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Synthesis of Quinoxaline Using Silica Supported Phosphomolybdic Acid as Reusable Heterogeneous Catalyst

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Using phosphomolybdic acid on silica as recyclable catalyst we have developed methodology for the synthesis of quinoxalines by condensation of phenacyl bromides and *o*-phenylene diamines in $ClCH_2CH_2Cl$ at 80 °C. The phosphomolybdic acid-silica catalyst can be reused for three successive runs with slight decrease in yield.

Keywords: Phenacyl bromide, Silica, 1,2-Dichloroethane, Phosphomolybdic acid, Recyclable.

INTRODUCTION

Organic synthesis is a broad area that requires more efficient chemical methods and synthetic routes [1]. Quinoxaline and its derivatives are very important in various fields of science like chemical, pharmaceutical and material industries [2]. Quinoxalines and its frame-works continue to play an important role in nitrogen heterocyclic chemistry. Molecules that contain quinoxaline subunits posses some interesting biological activities including anticancer, antimicrobial, anathematic, antidepressant and antifungal activities [3]. Various antibiotics such as echinomycin, levomycin and actinomycin [4] having quinoxaline moieties leads to inhibit the growth of Gram-positive bacteria and are active against several transplantable tumors. They have been employed as dyes [5], organic semiconductors [6], chemically controllable switches [7], efficient electroluminescent materials [8]. Quinoxaline derivatives are generally synthesized by condensation of 1,2-diamines with α-diketones in MeOH under microwave irradiation [9], oxidative coupling of epoxides with ene-1,2-diamines [10]. Additionally synthesis of quinoxalines by using solid-phase synthesis [11], β-cyclodextrin [12], DABCO [13] oxidation trapping of α-hydroxy ketones with 1,2-diamines. The above methods suffer from limitations, preparations of starting materials, long reactions, unsatisfactory yields, expensive metal precursors and harsh reaction conditions and difficult experimental procedures. Therefore, development of efficient and versatile procedure for the synthesis of quinoxaline derivatives still remains strongly desirable.

Silica is broadly used as inorganic space filler. Based on this we can transform the surface of silica with various inorganic or an organic moieties leads to many organic transformations. Additionally, heterogeneous catalysts have gained considerable importance because of environmentally friendly alternative to the more wasteful traditional catalysts, easy to handle, not moisture sensitive and economic considerations. We have observed that phosphomolybdic acid supported on silica (PMA-SiO_2) is most suitable to catalyze the synthesis of quinoxalines. It can be easily recovered from the reaction mixture by simple filtration and can be re-used. Phosphomolybdic acid-SiO_2 can be reused four successive runs with slight decrease in yield and slight increase in reaction time. Here we report the utilization of a heterogeneous catalyst for the preparation of quinoxalines from phenacyl bromide and phenylene diamines.

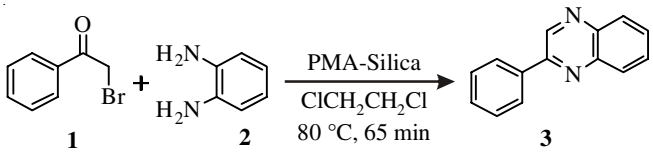
EXPERIMENTAL

Product purification by column chromatography by using Merck silica gel 60-120 mesh was performed. Melting points were determined in capillary tubes with a veego model: VMP-DS aPMAratus (heating rate 5 °C/min) and are given uncorrected. Infrared spectra were recorded using Thermo Nicole Nexus 670 FT-IR spectrometer. NMR spectra were recorded on either a Bruker Advance 300 or Advance 400 spectrometer. Chemical shifts (δ) are given in ppm using internal references or TMS as external reference for $CDCl_3$. Mass spectra were recorded on Finnigan MAT 1020 mass spectrometer operating at 70 eV.

Synthesis of PMA-silica: Phosphomolybdic acid (1 g) was charged in the 100 mL round-bottom ask and $CHCl_3$ (50 mL) was added. After the mixture was stirred at 50 °C for 1 h, 2.3 g of 60-120 mesh SiO_2, was added to the solution and the

mixture was stirred for another 1 h. The $CHCl_3$ was removed with rotary evaporator and the resulting solid was dried in vacuum at room temperature for 3 h. Used PMA/SiO_2 was regenerated as follows: PMA/SiO_2 was recovered by ltration from the reaction mixture and then it was put in the 50 mL round-bottom ask and dried in vacuum at 100 °C for 2 h.

General procedure: The phenacyl bromide **1a** (1 mmol) and *o*-phenylenediamine **2a** (1 mmol) were dissolved in 1,2-dichloroethane (3 mL). A catalytic amount (5 mol %) of PMA-silica was added slowly at room temperature then it was stirred at 80 °C for 60 min. After completion of the reaction monitered by TLC the reaction mixture was filtered. The catalyst was washed with Et_2O 2-3 times for reuse. The filtrate was concentrated and the residue was subjected to column chromatography (Hexane-EtOAc) to obtain pure quinoxaline **3a**. The recovered catalyst was reused for the synthesis of quinoxaline (**Scheme-I**).



Scheme-I: Synthesis of quinoxaline

2-Phenylquinoxaline (3a) [15]: Yield: 95 %; Milky white colour solid; m.p.: 75-78 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.61-7.40 (3H, *m*, Ar-H), 7.82-7.66 (2H, *m*, Ar-H), 8.16-8.06 (2H, *m,*Ar-H), 8.25-8.17 (2H, *m,* Ar-H), 9.31 (1H, *s,* Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 127.3, 129.0, 129.1, 129.5, 129.6, 130.1, 130.2, 136.7, 141.5, 142.2,143.3, 151.7; MS (ESI) *m/z* 207 $(M+H)^+$; HRMS (ESI) calcd. for $C_{14}H_{10}N_2$ $(M+H)^+$ 207.0922, found 207.0929.

2-*p*-Tolylquinoxaline (3b): Yield: 95 %; Brown colour solid; m.p. 90-92 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.45 (3H, *s,*Ar-CH_3), 7.37-7.29 (2H, *m,* Ar-H), 7.77-7.64 (2H, *m,* Ar-H), 8.14-8.04 (4H, *m,* Ar-H), 9.28 (1H, *s,*Ar-H); ^{13}C NMR (75 MHz,$CDCl_3$, δ ppm): 21.4, 127.4, 129.0, 129.2, 129.5, 129.8, 130.1, 133.9, 140.4, 141.4, 142.2, 143.2, 151.7; MS (ESI) *m/z*: 220 $(M+H)^+$; HRMS (ESI) calcd. for $C_{15}H_{12}N_2$ $(M+H)^+$ 220.1080, found 220.1083.

2-(4-Fluorophenyl)quinoxaline (3c) [16]: Yield: 90 %; Yellow colour solid; m.p.: 120-122 °C; ^{1}H NMR (JCAMP., $CDCl_3$, δ ppm): 7.18-7.28 (2H, *m,* Ar-H), 7.67-7.82 (2H, *m,* Ar-H), 8.06-8.12 (2H, *td,* Ar-H), 8.18-8.27 (2H, *m,* Ar-H), 9.27 (1H, *s,* Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 116.0, 116.3, 129.1, 129.4, 129.5, 129.5, 130.3, 132.9, 142.8, 150.6, 165.8; MS (ESI) *m/z* 225 $(M+H)^+$; HRMS (ESI) calcd. for $C_{14}H_9FN_2$ $(M+H)^+$ 225.0924, found 225.0929.

2-(4-Nitro-phenyl)quinoxaline (3d): Yield: 85 %; Yellow colour solid; m.p. 187-189 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.77-7.85 (2H, *m,* Ar-H), 8.11-8.18 (2H, *m,* Ar-H), 8.40 (4H, *s,* Ar-H), 9.36 (1H, *s,* Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 127.7, 128.4, 129.2, 130.1, 130.8, 131.4, 133.0,138.6, 142.8, 147.0, 149.1; MS (ESI) *m/z* 252 $(M+H)^+$; HRMS (ESI) calcd. for $C_{14}H_9N_3O_2$ $(M+H)^+$ 252.0756, found 252.0766.

4-Quinoxalin-2-yl-aniline (3e): Yield: 90 %; Black colour solid; m.p. 167-169 °C; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 6.76 (1H, dd, $J_{(1,2)}$ = 8.9, $J_{(1,3)}$ = 3.0, Ar-H), 7.29 (1H, *t, J* = 7.9, Ar-H), 7.45-7.58 (2H), *m,* 7.64-7.79 (2H, *m,* Ar-H), 8.09 (2H, *t, J* = 10.8, Ar-H), 9.25 (1H, *s,* Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm):113.7, 116.9, 117.6, 129.0, 129.3, 129.4, 129.9, 130.1, 137.7, 141.4, 142.1, 143.4, 147.2; MS (ESI) *m/z* 222 $(M+H)^+$; HRMS (ESI) calcd. for $C_{16}H_{11}N_3$ $(M+H)^+$ 222.1392, found 242.1410.

6-Methyl-2-phenylquinoxaline (3f): Yield: 96 %; White colour solid; m.p. 134-136 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.62 (3H, *s,* Ar-CH_3), 7.61-7.42 (4H, *m,* Ar-H), 8.03-7.82 (2H, *m,* Ar-H), 8.18 (2H, *m,* Ar-H), 9.24 (1H, *d, J* = 7.3 MHz, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 20.1, 127.2, 127.9, 128.4, 128.8, 129.6, 136.9, 139.9, 140.3, 140.6, 140.9, 142.2, 150.8; MS (ESI) *m/z* 220 $(M+H)^+$; HRMS (ESI) calcd. for $C_{15}H_{12}N_2$ $(M+H)^+$ 220.1082, found 220.1085.

6,7-Dimethyl-2-phenylquinoxaline (3g): Yield: 98 %; Light yellow colour solid; m.p. 122-124 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.51 (6H, *s,* Ar-CH_3), 7.56-7.41 (3H, *m,* Ar-H), 7.89-7.79 (2H, *m,* Ar-H), 8.20-8.12 (2H, *m,* Ar-H), 9.19 (1H, *s,* Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm):20.3, 20.4, 127.3, 128.1, 128.6, 129.0, 129.8, 140.1, 140.8, 142.4; MS (ESI) *m/z* 234 $(M+H)^+$; HRMS (ESI) calcd. for $C_{16}H_{14}N_2$ $(M+H)^+$ 234.1220, found 234.1223.

6-Methyl-2-*p*-tolylquinoxaline (3h): Yield: 96 %; Milky white colour solid; m.p. 146-147 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2,45 (3H, s, Ar-CH_3), 2.61 (3H, *s,* Ar-CH_3), 7.31 (3H, *d*, *J* = 8.3, Ar-H), 7.59-7.47 (1H, *m,* Ar-H), 8.02-7.79 (2H, *m,* Ar-H), 8.07 (2H, *d, J* = 8.3, Ar-H), 9.22 (1H, *d, J* = 7.5, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 21.3, 128.7, 129.1, 129.2, 129.3, 129.4, 130.3, 142.7, 142.8, 150.9; MS (ESI) *m/z* 234 $(M+H)^+$; HRMS (ESI) calcd. for $C_{16}H_{14}N_2$ $(M+H)^+$234.1230, found 234.1237.

6,7-Dimethyl-2-*p*-tolylquinoxaline (3i): Yield: 97 %; Light brown colour solid; m.p. 127-129 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.45 (3H, *s,* Ar-CH_3), 2.51 (6H, *s,* Ar-CH_3), 7.30 (2H, *d, J* = 8.0, Ar-H), 7.82 (2H, *d, J* = 9.5, Ar-H), 8.05 (2H, *d, J* = 8.0, Ar-H), 9.17 (1H, *s,* Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 21.3, 22.9, 128.5, 129.0, 129.1, 129.3, 139.9, 140.3, 141.3, 142.9, 151.9; MS (ESI) *m/z* 248 $(M+H)^+$; HRMS (ESI) calcd. for $C_{16}H_{14}N_2$ $(M+H)^+$ 248.1390, found 248.1398.

2-(3-Nitrophenyl)quinoxaline (3j): Yield: 80 %; Light orange colour solid; m.p. 185-187 °C; ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 7.72-7.90 (3H, *m,* Ar-H), 8.11-8.25 (2H, *m,* Ar-H), 8.30 (1H, *td,* $J_{1,2}$ = 8.3, $J_{1,3}$ = 2.3, $J_{1,3}$ = 1.5, Ar-H), 8.6 (1H, *d, J* = 8.3, Ar-H), 9.09-9.15 (1H, *m,* Ar-H), 9.41 (1H, *s,* Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 122.5, 124.7, 129.2, 129.8, 130.2, 130.5, 130.9, 133.1, 142.5; MS (ESI) *m/z*: 252 $(M+H)^+$; HRMS (ESI) calcd. for $C_{14}H_9N_3O_2$ $(M+H)^+$ 252.1652 found 252.1657.

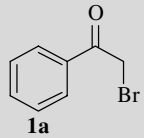
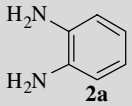
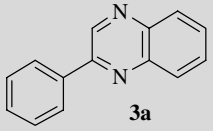
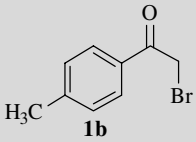
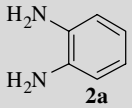
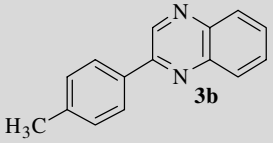
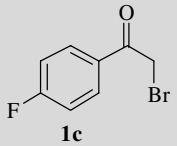
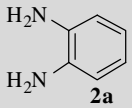
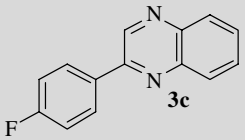
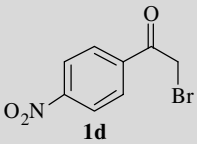
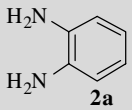
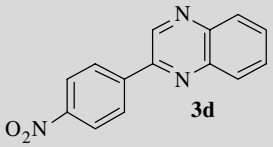
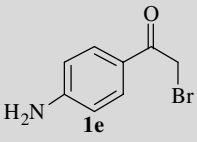
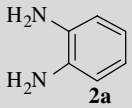
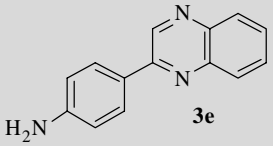
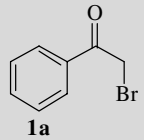
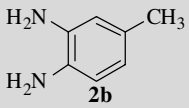
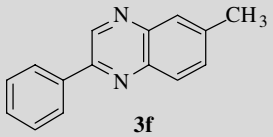
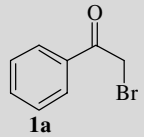
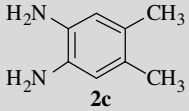
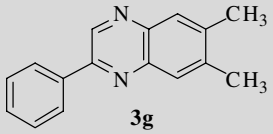
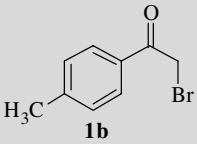
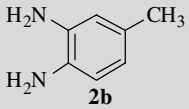
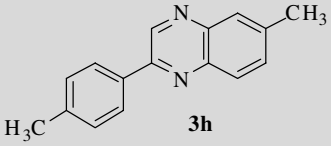
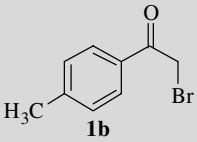
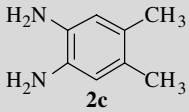
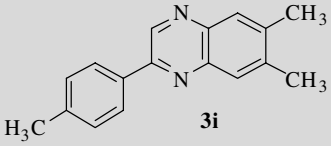
3-(Quinoxalin-2-yl)benzenamine (3k): Yield: 97 %; Yellow colour solid; m.p. 163-165 °C; ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm): 3.80 (2H, *bs,* -NH_2), 6.76 (1H, *dd,* $J_{1,2}$ = 2.9, $J_{1,3}$ = 8.9, Ar-H), 7.20-7.33 (1H, *m,* Ar-H), 7.45-7.59 (2H, *m,* Ar-H), 7.64-7.80 (2H, *m,* Ar-H), 8.09 (2H, *s, J* = 10.9, Ar-H), 9.25 (1H, *s,* Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 113.8, 117.0, 117.8, 129.1, 129.4, 129.5, 130.1, 130.2, 137.8, 141.6, 142.2, 143.5, 147.3, 152.0; MS (ESI) *m/z* 222 $(M+H)^+$; HRMS (ESI) calcd. for $C_{16}H_{11}N_3$ $(M+H)^+$ 222.1249, found 222.1258.

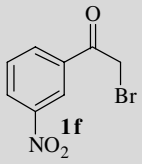
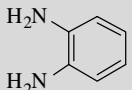
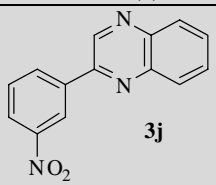
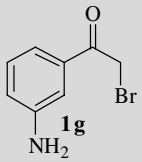
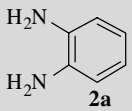
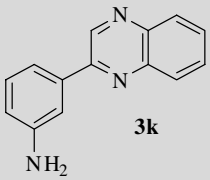
RESULTS AND DISCUSSION

A model reaction using phenacyl bromide and *o*-phenylenediamine was carried out in the 1,2-dichloroethane in presence of PMA-silica to investigate best reaction condition as shown in Table-1. The reaction was carried out at 80 °C the resultant compound formed with good yield but at room temperature slows down the reaction resulting in incomplete reaction with lower yield. It was clear that phenacyl bromides bearing electron-donating groups completed the reaction in shorter time than those bearing electron-withdrawing groups. The couplings of electron-rich 2-bromo-4'-methylacetophenone with diamines provided the product in 95 % yield in 60 min, (Table-1, entry 2). In the case of electron-poor 2-bromo-4'-nitroacetophenone, the corresponding products rapidly in low yield (Table-1, entry 4), which were also far more efficient than those in reported recyclable catalytic systems. It was worth noting that using electron rich *o*-phenylenediamine as the coupling partner, resulted in formation of desired product in good yield (Table-1, entries 6-9).

One of the main aims of our revise was to examine the reuse and recycling the catalyst. To conclude, we explored the reusability of the PMA-Silica catalytic system using the reaction of phenacyl bromide and *o*-phenylenediamine as the model reaction. After the completion of the reaction, remove the solvent and the reaction mixture was diluted with Et_2O and decanted, the remained catalyst was washed with Et_2O

TABLE-1
PMA-SILICA CATALYZED SYNTHESIS OF QUINOXALINES[a]

Entry	Phenacyl bromide (**1**)	*o*-Phenylenediamine (**2**)	Product (**3**)	Time (min)	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	65	95
2	 **1b**	 **2a**	 **3b**	60	95
3	 **1c**	 **2a**	 **3c**	70	90
4	 **1d**	 **2a**	 **3d**	80	85
5	 **1e**	 **2a**	 **3e**	75	90
6	 **1a**	 **2b**	 **3f**	64	96
7	 **1a**	 **2c**	 **3g**	59	98
8	 **1b**	 **2b**	 **3h**	60	96
9	 **1b**	 **2c**	 **3i**	58	97

Entry	Phenacyl bromide (**1**)	*o*-Phenylenediamine (**2**)	Product (**3**)	Time (min)	Yield (%)[b]
10	 **1f**	 **2a**	 **3j**	74	80
11	 **1g**	 **2a**	 **3k**	70	97

[a]Reaction conditions: Phenacyl bromide (1 mmol), *o*-phenylene diamine (1.1 mmol), PMA-Silica (5 mol %), 1,2-dichloroethane (3 mL); Nitrogen atmosphere was used; [b]Isolated yield.

for several times and reused directly under the conditions mentioned above. The results listed in Table-2 and showed the catalytic system could be reused up to 4 runs while retain the catalytic activity.

TABLE-2
REUSE OF CATALYTIC SYSTEM FOR THE SYNTHESIS OF QUINOXALINE BY THE REACTION OF PHENACYL BROMIDE AND *o*-PHENYLENEDIAMINE[a]

Run	1	2	3	4
Yield (%)[b]	95	93	92	90

[a]Reaction conditions: Phenacyl bromide (1.0 mmol), *o*-phenylene diamine (1.1 mmol), PMA-Silica (5 mol %), 1,2-dichloroethane (3 mL). [b]Isolated yield.

Conclusion

Phosphomolybdic acid-silica dioxide catalyst is proved to be highly efficient for the synthesis of quinoxaline. Furthermore, the phosphomolybdic acid-silica catalyst can be easily separated and recovered from the reaction mixture by filtration and reused for up to 4 runs without noticeable losing activities. This method has several advantages, such as low cost, short reaction time, excellent yield, simple experimental as well as isolation procedures. This greener methodology will be useful in synthesis of libraries of compounds having such different bioactivities as pharmaceuticals and agrochemicals.

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