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Communication

A recyclable and highly effective sulfated TiO_2-P25 for the synthesis of quinoxaline and dipyridophenazine derivatives at room temperature

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ABSTRACT

Sulfated TiO_2-P25 has been prepared using H_2SO_4 and used for the synthesis of quinoxaline and dipyridophenazine derivatives. Sulfate loading by H_2SO_4 increases the Lewis acidity of TiO_2-P25. This catalyst gives excellent yield with less reaction time and it is an inexpensive, easily recyclable catalyst for this reaction.

1. Introduction

Catalysis is one of the fundamental pillars of green chemistry. The design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances has lead to the design and application of catalysts and catalytic systems to achieve the dual goals of environmental protection and economic benefit [1]. Degussa TiO_2-P25 (80% anatase, 20% rutile) is a well known and widely investigated photocatalyst. Acid–base and redox properties are one of the most important types of surface chemical properties of metal oxide catalysts. From a catalytic point of view, transition metal oxide TiO_2 possesses a unique type of surface involving both redox and acid–base sites. In addition to high thermal stability, its amphoteric character makes titania a promising catalytic material. The textural and acid–base properties of titania depend greatly on method of preparation. Doping of sulfate using H_2SO_4 makes the catalyst more acidic [2] when compared to TiO_2-P25. Since the surface of TiO_2-P25-SO_4^{2-} is positively charged due to protonation as shown in Scheme 1 it acts as a strong Lewis acid. Surface acidity was determined by the spectrophotometric method on the basis of irreversible adsorption of organic base pyridine [3–5]. The amount of pyridine adsorbed by 0.1 g of TiO_2-P25 and TiO_2-P25-SO_4^{2-} are 40 and 170 μg, respectively. This reveals that TiO_2-P25-SO_4^{2-} has more acidic sites when compared to bare TiO_2-P25.

Quinoxaline derivatives are the subject of considerable interest from both academic and industrial perspectives because they are significant intermediates for the manufacturing of pharmaceuticals and advanced materials [6,7]. They have been shown to possess a broad spectrum of biological activities such as antiviral, antibacterial, anti-inflammatory, antitumor and antidepressant activities [8–10]. Dipyridophenazines were used as a metal ligand for the formation of metal-ligand complexes with attractive features [11]. A number of synthetic strategies have been developed for the preparation of substituted quinoxalines and dipyridophenazines [11–13]. The most common method is the condensation of an aryl-1,2-diamine with a 1,2-dicarbonyl compound in refluxing ethanol or acetic acid [14].

Lewis acids and many other catalysts including sulfamic acid [15], montmorillonite K-10 [16], polyaniline-sulfate salt [17], $H_6P_2W_{18}O_{62}\cdot 24H_2O$ [3], $InCl_3$ [18], $CuSO_4\cdot 5H_2O$ [19] have been explored. There are a few constraints like the use of strong acids and high reaction temperatures. Recent research has been focused on finding new catalysts to improve the yield of this condensation reaction.

Jing Cai et al. [20] reported the synthesis of quinoxaline derivatives using gallium(III) triflate in good yield and less reaction time. But this catalyst is acidic, hygroscopic and hazardous in nature. Ahmad shaabani et al. [21,22] reported two solid acid catalyst cellulose sulfuric acid (CSA) and silica sulfuric acid (SSA) for this synthesis. Though they give good yield with reusability, preparation of these

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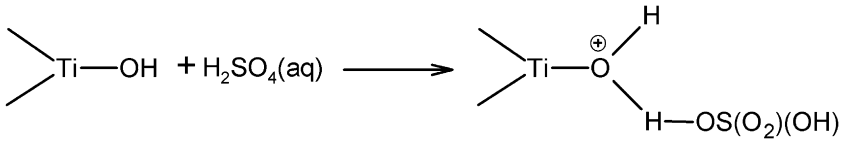
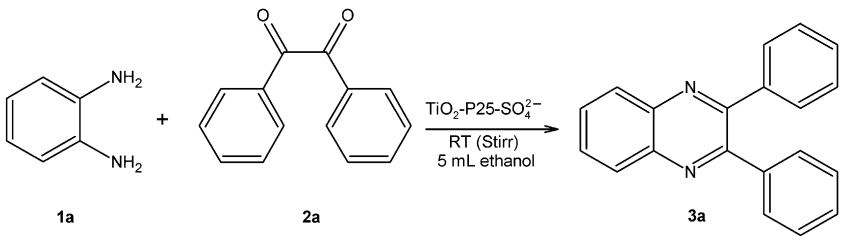


Scheme 1. Protonation of TiO_2-P25-SO_4^{2-}.



Scheme 2. The condensation reaction of 1,2-phenylenediamine **1a** with benzil **2a** catalyzed by TiO_2-P25-SO_4^{2-}.

catalysts involves the evolution of HCl. As the aforesaid methods are not compatible with heat or acid sensitive substrates, there is a need to develop an effective synthesis of quinoxalines employing more eco-friendly catalysts. Our laboratory has been engaged mainly on the development of modified semiconductor photocatalysts for environmental remediation and organic synthesis [5,23–25] Herein, we report the preparation of a recyclable, easily separable, eco-friendly and highly effective solid acid catalyst TiO_2-P25-SO_4^{2-} for the green synthesis of quinoxaline and dipyridophenazine derivatives at room temperature.

2. Results and discussion

2.1. Effect of different catalysts and solvents

In order to optimize the condensation reaction conditions such as percentage of sulfate in the catalyst and also to check the versatility of this method with substituted 1,2-phenylenediamines, the reaction was carried out under various conditions. The condensation reaction of 1,2-phenylenediamine **1a** and benzil **2a** (Scheme 2) was carried out in the presence of TiO_2-P25 and TiO_2-P25-SO_4^{2-} with different concentrations of sulfate at room temperature for 5 min in ethanol medium. The yield with TiO_2-P25 was found to be 91.8% (Table 1, entry 1). It was surprising to find that the reaction with TiO_2-P25-SO_4^{2-} could be completed in 5 min to give quantitative yield of 98.0% of product quinoxaline **3a** (Table 1, entry 2). Structure of this product has been confirmed by spectral and GC–MS data. The percentage yield of the product with 3 and 5 wt.% of sulfate concentrations are 94.5 and 98.0%, respectively (Table 1, entries 5, 2). The same reaction when performed without catalyst for 3 h gave no product. When the sulfate content was increased to 7 wt.%, the product yield decreased to 95.8% (Table 1, entry 6). Hence 5 wt.% of sulfate was found to be the optimum level.

The reaction between 1,2-phenylenediamine and benzil was carried out in the solvents acetonitrile, water and 95% ethanol in water under the same reaction conditions. In the solvents acetonitrile and ethanol the reaction could be completed in 5 min with a quantitative yields of product 95.7 and 98.0%, respectively (Table 1, entries 3, 2). It was found that reaction in water required a longer time (15 min) to give 90.4% (Table 1, entry 4) yield of product. Because of high product yield with less reaction time and easy availability, 95% ethanol was chosen as a solvent for further reactions.

Table 1
Effect of different solvent and catalyst (0.1 g) on condensation of *o*-phenylenediamine (1 mmol) and benzil (1 mmol) under room temperature.

Entry	Catalyst	Solvent	Yield[a] (%)
1	TiO_2-P25	95% ethanol (5)	91.8
2	5 wt.% of TiO_2-P25-SO_4^{2-}	95% ethanol (5)	98.0
3	5 wt.% of TiO_2-P25-SO_4^{2-}	(CH_3CN (5)	95.7
4	5 wt.% of TiO_2-P25-SO_4^{2-}	(H_2O) (15)	90.4
5	3 wt.% of TiO_2-P25-SO_4^{2-}	95% ethanol (5)	94.5
6	7 wt.% of TiO_2-P25-SO_4^{2-}	95% ethanol(5)	95.8

Values within parentheses are indicating reaction time in min.
[a] Yields with respect to 1,2-diamine.

2.2. Effect of catalyst loading

The effect of catalyst loading on the formation of quinoxaline was investigated by varying the catalyst amount from 0.05 to 0.2 g (Fig. 1). Increase in catalyst amount from 0.05 to 0.1 g increases the formation of quinoxaline from 92.5 to 98.0%. This is due to increase in the number of TiO_2-P25-SO_4^{2-} particles. Above 0.1 g of the catalyst, no significant change in the conversion occurred. The

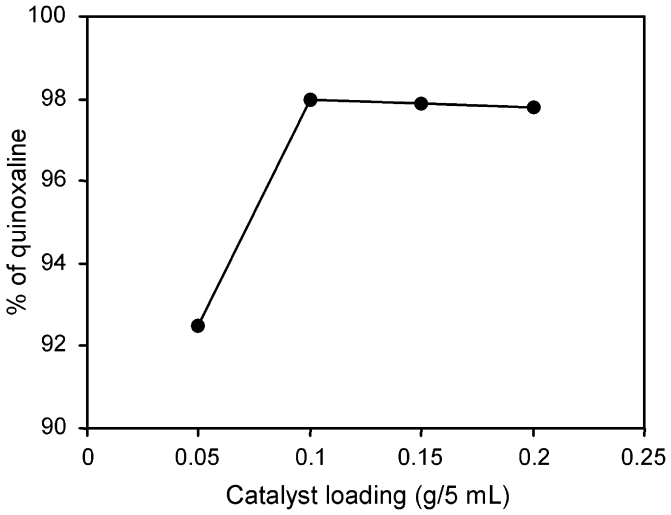
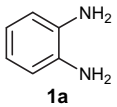
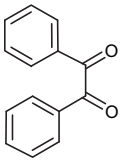
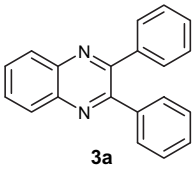
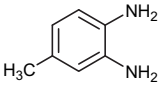
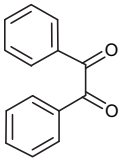
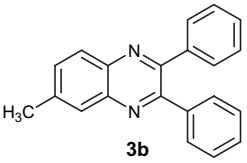
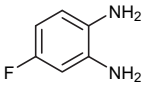
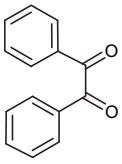
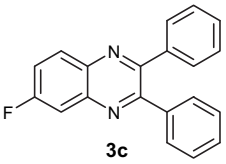
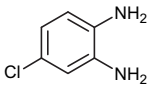
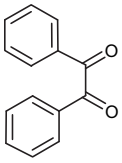
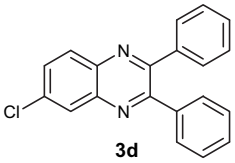
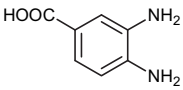
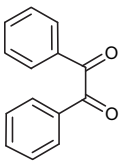
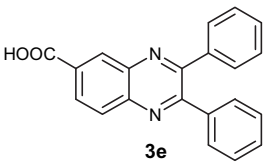
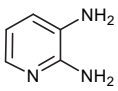
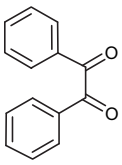
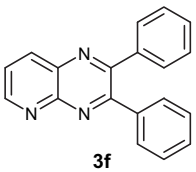
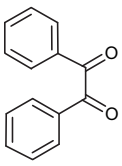
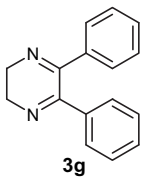


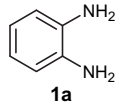
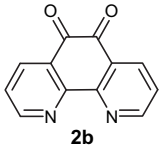
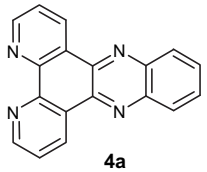
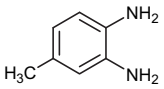
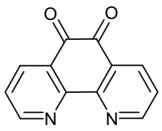
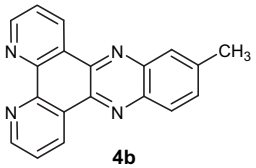
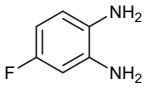
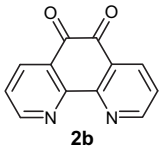
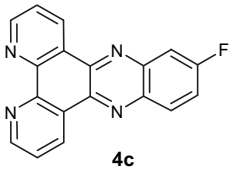
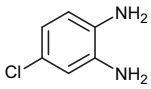
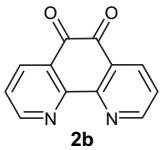
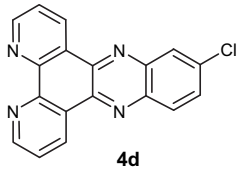
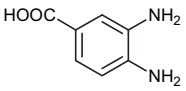
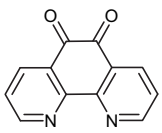
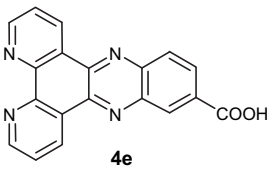
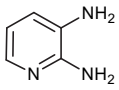
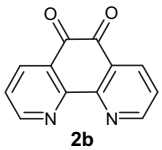
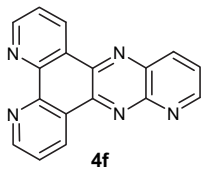
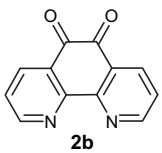
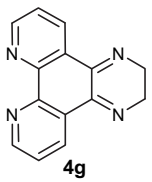
Fig. 1. Effect of catalyst loading: *o*-phenylenediamine = 1 mmol, benzil = 1 mmol, solvent = 95% ethanol in water (5 mL), time = 5 min (stirring at room temperature).

Table 2
Quinoxaline derivatives from different 1,2-diamines and 1,2-diketone (benzil) catalyzed by TiO_2-P25-SO_4^{2-}.

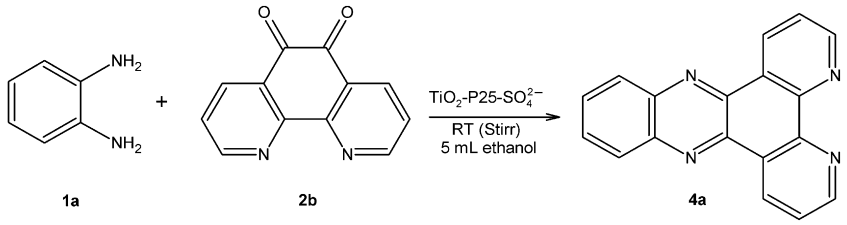
Entry	1,2-Diamine	1,2-Diketone	Product	Time (min)	Yield[a] (%)
1	 **1a**	 **2a**	 **3a**	5	98.0
2	 **1b**	 **2a**	 **3b**	45	97.6
3	 **1c**	 **2a**	 **3c**	120	95.5
4	 **1d**	 **2a**	 **3d**	120	93.0
5	 **1e**	 **2a**	 **3e**	120	60.0
6	 **1f**	 **2a**	 **3f**	60	78.0
7	 **1g**	 **2a**	 **3g**	60	80.5

[a] Yields with respect to 1,2-diamine.

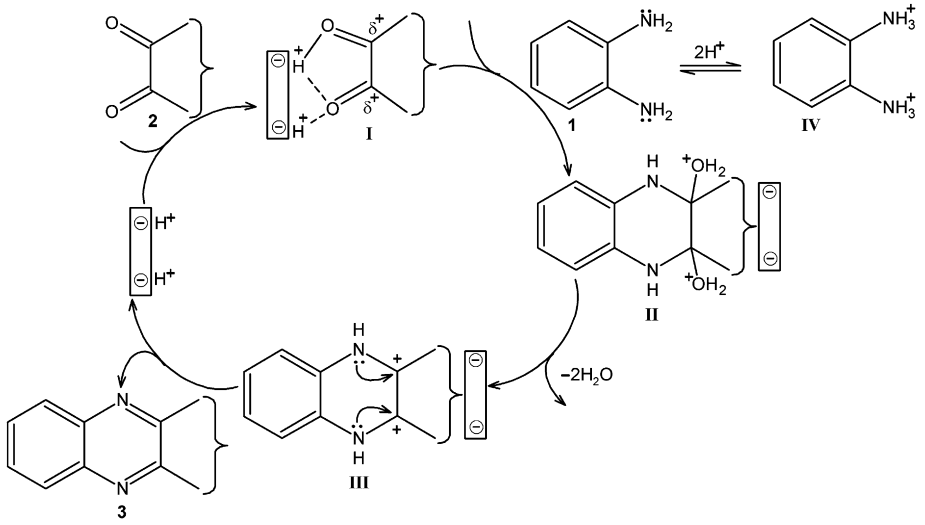
Table 3
Dipyridophenazine derivatives from different 1,2-diamines and 1,2-diketone (1,10-phenanthroline-5,6-dione) catalyzed by TiO_2-P25-SO_4^{2-}.

Entry	1,2-Diamine	1,2-Diketone	Product	Time (min)	Yield[a] (%)
1	 **1a**	 **2b**	 **4a**	4	99.0
2	 **1b**	 **2b**	 **4b**	30	98.5
3	 **1c**	 **2b**	 **4c**	60	96.0
4	 **1d**	 **2b**	 **4d**	60	94.9
5	 **1e**	 **2b**	 **4e**	60	65.0
6	 **1f**	 **2b**	 **4f**	60	78.5
7	 **1g**	 **2b**	 **4g**	60	85.2

[a] Yields with respect to 1,2-diamine.



Scheme 3. The condensation reaction of 1,2-phenylenediamine **1a** with 1,10-phenanthroline-5,6-dione **2b** catalyzed by TiO_2-P25-SO_4^{2-}.



Scheme 4. Proposed mechanism for the condensation reaction of 1,2-diamine with 1,2-dicarbonyl compounds catalyzed by TiO_2-P25-SO_4^{2-}.

optimum catalyst loading is found to be 0.1 g for the formation of quinoxaline.

2.3. Effect of different substrates

Encouraged by the remarkable results obtained with the above reaction conditions and in order to show the generality and scope of this new protocol, we used various substituted 1,2-phenylenediamines and the results obtained are summarized in Tables 2 and 3. To check the versatility of this method, we had also studied the condensation of 1,2-phenylenediamine with 1,10-phenanthroline-5,6-dione **2b** (Scheme 3) under the same conditions used for quinoxalines and the product dipyrido[3,2-a:2′,3′-c]phenazine **4a** (Table 3) was obtained in excellent yield (99%) within 4 min. Structure of this product was confirmed by spectral and GC–MS data. All the reactions with substituted 1,2-phenylenediamines proceeded very cleanly at room temperature and no undesirable side-reactions were observed, although the yields were highly dependent on the substituents. Results in Tables 2 and 3 show that electron-donating groups at the phenyl ring of 1,2-diamine favored the formation of product (Table 2, entry 2; Table 3, entry 2). In contrast, electron withdrawing groups such as fluoro, chloro and carboxylic slightly lower the yields (Table 2, entries 3–5; Table 3, entries 3–5) with longer reaction times. 2,3-diaminopydrine and aliphatic diamine (ethylene diamine) also gave moderate yields (Table 2, entries 6, 7; Table 3, entries 6, 7).

2.4. Mechanism of the reaction

This reaction is likely to follow the proposed mechanism of acid-catalyzed condensation reactions as shown in Scheme 4. This mechanism involves the complexation of TiO_2-P25-SO_4^{2-} with the diketone by acting as an acid and also playing a complex role in promoting the dehydration. As seen earlier by pyridine adsorption, the surface acidity of TiO_2-P25-SO_4^{2-} is much higher than TiO_2-P25. A similar mechanism has been proposed for this reaction with the catalyst montmorillonite K-10 [16]. The possibility of recycling the catalyst (TiO_2-P25-SO_4^{2-}) was examined for the reaction of *o*-phenylenediamine **1a** and benzil **2b**. When the reaction was complete, ethyl acetate was added to the solidified mixture and the insoluble catalyst was separated by filtration. The separated catalyst could be used five times without any treatment and, no appreciable loss in its catalytic activity was observed up to fifth run (95.3% - Table 4, entry 3). Efficiency of this solid acid catalyst, TiO_2-P25-SO_4^{2-}, in the synthesis of quinoxaline from *o*-phenylenediamine and benzyl is compared with the efficiencies of two solid acid catalysts cellulose sulfuric acid (CSA) and silica sulfuric acid (SSA) reported for the same reaction [21,22]. Table 4 gives the product yield in EtOH and H_2O for each catalyst and its reusability in EtOH. Among the three catalysts

Table 4
Comparison of catalytic efficiencies for the condensation of *o*-phenylenediamine and benzyl at room temperature.

Entry	Catalyst	EtOH (time/ Yield (%)[a])	H_2O (time/ Yield (%)[a])	Reference
1	Cellulose sulfuric acid (CSA)	60 min/93 (92, 95, 90, 90)[b]	2.30 h/72	[21]
2	Silica sulfuric acid (SSA)	15 min/98 (94, 90, 85, 78)[b]	–	[22]
3	Sulfated TiO_2-P25	5 min/98(98, 97.9, 96.5, 95.3)[b]	15 min/90.4	Present work

[a] Yield with respect to 1,2-diamine.
[b] The same catalyst was used for each of the five runs.

TiO_2-P25-SO_4^{2-} is more efficient as it gives 98% yield in 95% ethanol-water (5 min) and 90.4% in water (15 min). Even in fifth run the yield is 95.3% (5 min) which is higher than the yield with CSA (90% in 60 min) and SSA (78% in 15 min).

3. Conclusions

In conclusion, TiO_2-P25-SO_4^{2-} is introduced as an excellent solid acid catalyst for the synthesis of quinoxaline and dipyridophenazine derivatives at room temperature. In comparison with the previously reported methods, this novel and practical method has the advantages of mild conditions, quantitative yields of products, and very short reaction time at room temperature. Another attractive feature of this green process is its application in industrial processes due to simple preparation and reusability of TiO_2-P25-SO_4^{2-}. Water (green solvent) can also be used as a solvent.

4. Experimental

4.1. Preparation of sulfate loaded TiO_2-P25 photocatalysts

About 2.7 g of TiO_2-P25 [It is a mixture of 80% anatase and 20% rutile. It has a particle size of 30 nm and BET specific area 50 $m^2\ g^{-1}$] suspended in 100 ml of 2-propanol and to this solution 3.2 ml of 1 M H_2SO_4 was added dropwise under vigorous stirring. The resulting colloidal suspension was stirred for 4 h. The gel obtained was filtered, washed and dried in an air oven at 100 °C for 12 h. Addition of $BaCl_2$ to filtrate gave no precipitate indicating that all the sulfate ions were completely loaded on the gel. This catalyst contained 5 wt.% of SO_4^{2-}. Similarly catalysts with 3 and 7 wt.% of SO_4^{2-} were prepared with the same procedure.

4.2. Preparation of quinoxaline and dipyridophenazine derivatives – General procedure

To a mixture of an *o*-phenylenediamine (1 mmol, 0.108 g) and 1, 2-dicarbonyl compound (1 mmol, 0.210 g) in ethanol (5 mL), 0.1 g of TiO_2-P25-SO_4^{2-} was added and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, ethyl acetate was added to the solidified mixture and the insoluble catalyst was separated by filtration. The filtrate was dried over anhydrous Na_2SO_4. The solvent was evaporated and the pure product was obtained. Then it was subjected to GC and GC–MS analysis for the determination of the yield of the products. The structure of products obtained had been confirmed by FT-IR, ^{1}H NMR, ^{13}C NMR and GC–MS analysis. A variety of substituted 1,2-phenylenediamines were condensed with benzil and 1,10-phenanthroline-5,6-dione. The catalyst separated can be reused.

4.2.1. 2,3-Diphenylquinoxaline, **3a**

m.p. = 125–126 °C; IR (KBr) (cm^{-1}) = 3055, 2921, 1542, 1344, 768, 696; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.19 (dd, 2H), 7.76 (dd, 2H), 7.5 (m, 4H), 7.34 (m, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ = aromatic carbons are observed at 128.30, 128.83, 129.05, 129.23, 129.87, 129.99, 134.90, 139.10, 141.24 and 153.49 (C=N); GC–MS (*m/z*) = 283.2 (M+1).

4.2.2. Dipyrido[3,2-a:2′,3′-c]phenazine, **4a**

m.p. = 246–247 °C; IR (KBr) (cm^{-1}) = 3073, 2852, 1577, 1498, 1415, 1361, 1337, 739, 669; ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 9.65 (2d, 2H), 9.27 (d, 2H), 8.36 (t, 2H), 7.94 (q, 2H), 7.82 (q, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ = aromatic carbons are observed at 124.17, 127.62, 129.56, 130.69, 133.81, 141.14, 142.51, 148.40 (C=N of pyridine ring) and 152.53 (C=N of phenazine ring); GC–MS (*m/z*) = 282.9 (M+1).

Acknowledgements

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