Quinoxaline as a potent heterocyclic moiety

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ABSTRACT: Various novel, mild, eco-friendly and efficient methods has been developed for the preparation of quinoxaline derivatives in high yields via condensation of aromatic diamine and 1,2-dicarbonyl compounds or alphahydroxyketones in the presence of different catalyst such as CuSO4/KMnO4, iodine, phenol similarly by using different solvents such as water, ethanol. As part of current studies, we here in report efficient practical techniques like sonication (sonochemistry synthesis), heating, grinding and simple mortal-pastel methods (mechanochemistry). However, all results suggest a mild and heterogeneous nature of these mechanisms, shorter time of reaction and higher yield or similar to reported older methods, the review here is to highlight some convenient methods of synthesis with keeping an eye to their various biological importances.

KEYWORDS - alphahydroxyketones, sonochemistry, antioxidantactivity.

Methods for synthesis of quinoxaline:

I. INTRODUCTION:

Fig: Structure of quinoxaline

The current review mainly concern with the catalytic method of synthesis of quinoxaline derivatives. Due to the important role in lead optimization as well as for the synthesis of derivatives, effective and convenient methods are a serious need for medicinal chemistry. Quinoxaline is commonly called as or benzopyrine. Quinoxaline and its derivatives are mostly of synthetic origin. The fusion of one or two benzene rings in quinoxaline and phenazine increases the number of resonance structure, which are available to these systems. It posses the dipole moment of zero. Considering these properties, various research workers have shown a keen interest in this small heterocyclic moiety as target structure for evaluation of many pharmacological activities. This review includes various synthetic routes and guidelines for the development of new quinoxalines.

Nitrogen containing heterocyclic compounds are indispensable structural units for both the chemists and biochemists. Among the various classes of benzene fused six-membered nitrogen containing heterocyclic compounds, quinoxaline derivatives form an important class of pharmacologically active compounds. The numbering and chemical structure is as shown above. Numerous quinoxaline derivatives have important biological activity such as antibacterial[1], anticancer[2], anti-inflammatory agents[3], antitubercular and antifungal[4], cytotoxic[5], Antioxidant[6], Anticonvulsant[7], antiviral[8], SR protein-specific kinase-1 inhibitor[9] activity.

II. CHEMISTRY

Quinoxaline is a low melting solid, m.p 29-30°C and is miscible with water. It is weakly basic pKa 0.56. Quinoxaline forms salts with acids. Nitrilation occurs only under forcing conditions (Conc. HNO3, Oleum,90°C) to give 5-nitroquinoxaline (1.5%) and 5,7-dinitro-quinoxaline (24%).
Oxidation of quinoxaline results in the formation of the product depending on the nature of the oxidizing agent employed. With alkaline potassium permanganate pyrazine 2,3-dicarboxylic acid is formed, while with peracid quinoxaline di-N-oxide results.[10]

![Quinoxaline reaction diagram]

**SYNTHESIS:**

1. Atghia and Beigbaghlou examined the reaction of 1,2-phenylenediamine (1 mmol) with benzil (1 mmol) in various solvents (EtOH, THF, MeCN, EtOAc, and toluene) and also under solvent-free classical heating conditions in the presence of different amounts of the catalyst. The best result was achieved by carrying out the reaction in the presence of 10 mg of TiO2-Pr-SO3H in EtOH[11].

![Reaction equation]

2. Sajjadifar developed a novel, mild, eco-friendly and efficient method for the preparation of quinoxaline derivatives in high yields via a one-pot condensation of aromatic diamine and 1,2-dicarbonyl compounds in the presence of [2-(sulfooxy)ethyl]sulfamic acid (SESA)[12].

![Reaction equation]

3. Karami And Khodabakhshi produced a Convenient and simple procedures for the synthesis of phenazine and quinoxaline derivatives were developed via a reaction of o-phenylenediamines and 1,2-dicarbonyl compounds. In addition, the synthesis of two new 1,4-benzodiazine derivatives and the catalytic activity of magnesium sulfate heptahydrate (MgSO4·7H2O) in the room temperature condensation of o-phenylenediamines and 1,2-dicarbonyl compounds in ethanol as solvent are reported[13].
4. Heravi et al. Iodoxybenzoic acid (IBX), a readily available hypervalent iodine (V) reagent, was found to be highly effective in synthesis of quinoxaline derivatives, from 1,2-diketones and ophenylenediamines at room temperature in very high yields [14].

5. Fan and Hua studied, Yb immobilized NaY zeolite catalyst (Yb/NaY) which was obtained by a hydrothermal method and characterized by XRD, BET, FT-IR, ICP-AES, and NH₃-TPD. The catalyst displayed good catalytic activity when applied to the synthesis of quinoxalines via condensation of α-hydroxyketones with 1,2-diamines, and could be reused several times without any loss of catalytic activity [15].

6. Nagarapu and et al synthesized Quinoxaline derivatives 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 withdrawing 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 [16].
7. Soleymani et al synthesized compounds based on condensation of Aryl-1,2-di amine with 1,2-di carbonyl in the acidic condition, some new compounds was obtained from Quinoxaline family that for the first time some new catalysts was used for increasing of efficiency and reducing of process time. Used catalysts were CrCl2.6H2O, PbBr2 and CuSO4.5H2O compounds that preparation of these catalysts is economically, cost-effective and saves time. All mechanisms were done in ethanol solvent at room temperature[17]

8. Sajjadifar et al described a simple, highly efficient and green procedure for the condensation of aryl and alkyl 1,2-diamines with α-diketones in the presence of catalytic amount of citric acid at room temperature. Using this method, quinoxaline derivatives as biologically interesting compounds are produced in high to excellent yields and short reaction times under mild and green condition. In this research, new quinoxaline derivatives were produced.[18]

![Image of chemical structures and reactions](image-url)

**Figure 1- Citric acid structure as a trifunctional Bronsted acid**
9. Biswas et al developed an operationally simple and efficient cascade strategy to access substituted isoindolo[2,1-a]quinoxalines via one step copper-catalysed C-N coupling of substituted 2H-isindole-1-carbaldehyde and substituted 2-halophenylamines. Another straightforward procedure to prepare substituted isoindolo[2,1-a]quinoxalin-6(5H)-ones involving transformation of substituted 2H-isindole-1-carboxylic acids to acid chloride, coupling with substituted 2-iodophenylamines and copper-catalysed C-N coupling is described[19].

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{NH}_2\cdot\text{HCl} \\
+ & \quad \text{CHO} \\
\text{CuI} & \quad \text{R} \\
\rightarrow & \quad \text{R} \\
1. \text{LiAlH}_4 & \quad \text{NH} \\
2. \text{MnO}_2 & \quad \text{CO}_2\text{Me} \\
& \quad \text{CHO}
\end{align*}
\]

Scheme 2. A plausible mechanism for the synthesis of isoindolo[2,1-a]quinoxaline

10. Shi et al described an efficient and clean method for the synthesis of 1,5-benzodiazepines from o-phenylenediamine and ketones catalyzed by sodium tetrachloroaurate(III) dihydrate under mild conditions. The catalyst was shown to be equally effective for the synthesis of quinoxalines from o-phenylenediamine and α-bromo ketones under the similar reaction conditions. This method produced good yields[20].

\[
\begin{align*}
\text{NH}_2\text{NH}_2 & \quad \text{CHO} \\
\text{1} & \quad \text{2e} \\
\text{Solvent, r.t} & \quad \text{Gold catalyst} \\
\text{(2% mole fraction)} & \quad \text{3e}
\end{align*}
\]

11. Yun-fei et al described Ga(ClO₄)₃-catalyzed reaction of 1,2-aryldiamines and α-bromoketones to afford 2-substituted quinoxalines in good yields. The reaction proceeded via grinding process with 10%(molar fraction) catalyst under solvent-free conditions at room temperature[21].
11. Huang et al found Keggin type heteropolyacids to be an efficient and reusable catalyst for the synthesis of biologically active quinoxaline derivatives from the condensation of 1,2-diamine with 1,2-dicarbonyl compounds in excellent yields in water. This method provides a new and efficient protocol in terms of small quantity of catalyst, a wide scope of substrates, and simple work-up procedure[22].

12. Cartigny et al developed a highly efficient and general iridium-difluorphos-catalyzed asymmetric hydrogenation of diverse 2-alkyl- and 2-aryl-substituted quinoxalines into biologically and pharmaceutically relevant 2-substituted-1,2,3,4-tetrahydroquinoxaline units has been developed. High isolated yields and excellent enantioselectivities of up to 95% for 2-alkyl-substituted quinoxalines and of up to 94% for 2-aryl-substituted quinoxalines were obtained.[23]

13. Pawar et al synthesized quinoxaline derivatives in high to excellent yields in the presence of thiamine hydrochloride (VB1) as an inexpensive, nontoxic and metal ion free catalyst at ambient temperature.[24]

14. Heravi et al found o-Iodoxybenzoic acid (IBX), a readily available hypervalent iodine (V) reagent, to be highly effective in synthesis of quinoxaline derivatives, from 1,2-diketones and o-phenylenediamines at room temperature in very high yields.[25]
15. Bandyopadhyay et al produced a microwave-induced iodine-catalyzed simple, rapid and convenient synthesis of different types of quinoxalines via condensation of 1,2-diamines with 1,2-dicarbonyl compounds.[26]

16. Das and Sarkar carried out an efficient environmentally benign condensation of 1,2 diketones and 1,2-diamines for a facile synthesis of quinoxalines was carried in aqueous medium in the presence of tetraethylammonium bromate. [27]

<table>
<thead>
<tr>
<th>S.NO.</th>
<th>CHEMICAL STRUCTURE</th>
<th>CHEMICAL NAME</th>
<th>ACTIVITY</th>
<th>REF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>Acetaminophen</td>
<td>Anticancer and Cytostatic</td>
<td>[2]</td>
</tr>
<tr>
<td>2.</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>2-(benzylthio)-3-methylquinoxaline</td>
<td>Antiinflammatory</td>
<td>[3]</td>
</tr>
<tr>
<td>3.</td>
<td><img src="image" alt="Quinoxaline-6-Carabaldehyde" /></td>
<td>Quinoxaline-6-Carabaldehyde</td>
<td>Antimicrobial</td>
<td>[28]</td>
</tr>
<tr>
<td>4.</td>
<td><img src="image" alt="Quinoxylamino-1,3-diazacycloalkanes" /></td>
<td>Quinoxylamino-1,3-diazacycloalkanes</td>
<td>Hypotensive</td>
<td>[29]</td>
</tr>
<tr>
<td>5.</td>
<td>![1,2,4]triazolo[4,3-a]quinoxaline](image)</td>
<td>[1,2,4]triazolo[4,3-a]quinoxaline</td>
<td>Anticonvulsant</td>
<td>[*]</td>
</tr>
</tbody>
</table>

**1a–e**

R = H, CH₃, CF₃, substituted phenyl  
R₁ = substituted phenyl

| 6. | ![1-[(4-(1H-benzimidazol-2-yl)phenyl)amino]methyloxazoline](image) | 1-[(4-(1H-benzimidazol-2-yl)phenyl)amino]methyloxazoline | Antiviral | [8] |
| 7. | ![Antiplasmodial](image) | Antiplasmodial | [*] |
| 8. | ![4-Acetyl-2-phenyl-1,3,4-oxadiazino[5,6-e]quinoxaline](image) | 4-Acetyl-2-phenyl-1,3,4-oxadiazino[5,6-e]quinoxaline | Antidepressant | [31] |
| 9. | ![Tricyclic benzof[g]quinoxaline leads.](image) | Tricyclic benzof[g]quinoxaline leads. | SR protein-specific kinase-1 inhibitor | [32] |
III. CONCLUSION

This review gives an overview of the various synthetic routes used to form a biologically rich quinoxaline moiety. This paper proves to be helpful for further research work on the bioactive quinoxaline ring and as an important tool for the development of better medicinal agents and newer compounds possessing quinoxaline moiety that could be better agents in terms of efficacy and safety.

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