

RESEARCH PAPER

Synthesize of Folic acid Functionalized Dendritic Fibrous Nano-silica and its Application as an Efficient Nanocatalyst for Access to direct Amidation of Carboxylic Acids with Amines

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ABSTRACT

A new nanomaterial based on folic acid functionalized dendritic fibrous nano-silica (FA-KCC-1-NH₂) was synthesized and used as a recyclable solid acid and heterogeneous nanocatalyst towards efficient amidation of a variety of carboxylic acids with amines in toluene under reflux conditions. KCC-1 porous nanomaterials were produced utilizing a hydrothermal technique and next functionalized with folic acid moieties to yield KCC-1-NH-FA nanocatalyst. The morphology, surface charge and size of KCC-1, KCC-1-NH₂ and KCC-1-NH-FA nanoparticles were verified by field emission scanning electron microscope (FESEM), dynamic light scattering (DLS), zeta potential and transmission electron microscopy (TEM), respectively. The pore size of KCC-1-NH-FA nanoparticles were moreover investigated with Brunauer-Emmett Teller (BET) where results revealed that the surface of this nanocomposite was expanded. The synthesized KCC-1-NH-FA nanoparticles showed effective catalytic activity in amidation of carboxylic acids with amines affording in high yields (76-89%) in short period of times. Moreover, other advantages of present method are easy workupcondition and recyclability of catalyst which gives economic rewards.

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INTRODUCTION

The compounds containing amide moiety are one of the most significant functional structures in organic chemistry and biology [1]. The amide bond is extensively present in the most of pharmaceutically interesting materials, drug candidates and natural products, as well as in majority of industrial compounds, including detergents, polymers and even lubricants [2, 3]. Also, this bond constitutes the backbone of the proteins, peptides and other biologically-related molecule structures [4, 5]. Recent surveys revealed that 25% of registered drugs have at least

one amide bond in their structures and therefore amidation reactions are the most common reactions in the synthesis of pharmaceuticals. Some examples of these drugs are shown in Fig. 1 [6]. Usually the synthesis of amides can be performed by the reaction of amines with carboxylic acids [7-9] or other derivatives including carboxylic salts [10], esters [11,12] and halides [13]. Various methods have been developed for amide bond synthesis such as rearrangement of aldoximes [14], direct coupling of amides with aryl halides [15], transamidation of amides with amines [16], hydration of nitriles [17,18], aminocarbonylation

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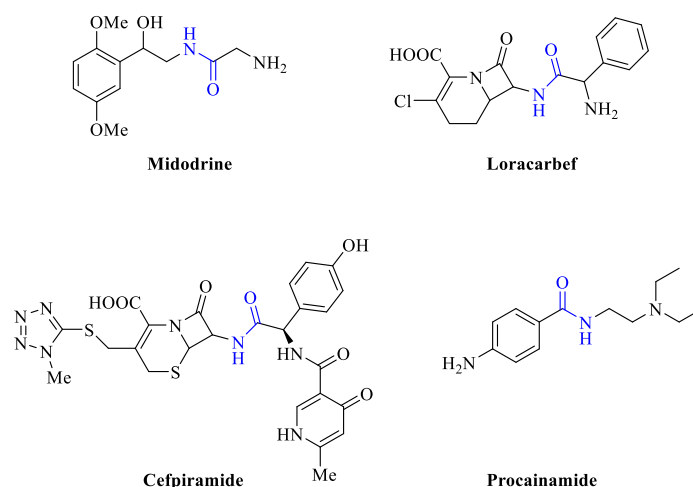


Fig. 1. Some drugs contain amide bond

of aryl halides [19] and Ugi reaction [20]. New efficient synthetic protocols with catalytic procedures have been expanded for oxidative amidation of alkylarenes [21], alcohols [22] and aldehydes [23] with various amine derivatives and amine salts that have important advantages from green chemistry and atom economy viewpoints [24-30]. Recently, using from N-bromosuccinimide as an oxidant for the preparation of amides from aromatic aldehydes with amines has been proposed [23]. Bantreil et al. reported a direct synthesis method of benzamides using copper salt from benzyl alcohols [31]. Also, Wang et al., utilized tetrabutyl-ammonium iodide and FeCl₃ as a co-catalysis for direct amidation by using free amines and methylarenes in water by tert-butyl hydroperoxide as an ecofriendly benign oxidant [21, 32-36]. Considering the various methods used highly hazardous reagents or contained poor atom efficiency, so it was necessary to observed from both environmentally friendly and atom economy points of view. Acidic materials such as solid acids and acidic carbons are cheap and environmentally benign for direct amidation without side problems [37]. Recently, Polshettiwar et al., synthesized fibrous nano-silica (KCC-1), with the high surface area (typically >700 m²/g), large pore sizes [38], low density, ease of surface modification and weak toxicity with well biocompatibility [39]. Also, these dendritic porous nanocomposites have been successfully used as suitable heterogeneous nano-silica catalysts for several organic synthesis [40-44] and therapeutics [45]. Folic acid (FA) is a well-known compound (vitamin B9) which generally

known as a biological molecule. FA is essential in cell division, nucleic acid preparation and cells metabolic [46].

In our previous works, we reported two kinds of KCC-1 based nanocomposites with high surface area, good catalyst activity and different specifications where KCC-1-NH₂-DPA and magnetic Fe₃O₄@KCC-1-npr-NH₂ nanocatalysts used as efficient and recyclable materials for synthesizing of tetrahydrodipyrzolo-pyridine and sulfonamide derivatives, respectively [41,42].

In our research, an appropriate procedure for the synthesis of folic acid-based catalyst (KCC-1-NH₂-FA) has been described. The catalytic activity of KCC-1-NH₂-FA as a recyclable solid acid and efficient nanocatalyst was further examined for the direct amidation of carboxylic acids with amines into the desirable amides in toluene under reflux condition.

MATERIALS AND METHODS

All solvents and chemical materials were purchased from Sigma Aldrich and Nano Eksir Sina (Iran) chemical companies and used without further purification. X-ray diffraction (XRD) configurations were conducted on a Siemens D 5000x-Ray diffractometer (Texas, USA) with a Cu K α anode ($\lambda=1.54 \text{ \AA}$) operating at 40 kV and 30 mA. The surface morphology and energy dispersive X-ray (EDX) and FESEM analysis were conducted on TESCAN system of FEG-SEM MIRA3 TESCAN (Brno, Czech Republic). Transmission electron microscopy (TEM) images were recorded by a Carl Zeiss LEO 906 electron microscope operated at 100 kV

(Oberkochen, Germany). Brunauer-Emmett-Teller (BET) was measured by Micromeritics NOVA 2000 apparatus at 77 K using nitrogen as the adsorption gas (Florida, USA). Particle size distribution values and zeta potential were measured by Malvern particle size analyzer (Malvern, UK).

Synthesis of KCC-1

Mesoporous KCC-1 was prepared following to the described process by Bayal et al. (2016) [47]. Briefly, 5 mL of NaOH (2 M) and 1.0 gr of CTAB and 230 mL of deionized water were mixed and sonicated for 20 min. After that 0.6 g urea was added to the mixture and stirred for 5 h at 30 °C. In continue, 3 gr of TEOS was added drop-wise in the reaction ambient and then 45 mL cyclohexane and 2 mL hexanol were mixed and added to the reaction ambient and sonicated for 1 hr. Next, the resultant solution was refluxed at 90 °C for 20 hr. Afterward, the mixture was cooled and obtained white sediment were filtrated and to collect the KCC-1 particles. Next the white precipitation was washed tree times with deionized water and absolute ethanol and was dried at 70 °C in the oven. Eventually, the prepared KCC-1 was calcinated at 560 °C for 5 h to eliminate the extra CTAB in the oven [48].

Synthesis of KCC-1-NH₂

In order to synthesis of KCC-1 nanoparticles functionalized with amine groups, firstly, 260 mg of KCC-1 nanocomposite was added to the 10 mL of HCl solution and sonicated for 30 min. Then, 6 mL of ethanol and 790 µL of APTES were added to the solution and stirred at room temperature for 6 h. Next, the obtained suspension was centrifuged and washed several times with absolute ethanol. Then, washed KCC-1-NH₂ white solids were dried at room temperature.

Synthesis of KCC-1-NH₂-FA

For the synthesise of FA-NHS by EDC/NHS, firstly, 70 mg of folic acid, was mixed to with 15 mL of DMSO and 160 µL of TEA and stirred vigorously. Then, 13 mg of NHS and 11 mg of EDC were added and stirred vigorously at 37 °C for 20 hr. Next, TEA was eliminated by vaporization and synthesized folic acid-NHS was kept in a refrigerator for next stage of synthesis.

In continue, 190 mg of KCC-1-NH₂ nanoparticles were mixed with 30 mL of PBS (pH 7.0, 55 mM) and next 15 mL of the synthesized FA-NHS solution

was mixed with the solution. Next, the mixture of KCC-1-NH₂ and prepared folic acid-NHS was stirred at room temperature for 6 hr. After that, KCC-1-NH-FA white-yellow precipitate was filtered and washed several times with deionized water and dried at 60 °C.

General process for the direct amidation of carboxylic acids with amines

In order to the synthesis of desired compounds 1 mmol carboxylic acid and 1 mmol amine was mixed in toluene and then 20 mg of synthetic KCC-1-NH-FA was added to the solution as a catalyst. The resulting solution was refluxed for a specified period of time (Table 1).

After 3 h which the reaction of amine and acid was completed (monitored by TLC), the solution was mixed with about 30 ml of ethyl acetate and KCC-1-NH-FA nanoparticles were separated by filtration. Then, the solvent was evaporated under vacuum and resultant precipitate was purified by preparative layer chromatography on silica gel using EtOAc/n-hexane (1: 4 V/V) to give **4a-p**. Finally, separated catalyst was washed several times with absolute acetone and deionized water and reused for next reaction without the significant losses of its performance (Fig. 2).

RESULTS AND DISCUSSION

Characterization of the KCC-1-NH₂-FA nanocatalyst

The process of functionalization of the KCC-1 with NH₂ and FA moieties was monitored by FT-IR spectrums. As could be seen in Fig. 3, the typical transmittance peaks of silica-based composites could be attributed in the range of 1020-1110 cm⁻¹ signifying the asymmetric stretching of Si-O-Si mode. Also, Si-OH spectrum which located at 960 cm⁻¹ denotes the asymmetric bending and stretching vibration. However, peak at around 1500 cm⁻¹ is related with amide II bonds between carboxyl's of FA molecules and amine's of KCC-1-NH₂ [41,58].

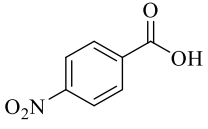
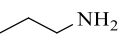
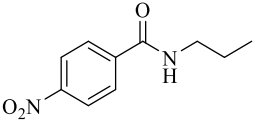
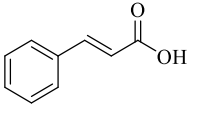

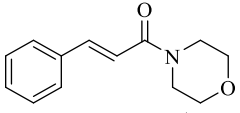
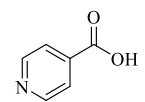
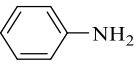
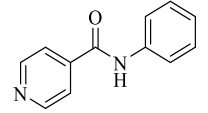
In order investigating the surface morphology and size of nanoparticles, FE-SEM and TEM images of the KCC-1, KCC-1-NH₂ and KCC-1-NH-FA were recorded (Fig. 4 (a, b and c)). The TEM and FESEM pictures showed the fibrous shape, morphological and structural features of the nanoparticles which approximate average sizes of KCC-1, KCC-1-NH₂ and KCC-1-NH-FA are determined to be about 175, 190, and 200 nm, respectively.

The EDX (Energy-Dispersive X-ray) analysis was

Table 1. Direct amidation of different acids with amines using KCC-1-NH-FA catalyst.

Entry	Products	Acid	Amine	Amide	Time	Yield ^a (%)
1	3a				3h	89 [14]
2	3b				3h	80 [14]
3	3c				3h	78 [49]
4	3d				3h	85 [50]
5	3e				3h	75 [15]
6	3f				3h	75 [11]
7	3g				3h	74 [11]
8	3h				3h	80 [51]
9	3i				3h	78 [52]
10	3j				3h	83 [53]
11	3k				3h	74 [54]
12	3l				3h	76 [55]

Continued Table 1. Direct amidation of different acids with amines using KCC-1-NH-FA catalyst.

Entry	Products	Acid	Amine	Amide	Time	Yield ^a (%)
13	3m				3h	84 [56]
14	3n				5h	61 [57]
15	3o				5h	68 [57]

^a Isolated product.

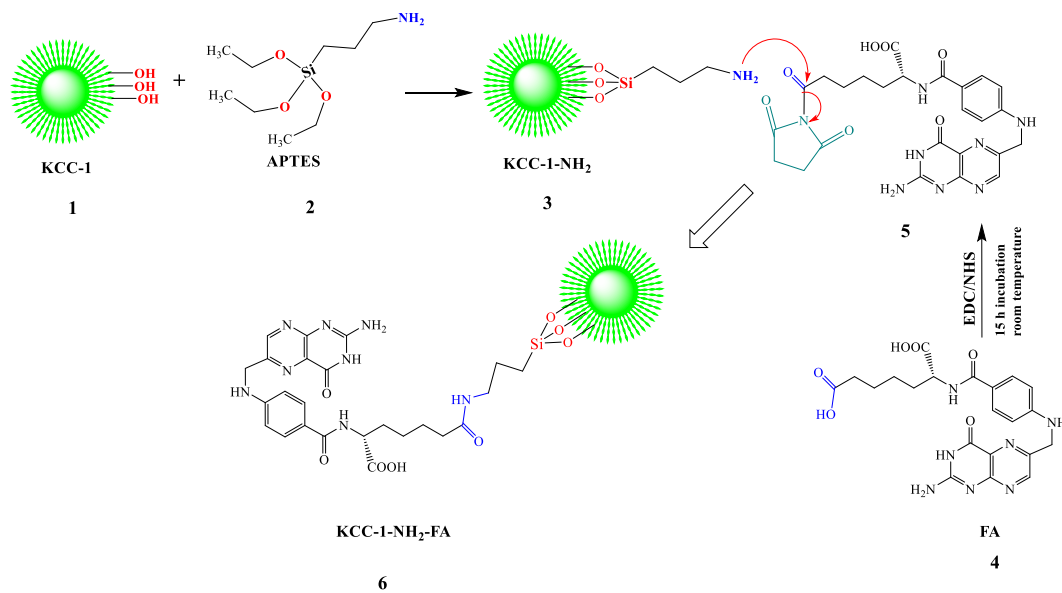


Fig. 2. Schematic procedure for the synthesis of KCC-1-NH-FA.

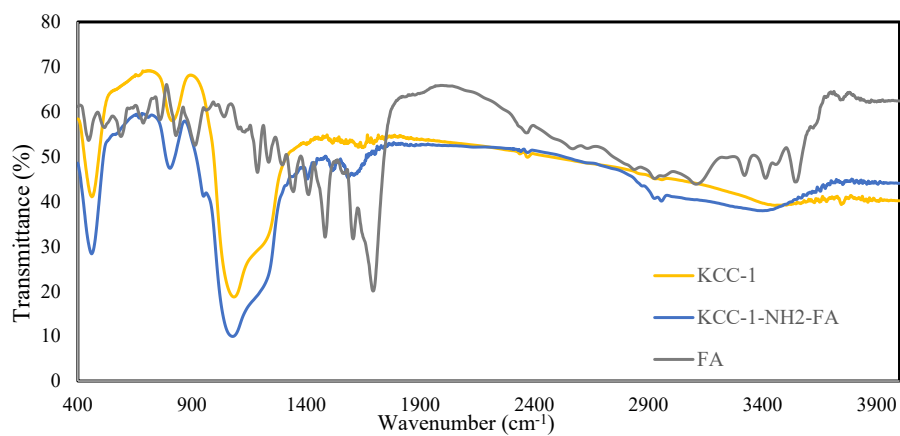


Fig. 3. FTIR spectra of the KCC-1, KCC-1-NH-FA and FA.

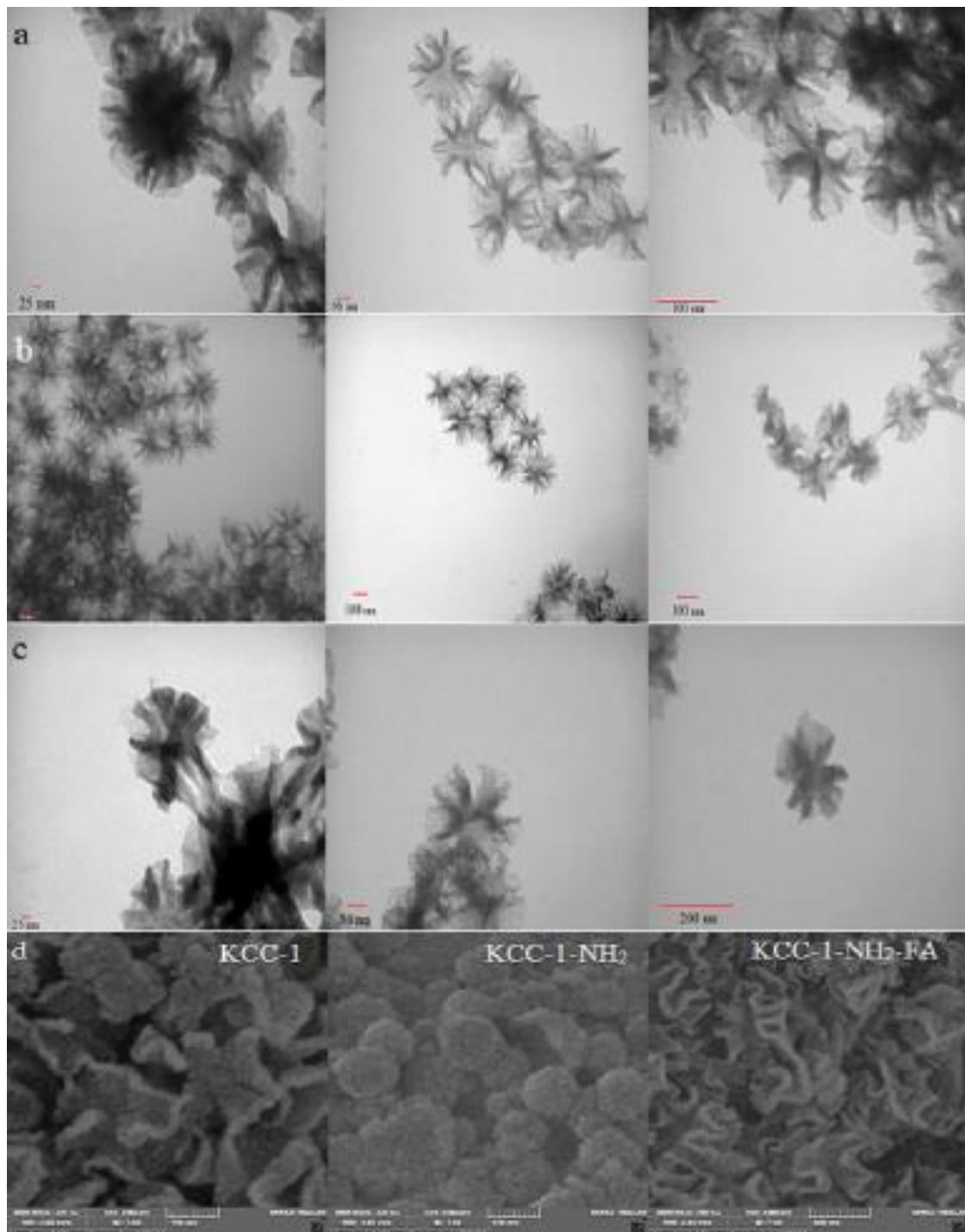


Fig. 4. TEM (a, b and c) and FESEM (d) images of KCC-1, KCC-1-NH₂ and KCC-1-NH₂-FA.

also applied for elementary analysis (Fig. 1S). EDX analysis proved that KCC-1-NH-FA contain the C, O, N and Si elements that exhibit the mass percent

of N, O and C are increased which confirm the efficient surface modification of KCC-1 with APTES and FA.

Table 2. The obtained results from BJH, BET analysis

Material type	Pore size (nm) ^a	Pore volume (cm ³ g ⁻¹) ^b	Surface Area (m ² g ⁻¹)
KCC-1	9.9	1.5	617
KCC-1-NH ₂	11.9	1.1	367
KCC-1-NH-FA	13.2	1.3	397

^a Pore size was measured by BET method. ^b Pore volume investigated from nitrogen physisorption isotherm

The X-ray diffraction (XRD) was employed to investigate the crystallinity of KCC-1, KCC-1-NH₂ and KCC-1-NH-FA (Fig. 2S). Two main spectra which could be seen in Fig. 2S prove the increasing the crystallinity from KCC-1 to KCC-1-NH₂-FA. The wide peak at $2\theta = 20^\circ$ and 30° is related to the formless silica. Moreover, comparison of the three spectra of the KCC-1, KCC-1-NH₂ and KCC-1-NH-FA shows that peaks were transmitted to the upper 2θ values where is a logical cause for the superficial functionalization of KCC-1 and preparation catalyst [44,58].

The BJH, BET analysis and the N₂ adsorption/desorption isotherms of the KCC-1, KCC-1-NH₂ and KCC-1-NH-FA were applied to evaluate the porous essence, porous volume and specific surface area of the nanocomposites (Fig. 3S). The average pore size, surface area and pore volume of KCC-1, KCC-1-NH₂ and KCC-1-NH-FA are seen in Table. 2. As could be seen, the porous volumes of KCC-1, KCC-1-NH₂ and KCC-1-NH-FA are 1.52 to 1.1 and 1.3 cm³/g and the revealed results proved that surface area of KCC-1, KCC-1-NH₂ and KCC-1-NH-FA are 617 m²/g to 367 and 397 m²/g, respectively. Also, average porous diameter broadcast of the KCC-1, KCC-1-NH₂ and KCC-1-NH-FA composites are 9.9, 11.9 and 13.2 respectively (Table. 2).

The zeta potential analysis of KCC-1, KCC-1-NH₂ and KCC-1-NH-FA were determined at pH 7.5 to investigate the surface charge to found the possible surface modification. Also, the KCC-1 simple dendritic nanocomposites show negative charge at pH 7.5 where could be caused from Si-OH functional structures. Moreover, the zeta potential analysis of the KCC-1-NH₂ and KCC-1-NH-FA confirmed the positive charges of these nanocomposites which approve the anchoring amine and FA moieties on the surface of the porous nanocomposite. Also, this positive charge was shown the acidic activity of FA group in the direct amidation reaction.

Also, dynamic light scattering (DLS) analysis of the KCC-1, KCC-1-NH₂ and KCC-1-NH-FA confirmed that the hydrodynamic diameter of

nanocomposite increased from KCC-1 to KCC-1-NH-FA which confirm the accurate surface functionalization with NH₂ and FA groups.

Catalytic activity of the KCC-1-NH-FA nanocatalyst in the direct amidation of carboxylic acids with amines

The catalytic performance of the nano-silica KCC-1-NH-FA and the effect of several parameters were investigated in the direct amidation of carboxylic acids with amines. Initially, the direct amidation of acetic acid (1 mmol) with aniline (1 mmol) under solvent free conditions at 25 °C and was performed as a model reaction. Then, the effect of temperature and reflux conditions to increase the yield of synthetic products was studied. To finding the optimize conditions of the reaction, first investigations were applied under various conditions. As could be seen the results are shown in Table 3. The direct amidation of acetic acid (1 mmol) with aniline (1 mmol) without using the nanocatalyst at 25 °C under solvent-free conditions the corresponding amide in 5% after 48 h was investigated (**entry 1, Table 3**). When the amidation reaction was performed with using of 20 mg of KCC-1 under solvent free conditions, the desired amide was obtained in 5% yield after 48 h (**entry 2, Table 3**). Also, when reaction was performed with using of 20 mg of KCC-1-NH₂ in the similar conditions obtained product in 5% yield after 48 h (**entry 3, Table 3**). Moreover, when reaction was performed with using of 20 mg of KCC-1-NH-FA as a catalyst, the obtained product was isolated in 20% yield respectively after 48 h (**entries 4, Table 3**). In continue, we tested the influence of ultrasonic irradiation and heating on this chemical amidation and the results weren't considerable (entries 5 and 6, Table 3). Then the influence of different solvent on the chemical transformation was tested and toluene was the best solvent to improve the yield of synthetic compounds. Therefore, the reaction was proceeding in the presence of 20 mg of KCC-1-NH-FA in toluene under reflux condition (entries

Table 3. Various conditions for the direct amidation of acetic acid with aniline ^a.

Entry	Catalyst	Conditions	Time	Yield (%)
1	-	Solvent free, room temperature		
2	KCC-1	Solvent free, room temperature	48 h	5
3	KCC-1-NH ₂	Solvent free, room temperature		
4		Solvent free, room temperature		20
5		Bath ultrasonic, solvent-free, r.t.	24 h	
6		Bath ultrasonic, solvent-free, 60 °C		29
7		Water, room temperature		20
8		Water, reflux		37
9	KCC-1-NH-FA (20 mg)	Ethanol, room temperature	48 h	23
10		Ethanol, reflux		39
11		Acetonitrile, room temperature		25
12		Acetonitrile, reflux		52
13		Toluene, room temperature	24 h	40
14		Toluene, reflux	3 h	89

^a Reaction conditions: acetic acid (1 mmol) and aniline (1 mmol).

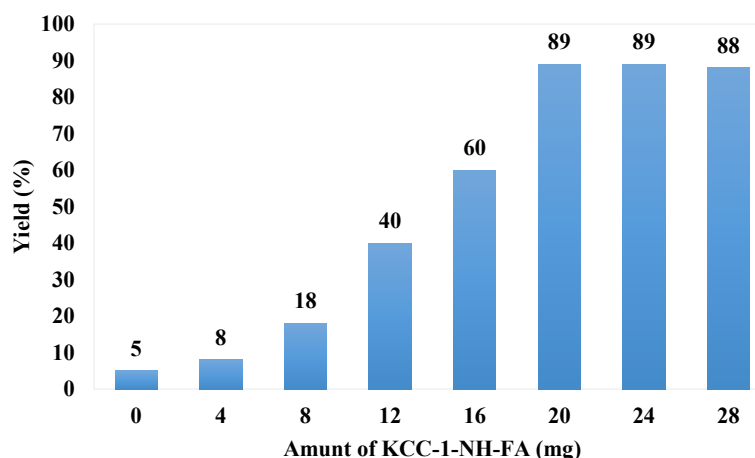


Fig. 5. Optimization of the condition for direct amidation of various acids (1.0 mmol) with amines (1.0 mmol) using KCC-1-NH-FA catalyst, toluene (4 mL), reflux, 3 h.

7-14, Table 3). It is observed that the reaction time decreased and the product was isolated in 89% yield after 3 h (entry 14, Table 3).

Thus, these result clearly confirmed the impressive effect of KCC-1-NH-FA catalyst on the amidation process. Increasing the amount of nanocatalyst to 25, 30 mg didn't have increasing in the yield of the reaction (Fig. 5).

After obtain the optimized reaction conditions, we then tested the possibility of applying this procedure by utilizing of different carboxylic acids with a various amines using of KCC-1-NH-FA (20 mg) in toluene under reflux conditions. (3a-o). As a result, different products of amides (4a-m)

were achieved in high yields without any side products (Table 1). By using of these conditions, the reaction of aliphatic, hetro aromatic, cyclic and linear aliphatic amines with aliphatic carboxylic acid produced the desired amides in 74-89% yields after period of time. (Entries 1-9, Table 1). Also, direct amidation of aromatic carboxylic acid with four class of amines obtained the formation of the desired amide derivatives in 61- 84% yields (entries 10-15, Table 1).

The reusability of the nanocatalyst is an advantage for organic synthesis so this important factor was tested by applying the model reaction and our synthetic nanocomposite was recovered

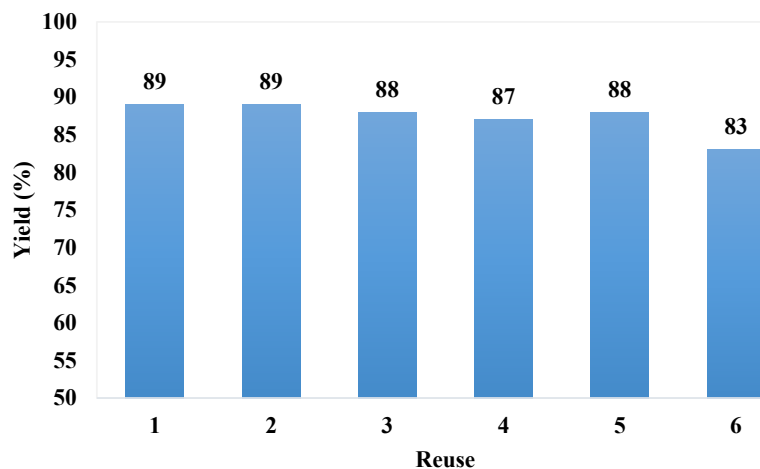


Fig. 6. Reusability of KCC-1-NH-FA.

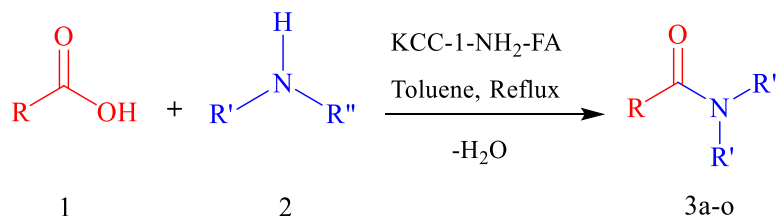
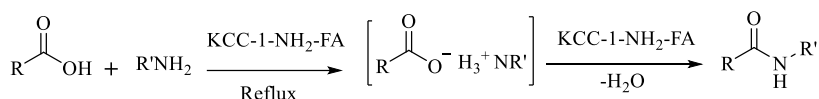


Fig. 7. Direct amidation of carboxylic acids with amine products using KCC-1-NH-FA.

(a)



(b)

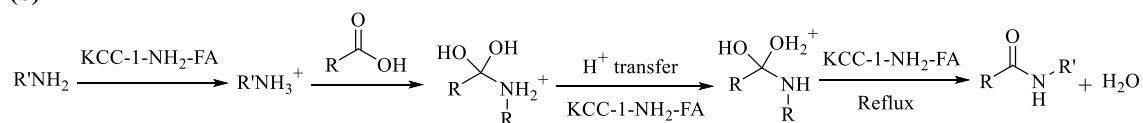


Fig. 8. Probable mechanism for direct amidation of carboxylic acids with amines catalyzed by KCC-1-NH-F

up to six times without significant losses in the catalyst performance (Fig. 6). Thus, at any cycle ethyl acetate was mixed in the solution and was filtered through a sintered funnel to recover the catalyst. Then, the used catalyst was washed several times with absolute acetone and deionized water and dried under vacuum.

Mechanism study

To the best of our knowledge, the mechanism is not very clear. However, the suggested mechanism

of direct amidation of carboxylic acids with amines is postulated in Fig. 7.

Pathway (a): The reaction can initiate with construction of a stable ammonium carboxylate salt with using of high acid capacity of KCC-1-NH-FA nanocatalyst and finally, dehydration resulting the construction of desired amide products (Fig. 8a).

Pathway (b): the synthesized nanocatalyst leads to the alteration of amine into ammonium salt. Then, ammonium salt and carboxylic acid were reacted together and resulted in intermediate

l. in continue a proton transfer as well as water elimination leading to the construction of amide bond (Fig. 8b).

CONCLUSION

We reported an effective nanocatalyst based on KCC-1-NH-FA nanoparticles. The synthesized nanocomposite was efficaciously utilized for direct amidation of carboxylic acids with amines through a reaction under reflux conditions. In addition, this methodology characterized by advantages such as good yields, short reaction times, excellent catalytic activity and reusability of the heterogeneous nanocatalyst without any important losses in the overall yield.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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