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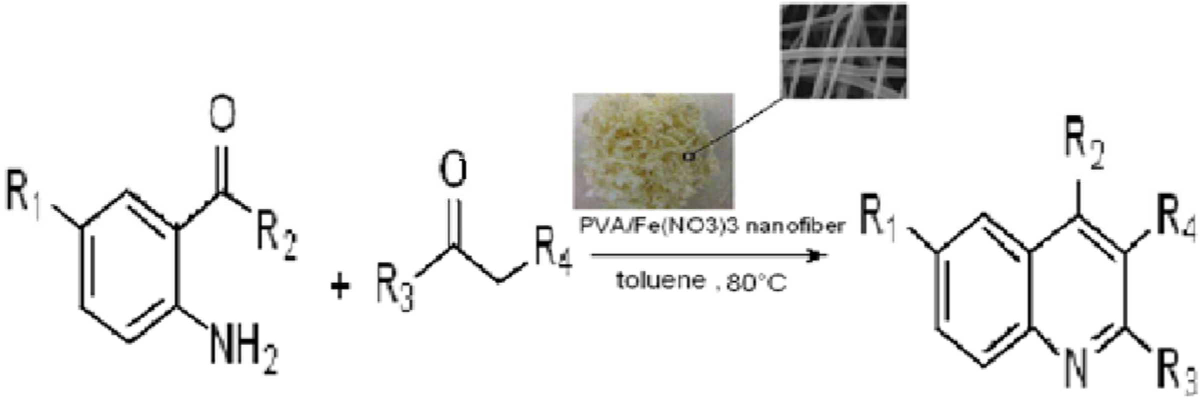
Graphical abstract:



PVA/Fe(NO$_3$)$_3$nanofiber mats: an efficient, heterogeneous and recyclable catalyst for the synthesis of quinolines via Friedländer annulations

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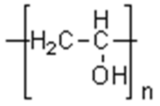
PVA/Fe(NO$_3$)$_3$nanofiber mats is found to be a heterogeneous recyclable catalyst for the efficient synthesis of quinoline derivatives in the Friedländer condensation of 2-aminoarylketones with carbonyl compounds and β-keto esters. The novel catalytic system could be recovered and reused at least 5 times without any loss of catalytic activity.

Quinoline derivatives are an important class of heterocycles, structural unit in alkaloids, therapeutics and synthetic analogues.[1] These compounds have interesting biological activities such as antimycobacterial,[2] antimalarial,[3] anti-inflammatory[4] and anticancer.[5]Quinolines are also valuable reagents for the synthesis of nano and meso structures with enhanced electronic and photonic properties.[6] Due to their importance in a wide range of synthetic and natural products, significant efforts continue to be directed in to the development of novel procedures and catalysts for preparation of quinoline derivatives including Skraup,[7] Pfitzinger,[8] Friedländer[9] and Combes reactions.[10] Among them, Friedländer reaction is one of the most straightforward and excellent methods. This procedure usually involves acid or base catalyzed condensation between a 2-aminoarylketone or aldehyde and a carbonyl compound possessing a reactive α-methylene group.[11]Lewis acid catalysts such as Zr(NO$_3$)$_4$,[12] Y(OTf)$_3$,[13]AgOTf,[14] ZnCl$_2$[15] and PdCl$_2$[16] have been used in the Friedländer reaction. However, many of these procedures have some limitations such as low yield, low selectivity, long reaction time, harsh reaction conditions and need to excess amount of catalysts. Recently FeCl$_3$,[17] FeCl$_2$[18] and Fe(NO$_3$)$_3$[19]have been reported for the effective synthesis of quinolinesas Iron based Lewis acids catalyst. In spite of their high yield and short reaction time, homogeneity of catalyst, tedious work-up, non-reusability, deactivation (due to aggregation of particles) and product contamination by residual transition metal are main problems in the use of these catalysts. A general scope in catalysis is conversion of a homogeneous catalyst into a heterogeneous catalytic system.[19]The immobilization of homogeneous catalysts on solid supports opens up new route for design and engineering of novel catalysts. These structures are easily separable from the reaction mixture, allowing the recovery of the solid and eventually its reuse. But the heterogenization of a homogeneous catalysis decreases catalytic activity because it reduces the accessible catalytic center and make it difficult to diffuse the reactants to the catalyst site.[20]To enhance the availability of the active site, materials with porous structure and different smaller size structure such as nanoparticles and nanofibers have been utilized.[21]

Poly(vinyl alcohol) (PVA) is a water soluble and biodegradable synthetic polymer.Polymerizationof vinyl acetate, followed by hydrolysis ofthe product, leads toproduction of PVA. It is white (colourless), odourless and granular in the commercial form. The poly hydroxy structure of this polymer is shown below.



PVAis usedinvariousindustries such as membrane, coatings, textile sizing, adhesive and medical devises because of biocompatibility, good chemical resistance and physicalproperties.[22]

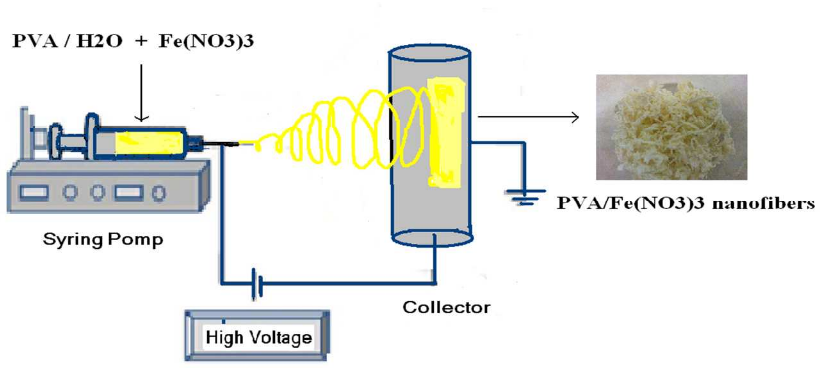
This Inexpensive and non-toxic polymeris a good candidate as the supported matrix to immobilize Lewis acid catalyst. Transition metal species can be chelated with numeroussurface hydroxyl functional groups of PVA to prepare heterogen solid support which are insoluble in most organic solvents and can also be functionalized.But semi crystalline structure, high melting point and low active site of bulk PVA make it difficult to fabricate in to suitable solid matrix for catalytic application.[23]Electrospinning is a versatile method for preparation of ultra-long one-dimensional PVA nanofibers. This method uses an electromagnetic field with a voltage sufficient to overcome the surface tension of a polymer solution and to draw ultrafine nanofiber.The electrospunnanofibers exhibit a number of unique features and properties such as 1D morphology, extraordinary length, high surface area, and hierarchically porous structure.[24] Against the nanoparticles, electrospunnanofibers can be easily prepared as membranes (supported or free-standing, and nonwoven or woven) that can be conveniently handled and manipulated during an application.[25]Few studieshave been reported on thecatalytic activity of PVA nanofibers. L. Shao used Pd/PVA nanofiber mates as catalyst in coupling reaction.[26]However, to our best knowledge, no study has been conducted on the use of electrospun PVA nanofiber mats as a heterogeneous Iron salt catalyst. We herein report the use of PVA/Fe(NO$_3$)$_3$nanofiber mats as an effective heterogeneous catalyst in quinolines synthesis via Friedländer annulations. This catalyst showed good catalytic activity and high selectivity under mild conditions. Besides it can be separated easily by forceps or simple filtration and reused at least 5times without any catalytic activity loose.

Results and Discussion

Preparation and characterization of PVA/$Fe(NO_3)_3$nanofiber mats

Herein aguesPVA/$Fe(NO_3)_3$ solution was electrospun to produce nanofiber mates that are insoluble in the most solventunlike the $Fe(NO_3)_3$. This Freestanding membrane-like structure was used as a novel reusable Iron catalyst in Friedlander reaction.

Uniform and bead-free structure of the nanofiber mats could be achieved when the PVA weight concentration was at 6.0 - 8.0% in water.[27] The PVA weight (8.0 wt %) was chosen for preparation of PVA solution and was mixed with ferric nitrate.[28] Then electrospinning of solution producedPVA/$Fe(NO_3)_3$ nanofiber mats (scheme 1).The SEM images in Fig.1 (a-b) show the morphologies of the PVA/$Fe(NO_3)_3$nanofibers with different magnifications. As this figure shows the nanofibers appear uniform in size, smooth surfaces and no significant bead in the samples. The resultantnanofiber mats offer unique properties like high surface area to volume ratio, porousmembrane structure, good interconnectivity of pores and potential to functionality onnanoscale. The obtained histograms (Fig. 1c) confirm the narrow diameter distribution for 50 observed nanofibers. The diameter of PVA/$Fe(NO_3)_3$ nanofibers is between 80-200 nm. Figure 2 provides the FT-IR spectra of PVA, $Fe(NO_3)_3.9H_2O$ and PVA/$Fe(NO_3)_3$nanofibers. The FT-IR spectra of PVA/$Fe(NO_3)_3$ nanofiber mates are similar to those of the PVA with only slight increasing the transmittance.Also thethe peaks corresponds to $Fe(NO_3)_3$ stretch were eliminatedindicating that the $Fe(NO_3)_3$ were well retained in the PVA matrix. The X-ray diffraction analysis (Fig. 3) has indicated that the nanofibershave approximately amorphous structure andthe crystallites of PVA powder diminished during the solution preparation followed byelectrospining. As well asthere is no characteristic diffraction peak for the ferric nitrate, suggesting that the metal salt dispersed on the PVA nanofiber mats has amorphous structure and chelated to PVA successfully.[29] Previously, groups of researchers have studied the binding energy of O1s and Fe2pduring the formation of the PVA—Fe(Ⅲ) complex in nanofibers. These results indicated the bonding of hydroxyl in PVA with metal ion through the Fe-O-C bond.[30]



Scheme 1 Preparation of PVA/$Fe(NO_3)_3$nanofiber mats

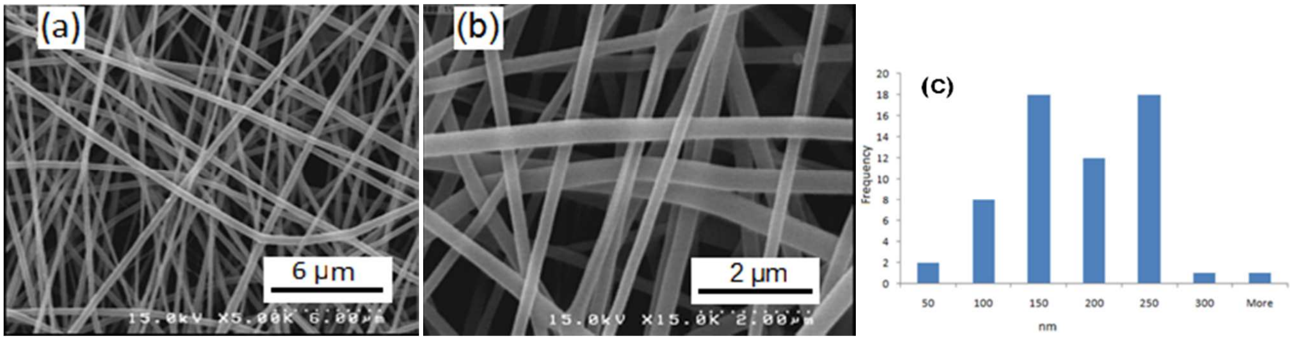


Fig. 1 a,b) SEM image of electrospunPVA/$Fe(NO_3)_3$fiber with different magnification, c) Fiber diameter distribution of electrospun PVA/$Fe(NO_3)_3$fibers

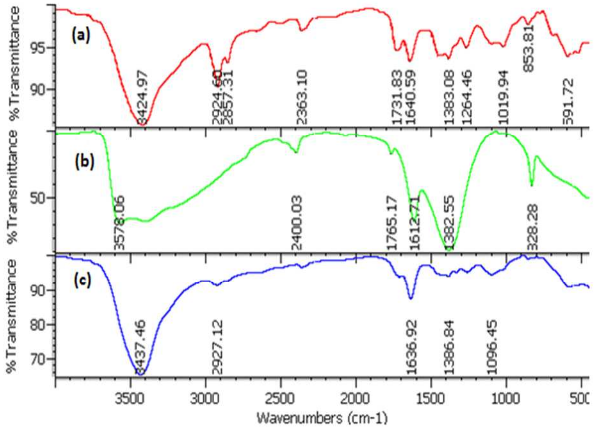


Fig. 2 FT-IR spectra of a) PVA b) $Fe(NO_3)_3.9H_2O$ c) PVA/$Fe(NO_3)_3$ nanofibers

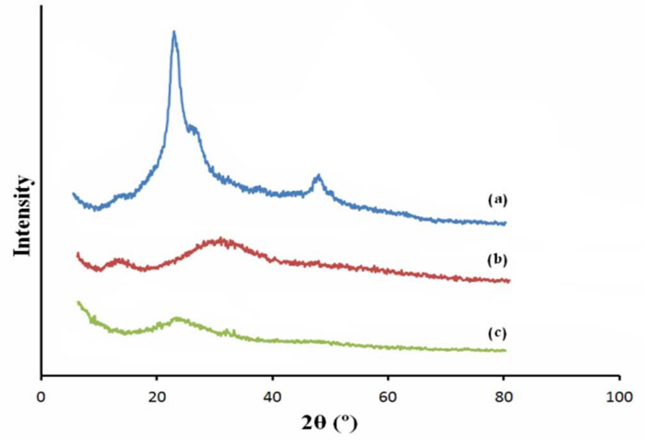
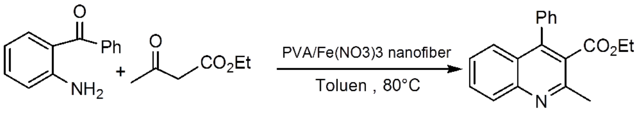


Fig.3 XRD pattern of a) PVA b) $Fe(NO_3)_3.9H_2O$ c) PVA/$Fe(NO_3)_3$ nanofibers

Synthesis of quinolines catalyzed by PVA/$Fe(NO_3)_3$ nanofiber mats

After catalyst preparation, we investigated the reaction of 2-aminobenzophenone with ethyl acetoacetate in the presence of PVA/$Fe(NO_3)_3$ nanofibers as a model reaction to check catalyst activity in Friedländer reaction (Scheme 2).



Scheme 2 Synthesis of ethyl 2-methyl-4-phenylquinoline-3-carboxylate

The reaction normally was done in toluene as solvent that is the normal solvent for Friedlander reaction.[31] As well-known, $Fe(NO_3)_3$ in homogenous form was effective for synthesis of quinoline (Table 1, entry1). This reaction proceeded in lower time and good yieldbecause of the accessibility of catalytic Fe^{3+}center in solution, but the salt was soluble and homogenous in the solvent resulting to contamination of product by salt and difficult work up without catalyst reuse. In the presence ofheterogeneousPVA/$Fe(NO_3)_3$nanofibers, the reaction proceeded clean and simple and the condensation product precipitated in excellent isolated yield (Table 1, entry 2). Our result showed that this catalyst was insoluble in toluene after 1 weeks reflux. To optimize the reaction conditions and improve the yield, our attention was drawn to the role of temperature. It was noticed that increasing the temperature to 80 °C considerablyenhancesthe yield amount. By elevating the temperature up to 80 °C, the yield remained unchanged (Table 1, entries 3 and 4). In the next steps, different amounts of catalyst were used for this transformation (Table 1, entry 5 and 6). Increasing the amount of catalyst increased the yield of quinolines. In the absence of the catalyst the reaction takesmore than 24 h to complete (Table 1, entry 7). The PVA nanofibers catalysts react with very low yield during long time (Table 1, entry 8). Using catalyst containing 3 mol % of Fe^{3+} is most effective in term of both time and yield. Therefore, the optimum conditions for this reaction are asfollows: PVA/$Fe(NO_3)_3$nanofiber containing 3 mol% of Fe^{3+} at 80°C.

Table 1 Optimization of the reaction conditions using the model system[a]

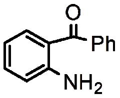
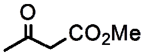
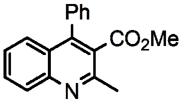
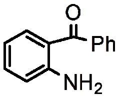
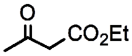
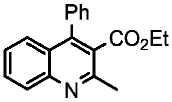
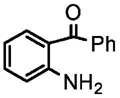
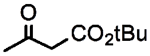
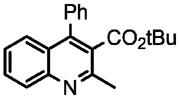
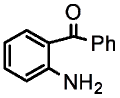
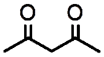
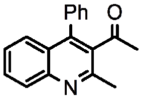
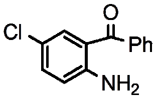
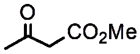
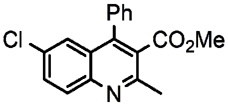
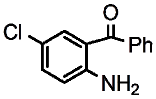
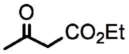
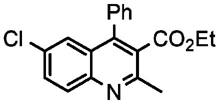
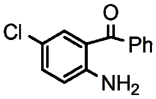
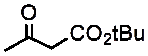
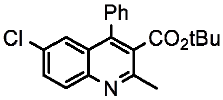
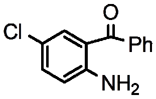
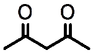
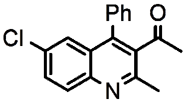
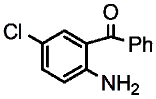
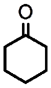
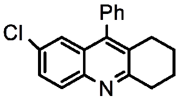
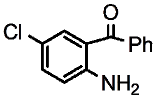
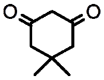
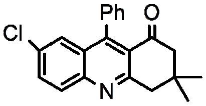
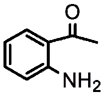
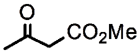
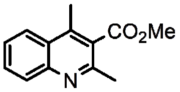
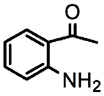
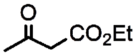
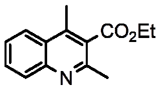
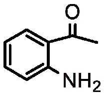
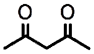
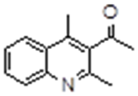
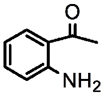
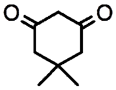
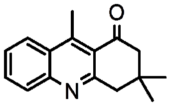
Entry	Catalyst(mol%)[b]	Temp. .(°C)	Time (h)	Yield (%)[c]
1	$Fe(NO_3)_3.9H_2O$ (1)	60	2	84
2	PVA/$Fe(NO_3)_3$nanofiber (1)	60	10	70
3	PVA/$Fe(NO_3)_3$nanofiber (1)	80	10	78
4	PVA/$Fe(NO_3)_3$nanofiber (1)	100	5	80
5	PVA/$Fe(NO_3)_3$nanofiber (2)	80	4	85
6	PVA/$Fe(NO_3)_3$nanofiber (3)	80	4	96
7	No catalyst	80	24	0
8[d]	PVA nanofiber (0)	80	12	trace

[a] Reaction conditions: 2-aminobenzophenone (2mmole), ethyl acetoacetate(2mmol), toluene (5mlit).
[b] mol % Fe $^{3+}$ in catalyst.
[c] Isolated yields.
[d] Reaction completed after 18 h.

We extended this condition to a variety of 2-aminoarylketones with carbonyl compounds. As shown in Table 2, this method is equally effective for substituted 2-aminoarylketones such as 2-aminobenzophenone or 2-amino5-cholorobenzophenone and 2-aminoacetophenone. Various 1,3-diketone and β-ketoesters reacted with 2-aminoarylketones to give the correspondingquinolines. Under the same conditions cyclohexane as a simple cyclic ketone gave the tricyclic quinoline, however, the reaction needed excess amount of ketone and proceeded slower than other reactants (Table 2, entry I).

The reusability of the nanofibers was also examined. After completing the first run of model reaction, the catalyst was washed with CH_2Cl_2 three times then was dried in a vacuum and reused in the subsequent reaction. Large structure of nanofiber mats catalyst leads to easy separation process using forceps. No significant loss of catalyst activity was observed even after 5 times of reuse (Fig. 4).Negligible decrease of the catalyst activity, rule out the deactivation of catalyst in fridlander reaction.

Table 2: Preparation of quinoline derivatives in the presence of PVA/Fe$(NO_3)_3$ nanofiber[a]

Entry	Compound 1	Compound 2	Product 3	Melting point (°C)	Time (h)	Yield (%)[b]	TON[c]	TOF(h^{-1})[d]
a				107	4	95	32	8
b				100	4	96	32	8
c				108	4	90	30	7.5
d				108	6	80	27	4
e				131	4	96	32	8
f				100	4	98	33	8
g				135	4	90	30	8
h				156	6	75	25	4
I[e]				163	8	70	23	3
j				215	4	78	26	6.5
k				100	5	85	28	6
l				oil	5	85	28	6
m				oil	5	78	26	5
n				105	6	70	23	4

[a] Reaction conditions: compound 1 (2mmole), compound 2 (2 mmole.), PVA/Fe$(NO_3)_3$nanofibers(3 mol% Fe^{3+}), toluene (5mlit), 80°C.

[b] Isolated yields. [c] Turnover number (total number of product moles per mole of the catalyst).[d] Turnover frequency (turnover number per hour).

[e]2 eq of compound 2 was used.

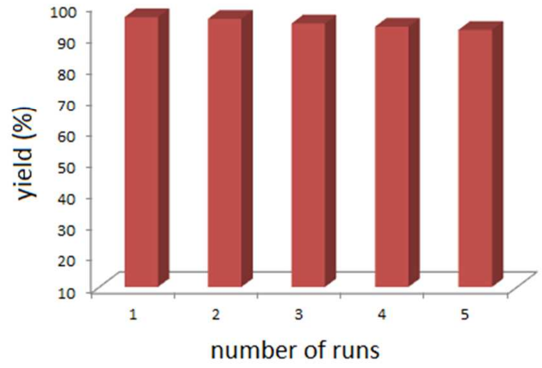


Fig. 4 Reusability of PVA/Fe$(NO_3)_3$nanofibers in reaction between 2-amino benzophenone with ethyl acetoacetate

Leaching of Fe$(NO_3)_3$ from nanofiberto solvent was analysed by ICP. We analysed concentration of Fe^{3+} in PVA/Fe$(NO_3)_3$nanofibers catalyst before and after the reaction. The Fe^{3+} contents have been determined to be 0.055 and 0.052 mg for each mg of fresh and used catalyst respectively. After completion of the reaction (monitored by TLC), catalyst and product were separated from the solvent. Having evaporated the solvent, water added as the new solvent. The resultant aqua solution wasanalysed by ICP. The content of Fe in solutionwas 0.0002 mg for each mg of catalyst, indicating that the Fe leaching is less than 1%. These results show that the Fe leaching from PVA/Fe$(NO_3)_3$nanofiber mats is not significant during the reaction. The SEM analysis of nanofibers after reaction(Fig. 5) showed that this catalyst is stable in reaction condition and was insoluble in toluene. Also the SEM of nanofibers after using for 5 run showed no distinct change in morphology.

Experimental

Instrumental and characterization

All chemicals were purchased from Merck chemicals Co. (Germany). Reagents were used without further purification and deionized water was used as solvent.

The electrospinning process was carried out using Electroris (FNM Ltd., Iran, www.fnm.ir) as an electrospinner device having a high voltage and a syringe pump controllable in range of 1–35 kV and 0.1– 100 mL/h, respectively. This device can control the electrospinning parameters such as injection rate, drum rotating speed, working distance, needle scanning rate and temperature of the electrospinning media. Electroris has also the industrial size for preparation of nanofibers in large amounts.SEM images were observed using SEM (Philips XL 30 and S-4160) with gold coating equipped. Powder XRD spectrum was recorded at room temperature by a Philips X'pert 1710 diffractometer using Co Kα (α = 1.54056 Å) in Bragg-Brentano geometry (θ-2θ). FT-IR spectra were obtained over the region 400-4000 cm-1 with NICOLET IR100 FT-IR and spectroscopic grade KBr.NMR spectra were recorded in $CDCl_3$ (Bruker, 250 MHz, Switzerland) and the proton chemical shifts are reportedin ppm relative to TMS as the internal reference.

Catalyst preparation

0.800 g of PVA powder was added to 10.0 ml of deionized water (8.0 wt %).Then 0.400 g ferric nitrate (Fe$(NO_3)_3$.9H_2O) was added to the above PVA aqueous solution with stirring for 6 h.

The electrospinning process was carried out using Electroris as an electrospinner. The obtained solution was loaded into a plasticsyringe with 0.8 mm inner diameter of pinhead. In ourexperiment, a voltage of 20 kV was applied for electrospinning.

The rate of flow was 1.0 ml/h and aluminum foil served as the counter electrode. The distance between the capillary and the substrate electrode was 12 cm while all parameters were controlled by the device. The electrospun PVA/Fe$(NO_3)_3$nanofibers were placed in a vacuum oven for 12 h at room temperature in order to remove the solvent residuals, then peeled off from foil and used as catalyst.

General procedure for synthesis of quinolines

PVA/Fe$(NO_3)_3$nanofiber mates (61 mgr, 3 mol% Fe^{3+}) was added to a mixture of 2-aminoaryl ketones (2 mmol) and β-ketoester / 1,3-diketone / cyclic ketone (2 mmol) in toluene (5 mL) at 80 °C. The mixture was stirred until completion of the reaction, as indicated by TLC. The nanofiber mats were separated from the reaction mixture by forceps. The precipitated product was separated by filtration and vacuum dried. Then product was recrystallized in CH_2Cl_2.All the products were known compoundsand were characterized by IR, Mass, ^1H NMR spectroscopic data and respective melting points and were compared with those reported in the literature.[21,32]Some selected spectral data are given in supplementary data.

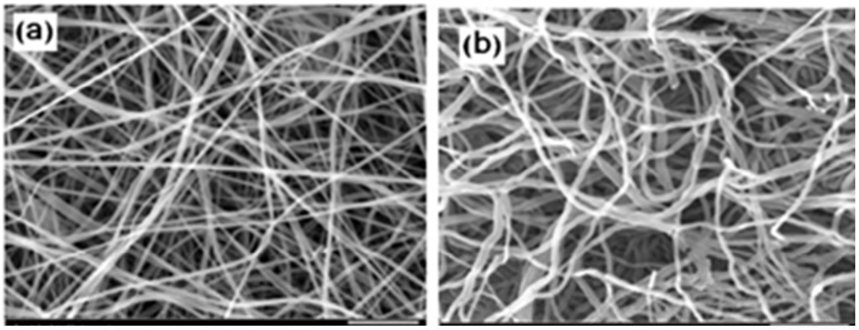


Fig. 5 SEM of electrospun PVA/Fe$(NO_3)_3$fibers (a) after reaction (b) after 5 times reusing

Conclusions

In summary the PVA/Fe$(NO_3)_3$nanofiber mates were prepared by electrospinning of solution of poly(vinylalcohol) (PVA) and Fe$(NO_3)_3$. The prepared nanofiber mates have been demonstrated as a novel, effective, heterogeneous and biodegredable catalyst for the synthesis of quinoline derivatives in the Friedländer condensation of 2-aminoarylketones with carbonyl compounds and β-keto esters. Recovery of the catalyst was simple, allowing its reuse without significant loss of its catalytic activity. The simple and fast catalyst preparation, mild reaction conditions, excellent yields, operational simplicity, product purity and therefore cost efficiency are the advantages of this protocol. In addition to this, environmentally benign membrane-like catalyst can be produced in large scales by industrial electrospinner.

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