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A novel eco-friendly method for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones in aqueous media under ultrasonication using $ZrOCl_2$-MCM-41 as a highly efficient nanocatalyst/nanoreactor

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Simple, convenient, and green synthetic protocols are developed for the one-pot synthesis of 2,3-disubstituted quinazolin-4(1*H*)-ones through one-pot condensation of arylaldehydes, isatoic anhydride and ammonium acetate in the presence of $ZrOCl_2$-MCM-41 as a highly efficient novel nanocatalyst/nanoreactor under sonication. The main advantages of this protocol include short reaction times, practical simplicity, high yields, recyclable catalysts, safety, and cheapness of benign solvents.

Keywords: $ZrOCl_2$-MCM-41**,** Nanocatalyst**,** Ultrasound irradiation**,** 2,3-Dihydroquinazolinone**,** Heterocycles**,** Multicomponent reactions**,** Solvent-free conditions

INTRODUCTION

Quinazolin-4-ones are pharmacologically the most important classes of heterocyclic compounds and occur widely in natural products such as rutaecarpine (Figure 1) [1]. These compounds possess versatile types of biological activities; some of these are well known for their anticancer [2,3], antitubercular [4], antibacterial [5], antifungal [6], anti-HIV [7], antihelminthic [8], anti-inflammatory [9] and antihypertensive activities [10].

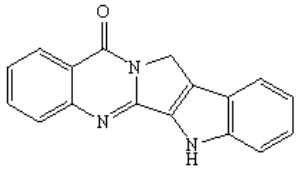

Fig. 1. Structure of rutaecarpine

Multicomponent reactions (MCRs) leading to interesting heterocyclic scaffolds are particularly useful for the creation of diverse chemical libraries of drug-like molecules for biological screening [11]. Some reported synthetic routes include the reaction of isatoic anhydride and aldehydes with ammonium acetate or primary amine in the presence of various reagents or catalysts [12-28].

Recently, we have reported the preparation of 2,3-disubstituted quinazolin-4(3H)-ones via multi-component reactions [29]. Now, a three-component one-step synthesis of 2,3-dihydroquinazolin-4(1H)-ones has been designed. For this, the use of $ZrOCl_2$ incorporated in MCM-41, which is relatively non-toxic and inexpensive, was at the centre of our study. In the course of our work on the application of zirconium containing MCM-41 in different organic reactions, we have found it as an effective promoter for the preparation of 2,3-dihydroquinazolin-4(1H)-ones.

Zirconia is a special transition metal oxide that is widely used in catalytic processes as a catalyst, a support, and a promoter [30]. However, its relatively low surface area (usually below 50 m^2 g^{-1}) limits the number of active sites [31]. Ordered mesoporous silicas with a tunable pore structure and tailored composition have received considerable interest with broad application ranging from adsorption [32], gas separation [33], and catalysis [34] to biological uses [35]. Some properties of these materials are: mechanically stable structure, high surface area, and large, ordered pores with narrow size distribution of an

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inorganic backbone. Therefore, it would be reasonable to consider these materials as numerous combined nanosized vessels of the same properties. One of the best-known nanosized inorganic backbones is MCM-41, which is a structurally well ordered mesoporous material with a narrow pore size distribution between 1.5 and 10 nm, depending on the surfactant cation and a very high surface area of up to 1500 m^2 g^{-1} [36]. While several types of solid sulfonic acids, based on ordered mesoporous silicas, have been created in recent years [34], there have been only a few reports of their applications as catalysts in chemical transformations. Herein, we report the preparation of $ZrOCl_2$-MCM-41 as a new modified Lewis acid.

The application of ultrasonic irradiation in reactions using heterogeneous catalysts is a promising technique. Compared with traditional methods, the procedure is more convenient and can be carried out in a shorter reaction time and milder conditions under ultrasound irradiation to give a higher yield of products. Sonication accelerates the reaction by providing driving energy by cavitation and formation and collapse of bubbles (production of high pressure and high temperature) and ensures a better contact, increasing the reaction rate and selectivity [37]. Our efforts for development of new green synthetic methods for various heterocyclic compounds prompted us to investigate the utility of $ZrOCl_2$-MCM-41 as a heterogeneous nanocatalyst under sonication to afford substituted quinazolinones.

Therefore, we present a versatile procedure for the selective production of mono and di-substituted 2,3-dihydroquinazolin-4(1H)-ones in the presence of $ZrOCl_2$-MCM-41 employing three-component reactions of isatoic anhydride with aldehydes and primary amines (or ammonium salts) (Scheme 1).

EXPERIMENTAL

Reagents

All the chemicals used were of analytical grade (E. Merck or Fluka).

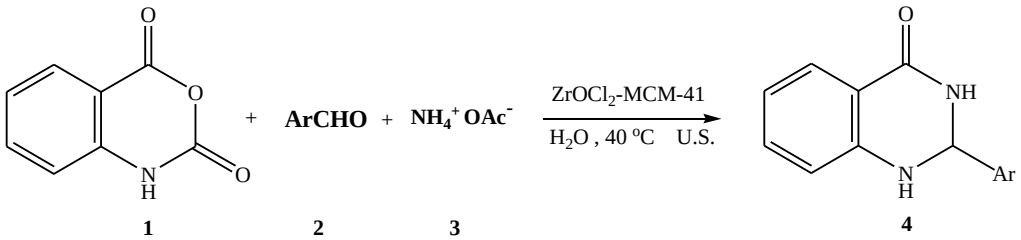
Apparatus

Nanocatalyst: A Philips X'pert powder diffractometer system with Cu-Kα (λ=1.541Å) radiation was used for the X-ray studies. Nitrogen sorption studies were made with a Quantachrome NOVA instrument and scanning electron micrographs were recorded using a Philips microscope XL30. FT-IR spectra were obtained using a Bruker FT-IR spectrophotometer model Vector-22. Thermogravimetric analysis was performed on a Rheometric Scientific model STA-1500.

Products: Melting points were measured on a Buchi B-540 apparatus. IR spectra were obtained on an ABB Bomem Model FTLA200-100 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-300 spectrometer at 300 and 75 MHz, using TMS as an internal standard. Mass spectra were obtained on a Shimadzu QP 1100 EX with an ionization potential of 70 eV.

Preparation of Mesoporous Zirconium Silicate

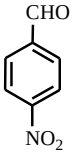
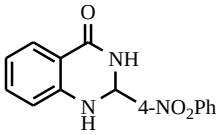
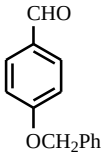
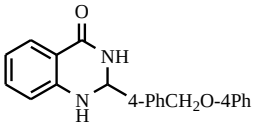
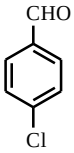
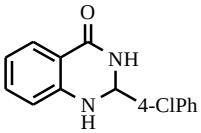
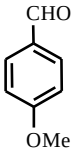
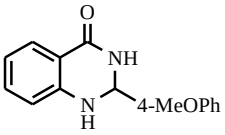
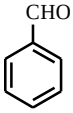
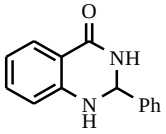
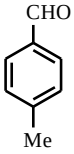
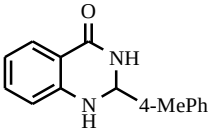
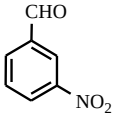
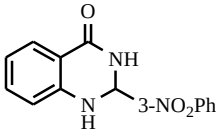
Five different samples of mesoporous zirconium silicate were prepared by mixing sodium silicate as a silicon source, zirconium oxychloride as a zirconium source, and cetyltrimethylammonium bromide (CTMABr) as a surfactant under non-thermal conditions. In a typical procedure, 0.6 g of CTMABr was added in 23 g of demineralized water, the mixture was stirred at 3270 H for 15 min (140 rpm), after that 3 g of sodium silicate was added to the mixture and it was further stirred for 30 min. The pH value was adjusted at 9 by adding sulfuric acid (2M). Then a solution of $ZrOCl_2.8H_2O$ (0.45 g in 50 mL demineralized water) was dropwise added. The stirring was continued for 4 h. A bulky white precipitate was formed. It was filtered, washed five times with demineralized water, and dried in an air oven at 50°C for 48 h. A small portion of this material was calcined at 600 °C for 6 h. The material was digested in 0.1M HNO_3 for 24 h and then washed with demineralized water. The samples prepared had Si/Zr molar ratios: 10; 20; 40; and 80. They were marked as: ZrxMCM-41 where x indicated the Si/Zr molar ratio and MCM-41 indicated a hexagonal ordered mesoporous silicate.



1 **2** **3** **4**

Scheme 1. Synthesis of new substituted 2,3-dihydroquinazolinones.

Table 1. Synthesis of 2-aryl substituted 2,3-dihydroquinazoline-4(1H)-ones in the presence of $ZrOCl_2$-MCM-41.

Entry	Ar	Product		Time (min)	Yield (%)[a]	M.P. (°C) Found	M.P. (°C) Reported [Ref]
1			**(4a)**	8	87	300-302	310–312[29]
2			**(4b)**	5	79	238-240	238–240[29]
3			**(4c)**	10	75	207-208	207–208[29]
4			**(4d)**	15	75	183-184	183–184[29]
5			**(4e)**	20	86	225–226	225–226[29]
6			**(4f)**	25	70	228–230	229-231[29]
7			**(4g)**	8	87	180–182	180–182[29]

[a]Isolated yields

General Procedure for the Synthesis of 2, 3-Dihydroquinazolin-4(1H)-ones

A mixture of 0.163 g isatoic anhydride (1 mmol), aromatic aldehyde (1 mmol), and ammonium acetate (1.2 mmol) was added to 5 mg of $ZrOCl_2$-MCM-41(Zr/Si molar ratio 0.27) and water (5 mL) and the temperature was then raised to 40 °C and maintained under ultrasonic irradiation (25 kHz) for the appropriate time (Table 1). When the reaction was complete (TLC; n-hexane–EtOAc, 2:1) the water was evaporated, $CHCl_3$:methanol (10 mL, 3:1) was added. The mixture was stirred for at least 10 min and the solid catalyst was separated by filtration. The mixture was evaporated in vacuum; the residues were purified by recrystallization from EtOH.

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*Compound **4a***

IR (KBr): $\bar{\nu}$ = 3360, 3345, 3065, 1679, 1608 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), δ: 7.56(t, *J*=6/0 Hz, 1H, 1CH), 7.86(m, 3H, 2CH, 1NH), 8.16(d, *J*=6/0 Hz, 1H, CH), 8.39(m, 5H, CH), 12.8(s, 1H, NH) *ppm*; ^{13}C-NMR (75 MHz, DMSO-d_6), δ: 65.5, 121.2, 123.6, 125.9, 127.7, 129.3, 134.8, 138.6, 148.3, 149.0, 150.8, 162.1 *ppm*; MS, m/z (regulatory intensity): 50(45), 76(50), 92(29), 119(97.5), 192(24), 221(43), 267(100), 269(2.5)[M^+].

*Compound **4d***

IR (KBr): $\bar{\nu}$ = 3291, 3178, 3060, 2931, 2829, 1663 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), δ: 3.84-3.9(s, 3H, CH_3), 4.34(s, 1H, NH), 5.72(s, 1H, NH), 5.86(s, 1H, CH), 6.65-6.8(d, *J*=8.0 Hz, 1H, CH, Ph), 6.88-7.00(m, 3H, CH, Ph), 7.31-7.36(d, *J*=7.8Hz, 1H, CH, Ph), 7.51-7.53(d, *J*= 8.6 Hz, 2H, CH, Ph), 7.93-7.96(d, *J*=7.7Hz, 1H, CH, Ph) *ppm*.

*Compound **4g***

IR (KBr): $\bar{\nu}$ = 3350, 3245, 3050, 2910, 1608 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6), δ: 5.93(s, 1H, CH), 6.66(t, *J*= 6.0Hz, 1H, CH), 6.77(d, *J*=6.0Hz, 1H, CH), 7.26(d, t, J_1=1.2Hz, J_2=9.0Hz, 1H, CH), 7.33(s, 1H, NH), 7.59(d, *J*=9.0Hz, CH), 7.83(m, 1H, CH), 7.92(d, 1H, *J*=9.0Hz, CH), 8.19(d, *J*=6.0Hz, 1H), 8.34(s, 1H, CH), 8.54(s, 1H, NH) *ppm*; ^{13}C-NMR (75 MHz, DMSO-d_6), δ: 65.1, 114.6, 114.9, 117.5, 121.6, 122.7, 123.3, 125.9, 127.4, 131.3, 133.4, 133.6, 134.7, 144.3, 147.3, 147.7, 163.3 *ppm*; MS, m/z (regulatory intensity): 50(15), 92(35), 119(29), 120(40), 147(100), 221(15), 269(6.7) [M+].

RESULTS AND DISCUSSION

In continuation of our search for application of functionalized ordered mesoporous silicas [38], our attempt was focused on the application of novel nanoreactors for ultrasound assisted synthesis of substituted quinazolinones. These Lewis acidic nanoporous zirconium silicates were prepared with various mole ratios of Si/Zr. Infrared spectra of these nanocatalysts were measured by a standard KBr disc technique. The FT-IR spectrum of the Zr10MCM-41 nanocatalyst shown in Fig. 2 is closely similar to that of mesoporous molecular sieves which also show a series of bands that are characteristic of the SiO_4 tetrahedron and its modification by introduction of metal ions [39]. The spectrum shows five main absorption bands in the regions 3000–3700, 1055–1090, 960–970, 790–850, 440–465 cm^{-1}. The band in the region 1055–1090 cm^{-1} is due to the internal asymmetric stretching mode of SiO_4 (TO_4) skeleton, the strongest band in the spectra of silicates [40]. The peak in the region 960–970 cm^{-1} is generally considered as a proof for the incorporation of a heteroatom into the framework [41]. Camblor *et al*. have proposed that the band at 960 cm^{-1} is due to the Si-O stretching vibrations of the Si-OH groups present.

The SEM image of the mesoporous Zr10MCM-41 was taken using gold coating during 2 minutes for high magnification and is shown in Fig. 3. The SEM image of the mesoporous Zr10MCM-41 exhibits uniform spherical crystallites ~0.4–0.8 mm in size.

XRD analysis was performed from 1.5° (2Θ) to 10.0° (2Θ) at a scan rate of 0.02° (2Θ)/sec. The XRD patterns after calcination of the synthesized zirconium silicate samples are presented in Fig. 4. There is a strong diffraction at 2Θ smaller than 3° along with the presence of small peaks, which confirms the formation of mesoporous materials [42].

The thermogravimetric analysis of these nanocatalysts was performed from ambient temperature to 900°C at a heating rate of 10°C/min. The thermograms of the nanocatalysts are presented in Fig. 5. The thermograms of the uncalcined samples show a gradual weight loss up to 900°C. The TGA curve of the samples shows five steps of weight loss (35-130, 130-300, 300-380, 380-480, and 480-600 °C). The weight loss is ~4.0% in the first step and is due to desorption of the physisorbed water in the pores of the uncalcined samples. The weight losses in the second (~20.0%) and third (~7.0%) steps are mainly associated with oxidative decomposition of templates; in the fourth step, the weight loss (~7.0%) is due to removal of coke formed in the previous steps by the decomposition of templates. In the final step, the weight loss (~2.0%) is mainly due to the loss of water formed by condensation of the silanol groups.

In the present communication, we report a simple and ecofriendly synthesis of 2-aryl substituted 2,3-dihydroquinazoline-4(1H)-ones by treatment of isatoic anhydride, aromatic aldehyde, and ammonium acetate in the presence of $ZrOCl_2$-MCM-41 as catalyst under ultrasound irradiation (Scheme 1).

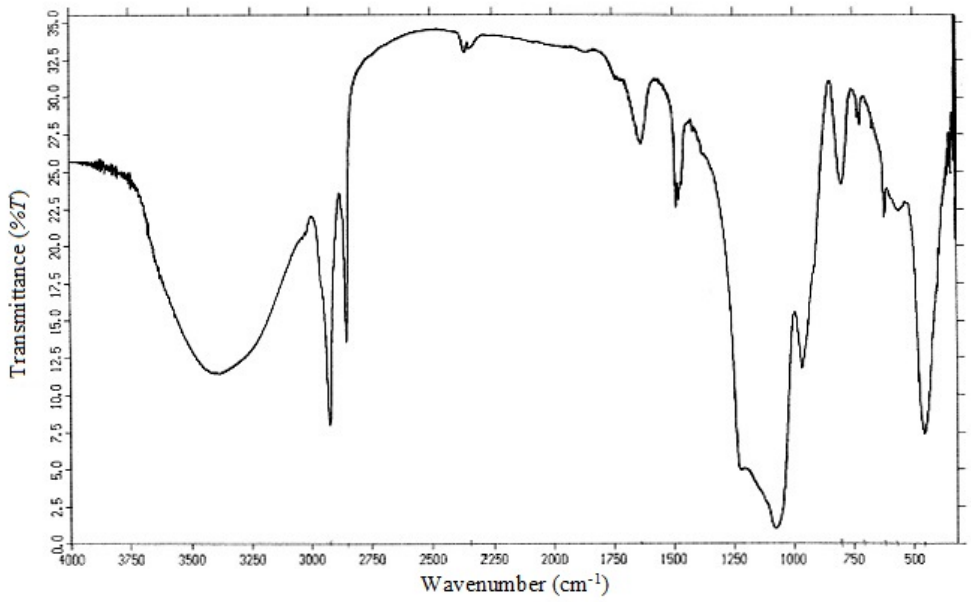


Fig. 2. FT-IR spectrum of the synthesized $ZrOCl_2$-MCM-41.

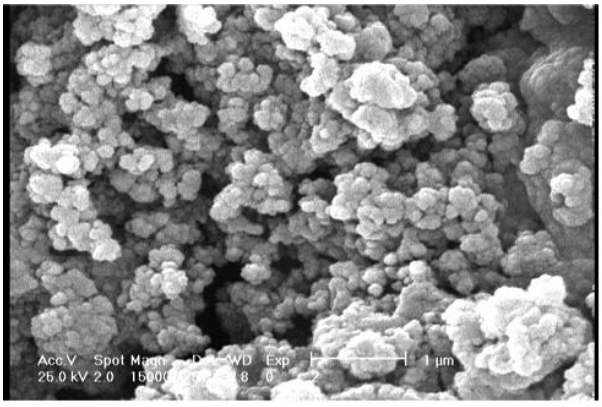


Fig. 3. SEM image of $ZrOCl_2$-MCM-41.

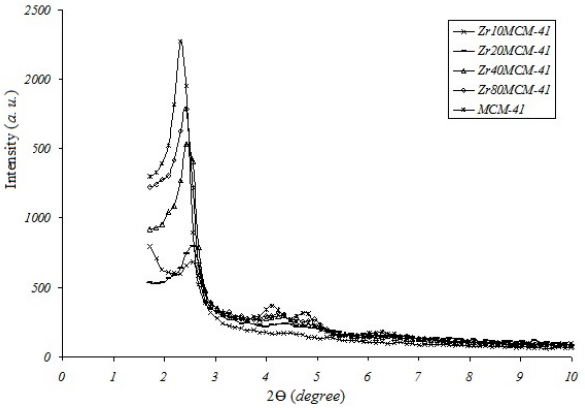


Fig. 4. XRD patterns of the synthesized $ZrOCl_2$-MCM-41and MCM-41

The results showed that the reaction without ultrasound irradiation needs very long time and gives relatively low yields. Thus, it seemed that ultrasound irradiation played the main role in enhancement of the reaction rate and the combination of ultrasound and $ZrOCl_2$-MCM-41 was found to be ideal for the faster synthesis in high yield.

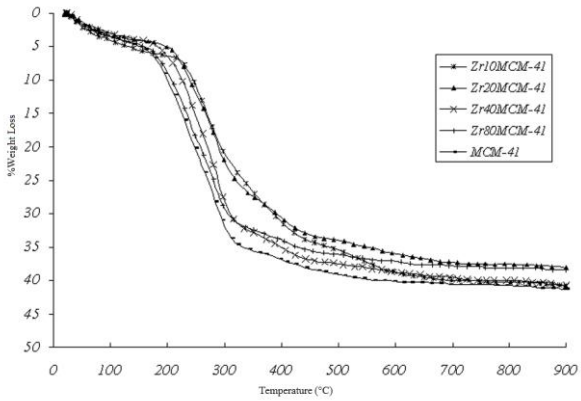
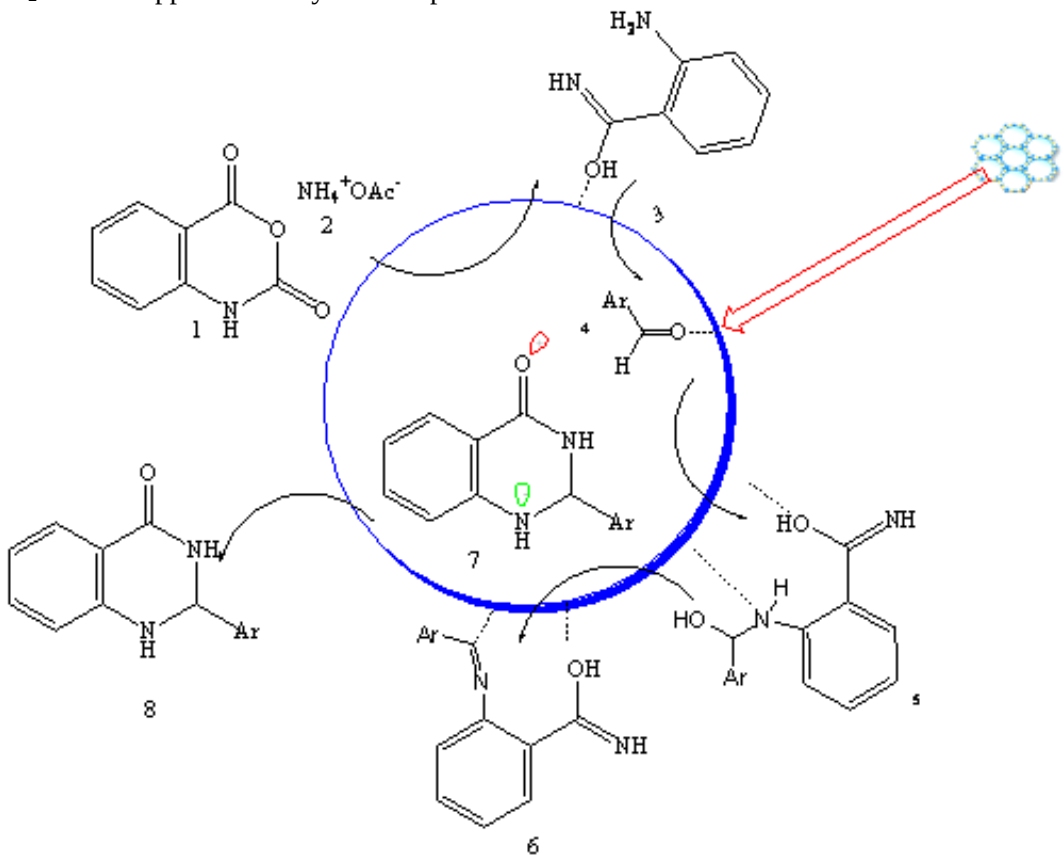


Fig. 5. TGA curve of the of the synthesized $ZrOCl_2$-MCM-41 and MCM-41.

A variety of aldehydes including heterocyclic and aromatic aldehydes, possessing both electron-donating and electron-withdrawing groups, were employed for the formation of 2,3-dihydroquinazolin-4(1H)-ones. In all cases, the yields were excellent (Scheme 1, Table 1). Among the various benzaldehydes tested, the reaction worked well with electron-donating groups (Me, MeO) (entries 6 and 4, Table 1), as well as electron-withdrawing groups (NO_2, Cl) (entries 1 and 3, Table 1) giving various 2,3-dihydroquinazolin-4(1H)-ones in 75–87% yields.

We have found that $ZrOCl_2$-MCM-41 is an effective eco-friendly and efficient promoter for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones. A plausible mechanistic pathway to 2-aryl-substituted

2,3-dihydroquinazolin-4(1H)-ones is illustrated in Scheme 2. In the initial step, the reaction of isatoic anhydride (1), and ammonium acetate (2) within the $ZrOCl_2$-MCM-41 tunnels, together with decarboxylation, gives 2-aminobenzamide (5). The intermediate (3) is formed through nucleophilic attack of the amino group in 2-aminobenzamide at the activated carbonyl group in the aldehyde by $ZrOCl_2.8H_2O$ as a supported catalyst. Also part of the amide in the imine intermediate (5) is converted into its tautomer in the presence of the catalyst. Then the Schiff base intermediate (6) is produced by intermediate (5) dehydration. The intramolecular nucleophilic addition reaction between the amide group nitrogen and the activated Schiff base carbon gives intermediate (7), which is followed by a 1,5-proton transfer giving the products.



Scheme 2. Proposed reaction mechanism

CONCLUSION

In conclusion, a simple green method for the synthesis of a novel class of the quinazolinone family is developed. $ZrOCl_2$-MCM-41 is an efficient nanoreactor for the synthesis of 2,3-dihydroquinazolinones. The method offers several advantages, such as avoiding toxic solvents or catalysts, simple work-up procedure without using any chromatographic method, and improved yields. Starting materials are inexpensive and commercially available. We believe that many biologically active derivatives could be synthesized by this multi-component reaction with high atomic economy.

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НОВ ЕКОЛОГИЧНО СЪВМЕСТИМ МЕТОД ЗА СИНТЕЗА НА 2,3-ДИХИДРОХИНАЗОЛИН-4(1Н)-ОНИ ВЪВ ВОДНА СРЕДА ПРИ УЛТРАЗВУКОВО ВЪЗДЕЙСТВИЕ, ИЗПОЛЗВАЙКИ $ZrOCl_2$-MCM-41 КАТО ВИСОКОЕФЕКТИВЕН НАНОКАТАЛИЗАТОР/НАНОРЕАКТОР

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(Резюме)

Прости, удобни и „зелени“ рецептури са разработени за едностадийната синтеза на 2,3-дихидрохиназолин-4(1*Н*)-они чрез кондензация на арилалдехиди, изатинов анхидрид и амониев ацетат в присъствие на $ZrOCl_2$-MCM-41 като високоефективен нанокатализатор/нанореактор при ултразвуково действие. Главните предимства на метода са кратките времена, високите добиви, рециклирания катализатор, безопасността и ниската цена на разтворителя.