Solventless Synthesis of Quinoline Derivatives: Acceleration of Friedländer Reaction by Supported Heteropoly Acids

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ABSTRACT

Different Keggin type heteropoly acids (HPAs) and supported ones on solids with different nature and textural properties were used in the Friedländer reaction in order to obtain quinoline derivatives. This conversion has been preceded by tungstophosphoric acid supported on silica, KSF and activated carbon as optimized catalysts in high yields and short reaction times. The general applicability of this method is demonstrated by using various substrates including ketones, β-ketoesters and β-diketones. For most substrates the reaction worked well. These catalysts were found to be reusable and considerable catalytic activity could still be achieved after the fourth run.

KEYWORDS

Friedländer reaction, quinoline derivatives, heteropoly compound, supported catalysts, solvent-free condition.

1. Introduction

Many N-heterocyclic compounds are susceptible to microbial degradation. They often exist in biologically active natural products and synthetic compounds of medicinal interest.[1] Some quinoline derivatives have the potential of both inhibiting PrPres (Proteinase K-Resistant Prion Protein) formation *in vitro* and prolonging the incubation period of infected animals. Various bioactive compounds such as antibacterial, anti-asthmatic, antihypertensive, anti-inflammatory, and tyrosine kinase inhibiting agents have a quinoline ring in their structures.[2–5] In addition to medicinal applications, quinolines have been employed in the study of bioorganic and bioorgano-metallic processes.[6] These compounds are also known for their formation of polymers that combine enhanced electronic, opto-electronic, or non-linear optical properties with excellent mechanical properties.[7] Different procedures such as the Skraup[8], Pfitzinger[9], Combes[10], and Friedländer[11] methods have been developed for the synthesis of quinoline derivatives. Among them Friedländer annulations is still one of the most simple, straightforward, and popular approach for the synthesis of poly-substituted quinolines.[12–17] These reactions are generally carried out in the presence of a base or by heating a mixture of the reactants at high temperatures in the absence of catalyst. Recently, several Brönsted acid and Lewis acid have been utilized for this conversion.[15,18–31] Most of the synthetic methods suffer from at least one of the following disadvantages such as low yield of products, prolonged reaction times, harsh reaction conditions, and tedious workup. Hence, in order to overcome these limitations, the development of a simple, efficient, and high-yielding protocol, with short reaction time is still desirable.

Heteropoly acids, HPAs, and their salts, are commonly used as catalysts in homogeneous and heterogeneous systems because of their strong acidity and redox properties. Among them Keggin type HPAs are particularly important due to their high stability, availability, strong acidity, ease of handling, non toxicity, experimental simplicity, and environmental compatibility.[32] These compounds have been extensively investigated with respect to their properties and applications.[33] Beside various advantages of HPAs, the disadvantage of these catalysts is that their specific surface area is very low (<10 m^2 g^{-1}). In order to increase this parameter, various supports have been used for dispersion of HPAs on a high surface area. Immobilization of HPAs on supports leads to increased surface area, increased active site accessibility, and higher dispersion of acidic protons.

In this work, we have investigated the catalytic performance of commercially available HPAs on different carriers in the conden-sation reaction of 2-aminoacetophenone (**1a**) and various carbonyl compounds *via* Friedländer reaction.

2. Experimental

2.1. General

H$_3$PW$_{12}$O$_{40}$ (PW), H$_3$PMo$_{12}$O$_{40}$ (PMo) and H$_4$SiW$_{12}$O$_{40}$ (SiW) hydrate and γ-Alumina were obtained from Aldrich, activated carbon from Merck and KSF and K 10 montmorillonite were purchased from Fluka. Aerosil silica and titania were obtained from Degussa. Products were characterized by comparing their spectral data with those of authentic samples. ^{1}H NMR spectra were recorded on a Bruker Avance 200 MHz NMR spectrometer with CDCl$_3$ as the solvent and TMS as the internal reference. CHN compositions were measured by Hekatech elemental analysis model Euro EA 3000.

2.2. Preparation of Supported Catalysts

Supported PW catalysts (PW/support) were prepared by the wet impregnation method. Silica-supported PW (PW/SiO$_2$) catalysts were prepared by impregnating silica (3.0 g) with an aqueous solution of PW (2.0 g in 20 mL water). The mixture was stirred overnight at room temperature, followed by drying using a rotary evaporator.

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For preparation of the K 10-supported PW catalyst (PW/K 10), K 10 montmorillonite was dried in an oven at 120 °C for 2 h prior to its use as a support. After drying, 5.0 g of K 10 was taken. To prepare a catalyst with 40 % loading of PW, 2.0 g of PW was dissolved in 4 mL of dry methanol. This solution was added dropwise to predried K 10 with constant stirring with a glass rod. Initially, with addition of PW solution, the clay was in a powdery form, but on further addition of PW solution, the clay turned into a paste. The paste, on further stirring for 10 min, resulted in a free flowing powder. A similar procedure was followed for the synthesis of KSF-supported PW catalyst (PW/KSF). A catalyst based on PW supported on γ-Al$_2$O$_3$ (PW/γ-Al$_2$O$_3$) was also prepared. The solution of PW was prepared by dissolving 2.0 g PW in 25 mL of water and 25 mL of methanol. Then 5.0 g γ-Al$_2$O$_3$ was dropped into the above solution under vigorous stirring for 24 h.

For the preparation of carbon-supported PW catalyst (PW/C), carbon was first subjected to an acid and base treatment to remove impurities. This catalyst was prepared by the pore filling impregnation technique with a PW solution. After the impregnation, the catalyst was dried at room temperature for 24 h, and calcined at 200 °C for 3 h.

All catalysts were characterized and identified by comparing their spectral and analytical data with those of authentic samples.[34]

2.3. Typical Procedure for Synthesis of Compounds 3a–i

A mixture of 2-aminoacetophenone **1a** (1.0 mmol), substrates **2a–i** (1.2 mmol), and an appropriate amount of catalyst, were crushed at 100 °C under solvent-free condition. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with CH$_3$CN (5 mL) and filtered. The catalyst was recovered from the residue. The filtrate was concentrated and the product was purified by column chromatography on silica gel using EtOAc/hexane as eluent. All products were identified by comparing of their spectral data with those of authentic samples. The recovered catalyst was washed with CH$_3$CN or ether (3 10 mL) and reused.

From the reaction of **1a** with ethyl acetoacetate (**2a**), *ethyl-2,4-dimethylquinoline-3-carboxylate* **3a** (94–98 %) was obtained as an oil; δ_H (200 MHz, CDCl$_3$): 1.40 (3H, t, *J* 7.1 Hz, CH$_3$), 2.57 (3H, s, CH$_3$), 2.68 (3H, s, CH$_3$), 4.42 (2H, q, *J* 7.1 Hz, OCH$_2$), 7.46–7.51 (1H, m, CH), 7.62–7.65 (1H, m, CH), 7.91 (1H, d, *J* 8.0 Hz, CH), 7.98 (1H, d, *J* 8.0 Hz, C-CH); δ_c (200 MHz, CDCl$_3$): 14.0, 19.8, 22.4, 60.7, 124.0, 125.3, 126.0, 128.1, 131.1, 144.7, 147.9, 158.6, 165.5; HRMs found: M, 229.272; Calc. for C$_{14}$H$_{15}$NO$_2$: 229.274; (Found: C, 73.45; H, 6.57; N, 6.04 %. Calc. for C$_{14}$H$_{15}$NO$_2$ (229.27); C, 73.34; H, 6.59; N, 6.11 %).

From the reaction of **1a** with methyl acetoacetate (**2b**), *methyl-2,4-dimethylquinoline-3-carboxylate* **3b** (91–98 %) was obtained as an oil; δ_H (200 MHz, CDCl$_3$): 2.58 (3H, s, CH$_3$), 2.70 (3H, s, CH$_3$), 3.96 (3H, s, OCH$_3$), 7.01–7.06 (1H, m, CH), 7.68–7.72 (1H, m, CH), 7.96 (1H, d, *J* 8.0 Hz, C-CH), 8.01 (1H, d, *J* 8.0 Hz, C-CH); δ_c (200 MHz, CDCl$_3$): 19.9, 22.5, 51.1, 123.9, 124.8, 126.0, 128.1, 131.8, 145.4, 148.8, 158.2, 166.1; HRMs found: M, 215.246; Calc. for C$_{13}$H$_{13}$NO$_2$: 215.248; (Found: C, 72.61; H, 6.06; N, 6.47 %. Calc. for C$_{13}$H$_{13}$NO$_2$ (215.25); C, 72.54; H, 6.09; N, 6.51 %).

From the reaction of **1a** with dimedone (**2c**), *3,3,9-trimethyl-1,2,3,4-tetrahydro-1-acridinone* **3c** (95–98 %) was obtained as a solid; m.p. 105 °C; δ_H (200 MHz, CDCl$_3$): 1.11 (6H, s, CH$_3$), 2.50 (2H, s, CH$_2$), 3.04 (3H, s, CH$_3$), 3.20 (2H, s, CH$_2$), 7.99–8.03 (2H, m, CH), 8.32–8.37 (2H, m, CH); δ_c (200 MHz, CDCl$_3$): 20.0, 26.5, 33.0, 52.8, 56.7, 124.8, 125.7, 126.6, 127.7, 130.9, 132.0, 144.1, 145.0, 160.1, 196.4; HRMs found: M, 239.313; Calc. for C$_{16}$H$_{17}$NO: 239.312;

(Found: C, 80.36; H, 7.14; N, 5.81 %. Calc. for C$_{16}$H$_{17}$NO (239.31); C, 80.30; H, 7.16; N, 5.85 %).

From the reaction of **1a** with benzoylacetone (**2d**), *2,4-dimethyl-3-benzoylquinoline* **3d** (81–96 %) was obtained as a solid; m.p. 109 °C; δ_H (200 MHz, CDCl$_3$): 2.55 (3H, s, CH$_3$), 2.62 (3H, s, CH$_3$), 7.52–8.09 (9H, m, Ar); δ_c (200 MHz, CDCl$_3$): 20.0, 22.5, 125.6, 126.7, 127.7, 128.8, 129.2, 129.9, 131.8, 132.2, 133.2, 134.7, 144.3, 145.7, 157.5, 196.8; HRMs found: M, 261.317; Calc. for C$_{18}$H$_{15}$NO: 261.318; (Found: C, 82.78; H, 5.76; N, 5.34 %. Calc. for C$_{18}$H$_{15}$NO (261.32); C, 82.73; H, 5.79; N, 5.36 %).

From the reaction of **1a** with acetylacetone (**2e**), *3-acetyl-2,4-dimethylquinoline* **3e** (74–97 %) was obtained as an oil; δ_H (200 MHz, CDCl$_3$): 2.58 (3H, s, CH$_3$), 2.63 (3H, s, CH$_3$), 2.65 (3H, s, CH$_3$), 7.44–7.50 (1H, m, CH), 7.61–7.64 (1H, m, CH), 7.94 (1H, d, *J* 8.0 Hz, C-CH), 7.99 (1H, d, *J* 8.0 Hz, C-CH); δ_c (200 MHz, CDCl$_3$): 19.9, 22.5, 30.0, 125.7, 125.8, 127.7, 128.8, 131.8, 132.0, 144.1, 145.7, 157.2, 199.2; HRMs found: M, 199.246; Calc. for C$_{13}$H$_{13}$NO: 199.248; (Found: C, 78.43; H, 6.55; N, 6.99 %. Calc. for C$_{13}$H$_{13}$NO (199.25); C, 78.36; H, 6.58; N, 7.03 %).

From the reaction of **1a** with cyclohexanone (**2f**), *5-methyl-1,2,3,4-tetrahydroacridine* **3f** (51–52 %) was obtained as a solid; m.p. 78 °C; δ_H (200 MHz, CDCl$_3$): 1.83–1.89 (4H, m, CH$_2$), 2.29 (3H, s, CH$_3$), 2.61–2.64 (2H, m, C-CH$_2$), 2.79–2.83 (2H, m, N-C-CH$_2$), 7.48–7.52 (1H, m, CH), 7.59–7.63 (1H, m, CH), 7.89 (1H, d, *J* 8.1 Hz, CH), 8.31 (1H, d, *J* 8.1 Hz, CH); δ_c (200 MHz, CDCl$_3$): 21.1, 22.5, 23.6, 33.8, 35.9, 122.8, 125.4, 128.2, 127.7, 132.9, 140.5, 144.9, 165.0; HRMs found: M, 197.275; Calc. for C$_{14}$H$_{15}$N: 197.276; (Found: C, 85.32; H, 7.63; N, 7.05 %. Calc. for C$_{14}$H$_{15}$N (197.28); C, 85.24; H, 7.66; N, 7.10 %).

From the reaction of **1a** with cyclohexanone (**2f**), *1-(2-(cyclohexenyl amino)phenyl)ethanone* **4f** (39–70 %) was obtained as an oil; δ_H (200 MHz, CDCl$_3$): 1.54–1.95 (8H, m, CH$_2$), 2.71 (3H, s, CH$_3$), 5.09 (1H, m, CH), 6.42–7.35 (4H, m, Ar), 11.02 (1H, brs, NH); δ_c (200 MHz, CDCl$_3$): 21.7 24.9, 26.2, 29.2, 100.5, 115.8, 118.6, 119.1, 129.1, 134.4, 148.0, 148.6, 199.2; HRMs found: M, 215.290; Calc. for C$_{14}$H$_{17}$NO: 215.291; (Found: C, 78.07; H, 7.94; N, 6.58 %. Calc. for C$_{14}$H$_{17}$NO (215.29); C, 78.10; H, 7.96; N, 6.51 %).

From the reaction of **1a** with 4-nitroacetophenone (**2g**), *4-methyl-2-(4-nitrophenyl)quinoline* **3g** (95–96 %) was obtained as a solid; m.p. 126 °C; δ_H (200 MHz, CDCl$_3$): 2.63 (3H, s, CH), 7.61 (1H, s, CH), 7.75–8.23 (4H, m, Ar), 8.31–8.42 (4H, m, Ar); δ_c (200 MHz, CDCl$_3$): 22.5, 121.5, 123.7, 124.5 126.9, 129.0, 129.9, 141.7, 146.2, 146.6, 147.1, 157.2; HRMs found: M, 264.278; Calc. for C$_{16}$H$_{12}$N$_2$O$_2$: 264.279; (Found: C, 72.79; H, 4.56; N, 10.55 %. Calc. for C$_{16}$H$_{12}$N$_2$O$_2$ (264.28); C, 72.72; H, 4.58; N, 10.60 %).

From the reaction of **1a** with 4-methylacetophenone (**2h**), *4-methyl-2-(4-methylphenyl)quinoline* **3h** (90–95 %) was obtained as a oil; δ_H (200 MHz, CDCl$_3$): 2.48 (3H, s, CH$_3$), 2.68 (3H, s, CH$_3$), 7.19–7.25 (2H, m, Ar), 7.42 (1H, s, CH), 7.56–7.67 (2H, m, Ar), 7.86–8.13 (4H, m, Ar); δ_c (200 MHz, CDCl$_3$): 22.5, 24.7, 121.5, 124.5, 126.8, 127.8, 128.6, 129.4, 133.7, 137.5, 145.9, 147.1, 157.2; HRMs found: M, 233.307; Calc. for C$_{17}$H$_{15}$N: 233.308; (Found: C, 87.56; H, 6.49; N, 5.97 %. Calc. for C$_{17}$H$_{15}$N (233.31); C, 87.52; H, 6.48; N, 6.00 %).

From the reaction of **1a** with acetophenone (**2i**), *4-methyl-2-phenylquinoline* **3i** (90–98 %) was obtained as an oil; δ_H (200 MHz, CDCl$_3$): 2.69 (3H, s, CH$_3$), 7.51 (1H, s, CH), 7.55–7.62 (3H, m, Ar), 7.66–7.80 (2H, m, Ar), 8.07–8.34 (4H, m, Ar); δ_c (200 MHz, CDCl$_3$): 22.6, 121.5, 124.5, 126.8, 127.8, 128.1, 129.4, 129.9, 137.2, 145.9, 147.1, 157.2; HRMs found: M, 219.282; Calc. for C$_{16}$H$_{13}$N: 219.281;

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S. Afr. J. Chem., 2011, **64**, 95–100,
<http://journals.sabinet.co.za/sajchem/>.

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(Found: C, 87.69; H, 5.99; N, 6.35 %. Calc. for $C_{16}H_{13}N$ (219.28); C, 87.64; H, 5.98; N, 6.39 %).

3. Results and Discussion

The reaction of **1a** and **2a** as model reactants (Scheme 1) was studied in the presence of 0.2 g of PW catalyst under solvent-free condition at different temperatures.

In the presence of this catalyst, no desired product was observed at room temperature and 60 °C after 1 h (Table 1, entries 1 and 2). When the temperature increased to 100 °C, the yield of product is significantly increased to 95 % after 30 minutes (Table 1, entry 3). In the presence of 0.2 g of other HPAs including SiW and PMo, quinoline product were obtained in lower yields in comparison with PW (Table 1, entries 3–5). Thus, the reaction of **1a** and **2a** in the presence of 0.2 g PW was chosen as a model for further investigations. Supported HPA catalysts are preferred from an environmental and economical point of view. In order to choose a suitable carrier, the model reaction was checked in the presence of different solid supports. K 10 montmorillonite resulted in good catalytic activity and in the presence of it an excellent yield of product was obtained in relatively short reaction time (Table 1, entry 6). The reaction did not proceed in the presence of activated carbon and γ-Al$_2$O$_3$ (Table 1, entries 7 and 8). SiO$_2$ and KSF showed moderate yields for this transformation (Table 1, entries 9 and 10). It was found that immobilization of PW on K 10 montmorillonite had no significant effect on reactivity of the solid support, but PW/SiO$_2$, PW/KSF and PW/C showed higher reactivity compared to the support alone on a unit weight basis (Table 1, entries 11–14). Based on these observations, SiO$_2$, KSF and activated carbon were chosen as suitable supports for further investigation. From previous studies[34,35], a 40 wt.% loading of PW was identified as giving the best results and thus was used in the present study.

In an effort to achieve optimal conditions, the model reaction was performed in the presence of different amounts of PW/SiO$_2$, PW/KSF and PW/C at 100 °C (Table 2). It was found that the use of 0.2 g of catalysts was sufficient to promote the reaction (Table 2, entries 2, 4, 6).

With respect to these optimized conditions, the reaction was extended to other carbonyl compounds such as β-ketoesters and cyclic or acyclic ketones and β-diketones. The results are summarized in Table 3. In the presence of PW/SiO$_2$, PW/KSF, and PW/C, high to excellent yields of products were obtained in short reaction times without any formation of undesirable side products. The catalytic activities of PW/SiO$_2$ and PW/C were relatively similar and in the presence of these catalysts the yields of products were better than PW/KSF. In the presence of PW/SiO$_2$ and PW/C both cyclic and acyclic β-diketones as well as β-ketoesters worked successfully in formation of quinoline derivatives, giving a high yield of products (Table 3, entries 1–5). The synthetic utility of the reaction, under the optimized reaction conditions, was evaluated by performing the reaction between **1a** with a variety of ketones. However, the reaction with cyclohexanone (**2f**) proved to be sluggish as compared to that with other ketones, β-diketones or β-ketoesters and yield of the corresponding product was lower with the formation of the

Table 1 Effect of temperature and catalysts in the reaction of **1a** and ethyl acetoacetate.

Entry	Catalyst	Temperature /°C	Time/min	Yield/% [a]
1	PW	r.t.	60	0
2	PW	60	60	0
3	PW	100	30	95
4	SiW	100	30	84
5	PMo	100	30	42
6	K 10	100	20	90
7	Activated carbon	100	60	0
8	γ-Al$_2$O$_3$	100	60	0
9	SiO$_2$	100	15	65
10	KSF	100	5	28
11	40 wt. % PW/KSF	100	10	96
12	40 wt. % PW/SiO$_2$	100	15	98
13	40 wt. % PW/C	100	10	94
14	40 wt. % PW/γ-Al$_2$O$_3$	100	5	54

[a] Isolated yield.

In an effort to achieve optimal conditions, the model reaction was performed in the presence of different amounts of PW/SiO$_2$, PW/KSF and PW/C at 100 °C (Table 2). It was found that the use of 0.2 g of catalysts was sufficient to promote the reaction (Table 2, entries 2, 4, 6).

Table 2 Effect of catalyst loading in the reaction of **1a** and ethyl acetoacetate.

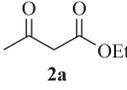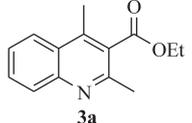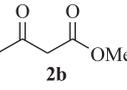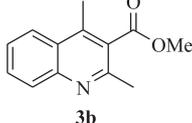| Entry	Catalyst/g	Yield/% [a]
1	PW/SiO$_2$ (0.1 g)	84
2	PW/SiO$_2$ (0.2 g)	98
3	PW/KSF (0.1 g)	82
4	PW/KSF (0.2 g)	98
5	PW/C (0.1 g)	82
6	PW/C (0.2 g)	98

[a] Isolated yield after 15 min.

enamine (**4f**) as by product (Table 3, entry 6). Thus, it seems that no cyclization was observed for 50 % of the final mixture in the presence of PW/SiO$_2$. In the case of PW/KSF and PW/C no cyclization was observed and 70 % and 50 % of the corresponding enamine was produced respectively (Table 3, entry 6). The reaction of open chain ketones was faster than cyclic analogues and cyclization occurred completely (Table 3, entries 7–9). The applicability of this method for the large-scale operations was investigated in the reactions of **1a** (10.0 mmol) with **2a**, **2c** and **2g** (12.0 mmol) under optimized conditions (Table 3, entries 1,3 and 7). As can be seen, PW/support catalysts are good candidates for large-scale synthesis of quinoline derivatives.

The reusability of a catalyst is of fundamental importance in industrial consumption and has economic benefits. After each run, the catalyst was recovered by filtering, washed and dried in an oven at 120 °C for 2 h, to remove the adsorbed reactants or product. When the catalysts were washed with CH$_3$CN, selectivity of the reaction was changed due to the formation of unwanted side-products (Figs. 1–3). Furthermore, the reusability of PW/KSF
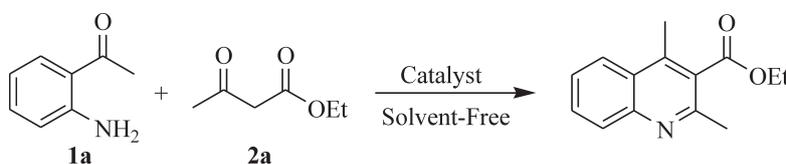
Scheme 1
Model reaction.

Table 3 Synthesis of quinoline derivatives in the presence of supported PW catalysts.

$$ 1a \; + \; \underset{2a\text{-}i}{R^1 \overset{O}{\diagup\!\!\diagdown} R^2} \xrightarrow[\text{Solvent-Free, } 100\,°C]{\text{Catalyst (0.2 g)}} \; \text{Product 3a-i} $$

Entry	Substrate **2**	Product	Time/min / Yield/% [a]		
			PW/SiO$_2$	PW/KSF	PW/C
1	**2a**	**3a**	15/98 (60/98) [b]	10/96 (45/95) [b]	10/94 (40/90) [b]
2	**2b**	**3b**	5/98	15/91	10/91
3	**2c**	**3c**	10/98 (50/95) [b]	15/95 (65/90) [b]	5/98 (30/98) [b]
4	**2d**	**3d**	10/81	5/82	20/96
5	**2e**	**3e**	10/97	10/74	20/92
6	**2f**	**3f** / **4f**	60/98 [c]	15/70 [d]	40/91 [e]
7	**2g**	**3g**	10/95 (30/90) [b]	15/95 (45/95) [b]	25/96 (70/95) [b]
8	**2h**	**3h**	15/95	5/90	20/91
9	**2i**	**3i**	10/98	10/90	10/93
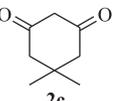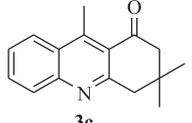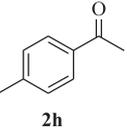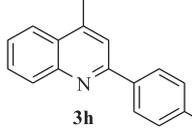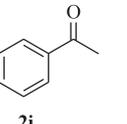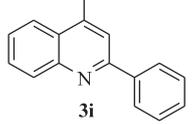
[a] Isolated yield; [b] results in brackets refer to large scale syntheses; [c] conversion (yield: 51 %); [d] yield of corresponding enamine (**4f**); [e] conversion (yield: 52 %).

Scheme 2
Suggested mechanisms.

Figure 1 Reusability of PW/SiO$_2$.

and PW/C was not favourable and in the presence of these catalysts, conversion of the reaction was significantly decreased (Figs 2,3). This may be due to the weak interaction between PW and support resulting in its leaching in polar media which lead-

ing to their poor reusability. But with use of ether as eluent, the reusability of all the catalysts was found to be favourable and conversion and selectivity of the reaction were only slightly decreased in all runs (Figs 1–3).

The authors suggest two possible reaction mechanisms that are shown in Scheme 2. Results that are observed in the reaction of **2f** with **1a** confirmed that mechanism **b** is the mechanism of the reaction in which enamine was formed as an intermediate. Proton conductivity of HPAs, as acid catalysts, is essential to activate carbonyl compounds for before reaction. In the Friedländer synthesis, a crossed–aldol reaction takes place initially, creating an amino ketone. This intermediate subsequently condenses with itself, generating the ring with concomitant formation of the carbon-nitrogen double bond.

Finally, the efficacy of the PW/support catalysts were compared with other reported catalysts listed in Table 4. It is evident that PW/support catalysts are efficient, cost-effective and environmentally benign catalysts useful in the synthesis of quinoline derivatives. Preparation of these catalysts is easy from readily available reagents and the reaction proceeded under solvent-free conditions. In addition, they could be recovered by simple filtration and recycled in subsequent reactions.

Figure 2 Reusability of PW/KSF.

Figure 3 Reusability of PW/C.

Table 4 Comparison of the efficiency of PW/support catalysts for synthesis of **3a**.

Entry	Reaction conditions	Time/min / Yield/%	Disadvantages	Ref.
1	NaHSO$_4$.SiO$_2$, 70 °C, solvent-free	240/80	Long reaction time	36
2	Amberlyst-15, EtOH, reflux	150/87	Long reaction time, use of organic solvent	37
3	Nano Al$_2$O$_3$, CHCl$_3$, reflux	90/97	Long reaction time, use of organic solvent	38
4	Al-SBA-15, 90 °C, toluene	120/62	Long reaction time, use of toxic solvent, low selectivity	39
5	PEG support, MeONa (1N)/MeOH, r.t.	1080/93	Long reaction time, use of organic solvent, Harsh reaction condition, difficulties in the work-up procedure	40
6	o-Benzenedisulfonimide, 80 °C, solvent-free	960/85	Long reaction time, difficulties in the catalyst synthesis and recovery	41

4. Conclusion

In conclusion, in this article we described a rapid, efficient, environmentally and economically benign method for the synthesis of quinoline derivatives by the Friedländer condensation under solvent-free conditions in the presence of low amounts of PW/SiO$_2$, PW/KSF and PW/C. The yields were excellent and the reaction times short.

Acknowledgements

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