KCC-1/Pr-SO₃H: an efficient heterogeneous catalyst for green and one-pot synthesis of 2,3-dihydroquinazolin-4(1H)-one

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ABSTRACT
KCC-1/Pr-SO₃H is found to be a considerable efficient nanocatalyst for the one-pot three-component condensation coupling of aromatic aldehydes, isoatoic anhydride, and primary amines for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones in ethanol as a green solvent under reflux conditions with excellent yields. The influence of different reaction parameters such as the effects of solvent, temperature, time, and concentration of catalyst for the synthesis of 2,3-dihydroquinazolin-4(1H)-one (4f) were studied. KCC-1/Pr-SO₃H is easily recyclable without the significant loss of catalytic activities after seven times. This mild and simple synthesis method offers some worthwhile advantages including short reaction time, high yield, and convenient work-up procedure.

GRAPHICAL ABSTRACT

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1. Introduction
The development of nanoscience and nanotechnology in the field of catalyst is one of the important goals of organic chemistry. In recent years, the catalyst applications of these nanoparticles have been investigated. Some reports showed a wonderful performance of these catalysts in terms of reactivity, selectivity, and improved yields of products [1]. Moreover, the enhanced surface area of nanoparticles provides more accessible sites for further functionalization. Thus, recently interest in nanocatalyst has increased significantly because of their high efficiency in organic synthesis reaction conditions [2]. As an example of the continuous interest in KCC-1-based catalysis, several studies have established the catalytic activity of sulfuric acid functionalized dendritic fibrous nano-silica 1 (KCC-1) in organic reactions [3, 4]. Recently, surface functionalized mesoporous materials have been reported as one of the most important research areas relating to advanced functional materials. Specifically, KCC-1 was reported by Tamehet al. possessing high surface area (typically >700 m²/g), broad pore size distribution, large pore sizes [5], ease of surface modification, low density, stability, and low toxicity containing good biocompatibility [6]. This dendritic mesoporous nano-silica showed various applications in various fields such as heterogeneous catalysis [7–9], energy storage, gas capture, solar energy harvesting [10], targeting of drugs, medical diagnosis...
Recently, multicomponent reactions (MCRs) have been used as the most efficient and powerful way in organic synthesis for the synthesis of various biologically important compounds. Moreover, MCRs offer numerous synthesis compounds in a fast and simple fashion with atom economy [15]. 2,3-Dihydroquinazolin-4(1H)-ones (DHQZs) represent a well-known heterocycle scaffold containing nitrogen atom in medicinal chemistry and have a various pharmaceutical and biological properties such as antiviral [16], antitumor [17], anti-inflammatory [18], antihistamine [19], cytotoxic [17], anticonvulsant [20], and antihypertensive [21]. Figure 1 shows the structure of some members of these compounds as clinically significant DHQZ medications such as fenquizone, evodiamine, metolazone, and aquamox. Therefore, Nemours synthesis approaches have been developed for the synthesis of DHQZs. The most commonly used methods for the preparation of DHQZs include the condensation of aldehydes or ketones with anthranilamide or the three-component condensation of aldehydes, isatoic anhydride, and amines utilizing catalysts such as montmorillonite K-10 [22], Perchlorated Zirconia (HClO4/ZrO2) [23], Amino Acid [24], Nano-MgO [25], KAl(SO4)2.12H2O [26], Fe3O4-GO-SO3H [27], SnCl2.2H2O [28], phosphate fertilizers (MAP, DAP, and TSP) [29]. Also, some researchers used sulfonic acid-functionalized mesoporous silica catalyst for the synthesis of DHQZs. For example, SBA-Pr-SO3H [30] and MCM-41-SO3H [31] are two catalysts of these mesoporous silica materials that are used for the synthesis of DHQZs. However, many of these procedures have remarkable disadvantages such as harsh reaction conditions, long reaction times, use of toxic catalysts or media and low yields as well as tedious work-up procedure. Therefore, the development of an efficient method for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones is a desire.

Herein, we report a significant catalytic activity of KCC-1/Pr-SO3H in one-pot protocol for the synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives using a three-component condensation coupling of isatoic anhydride with aromatic aldehydes and primary amines in ethanol (Scheme 1). There are two main differences between this work and our previous study where we used KCC-1-nPr-NH2-DPA for the synthesis of tetrahydrodipyrazolopyridine derivatives [8]. In our previous work, we introduced KCC-1-NH2 functionalized with DPA while here we synthesized a novel sulfuric acid-based KCC-1 nanocatalyst (KCC-1/Pr-SO3H) which has strong acidic properties compared to KCC-1-NH2-DPA. We needed a strong acidic catalyst in order to synthesize a sulfuric acid-based catalyst to be used for the first time for the synthesis of 2,3 dihydroquinazolin-4(1H)-one derivatives. The advantages of our newly formed nanocomposite catalyst are short reaction time and low catalyst loading so we could separate easily this catalyst at the end of the reaction and reuse it several times while at the same time showing high yield.

2. Experimental

2.1. Materials and methods

All of materials and solvents were purchased from Merck (Kenilworth, NJ) and Sigma-Aldrich (St. Louis, MO) in high purity and used without further purification. Melting points were measured in open capillaries using an electrothermal MEL-TEMP apparatus (model 9200). FTIR spectra were obtained with a Bruker Tensor 27 spectrometer ((Bruker, Billerica, MA); v in cm\(^{-1}\) in the transmission mode in spectroscopic grade KBr tablets for all the powders. The \(^1\)H and \(^13\)C NMR spectra were observed with a Bruker Spectrospin Avance 400 spectrometer operating at 400 and 100 MHz, respectively. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid. X-ray diffraction (XRD) patterns of KCC-1 based materials were

![Figure 1. Some important drugs with 2,3-dihydroquinazolin-4(1H)-one skeleton.](image)

![Scheme 1. Schematic for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones.](image)
recorded by Siemens D 5000 X-ray diffractometer (Siemens, Houston, TX) with a Cu Ka anode ($\lambda = 1.54$ Å) operating at 40 kV and 100 mA. The scanning electron microscopy (SEM) images and energy-dispersive X-ray (EDX) were recorded with FEG-SEM MIRA3 TESCAN, Brno, Czech Republic) at 1000 kV. Transmission electron microscopy (TEM) analysis was conducted on a Carl Zeiss LEO 906 electron microscope operated at 100 kV (Oberkochen, Germany). Brunauer-Emmett-Teller (BET) was recorded by Micromeritics NOVA 2000 (Quanta Chrome Corporation, Boynton Beach, FL) apparatus at 77 K using nitrogen as the adsorption gas. The particle size distribution and zeta potential values were determined using Malvern particle size analyzer (Malvern, UK). The purity determination of the products and reaction monitoring was accomplished by TLC on silica gel polygram SILG/UV 254 plates.

2.2. Preparation of KCC-1

Briefly, 1 g of cetyl trimethylammonium bromide (CTAB) was added to 10 mL deionized water and after addition of 0.6 g urea, the mixture was stirred for about 3 h at room temperature. Then, 2 g of tetraethyl orthosilicate (TEOS), 30 mL cyclohexane, and 1.5 mL hexanol was added to the flask and sonicated for 30 min. So, the mixture was refluxed at 80 °C for 24 h. Afterward, the mixture was cooled to the room temperature and centrifuged to collect the KCC-1 as white sediment. The collected KCC-1 was washed several times with deionized water and ethanol and dried at 60 °C for 24 h. Finally, KCC-1 was calcinated at 550 °C for 6 h to remove the CTAB as templating agent.

2.3. General procedure for the synthesis of nanocatalyst (KCC-1/Pr-SO$_3$H)

In order to functionalize silica KCC-1 with sulfonic acid groups through post grafting method, 1 g of synthesized KCC-1 was added to the mixture of 20 mL anhydrous toluene and 1.5 mL mercaptopropytrimethoxysilane (MPTS) and the resulting solution was refluxed for 24 h. Then, the mixture was cooled to room temperature. After filtration, the white solid KCC-1/Pr-SH was washed with methanol repeatedly using a Soxhlet extractor and dried at 85 °C overnight. In order to change thiol groups into —SO$_3$H ones, obtained KCC-1/Pr-SH was added to 20 mL of 30% H$_2$O$_2$ by permanent stirring at ambient temperature for 24 h. The consequential sulfonated solid was washed with methanol several times, and dried at room temperature [3]. The synthesis process for heterogenous KCC-1/Pr-SO$_3$H is depicted in (Scheme 2).

2.4. General procedures for the synthesis of 2,3-dihydroquinazolin-4(1H)-one (4a-n)

A mixture of isotonic anhydride (1 mmol), aromatic aldehyde (1 mmol), and primary amine (1 mmol) and KCC-1/Pr-SO$_3$H (5 mg) in EtOH (3 mL) was magnetically stirred for 2-3 h under reflux condition. Then, the mixture monitored by TLC and after completion of the reaction (EtOAc: n-hexane, 1:2), the nanocatalyst was separated by filtration and washed with extra hot ethanol. Thus, the obtained precipitate was dissolved again in ethanol to afford the pure product by recrystallization from ethanol (75–95% yields). The products 4a-n, were known compounds which their authenticity was recognized by their melting points compared with reported data in literatures. Pure product 4n was obtained by recrystallization from ethanol which was unknown and recognized by its elemental analysis, IR, $^1$H NMR, $^{13}$C NMR, and melting point.

3. Results and discussion

To investigation the morphology of KCC-1/Pr-SO$_3$H, FESEM images were recorded (Figure 2(a)). Moreover, the structure and size of the KCC-1/Pr-SO$_3$H were evaluated utilizing TEM. As shown in Figure 2(b), the uniform fibers of the silica KCC-1 with high surface area have several Si—OH groups that could grow from the inner to outer. The TEM images revealed the porous, fibrous, and dendritic form of the nanomaterials which fibrous system is a result of using the MPTS for the NPs design while the fibrous-sphere reveals the formation of KCC-1. The size of the KCC-1/Pr-SO$_3$H is about 25 nm. As can be seen in Figure 2(a,b), the KCC-1/Pr-SO$_3$H has a constant particle size of 20 nm. EDX results indicate the atomic structure of the produced compound and that the KCC-1 is composed of only with Si and O. Though, the carbon is arising from the SEM grid and MPTS as a pattern agent. Moreover, functionalization of KCC-1 with MPTS,
the weight percent of S, O, and C are increased which confirmed successful functionalization of KCC-1 by n-propyl SO$_3$H. Moreover, the TEM images indicate that this dendritic morphology is not changed after functionalization (Figure 1S).

FTIR was employed to confirm the proper functionalization of the KCC-1 fibrous with propyl sulfonic acid groups and results are shown in Figure 2S. The typical peaks of the silica-based nanomaterials could be seen in the range of 1049–1075 cm$^{-1}$ representing the Si—O—Si asymmetric stretching mode. Also, Si—OH peak could be observed at 799 cm$^{-1}$ which shows the asymmetric bending and stretching vibration. In addition, the broad peak at 3645 cm$^{-1}$ representing free hydroxyl moieties and the low-intensity peak at 1650 cm$^{-1}$ which represents the water molecules adsorbed on the silica surfaces. Moreover, the adsorption peak which appeared at 820 cm$^{-1}$ is attributed to symmetrical stretching mode of Si—O—Si, and the stretching vibration of the C—H at 2874 cm$^{-1}$ confirms the grafting of mercaptopropyl moieties to the surface of KCC-1 material.

The XRD patterns of KCC-1/Pr-SO$_3$H are shown in Figure 3S. The XRD pattern of KCC-1/Pr-SO$_3$H NPs was recorded from 5.0° (2θ) to 100.0° (2θ) to investigate the crystallinity of the produced nanomaterial in order to obtain additional information about their molecular structures. The wide peak between 20° and 30° is related to the amorphous silica and proved the effective grafting of the silica with propyl sulfonic acid groups. It is important to point out that the XRD templates of the KCC-1/Pr-SO$_3$H are similar to the fibrous mesoporous silica (KCC-1).

The N$_2$ adsorption–desorption isotherms of KCC-1/Pr-SO$_3$H are shown in Figure 4S(b). The BET and BJH analyses of the KCC-1/Pr-SO$_3$H NPs were used to determine the porous structure of the synthesized nanocatalyst (Figure 4S(b)). The specific surface area and porosity of the nanomaterials were determined using the adsorption isotherm and calculated by BET. Also, BJH technique was used to evaluate the pore volume of the KCC-1 and KCC-1/Pr-SO$_3$H (Figure 4S(a and b)). The surface area of KCC-1 and KCC-1/Pr-SO$_3$H was measured at about
617 and 293 m²g⁻¹, and also the average pore size is 5.8 nm. The pore volumes, pore size, and surface area of KCC-1 and KCC-1/Pr-SO₃H are clearly proved by the reported results which were summarized in (Table 1S). It is clear that the specific surface area was reduced from 675 to 293 m²g⁻¹ and the variation pore volume of modified silica KCC-1 nanocatalyst is due to the combination of propyl sulfonic acid groups.

Zeta potentials of KCC-1/Pr-SO₃H were checked at pH 7.5 to control the surface charge to determine the possible surface modification. The zeta potential of the KCC-1/Pr-SO₃H shows negative charges which verify the propyl sulfonic acid groups on the surface of the fibrous system. Also, DLS result of the KCC-1/Pr-SO₃H approves again the successful functionalization of KCC-1 with propyl sulfonic acid moieties.

After characterization of KCC-1/Pr-SO₃H, the catalytical performance of this nanomaterial was evaluated for the synthesis of 2,3-dihydroquinazolin-4(1H)-one. In order to optimize the MCR conditions and obtain good catalytic activity, synthesis of 2,3-dihydroquinazolin-4(1H)-one (4f) was used as a model, and investigated under different reaction parameters including amount of the catalyst, time, temperature, and type of solvent. For this reason, isatoic anhydride (1), benzaldehyde (2a), and 4-nitroaniline (3a) were condensed as a model reaction in the presence of 3 mg KCC-1/Pr-SO₃H in water at ambient temperature and under reflux condition for 3 h (Table 1 (entries 1 and 2)). It is obtained that the solvent type and temperature do effect on the performance of the nanocatalyst. Desired 2,3-dihydroquinazolin-4(1H)-one derivative (4f) was obtained in 40% at room temperature and 55% under reflux condition after 3 h and no further increasing was noticed with additional time. Also, some aprotic polar solvents including THF, CH₃CN, and toluene lead to low efficiency (Table 1 (entries 3–5)). Interestingly, the other protic solvents

![Figure 4. Effect of time on yield of 2,3-dihydroquinazolin-4(1H)-ones: isatoic anhydride (1 mmol), aromatic aldehyde (1 mmol), and primary amine (1 mmol) and KCC-1/Pr-SO₃H (5 mg), EtOH (3 mL), under reflux conditions for 2 h.](image)
improved reaction performance. Methanol and iPrOH gave quinazolinone derivative in average yields (Table 1, entries 6 and 7). In contrast, the utilization of water caused an increased yield of 65%, while the yield was considerably increased up to 95% when ethanol was used as an organic solvent in the presence of KCC-1/Pr-SO₃H (Table 1 (entries 8 and 9)). Also, it is found that conventional heating under reflux conditions in ethanol as a solvent (Table 1) in 2 h and in the presence of 5 mg of KCC-1/Pr-SO₃H NPs is an optimum condition for the synthesis of quinazolinone derivative. In addition, water/ethanol (1:1) mixture gave quinazolinone derivative in average yield (Table 1, entry 10). As could be seen in Table 1, catalytic activity of KCC-1/Pr-SO₃H is excellent in protic solvents.

To further investigate the efficiency of the nanocatalyst, we compared the catalytic performance of the newly synthesized nanocatalyst with different nanosilica-based materials and the results are shown in Table 2. Originally, a standard reaction was accomplished using KCC-1, KCC-1-npr-NH₂, KCC-1-npr-NH₂-FA, KCC-1-npr-NH₂-DPA, Fe₃O₄@KCC-1-npr-NH₂, and KCC-1/Pr-SH. The results confirmed that the desired product was not formed (Table 2, entries 1 and 6) after 3 h of reaction time in any amount. When, KCC-1/Pr-SO₃H was used as the nanocatalyst, a reaction was performed and completed after 2 h (Table 2, entries 7). Thus, KCC-1/Pr-SO₃H was found to be the most effective catalyst among the various silica-based nanocatalysts and 5 mg of KCC-1/Pr-SO₃H proved to be optimal. Finally, the amount of nanocatalyst on the reaction efficiently was investigated. According to the obtained results, the variation in the KCC-1/Pr-SO₃H amount played a key role in reaction efficiency. The optimum amount of KCC-1/Pr-SO₃H was 5 mg, which obtained the desired product in 95% yields (Figure 3). It is important to point out that, we could achieve excellent yields of guinazolinone derivative using this nanocatalyst, in 2 h (Figure 4).

Thus, optimal synthesis conditions were carried out to evaluated this approach for the synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives using isatoic anhydride (1 mmol), various substituted aromatic amines (1 mmol) and aldehydes (1 mmol) in ethanol. As can be seen in Table 3, the type of substituents on the aromatic rings and electronic properties have extremely evident effects in terms of yields under the reaction conditions. Aromatic aldehydes containing electron-donating groups on the ring such as 4-methoxybenzaldehyde and 4-methylbenzaldehyde (Table 3, 4c, and 4b) have average yield. But, electron-withdrawing groups on the ring such as 4-nitrobenzaldehyde (Table 3, 4f) reacted well to afford the desired 2,3-

### Table 2. Influence of different KCC-1-based nanocatalysts for the synthesis of 2,3-dihydroquinazolin-4(1H)-one.

| Entry | KCC-1-based catalysts | Yield (%) |
|-------|-----------------------|-----------|
| 1     | KCC-1                 | –         |
| 2     | KCC-1-npr-NH₂         | –         |
| 3     | KCC-1-npr-NH₂-FA (folic acid) | –     |
| 4     | KCC-1-npr-NH₂-DPA (d-pencil amine) | – |
| 5     | Fe₃O₄@KCC-1-npr-NH₂  | –         |
| 6     | KCC-1/Pr-SH           | –         |
| 7     | KCC-1/Pr-SO₃H        | 95        |

Reaction conditions: isotonic anhydride (1 mmol), aromatic aldehyde (1 mmol) and primary amine (1 mmol) and KCC-1/Pr-SO₃H (5 mg), EtOH (3 mL), under reflux conditions for 2 h. Isolated yield (%).

### Table 3. Synthesis of 2,3-dihydroquinazolin-4(1H)-ones in the presence of the KCC-1/Pr-SO₃H catalyst in ethanol.

| Entry | Product | R | R¹ | Time(h) | Yield (%) | Found | Reported |
|-------|---------|---|----|--------|-----------|-------|----------|
| 1     | 4a      | Ph | Ph | 2      | 85        | 204–206 | 203–205 [34] |
| 2     | 4b      | Ph | 4-MeC₆H₄ | 2 | 78 | 212–215 | 214 [35] |
| 3     | 4c      | Ph | 4-MeOC₆H₄ | 2 | 75 | 204–206 | 205–204 [35] |
| 4     | 4d      | Ph | 4-BrC₆H₄ | 2 | 89 | 223–225 | 222–225 [34] |
| 5     | 4e      | Ph | 4-CIC₆H₄ | 2 | 91 | 213–215 | 214–217 [36] |
| 6     | 4f      | Ph | 4-NO₂C₆H₄ | 2 | 95 | 196–197 | 195–196 [34] |
| 7     | 4g      | 4-MeC₆H₄ | Ph | 2 | 92 | 198–199 | 196–198[34] |
| 8     | 4h      | 4-BrC₆H₄ | Ph | 2 | 82 | 222–224 | 224–226[34] |
| 9     | 4i      | 4-CIC₆H₄ | Ph | 2 | 81 | 217–220 | 216–218[37] |
| 10    | 4j      | 4-NO₂C₆H₄ | Ph | 2 | 76 | 186–188 | 185–187[37] |
| 11    | 4k      | 4-MeOC₆H₄ | Ph | 2 | 87 | 213–215 | 215–216[37] |
| 12    | 4l      | 4-MeC₆H₄ | Ph | 2 | 88 | 247–248 | 247–249[38] |
| 13    | 4m      | 2-CIC₆H₄ | Ph | 2 | 79 | 213–215 | 215–216[37] |
| 14    | 4n      | 4-PyrZoC₆H₄ | Ph | 2 | 95 | 235–236 | – |
dihydroquinazolin-4(1H)-ones in excellent yield with high purity. Also, the bromo- and chloro-substituted benzaldehydes gave the desired products 4d and 4e in 89% and 91% yields, respectively. When bromo- and chloro-substituted anilines (4h, 4i, and 4m) was used, they reacted smoothly with benzaldehyde without creating any dehalogenated products. In addition, electron-donating groups on the aromatic aniline afforded the corresponding products in good yield (4k and 4l) and electron-withdrawing group on the aniline ring afforded the desired quinazolinone in average yield (5j). We also observed that 4-pyrazoloaniline [32] which synthesized for prepare of our newly desired 2,3-dihydroquinazolin-4(1H)-one was well tolerated under our reaction conditions with 95% isolated yield (4o).

2.5. 3-(4-(1H-pyrazol-1-yl)phenyl)-2-phenyl-2,3-dihydroquinazolin-4(1H)-one (4t, C23H18N4O)

White solid; m.p.: 235–236°C; FT-IR (KBr): νmax/cm⁻¹ 3298 (NH), 3060, 3001, 2920, 2847, 2313, 2270, 1705 (C=O), 1673 (C=C), 1651 (C=N), 1489, 1451, 1370, 1358, 1311, 1245, 1159, 1055, 925, 866, 809, 757; 1H NMR (400 MHz, DMSO-d6): δ = 1.80 (s, 1H, Aliphatic), 6.34 (d, J = 2.26 Hz, 1H, CH, Pyrazole), 6.52 (t, J = 2.2 Hz, 1H, Pyrazole), 6.70–6.78 (m, 2H, Ar), 7.25–7.32 (m, 4H, Ar), 7.38 (t, J = 9.1 Hz, 4H, Ar), 7.66 (d, J = 2.22 Hz, 1H, Pyrazole), 7.72–7.73 (m, 2H, Ar), 7.77 (d, J = 8.8 Hz, 2H, Ar), 8.45 (d, J = 2.38 Hz, 1H, NH) ppm; 13C NMR (100 MHz, DMSO-d6): δ = 72.67 (C, Aliphatic), 107.96, 114.83, 115.16, 117.60, 118.45, 126.77, 127.44, 127.79, 128.03, 128.48, 132.17, 133.92, 137.34, 138.54, 140.51, 141.08, 146.77, 177.01 (CO) ppm. Anal. Calcd for C23H18N4O. Calcd. C, 75.39; H, 4.95; N, 15.29; O, 4.37%. Found, C, 75.32; H, 4.93; N, 15.20; O, 4.39%.

According to obtained results and by referring to the literature[33], the possible mechanism for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones from the three-component condensation of isatoic anhydride (1), aromatic amines (2), and aromatic aldehydes (4) in the presence of KCC-1/Pr-SO₃H has been shown in Scheme 3. As can be seen, at first stage the acidic sites of the catalyst activated the carbonyl group of isatoic anhydride. In the second step, a nucleophilic attack appeared from the aromatic amine to the activated carbonyl and intermediate 3 is formed and then released a CO₂ molecule. Finally, the aromatic amine group of mentioned intermediate attacks the activated carbonyl group of aromatic aldehyde and intermediate 5 is formed by releasing a H₂O molecule. Then, the amide attacks the imine group and in this step closes the ring and formed the product (compound 6). It is important to point out that, the acidic site of the nanocatalyst could active the imine group by coordinating its nitrogen.

It is undeniable that for a catalytic process, the recovery and reuse of catalyst materials are highly preferable. In this regard, the recyclability of the KCC-1/Pr-SO₃H was investigated using the model reaction of isatoic anhydride (1 mmol), aromatic amines (1 mmol), and aldehydes (1 mmol) under identical reaction conditions. After the completion of reaction, the recovered catalyst from the reaction mixture was washed with hot ethanol and dried at room temperature and reused for subsequent reactions. Thus, this catalyst could be recycled and reused up to seven consecutive trials without remarkable loss of its catalytic activity (Fig. 5) during the work-up procedure. Therefore, these results indicated that the synthesis nanocatalyst was stable and could tolerate the MCR conditions.

3. Conclusions

In conclusion, it is demonstrated that KCC-1/Pr-SO₃H could be used as a heterogeneous acidic nanocatalyst for the efficient one-pot three-component
synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives. High surface area of KCC-1, as well as the acidic property of the propyl sulfonic functionalized groups has increased the effective catalytic activity of the nanocatalyst. It found that KCC-1/Pr-SO$_3$H show good activity in protic solvents and was recovered and reused for seven times without considerable loss of catalytic activities. Proposed method has some advantages, containing short reaction times, mild reaction conditions, green solvent, low catalyst loading, re-usability of the solid catalyst, high yields, and convenient workup process.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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*Scheme 3. Plausible mechanism for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones.*
References

1. Astruc D. Palladium nanoparticles as efficient green homogeneous and heterogeneous carbon–carbon coupling precatalysts: a unifying view. Inorg Chem. 2007;46:1884–1894.

2. Ranu BC, Dey R, Chatterjee T, et al. Copper nanoparticle-catalyzed carbon—carbon and carbon heteroatom bond formation with a greener perspective. ChemSusChem. 2012;5:22–44.

3. Mohammadbagheri Z, Chermahini AN. KCC-1/Pr-SO3H as an efficient heterogeneous catalyst for production of n-butyl levulinate from furfuryl alcohol. J Ind Eng Chem. 2018;62:401–408.

4. Chermahini AN, Shahangi F, Dabbagh HA, et al. Production of 5-hydroxymethylfurural from fructose using a a spiraherically fibrous KCC-1 silica catalyst. RSC Adv. 2016;6:33804–33810.

5. Tameh FA, Safaei-Ghomi J, Mahmoudi-Hashemi M, et al. One-pot multicomponent reaction synthesis of spirooxindoles promoted by guanidine-functionalized magnetic Fe3O4 nanoparticles. RSC Adv. 2016;6:74802–74811.

6. Mitchell CJ, Ballantine SP, Coe DM, et al. Pyrazolopyridines as potent PDE4B inhibitors: 5-Heterocyclic SAR. Bioorg Med Chem Lett. 2010;20:5803–5806.

7. Shylesh S, Schüneemann V, Thiel WR. Magnetically separable nanocatalysts: bridges between homogeneous and heterogeneous catalysis. Angew Chem Int Ed. 2010;49:3428–3459.

8. Azizi S, Shadjou N, Hasanzadeh M. KCC-1-NH2-DPA: an efficient heterogeneous recyclable nanocomposite for the catalytic synthesis of tetrahydrodipyrazolopyridines as a well-known organic scaffold in various bioactive derivatives. Nanocomposites 2019;5:124–132.

9. Azizi S, Shadjou N, Hasanzadeh M. KCC1 amino-aryl-functionalized supported on iron oxide magnetic nanoparticles as a novel magnetic nanocatalyst for the green and efficient synthesis of sulfonamide derivatives. Appl Organometal Chem. 2019. doi: 10.1002/aoc.5321.

10. Huddleston JG, Visser AE, Reichert WM, et al. Characterization and comparison of hydrophobic and hydrophobic room temperature ionic liquids incorporating the imidazolium cation. Green Chem. 2001;3:156–164.

11. El-Borai MA, Rizk HF, Beltagy DM, et al. Microwave-assisted synthesis of some new pyrazolopyridines and their antioxidant, antitumor and antimicrobial activities. Eur J Med Chem. 2013;66:415–422.

12. Safaei-Ghomi J, Sadeghzadeh R, Shahbazi-Alavi H. A pseudo six-component process for the synthesis of tetrahydrodipyrazolopyridines using an ionic liquid immobilized on a FeNi3 nanocatalyst. RSC Adv. 2016;6:33676–33685.

13. Soleymani J, Hasanzadeh M, Somi MH, et al. Highly sensitive and specific cytosensing of HT 29 colorectal cancer cells using folic acid functionalized-KCC-1 nanoparticles. Biosens Bioelectron. 2019;132:122–131.

14. Shafiei-Irannejad V, Soleymani J, Azizi S, et al. Advanced nanomaterials towards biosensing of insulin: analytical approaches. TrAC Trends Anal Chem. 2019;116:1–12.

15. Gawande MB, Bonifácio VD, Luque R, et al. Benign by design: catalyst-free in-water, on-water green chemical methodologies in organic synthesis. Chem Soc Rev. 2013;42:5522–5551.

16. Wang Z, Wang M, Yao X, et al. Design, synthesis and antiviral activity of novel quinazolines. Eur J Med Chem. 2012;53:275–282.

17. Chinigo GM, Paige M, Grindrod S, et al. Asymmetric synthesis of 2, 3-dihydro-2-arylquinazolin-4-ones: methodology and application to a potent fluorescent tubulin inhibitor with anticancer activity. J Med Chem. 2008;51:4620–4631.

18. Abbas SE, Awadallah FM, Ibrahim NA, et al. New quinazoline–pyrimidine hybrids: synthesis, anti-inflammatory, and ulcerogenicity studies. Eur J Med Chem. 2012;53:141–149.

19. Smits RA, de Esch IJ, Zuiderveld OP, et al. Discovery of quinazolines as histamine H4 receptor inverse agonists using a scaffold hopping approach. J Med Chem. 2008;51:7855–7865.

20. Saravanan G, Alagarsamy V, Prakash CR. Design, synthesis and anticonvulsant activities of novel 1-(substituted/unsubstituted benzylidene)-4-(4-(6,8-dibromo-2-(methyl/phenyl)-4-oxoquinazolin-3(4H)-yl) phenyl) semicarbazide derivatives. Bioorg Med Chem Lett. 2012;22:3072–3078.

21. Rhee H-K, Yoo JH, Lee E, et al. Synthesis and cytotoxicity of 2-phenylquinazolin-4(3H)-one derivatives. Eur J Med Chem. 2011;46:3900–3908.

22. Rani CS, Suresh N, Rao MVB, et al. Montmorillonite K10 catalyzed one-pot synthesis of 2-aryl substituted N-(4-oxo-1,2-dihydroquinazolin-3(4H)-yl) aryl or alkylamide derivatives under ultrasound irradiation. Arab J Chem. 2019;12:3911–3920.

23. Hamid Z. Synthesis of 2, 3-dihydroquinazolin-4(1H)-ones catalyzed by Perchlorated Zirconia (HClO4/ZrO2) nanoparticles as a novel solid acid catalyst. Nanosci Nanotechnol. 2018;1:1.

24. Mostaqlou KM, Subramani A, Shabeer T, et al. Amino acid catalyzed synthesis of 2, 3-dihydroquinazolin-4(1H)-one derivatives. Lett Org Chem. 2018;15:246–250.

25. Kiyani H, Tazari M, Ghorbani F. Expeditious and green synthesis of 2, 3-dihydroquinazolin-4(1H)-ones catalyzed by nano-MgO. Lett Org Chem. 2018;15:523–529.

26. Mohammadi AA, Ahdenov R, Sooki AA. Design, synthesis and antibacterial evaluation of 2-alkyl- and 2-aryl-3-(phenylamino) quinazolin-4(3H)-one derivatives. Heterocycl Commun. 2017;23:105–108.

27. Abdi M, Rostamizadeh S, Zekri N. An efficient and green synthesis of 1H-2H-pyrrole [isoindoline-1, 2’-quinazoline]-3’, 4’(3’H)-dione derivatives in the presence of nano Fe3O4–GO–SO3H. Polycycl Aromat Comp. 2017;39:413–424.

28. Hassankhani A. Multicomponent reaction for the synthesis of 2, 3-dihydroquinazolin-4(1H)-ones using isatoic anhydride, aldehydes and NH4OAc under Solvent-free conditions. Iran Chem Commun. 2019;7:248–256.
29. Merroun Y, Chehab S, Ghailane T, et al. An effective method to synthesize 2, 3-dihydroquinazolin-4 (1H)-One using phosphate fertilizers (MAP, DAP and TSP) as green heterogeneous catalysts. J Turk Chem Soc Sect A Chem. 2018;5:303–316.

30. Ziarani GM, Badiei A, Aslani Z, et al. Application of sulfonic acid functionalized nanoporous silica (SBA-Pr-SO3H) in the green one-pot synthesis of triazoloquinazolinones and benzimidazoquinazolinones. Arab J Chem. 2015;8:54–61.

31. Rostamizadeh S, Amani AM, Mahdavinia GH, et al. Synthesis of some novel 2-aryl-substituted 2, 3-dihydroquinazolin-4 (1H)-ones under solvent-free conditions using MCM-41-SO3H as a highly efficient sulfonic acid. Synthesis 2010;2010:1356–1360.

32. Ghasemi Z, Azizi S, Salehi R, et al. Synthesis of azo dyes possessing N-heterocycles and evaluation of their anticancer and antibacterial properties. Monatsh Chem. 2018;149:149–157.

33. Razavi N, Akhlaghnia B. Hydroxyapatite nanoparticles (HAP NPs): a green and efficient heterogeneous catalyst for three-component one-pot synthesis of 2,3-dihydroquinazolin-4 (1H)-one derivatives in aqueous media. New J Chem. 2016;40:447–457.

34. Wang LM, Hu L, Shao JH, et al. A novel catalyst zinc (II) perfluorooctanoate [Zn (PFO) 2]-catalyzed three-component one-pot reaction: synthesis of quinazolinone derivatives in aqueous micellar media. J Fluor Chem. 2008;129:1139–1145.

35. Zhang ZH, Lü HY, Yang SH, et al. Synthesis of 2, 3-dihydroquinazolin-4 (1H)-ones by three-component coupling of isatoic anhydride, amines, and aldehydes catalyzed by magnetic Fe3O4 nanoparticles in water. J Comb Chem. 2010;12:643–646.

36. Rostamizadeh S, Amani AM, Aryan R, et al. Synthesis of new 2-aryl substituted 2, 3-dihydroquinazoline-4 (1H)-ones under solvent-free conditions using molecular iodine as a mild and efficient catalyst. Synth Commun. 2008;38:3567–3576.

37. Zhao K, Lei M, Ma L, et al. A facile protocol for the synthesis of 4-aryl-1, 4, 7, 8-tetrahydro-3, 5-dimethylpyrazolo [3, 4-b: 4′, 3′-e] pyridine derivatives by a Hantzsch-type reaction. Monatsh Chem. 2011;142:1169–1173.

38. Dabiri M, Salehi P, Koorshari M, et al. An efficient synthesis of tetrahydropyrazolopyridine derivatives by a one-pot tandem multi-component reaction in a green media. Arkivoc. 2014;2014:204–214.