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An efficient synthesis of quinoxalines catalyzed by monoammonium salt of 12-tungstophosphoric acid

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ABSTRACT

Monoammonium salt of 12-tungstophosphoric acid [$(NH_4)H_2PW_{12}O_{40}$] catalyst was used for the synthesis of biologically important quinoxaline derivatives in excellent yields from various aromatic 1,2-dicarbonyl and 1,2-diamines. The methodology has the advantages of mild reaction conditions with simple workup procedure, even for the synthesis of quinoxaline derivatives from sterically hindered diamine.

1. Introduction

Quinoxalines and its derivatives are an important class of benzoheterocycles [1,2] displaying a broad spectrum of biological activities [3-6] includes antiviral, antibacterial, anti-inflammatory *etc*. They have also found applications as dyes [7,8] and building blocks in the synthesis of organic semi conductors [9,10]. A number of synthetic strategies have been developed for preparation of substituted quinoxalines [11]. Most common method relies on the condensation of an aryl 1,2-diamine with 1,2-dicarbonyl compounds in refluxing ethanol or acetic acid for 2-12 h and this typically gives up to 70-80% yields.

Progresses has been made and can be noted in the literatures for the synthesis of quinoxaline derivatives compounds, such as the Bi-catalyzed oxidative coupling reaction [12], via a tandem oxidation process [13-15] using $Pd(OAc)_2$ or $RuCl_2$-$(PPh_3)_3$-TEMPO and MnO_2, heteroannulation of nitroketene N,S-arylaminoacetals with $POCl_3$ [16], a solid-phase synthesis on Synphase™ Lanterns [17], cyclization of α-arylimino oximes compounds under refluxing condition in acetic anhydride [18], the condensation of a 1,2-phenylene-diamines and 1,2-dicarbonyl compounds in MeOH/AcOH under microwave irradiation [19], and the molecular iodine catalyzed cyclocondensation reaction in DMSO and CH_3CN [20], $CuSO_4.5H_2O$ catalyzed cyclocondensation reaction in water, Zn[(L)proline] catalyzed cyclocondensation reaction in HOAc [21,22] and polyaniline-sulfate salt [23] catalyzed condensation reactions *etc*., and very recently Dong *et al.* reported the synthesis of quinoxaline derivatives catalyzed by task-specific ionic liquids [24]. However, most of the traditional processes suffer from several disadvantages, such as pollution, high cost, poor chemical yields, longer reaction time, and tedious work-up procedures, which limit their use under the aspect of environmentally benign processes. Despite remarkable efforts, the development of an effective method for the synthesis of quinoxalines is still an important challenge.

Keggin type heteropoly acids (HPAs) have gained lot of attention due to their economical and environmental advantages for both academic and industrial applications. They are useful as acid and oxidation catalysts for various reactions since their catalytic features can be varied at molecular level [25-27]. The most commonly used heteropolyacid is the dodecatungsto phosphoric acid (12-TPA). However, the main disadvantage with the usage of acid form of heteropoly compounds is their solubility in water and polar solvents. This problem can be overcome by converting it into its salt, like the ammonium salt. We have developed heterogeneous TPA catalyst by partial proton-exchange with ammonium carbonate to result water insoluble catalyst namely monoammonium salt of 12-tungstophosphoric acid and was employed for different applications [28-31]. In continuation to our previous work, we report herein a simple and convenient method for the synthesis of quinoxalines derivatives in good yields (85-98%) from 1,2-phenylenediamine and benzil diketone (Scheme 1) by employing monoammonium salt of 12-tungstophosphoric acid as heteropoly acid catalyst. The advantage of the present catalyst is that it does not require any additives or promoters. Furthermore, the preparation of the catalyst is very simple, inexpensive and reusable without any loss of activity. Monoammonium salt of 12-TPA has excellent catalytic properties with good selectivity and reusability [28].

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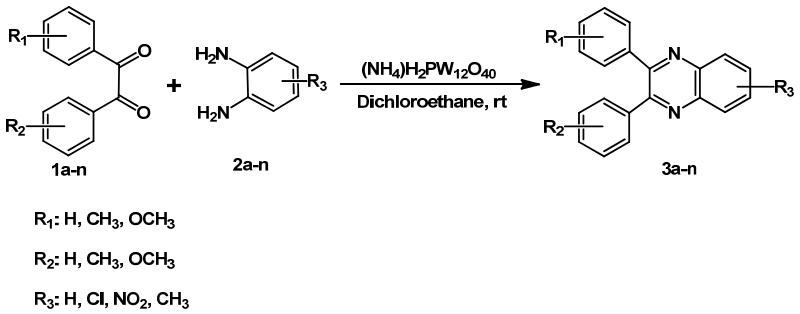


Scheme 1

2. Experimental

2.1. Materials and methods

All the commercial reagents and solvents were used without further purification unless otherwise stated. ^{1}H NMR spectra were recorded a BRUKER AMX 300-MHz spectrometer using TMS as an internal standard. IR spectra were recorded on Perkin FT-IR spectrometer. GC analysis was performed using Agilent 6850 Series Gas Chromatograph equipped with FID detector. GC-MS analysis was performed using Agilent 6890N Gas Chromatograph connected to Agilent 5973 Mass Spectrometer at 70 eV (*m/z*, 50-600; source at 230 ^{o}C and quadruple at 150 ^{o}C) in the EI mode with a HP-5 ms capillary column (30 m x 0.25 mm; 0.25 μm). All the reactions were monitored by thin layer chromatography performed on precoated silicagel 60F254 plates (Merck).

2.2. Procedure for the preparation of the catalyst

Monoammonium salt of 12-tungstophosphoric acid was prepared by simple ion exchange of 12-tungstophosphoric acid with a required amount of ammonium carbonate in aqueous medium [28]. Ammonium carbonate solution (0.167 g, 0.17 mmol, dissolved in 10 mL of distilled water) was added drop wise to an aqueous solution of 12-tungstophosphoric acid (10 g, 0.35 mmol, dissolved in 50 mL of distilled water) at 80 ^{o}C under stirring. The reaction mixture was stirred at 80 ^{o}C for 3 h, evaporated to dryness, and kept overnight at 120 ^{o}C. The catalyst was calcined in air at 350 ^{o}C for 4 h to obtain monoammonium salt of 12-tungsto-phosphoric acid. Yield: 9.25 g, 92%.

2.3. General procedure for the synthesis of quinoxalines

A mixture of 1,2 dicarbonyl (1 mmol) and aromatic 1,2 diamine (1 mmol) in 1,2-dichloroethane (5 mL) was stirred at room temperature in presence of monoammonium salt of 12-tungsto phosphoric acid catalyst (5 wt.% with respect to 1,2-dicarbonyl). The reaction was monitored by TLC. The reaction mixture was filtered to recover the catalyst and the filtrate was concentrated under vacuum. The crude product was purified by silica gel column chromatography (eluent-95:5 hexane-ethyl acetate) to give the pure product. The recovered catalyst was dried in oven at 110 ^{o}C for 2 h and reused for the next run. Representative examples of synthesized quinoxaline compounds:

2,3-Diphenyl quinoxaline (**3a**): FT-IR (KBr, cm^{-1}): 3059, 1478, 1345, 765. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 7.39-7.42 (m, 6H), 7.55 (m, 4H), 7.79 (dd, *J* = 6.3 Hz, 2H), 8.2 (dd, *J* = 6.30 Hz, 2H). GC-MS (EI, *m/z*): 282 (M$^+$).

6-Methyl-2,3diphenylquinoxaline (**3d**): FT-IR (KBr, cm^{-1}): 3056, 1660, 1480, 1208, 756. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 1.6 (s, 3H), 7.35-7.44 (m, 6H), 7.56 (m, 4H), 7.63 (dd, *J* = 8.56 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 8.1 (d, *J* = 8.5 Hz, 1H). GC-MS (EI, *m/z*): 296 (M$^+$).

2,3-Bis(4-methoxy-phenyl)quinoxaline (**3f**): FT-IR (KBr, cm^{-1}): 3003, 2958 , 1608, 1345, 1513, 1251, 1029, 757. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 3.81 (s, 6H), 6.85 (d, *J* = 7.9 Hz, 4H), 7.47 (d, *J* = 8.5 Hz, 4H), 7.68 (m, 2H), 8.1 (m, 2H). GC-MS (EI, *m/z*): 342 (M$^+$).

2,3-Bis(4-methyl-phenyl)quinoxaline (**3i**): FT-IR (KBr, cm^{-1}): 3031, 1613, 1592, 1342,1216,1057, 822, 756. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.4 (s, 6H), 7.39-7.42 (m, 4H), 7.55 (m, 4H), 7.79 (dd, *J* = 6.30 Hz, 2H), 8.2 (dd, *J* = 6.30 Hz, 2H). GC-MS (EI, *m/z*): 310 (M$^+$).

2,3-Bis(4-methyl-phenyl)6-nitroquinoxaline (**3k**): FT-IR (KBr, cm^{-1}): 3003, 2931, 1660, 1592, 1210, 1604, 1510, 1345, 1057, 876. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 2.4 (s, 6H), 7.10 (m, 4H), 7.56 (m, 4H), 8.24 (d, *J* = 9.1 Hz, 1H), 8.49 (dd, *J* = 9.1 Hz, 1H), 9.1 (d, *J* = 8.1 Hz, 1H). GC-MS (EI, *m/z*): 355 (M$^+$).

2,3-Di (furan-2-yl)quinoxaline (**3m**): FT-IR (KBr, cm^{-1}): 3120, 1568, 1522, 1484, 1345, 750. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 6.6 (d, 2H), 6.85 (dd, *J* = 6.3 Hz, 2H), 7.68 (d, *J* = 6.3 Hz, 2H), 7.72 (dd, *J* = 6.3 Hz, 2H), 8.20 (d, *J* = 9.2 Hz, 1H), 8.47 (dd, *J* = 9.2.1 Hz, 1H), 8.98 (s, 1H). GC-MS (EI, *m/z*): 307 (M$^+$).

Table 1. Effect of solvents for the synthesis of quinoxaline derivatives[a].

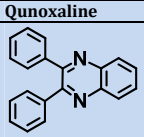
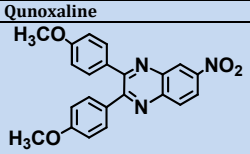
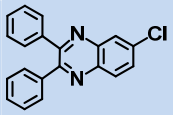
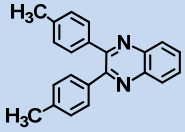
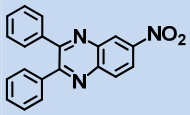
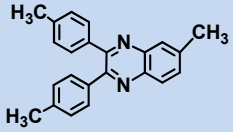
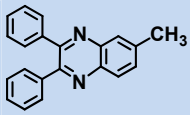
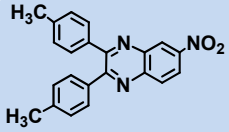
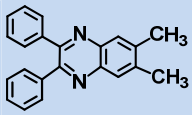
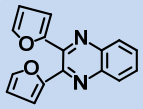
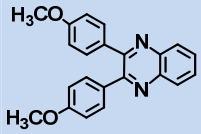
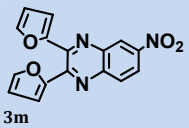
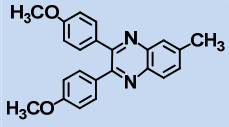
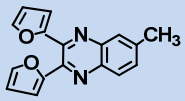
Entry	Solvents	Time (min)	Yield[b] (%)
1	Acetonitrile	40	96
2	Dichloromethane	30	97
3	Dichloroethane	15	98
4	Ethyl acetate	45	94
5	Toluene	45	93
6	Hexane	45	94
7	Methanol	45	89
8	Ethanol	45	92
9	Diethyl ether	45	91
10	Tetrahydrofuran	60	90

[a] 1,2-Phenylenediamine (1 mmol), Benzil (1 mmol), Catalyst (5 wt.% of benzil), Dichloroethane (5 mL), Room temperature.
[b] Isolated yields.

3. Results and discussion

Initially the reaction was conducted with benzil and 1,2-phenylenediamine (1:1 mmol) in acetonitrile at room temperature without using catalyst and obtained 2,3-diphenyl quinoxaline in very low yield even after 24 h of reaction, whereas use of the monoammonium salt of 12-TPA catalyst afforded the product in quantitative yield within 40 min. Different solvents with various polarity were screened (Table 1) for the condensation reaction in the presence of catalyst and found that all the solvents studied afforded the products in excellent yields with a slight variation in reaction period (15-60 min). Among all these solvents, dichloroethane (Table 1, entry 3) was found to be the best solvent of choice which not only afforded the product in 99% yield, but also with higher reaction rate (15 min).

Table 2. Synthesis of quinoxaline derivatives catalyzed by monoammonium salt of 12-TPA[a].

Entry	Quinoxaline	Reaction time (min)	Yield [b] (%)	Entry	Quinoxaline	Reaction time (min)	Yield [b] (%
1	 **3a**	10	98	8	 **3h**	30	90
2	 **3b**	20	92	9	 **3i**	30	90
3	 **3c**	30	90	10	 **3j**	10	86
4	 **3d**	15	93	11	 **3k**	30	85
5	 **3e**	10	94	12	 **3l**	10	92
6	 **3f**	10	92	13	 **3m**	30	93
7	 **3g**	15	91	14	 **3n**	15	34

[a] Diamine (1 mmol), 1,2-dicarbonyl compound (1 mmol), Catalyst (5 wt.% of substrate), Dichloroethane (5 mL), Room temperature.
[b] Isolated yields.

In order to evaluate the efficiency of this methodology, condensation of various 1,2-diketone compounds with different substituted 1,2-phenylenediamines were carried out (Table 2) by employing the catalyst in dichloroethane solvent at room temperature to obtain the corresponding quinoxalines **3a**-**n** in good yields (85-98%) and the results are summarized in Table 2. Condensation of 1,2-phenylenediamine with benzil gave quinoxaline **3a** in 98% yield within 10 min. The presence of electron donating substituents in the amine part, increased yields were obtained (**3d** and **3e**) within 10-15 min compared to electron withdrawing substituents (**3b** and **3c**) inspite of more reaction period of 20-30 min. On the other hand, electron-donating substituents on the aromatic ring attached to diketones gave the lowest yield among all the studied diketone substrates (Table 2, entry 10 and 11). Heterocyclic substrate furoin with 4-methyl-1,2-phenylenediamine gave 94% yield (Table 2, entry 14) in 15 min compared to 4-nitro-1,2-phenylenediamine (Table 2, entry 13, 30 min), indicating that electron donating methyl group in the diamines enhances its nucleophilicity. Over all the catalyst showed exceptionally high activity towards this reaction. After completion of the reaction, the catalyst was separated by simple filtration and washed several times with ethyl acetate. Later the catalyst was dried in air oven at 120 °C for 1 h and reused. The reusability of the catalyst was found to be effective up to three cycles without any loss in the activity. All the products were characterized by FT-IR, ^{1}H NMR, and GC-MS analysis.

4. Conclusion

In conclusion, we have demonstrated a very simple, efficient, clean, and practical method for the synthesis of various quinoxaline derivatives in good yields (85-98%) by employing monoammonium salt of 12-TPA as an efficient catalyst in dichloethane as more suitable solvent. It is applicable to a wide range of structural types; moreover, preparation of maono ammonium salt of 12-TPA catalyst is simple, and it is non-toxic, inexpensive and reusable.

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