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RESEARCH ARTICLE

An Efficient Synthesis of Quinaxoline Derivatives Using $Fe(DS)_3$ as a Lewis Acid-Surfactant-Combined Catalyst

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Abstract: A new and eco-friendly synthetic strategy for the synthesis of quinoxaline derivatives from various 1,2-diketones and 1,2-diamines using Lewis acid-surfactant-combined $Fe(DS)_3$ as a water stable catalyst is described. Use of water as reaction medium rendered this procedure cost-effective and environmentally benign. In addition to its efficiency and simplicity, this method provided high yields of biologically potent quinoxalines in shorter reaction time. This work not only may lead to environmentally benign systems but also will provide a new aspect of organic chemistry in water.

Keywords: 1,2-Diketones, 1,2-Diamines, Lewis acid-surfactant-combined catalyst and Aqueou medium

Introduction

Now a days, there is a great attention of synthetic chemist towards the development of sustainable and ecofriendly methodologies for the synthesis of heterocyclic compounds. The significant emphasis is towards the development of green chemical process. The important aspect of green chemistry is the utility of environmentally friendly solvents that are not harmful for environment as well as human health. Organic reactions in water have received considerable attention primarily because of its environmental acceptability, abundance and low cost[1,2].

Nitrogen-containing heterocyclic molecules are the fundamental structural units studied both by the chemists and biologists. Quinoxaline derivatives are one of the most important nitrogen-containing heterocyclic compounds which are the core constituents of many pharmacologically active agents[3]. Quinoxaline containing drugs, CQS (chloroquinoxaline sulfonamide) and XK469 were observed to have anticancer activity against solid tumors, (2-quinoxalinyloxy)phenoxy propanoic acid derivatives, such as Assure are well known to act as herbicide (Figure 1)[4]. Quinoxaline structural motif is found in several natural products and antibiotics such as echinomycin, leromycin and actinomycin[5], which are known to

inhibit the growth of gram-positive bacteria. Compounds with quinoxaline core are used as allosteric dual Akt1 and Akt2 inhibitors[6], human cytomegalovirus polymerase inhibitors[7], Src-Family Kinase p56^{Lck} inhibitors[8], SRPK-1 inhibitors[9], monoamine oxidase an inhibitors[10]. Some pyrrolo[1,2-a]quinoxaline derivatives are found to be potent and selective 5-HT_3 ligands[11-12]. Therefore, these compounds have distinguished themselves as heterocycles with chemical and biological significance. As a result of these significant properties, a variety of synthetic approaches have been reported for the synthesis of quinoxalines.

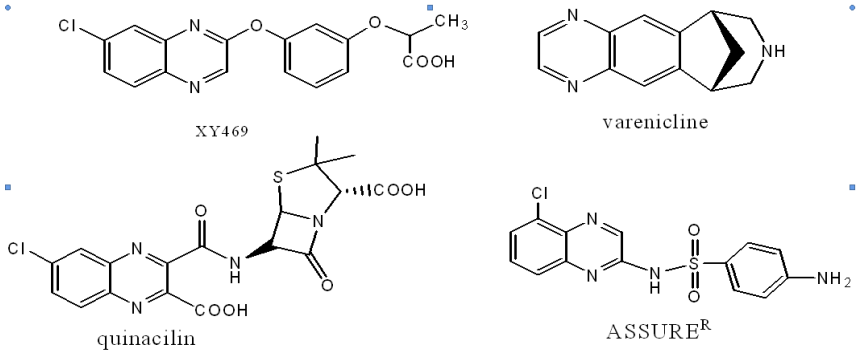


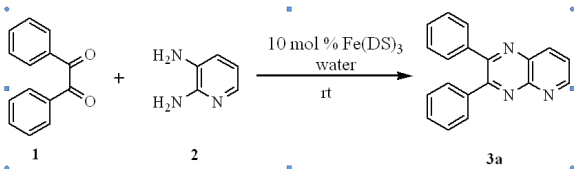
Figure 1. Representative quinoxaline containing drugs

The literature survey reveals several reports on the synthesis of quinoxalines using different catalysts such as *p*-TSA[13], ionic liquid (Hbim)BF_4][14], $Ga(OTf)_3$,[15] DMSO-PdI_2,[16] oxalic acid[17], silica bonded *S*-sulfonic acid[18], ZnI_2,[19] and amberlyte-15[20].

Recently, several workers have also improved the synthesis of quinoxalines using some modified catalysts and reagents like clayzic[21], silicagel[22], alumina[23], DABCO[24], PEG-400 in MW[25], PEG-water[26], glycerol[27], graphite[28] and using supported cobalt nano particles[29]. 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. In view of this, still a need was felt for designing a simple and recyclable catalytic system that will promote efficient one-pot synthesis of the functionalized quinoxaline derivatives.

Organic reactions in water are often limited in scope due to the poor solubility and hence to overcome this problem chemists use surfactants to increase the solubility in water and on the other hand Lewis acid catalysts are one of the most powerful catalysts in organic synthesis and they work in strictly anhydrous condition due to water-labile nature of most Lewis acids. Lewis acid-surfactant-combined-catalysts (LASC) are dual in nature and act as a Lewis acid catalyst as well as surfactant to form colloidal particles[30-31]. This catalyst can tolerate drastic reaction conditions such as high temperature and able to catalyze various acid catalyzed reactions.

During the course of our studies towards the synthesis of biologically active heterocycles[32-34] and encouraged by advantages of LASC, we demonstrated the high catalytic activity of Lewis acid-surfactant-combined catalyst ($Fe(DS)_3$ for the synthesis of substituted quinoxalines by the reaction of 1,2 diketones like phenanthrenequinone, benzoin, and acenathaquinone with *o*-phenylenediamine (Scheme 1) in aqueous media for the first time. The reported method has advantages of ambient reaction condition, environmentally acceptable solvent, high yields, simple work-up and easy catalyst recovery and reusability.



Scheme 1. Synthesis of quinoxalines

Experimental

Melting points were determined on a Toshniwal apparatus. The purity of compounds was checked on thin layers of silica gel in various non-aqueous solvent systems, *e.g.* benzene: ethylacetate (9:1), benzene : dichloromethane (8 : 2). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 400 Avance III using DMSO-d_6 at 400 and 100 MHz, respectively. TMS was used as internal reference. ESI Mass spectra of representative compounds were recorded on Waters UPLC-TQD Mass spectrometer. Lewis acid-surfactant-combined catalyst ($Fe(DS)_3$ was prepared by literature method[35].

*Synthesis of quinoxaline and pyrido[2,3-b]pyrazine derivatives (**3a-f**)*

Appropriate mixture of 1,2-diketone **1** (1.0 mmol), 1,2-diamine **2** (1.0 mmol) and $Fe(DS)_3$ (10 mol %) in water (10 mL) was taken in a flask. The reaction mixture was stirred at room temperature for required time. After the completion of the reaction, TLC was checked and the crude product was filtered and washed well with water to afford the pure product.

*2,3-Diphenylpyrido[2,3-b]pyrazine (**3a**)*

mp 136-138 °C (lit. 135-136 °C[20]); ^{1}H NMR (DMSO-d_6), δ: 7.18-7.23 (m, 5H), 7.40-7.48 (m, 5H), 7.71 (dd, 2H, *J* = 7.6 Hz, 8.0 Hz), 7.83 (t, 2H, *J* = 8.0 Hz), 8.65 (d, 1H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6), δ: 121.3, 123.6, 124.5, 127.8, 131.6, 131.8, 132.4, 135.7, 136.6, 139.1, 139.4, 139.8, 141.0, 142.3, 153.8, 154.6, 155.7; MS (ESI): *m/z* 284[M+H]$^{+}$.

*6-Nitro-2,3-diphenylquinoxaline (**3b**)*

mp 191-192 °C (lit. 192-193 °C[29]) ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.02-7.19 (m, 5H, Ar-H), 7.26-7.38 (m, 5H), 8.10- 8.17 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 124.7, 125.2, 125.4, 126.3, 127.0, 128.1, 128.6, 129.7, 130.3, 132.6, 133.9, 134.5, 135.8, 141.7, 142.3, 152.3, 152.9; MS (ESI): *m/z* 284[M+H]$^{+}$.

*5,6-Diphenyl-2,3-dihydropyrazine (**3c**)*

mp 162-164 °C (lit. 160-162 °C[17]); ^{1}H NMR (DMSO-d_6) δ: 3.56 (s, 5H), 7.08-7.19 (m, 5H, Ar-H), 7.38-7.67 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 38.9, 39.4, 125.7, 126.2, 127.4, 127.9, 128.3, 128.8, 129.3, 130.1, 131.2, 158.7, 159.3; MS (ESI): *m/z* 235[M+H]$^{+}$.

*2,3-Diphenylquinoxaline (**3d**)*

mp 125-127 °C (lit. 126-127 °C[21]); ^{1}H NMR (DMSO-d_6) δ: 7.02-7.19 (m, 5H, Ar-H), 7.26-7.38 (m, 5H, Ar-H), 7.56-7.98 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 124.1, 124.7, 125.2, 125.4, 126.3, 127.0, 128.1, 128.6, 129.7, 130.3, 132.6, 133.9, 134.5, 135.8, 141.7, 142.3, 152.3, 152.9; MS (ESI): *m/z* 283[M+H]$^{+}$.

*Dibenzo[a,c]phenazine (**3e**)*

mp 229-231 °C (lit. 228-229 °C[14]); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.64 (d, 2H, *J* = 7.2 Hz), 7.89 (dd, 2H, *J* = 5.6, 2.4 Hz), 8.07-8.96 (m, 8H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 121.3, 122.4, 122.8, 123.7, 124.6, 125.8, 126.9, 127.7, 128.5, 129.4, 130.6, 131.3, 133.4, 135.1, 141.8, 142.4, 143.2, 143.8; MS (ESI): *m/z* 281[M+H]$^{+}$.

*Dibenzo[f,h]-pyrido[2,3-b]quinoxaline (**3f**)*

mp 226-228 °C (lit. 228-229 °C [15]); ^{1}H NMR (400 MHz, DMSO-d_6), δ: 7.07 (d, 1H, J = 7.6 Hz), 7.18-7.26 (m, 4H), 7.39-7.47 (m, 4H), 7.86 (d, 1H, J = 7.0 Hz), 8.51 (d, 1H, J = 7.2 Hz); ^{13}C NMR (100 MHz, DMSO-d_6), δ: 123.9, 124.2, 127.8, 129.1, 129.8, 130.4, 131.2, 132.5, 137.3, 138.6, 139.1, 141.2, 142.4, 145.0, 145.9, 157.5, 158.2; MS (ESI): *m/z* 282[M+H]$^+$.

*Acenaphtho[1,2-b]quinoxaline (**3g**)*

mp 228-230 °C (lit. 224 °C[21]); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.69-7.92 (m, 6H), 7.83 (dd, 2H, J = 6.0, 2.8 Hz), 8.05 (d, 2H, J = 7.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 122.1, 122.7, 123.6, 124.8, 125.2, 125.9, 126.3, 126.8, 127.1, 128.3, 128.7, 130.4, 134.9, 140.2, 141.3, 141.9; MS (ESI): *m/z* 255[M+H]$^+$.

Results and Discussion

To achieve best conditions, the reaction of benzoin **1** and *o*-phenylenediamine **2** was chosen as the model reaction for synthesizing **3a**. In our initial study for the optimization of the reaction conditions, we performed the model reaction in water without using catalyst at room temperature (Table 1) and noticed that no reaction occurred even after stirring the reaction mixture for several hrs. The catalytic activity of various Bronsted and Lewis acids was also checked for the synthesis of **3** using water as solvent and the results are summarized in Table 1. It was found that very low yield of product was obtained in presence of Lewis acids like $FeCl_3$ and *p*-TSA due to lower solubility of reactants in water and to solve this solubility problem various surfactants *e.g.* SDS and DSA were added to the reaction mixture but yield of product did not improved effectively due to water labile character of Lewis acids. Hence, to overcome this problem, we synthesized water stable catalyst having both surfactant and strong Lewis acid property. The catalytic activity of synthesized Lewis acid-surfactant-combined catalyst ($Fe(DS)_3$ was examined for the present reaction and it was found that very good yield of product was obtained in aqueous mediums.

Table 1. Effect of different catalysts in aqueous medium

Entry	Catalyst	Time	Yield, %*
1.	-	1 h	Nil
2.	*p*-TSA	1 h	45
3.	Sulfamic acid	1 h	43
4.	$FeCl_3$	1 h	52
5.	$ZnCl_2$	1 h	49
6.	SDS	1 h	65
7.	CTAB	1 h	60
8.	$Fe[CH_3(CH_2)_{11}OSO_3$	10 min	94

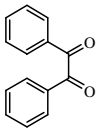
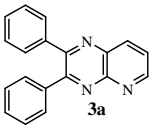
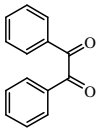
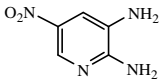
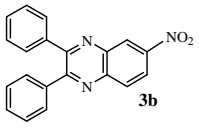
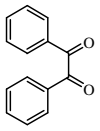
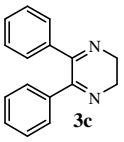
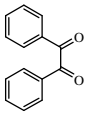
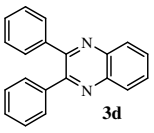
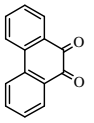
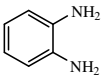
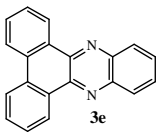
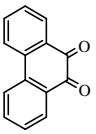
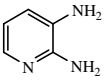
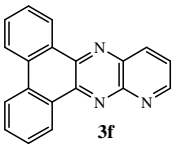
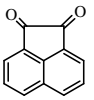
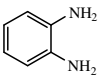
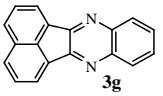
**Isolated Yield*

To generalize the scope and versatility of this protocol, different diketones and diamines were used for the synthesis of substituted quinoxalines (Table 2).

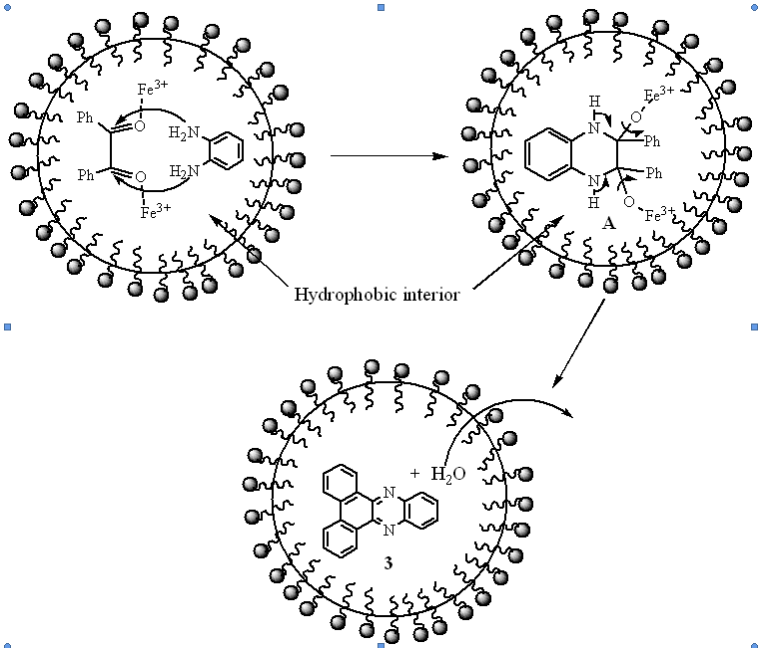
In this reaction Fe^{+3} acts as an efficient Lewis acid catalyst for this reaction. $Fe(DS)_3$ shows dual role in organic reactions as a catalyst to activate the substrate molecule and as a phase transfer catalyst to solubilize organic reactants to water. In the reaction mixture the Fe^{+3} coordinate with 1,2-diketones and during the micelles formation the Fe^{+3} ions enters in hydrophobic domain[36]. Diketones stabilized with interaction of Fe^{+3} by partial polarization of

carbonyl group which subsequently react with *o*-phenylenediamine to form a intermediate amino-1,2-diol (**A**). Then the intermediate **A** undergoes Fe^{+3} catalyzed elimination of water leads to the formation of desired products (Scheme 2).

Table 2. Synthesis of compounds (**3a-g**)

Entry	Carbonyl compound	Amine	Product	Time min	Yield %*
1			 **3a**	10	94
2			 **3b**	12	96
3			 **3c**	10	97
4			 **3d**	11	96
5			 **3e**	10	95
6			 **3f**	12	96
7.			 **3g**	10	93

In conclusion, we have developed a novel, efficient and eco-friendly synthetic strategy for the synthesis of quinoxaline derivatives from various 1,2-diketones and 1,2-diamines using separable Lewis acid-surfactant-combined catalyst ($Fe(DS)_3$). Use of water as a reaction medium rendered this procedure cost-effective and environmentally benign. In addition to its efficiency and simplicity, this method provided high yields of biologically potent quinoxalines in shorter reaction time.



Scheme 2. Plausible mechanism of formation of quinoxalines

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