (1)</th>
<th>Compound (2)</th>
<th>Product (3)</th>
<th>Time in Min</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td>45</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td>60</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td><img src="image9.png" alt="Image" /></td>
<td>55</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
<td>50</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /></td>
<td><img src="image15.png" alt="Image" /></td>
<td>65</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td><img src="image16.png" alt="Image" /></td>
<td><img src="image17.png" alt="Image" /></td>
<td><img src="image18.png" alt="Image" /></td>
<td>65</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td><img src="image19.png" alt="Image" /></td>
<td><img src="image20.png" alt="Image" /></td>
<td><img src="image21.png" alt="Image" /></td>
<td>50</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td><img src="image22.png" alt="Image" /></td>
<td><img src="image23.png" alt="Image" /></td>
<td><img src="image24.png" alt="Image" /></td>
<td>75</td>
<td>80</td>
</tr>
</tbody>
</table>
1. Reaction conditions: isatin (1) (147 mg, 1 mmol) and O-phenylenediamine (2) (108 mg, 1 mmol) fresh aqueous orange peel extract was added as catalyst (20 ml).

IV. CONCLUSION

In summary, a new facile, one-pot synthesis method for the synthesis of Indoloquinoxaline derivatives from the easily available isatin and O-phenylenediamine using fresh orange peel as a catalyst has been developed. In addition, this method is probable to be useful for the synthesis of a range of substituted heterocyclic compounds with comparable indoloquinoxaline structures other than simple substituted derivatives of compounds. Also short reaction time and readily available starting materials all combine to make this method striking for a wide range of application in organic synthesis and medicinal chemistry.

V. EXPERIMENTAL PROCEDURE

5.1 Synthesis of 6H Indolo [2, 3-b] quinoxaline (Entry 1)
To an equimolar solution of isatin (147 mg, 1 mmol) and O-phenylenediamine (108 mg, 1 mmol) and fresh aqueous orange peel extract was added as catalyst (20 ml), the reaction mixture was kept on magnetic stirrer, after 30 minutes the clear reaction mixture turns to turbid solution and finally get precipitate. The precipitate was filter, washed with water and recrystallized in ethanol to get pure product. The completion of reaction was monitored by TLC using ethyl acetate-hexane system (40:60).

Spectral data of compound 3-chloro-6H-indolo[2,3-b]quinoxaline (Entry, 13)
3-chloro-6H-indolo[2,3-b]quinoxaline (Entry, 13): White solid; IR: (solid, KBr, v max, cm⁻¹) 3381, 3018, 3022, 1655, 1615, 1524, 1335, 1033, 764; ¹H NMR: (300 MHz, CDCl₃) δ ppm 6.5-7.6 (3H, m), 7.2-7.5 (4H, m), 8.4 (1H, d), 12.6 (1H, s), ¹³C NMR: (CDCl₃, 75 MHz) δ ppm 114.48, 117.72, 123.31, 128.10, 129.98, 130.34, 131.11, 134.86, 147.70, 154.58; LC-MS: m/z (M+1) 154.0.

ACKNOWLEDGEMENTS

The authors wish to thanks to the Department of Chemistry, University of Mumbai, also thankful to principal MPASC College, Panvel.

REFERENCES


Copyright to IJARSCT www.ijarsct.co.in DOI: 10.48175/IJARSCT-3073