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Ce/SiO_2 composite as an efficient catalyst for the multicomponent one-pot synthesis of substituted pyrazolones in aqueous media and their antimicrobial activities

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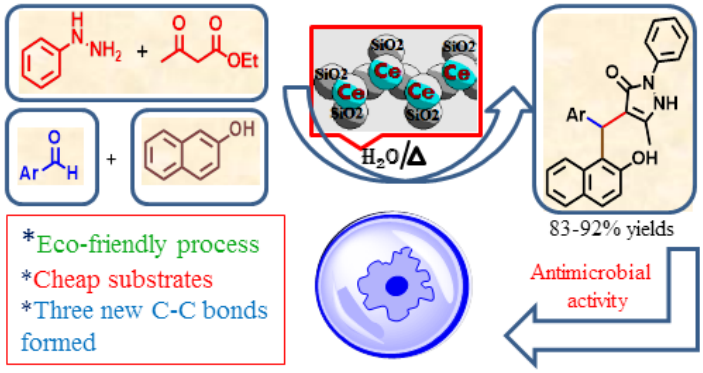
Graphical Abstract



Highlights

- ► Multicomponent reactions provide a convenient platform to construct complex polycyclic structural scaffolds.
- ► Ce-SiO_2 composite as a selective and reusable solid catalyst for the synthesis of polysubstituted pyrazolones.
- ► Eco-compatibility and aqueous medium protocols are added advantages of the reaction.
- ► New Pyrazolone derivatives exhibit good to promising antimicrobial activity.

ABSTRACT

We describe here the preparation and characterization of a Ce/SiO_2 catalyst and its application in an eco-friendly and convenient synthesis of pyrazolone derivatives via one-pot multicomponent reaction of 2-naphthol, aldehydes, phenylhydrazine and ethyl acetoacetate under aqueous media. The catalyst was prepared using sol-gel method and characterized by XRD, XPS, UV-DRS, SEM, TEM and surface area analysis. 2D-NMR technique was utilized to ascertain the pyrazolone tautomer. The new compounds were evaluated for anti-microbial activity and exhibited good to promising activity against most of the tested bacterial and fungal strains.

Keywords: Ce-SiO_2 catalyst, One-pot synthesis, Aqueous media, Substituted pyrazolones, antimicrobial activity.

1. Introduction

N-heterocyclic compounds are found extensively in biologically active pharmaceuticals and natural products such as hormones, vitamins, alkaloids and are also present in fine and speciality chemicals [1]. The pyrazolone nucleus is one of the most interesting and promising heterocyclic scaffolds that occur in many drugs and synthetic products [2]. Pyrazolone moieties are important components in many of the non-steroidal anti-inflammatory drugs (NSAIDs) however, in recent times they have also displayed versatile role in the treatment of cerebral ischemia and cardiovascular diseases [3]. The pyrazolone moiety has gained increasing attention due to its diverse pharmacological properties such as analgesic [4, 5], antitubercular [6], antifungal [7], antibacterial [8], anti-inflammatory [9, 10], antioxidant [11] and antitumor activities [12]. The ease of preparation and rich biological activities of pyrazolone framework makes it an interesting template for organic, combinatorial and medicinal chemistry [13-16].

The multicomponent reaction (MCR) strategy offers significant advantages over conventional multistep synthesis due to its flexible, convergent and atom economic nature [17-19]. These reactions represent environmentally friendly processes by virtue of reduced number of steps, lower energy consumption and minimized waste production [20, 21]. Diversified arrays of valuable heterocyclic ensembles can easily be constructed using such multicomponent reactions [22]. The adducts obtained from such reactions often display

pronounced biological activities [23]. The multicomponent reactions can be conducted in organic as well as aqueous media. Most often the organic media becomes the choice of solvent due to its ability to form single phase by dissolving all the components. Organic processes conducted in an environmentally benign reaction media are always preferred by the industry [24, 25]. Moreover, the water based MCRs for the constructions of bioactive heterocycles are currently gaining much interest [26]. Water, a readily available natural resource, has a huge potential as a media for chemical reactions. Water being non-hazardous, environment friendly, non-inflammable and inexpensive medium can be adopted to avoid the unwanted side reactions caused by the organic solvents [27-29]. According to recent reports in the literature, it has been demonstrated that organic reactions performed in water as a solvent are faster and display novel reactivity profiles [30]. In order to comply by the basic principles of green chemistry such as "minimization of waste" and "replacement of stoichiometric to catalytic reactions" [31], the focus of our research interest lies in the development of selective and reusable solid catalysts for the synthesis of heterocyclic molecules [32-35]. In continuation of this theme, we herein wish to report the synthesis of pyrazolone scaffolds through multicomponent reaction in water medium.

Cerium salts are frequently used for catalysis and their effectiveness can be endorsed by their moderate to low toxicity, ease of handling, reasonable cost and convenient usage as one-electron redox system. However, their use in stoichiometric amounts often impediment the economic and environmental aspects. Therefore, the use of heterogenized version of Ce salts is a preferable choice for green organic transformations. Silica is extensively used as a support due to its high specific surface area, greater flexibility and thermal durability. Silica supported active species in well-dispersed form provides a suitable environment for various applications over a wide range of temperatures [36]. The insoluble solid catalysts tend to minimize the waste generated due to catalyst separation and disposal. They can be easily incorporated into an economically attractive continuous flow processes for the industry [37]. There are quite a few conventional and catalytic methods for the synthesis of 2-aryl-5-methyl-1H-pyrazol-3(2H)-ones. Literature reports have indicated the use of ultrasound, microwave and thermal modes of synthesis. Among them, a four component reaction catalysed by PTSA [38] and copper iodide [39] catalyst has been utilized recently. Such reactions often involve high catalyst loading, elongated reaction time, drastic reaction conditions and formation of non-desirous side products. The intrinsic reaction conditions preferably utilize strong acidic media, high reaction temperatures and stoichiometric ratios

resulting in tedious work-up, operational complexity and waste generation. Thus, there is tremendous scope for the development of new greener synthetic protocols to assemble such frameworks.

In an earlier work, we have reported the synthesis of Ce-MCM-41 catalyst and its application in the multicomponent reaction which demonstrated a promising anti-microbial activity against many microbes [40]. We describe here, in continuation with our on-going research, the preparation of a new cerium–silica composite (Ce–SiO_2) and its application in the multicomponent reactions. The inherent properties of Ce-SiO_2 catalyst such as environmental compatibility, reusability, greater selectivity, operational simplicity, non-corrosiveness, low cost and ease of isolation makes this catalyst useful to carry out the reaction. This new solid acid catalyst was successfully employed in the one-pot preparation of a series of 2-aryl-5-methyl-1H-pyrazol-3(2H)-ones in water. These pyrazolone derivatives were further screened for their antimicrobial activities. A simple method for the synthesis of pyrazolone derivatives by using benzaldehyde, phenyl hydrazine, ethyl acetoacetate and 2-naphthol is shown in Scheme 1.

2. Experimental methods

2.1. General remarks

The Thin Layer Chromatography (TLC) was performed on Merck silica gel 60 F254 plates using ethyl acetate and hexane as eluting agents. Thin layer chromatography plates were visualized by exposure to UV-light/iodine and/or by immersion in an acidic staining solution of phosphomolybdic acid followed by heating on a hot plate. Purification of products was carried out by column chromatography using silica gel and a mixture of ethyl acetate and hexane as eluting agents. All the products were characterized by Mass, ^{1}H and ^{13}C-NMR spectroscopy. The NMR spectra of samples were acquired on a Bruker Avance 300 MHz, 500 MHz and 700 MHz spectrometer using TMS as an internal standard in $CDCl_3$ and Me_2SO-d_6. Mass spectra were acquired on a Thermo LCQ fleet ion trap mass spectrometer. High resolution mass spectra were acquired on a Q STAR XL Hybrid LC/MS/MS system, Applied Biosystems, USA. FT-IR data were acquired on a Thermo Nicolet Nexus 670 FT-IR spectrometer with DTGS KBr detector. XPS spectra were recorded on a Kratos AXIS 165 with a dual anode apparatus using the Mg Kα anode. X-ray powder diffraction data was collected on a Siemens/D-5000 diffractometer using Cu Kα radiation. Pore size distribution measurements were executed on Auto sorb-1 instrument (Quanta

chrome, USA) using by nitrogen physisorption. The particle size and external morphology of the samples were observed on a Philips TECNAI F12 FEI transmission electron microscopy (TEM). SEM-EDX was performed on a Hitachi SEM S-520, EDX-Oxford Link ISIS-300 instrument. Diffuse reflectance UV/Vis spectra for samples as KBr pellets were recorded on a GBC Cintra 10e UV-VIS spectrometer in the range 200 to 800 nm with a scan speed 400 nm per minute. The melting points were measured in open capillary tubes and are uncorrected.

2.2. Synthesis of Ce–SiO_2 composite by the sol–gel method

In a Becker cup, adapted with a magnetic stirrer, were placed 5 mL of ethanol, 2 mL of deionized H_2O and 3 drops of conc. HCl. Next, 5.0 mmol of anhydrous $CeCl_3$ was added in one portion. The mixture was vigorously stirred until total dissolution (ca. 15 min). To this clean homogeneous solution 20 mmol of TEOS was added in one portion in a continuous flow. This fresh mixture was stirred continuously for an additional 20 minutes. The magnetic stirrer bar was removed and the flask was covered with a clock glass and left to rest until the formation of a glass material (ca. 5 days). After this, the glass material was triturated in a mortar and the light yellow solid was subjected to the thermal treatment at 180 °C during 24 hours. After this time, the material was washed with 20mL of ethanol followed by 20 mL of deionized H_2O. The material was subjected again to the thermal treatment at 100 °C for additional 24 hours.

2.3. General procedure for synthesis of 2-phenyl-5-methyl-1H-pyrazol-3(2H)-ones

To a mixture of phenylhydrazine (1 mmol) and ethyl acetoacetate (1 mmol) in water (4 ml) (stirred at room temperature for 10-15 min), aromatic aldehyde (1 mmol), 2-naphthol (1 mmol) and Ce-SiO_2 (0.9 mol %) were added and heated to reflux for appropriate times (monitored by TLC). After completion of the reaction, the heterogeneous catalyst was recovered from the reaction media by simple filtration. The filtrate was evaporated to afford the crude solid product which was later purified by column chromatography. The solid catalyst was washed with hot ethanol and then dried in oven to reuse. The spectral data for some selected compounds are given below.

4-((2-hydroxynaphthalen-1-yl)(3,4,5-trimethoxyphenyl)methyl)-5-methyl-2-phenyl-1H-pyrazol-3(2H)-one:

Yellow solid, mp 128-130 °C; ^{1}H NMR (300 MHz, $CDCl_3$): 8.02 (t, 1H, J = 7.2 Hz, Ar-H), 7.80 (d, 1H, J = 7.9 Hz, Ar-H), 7.64 (d, 1H, J = 8.9 Hz, Ar-H), 7.47 (t, 1H, J = 7.5 Hz, Ar-H), 7.33 (t, 1H, J = 7.4 Hz, Ar-H), 7.18 (d, 2H, J = 7.7 Hz, Ar-H), 7.04 (d, 1H, J = 8.8 Hz, Ar-H), 6.90 (t, 2H, J = 7.5 Hz, Ar-H), 6.80 (t, 1H, J = 7.2 Hz , Ar-H), 6.32 (s, 2H, Ar-H), 5.97 (s, 1H, CH), 3.69 (S, 3H, OCH_3), 3.52 (s, 6H, OCH_3), 2.13 (s, 3H, CH_3); ^{13}C NMR (176 MHz, $CDCl_3$): δ 154.0, 152.8, 146.8, 136.4, 136.2, 135.1, 133.5, 129.4, 129.2, 129.1, 128.8, 126.5, 126.3, 122.7, 122.1, 121.6, 120.9, 120.4, 119.5, 106.8, 104.7, 60.7, 56.0, 36.3, 11.4; HRMS: m/z Calcd. for $C_{30}H_{29}N_2O_5$ $[M+H]^+$: 497.2071; Found, 497.2050 (Rel. Int.100%). FT-IR (KBr) *v* cm^{-1} : 3063, 2929, 1593, 1499, 1457, 1414, 1370, 1321, 1233, 1125, 1002, 821, 750, 691, 542.

4-((6-bromobenzo[d][1,3]dioxol-5-yl)(2-hydroxynaphthalen-1-yl)methyl)-5-methyl-2-phenyl-1H-pyrazol-3(2H)-one:

White solid, 178-179 °C; ^{1}H NMR (300 MHz, $CDCl_3$+Me_2SO-d_6): 11.0 (bs, 1H, NH), 9.89 (bs, 1H, OH), 7.94 (d, 1H, J = 8.9 Hz, Ar-H), 7.80 (d, 1H, J = 7.7 Hz, Ar-H), 7.69-7.72 (m, 3H, Ar-H), 7.41 (t, 3H, J = 7.5 Hz, Ar-H), 7.21-7.31 (m, 1H, Ar-H), 7.16-7.19 (m, 2H, Ar-H), 7.09 (d, 1H, J = 8.7 Hz, Ar-H), 6.71 (s, 1H, Ar-H), 6.01 (m, 2H, CH_2, CH), 5.98 (s, 1H, CH_2), 1.86 (s, 3H, CH_3); ^{13}C NMR (126 MHz, Me_2SO-d_6): δ 163.3, 153.3, 148.4, 146.5, 146.3, 137.1, 134.7, 133.5, 128.8, 128.6, 128.5, 126.3, 124.4, 122.6, 122.2, 119.4, 118.6, 118.2, 113.8, 112.2, 110.6, 107.0, 101.6, 38.2, 11.3; HRMS: m/z Calcd. for $C_{28}H_{22}BrN_2O_4$ $[M+H]^+$: 529.0757; Found, 529.0740 (Rel. Int.100%). FT-IR (KBr) ν cm^{-1}: 3450, 3062, 2906, 2797, 1732, 1598, 1550, 1501, 1475, 1411, 1373, 1312, 1249, 1158, 1104, 1038, 933, 859, 832, 813, 783, 748, 720, 686, 628, 570.

2.4. Evaluation of antimicrobial activity by plate method

Well plate method was followed for both antibacterial and antifungal activities for measuring the zone of inhibition by compounds against selected test organisms. Six bacterial strains which include three gram negative bacteria such as *Salmonella typhi, Salmonella paratyphi, Pseudomonas aeruginosa* and three gram positive bacteria such as *Bacillus subtilis, Micrococcus luteus* and *Streptococcus mutans.* While, *Candida albicans* and *Trichoderma viride* strains were used for determination of antifungal activity. Initially all the

above bacterial strains were grown in nutrient broth for 24 hours at 37^{o}C and fungal strains were grown in Czapek dox broth. All the synthesized compounds were diluted with DMSO to get final concentration of 1 mg/ml. Medium and the Petri plates were initially sterilized at 121^{o}C for 15 min. Under sterilized environment, the agar medium was poured into plates. After solidification, 60 µl of test inoculum was spread on the plates using sterile spreader. Wells were made with sterile cork borer and in each well exactly 100 µl of sample were loaded. Control and standard were also placed in separate wells in each plate. The plates were first incubated for 20 – 30 min at 4^{o}C to allow the compounds to diffuse into the agar, and then subsequently incubated for 24 h at 37^{o}C for antibacterial and 48 h for antifungal activity. Zone diameters were expressed in mm using calibrated scale. Experiment was performed in triplicate and average values were reported to minimize the deviations.

3. **Results and discussion**

Water, as a reaction media, enhances the synthetic efficiency of a multicomponent reaction while conserving the environmental benefits [41] and the use of such protocol can thus establish an ideal green synthetic reaction condition. Knoevenagel condensation reactions, often utilized for the construction of polyfunctional compounds, can be conveniently performed under aqueous environments. These polyfunctional compounds can be combined with other complexity-generating reactions such as inter- or intramolecular Diels–Alder, Michael addition reactions, etc., thereby forming different diverse heterocyclic structures [42]. Herein, the emphasis is focused on conducting a complex multi-component reaction in the presence of a solid acid catalyst under aqueous media to obtain poly-substituted pyrazolones. These pyrazolone derivatives will be screened for their antibacterial and antifungal activity in the hope of discovering new structural leads serving as antimicrobial agents.

3.1. Characterization of ceria–silica composite

Taking into account our interest to explore the ability of cerium (IV) compounds as Lewis acid catalysts [43-45], we decided to synthesize a new Ce–SiO_2 composite based on the sol–gel method [46]. Thus, requisite amounts of cerium chloride and tetraethylorthosilicate were taken under appropriate reaction conditions to yield the Ce-SiO_2 composite. The glassy composite was crushed and heated to give a fine pale yellow powder. Textural properties like BET specific surface area, pore volume, and average pore diameter of Ce-SiO_2 have been assessed from N_2 adsorption–desorption isotherm measurements. The

specific surface area of the Ce/SiO_2 composite, analysed through BET method, was found to be 197 m^2g^{-1}. The sample showed isotherm of type IV having inflection around P/P_0 =0.7–0.85. The BJH analysis showed a pore diameter of 66.4 Å and a pore volume of 0.9 cm^3g^{-1}, for Ce-SiO_2 composite, suggesting a mesoporous material (Fig. 1) [47, 48].

The chemical purity of the sample as well as their stoichiometry was analysed by EDAX studies. The EDAX spectrum (Fig. 2) showed the presence of cerium, oxygen and silicon as the only elementary components. The wide angle powder X-ray diffraction (XRD) patterns of ceria–silica sample are shown in Fig. 3. Peaks observed at 2θ = 28.6, 32.8, 47.5, 56.3 and 76.7 degrees in both the samples (Fig. 3a and 3b) are attributed to the (111), (200), (220), (311) and (331) reflection planes of typical face-centred cubic CeO_2 [49, 50]. These diffraction peaks clearly specify that Ce(III) ion incorporated in the silica framework has been oxidized to more stable Ce(IV) species during sol–gel synthesis and calcination process in presence of air. The similar diffraction patterns in both fresh and used (after 5^{th} cycle) samples relate to framework similarity in the catalysts.

XPS technique has been used to understand the chemical nature of cerium in silica matrix and interaction between supported CeO_2 with silica frameworks. Fig. 4a and 4b shows Ce 3d and Si 2p electron core level X-ray photoelectron spectra of Ce-SiO_2 composite. The XPS signal, at binding energies 887.45 eV and 905.25 eV (Fig. 4a), can be assigned to the Ce $3d_{5/2}$ and Ce $3d_{3/2}$ respectively [51-53]. The only peak near BE value ca. 103 eV in Si 2p XPS spectra (Fig. 4b) corresponds to the presence of SiO_2 species in the catalyst. The UV-vis absorbance of Ce-SiO_2 originates from a charge transfer transition from (ligand→metal) O 2p to Ce 4f and the spectrum (Fig. 5) displays two absorption peaks with intensity maxima around 220 and 330 nm which can be attributed to the presence of two different types (tetra-coordinated and hexa-coordinated) of Ce^{4+} species [47, 48, 50].

The SEM and TEM images of the Ce/SiO_2 composite after five cycles (Fig. 6) did not show any substantial changes in the morphology of the catalyst, which specifies that the integrity of the catalyst is preserved throughout the recycling studies. The above studies thus endorse a stable structure of the catalyst and cerium is tightly bound to the support, which in turn facilitates efficient recycling (Fig. 7). The ICP-AES analysis revealed that the concentration of Ce in both fresh (4.54 wt. % Ce) and after 5^{th} cycle catalyst (4.48 wt. % Ce) was almost similar. This denotes that Ce is tightly bound to the support and no leaching of the catalyst occurs upon it reuse.

3.2. Optimization studies

In the first series of experiments, the effect of the catalyst loading, the nature of the solvent, the optimum reaction time and temperature were examined. The four component reaction conducted on a 1 mmol scale reaction of benzaldehyde, 2-naphthol, phenyl hydrazine and ethyl acetoacetate at reflux temperature, under catalyst free conditions, formed trace amount of the product (Table 1, entry 1). To enhance the yield of the product and to optimize the reaction conditions, a number of alternative cerium based catalysts, preferably various cerium salts and different loadings of Ce-SiO_2 were investigated (Table 1). Heterogeneous Ce-SiO_2 composite exhibited better catalytic activity among various cerium catalysts under aqueous conditions (Table 1, entry 5).

Further, different loadings of Ce-SiO_2 were examined under given reaction conditions. The increase in the amount of Ce-SiO_2 from 0.3 to 0.9 mol% shortened the reaction time as well as enhanced the yield of product from 62% to 92% (Table 1, entries 5-9). An increase in the catalyst quantity had no significant effect on reaction time and the yield of product (Table 1, entry 10). A gradual increase in the reaction temperature from 60°C to 80°C to reflux temperature hastened the reaction to give the desired product in optimum yield (Table 1, entries 7, 8 and 9). The effect of solvents such as H_2O (Table 1, entry 9), CH_3CN (Table 1, entry 11), CH_3OH (Table 1, entry 12), EtOH (Table 1, entry 13) and toluene (Table 1, entry 14) was also examined at reflux temperatures and it was observed that the best result were obtained in the presence of water as a solvent. Catalytic amount of pure SiO_2 did not show valued effect on the reaction system emphasizing the role of cerium metal as a crucial species in the Ce/SiO_2 composite (Table 1, entry 15).

The optimized reaction conditions were then extended for a series of different aldehydes (1a–p) to assess the versatility of the Ce/SiO_2 catalysis. The results are summarized in Table 2. The reaction progressed almost with same ease with aromatic, heterocyclic and aliphatic aldehydes. Various functional groups such as nitro (NO_2), halo (X), hydroxyl (OH), methoxy (OCH_3) and methyl (CH_3) were tolerated. No significant change in the yield was observed when more than one substituent was present in the phenyl ring (Table 2, entries 9-12 and 15). Hence, electronic and steric factors played a negligible role in this protocol.

3.3. Catalyst Recycling

The catalyst recycling experiment was done using the model reaction of benzaldehyde, 2-naphthol, phenyl hydrazine and ethyl acetoacetate and 0.9 mol% of the catalyst in H_2O at reflux temperature. After completion of the reaction, the catalyst was easily separated by filtration and washed with hot ethanol, dried under oven and reused in the subsequent reaction. In addition, the absence of any leached cerium in the ICP-AES analysis of the filtrate confirmed that the catalytic process was completely heterogeneous. Almost quantifiable catalyst could be recovered from each run. The reusability of the catalyst was tested up to 5 successive runs (Fig. 7), with only marginal decrease in catalytic activity (Table 2, entry 1). It was found that the catalyst maintained good activity for a minimum of five cycles. The TEM images of the catalyst after five cycles (Fig. 6c and 6d) showed that the structure of the catalyst does not alter during the course of study. The catalyst was further reused for the 6^{th} and 7^{th} cycle. A drastic change in the recovery amount and yields (78% and 59% respectively for 6^{th} and 7^{th} cycles) of the desired product was observed due to loss of catalyst activity. Moreover, a change in the catalyst morphology (as evident from the TEM analysis) was also observed on further recycling experiments (See supplementary information).

3.4. 2D NMR studies

The structure of the final product was unequivocally established from the extensive 1D- (^{1}H and ^{13}C) and 2D- (^{1}H-^{1}H DQFCOSY, ^{1}H-^{1}H ROESY, ^{1}H-^{13}C multiplicity edited HSQC, ^{1}H-^{15}N HSQC and ^{1}H-^{13}C HMBC) NMR spectroscopy analysis of selected compound 8o (Fig. 8). The NMR spectra were acquired on Bruker Avance 500 MHz (for ^{1}H) and 700 MHz (for ^{1}H) spectrometers and are referenced to δ 2.50 ppm and δ 39.51 ppm in DMSO-d_6 solvent for ^{1}H and ^{13}C, respectively. The chemical shift values are presented in ppm (parts per million) units. The existence of NH form of the final product among the three possible CH, OH and NH forms (Fig. 9), was unambiguously confirmed from the observed characteristic ^{1}H- ^{15}N HSQC cross peak between N-3/H-3 (Fig. 10a) and noe cross peak between CH_3/NH protons (Fig. 10b). In the ^{1}H NMR spectrum of compound 8o, the NH and OH protons appear as broad singlets at 11.0 and 9.89 ppm, respectively. The chiral proton (H-7) gives a singlet at 6.00 ppm and show HSQC correlation with carbon (C-7) at 38.19 ppm (see SI). Furthermore, the H-7 proton shows HMBC correlations with C-6, C-13, C-1", C-8, C-4, and C-1 at 107.0, 113.8, 118.6, 134.7, 148.4 and 163.3 ppm, respectively (see SI).

The methyl protons appear as a singlet at 1.86 ppm and the methyl carbon (C-5) appear at 11.3 ppm (see SI). Moreover, the methyl protons show HMBCs with C-6 and C-4 at 107.0 and 148.4 ppm, respectively (see SI).

3.5. A tentative mechanistic pathway for the multicomponent reaction

A tentative mechanism for the formation of compound 8 is proposed in Scheme 2. The condensation of aldehyde (1), 2-naphthol (2), and 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (3) may occur by Knoevenagel condensation and Michael addition via two pathways (Scheme 2) [38, 39]. As shown in Scheme 2, the solid acid catalyst Ce-SiO_2 (≡ Ce (IV)) activates the reactants and the intermediates in this reaction. In the first pathway, the intermediate 4 is formed by Knoevenagel condensation of 1 and 2 in the presence of Ce-SiO_2, followed by Michael addition of 3 to 4 to form product 8. In the second pathway, the intermediate 5 is formed by Knoevenagel condensation of 1 and 3 in the presence of catalyst, followed by Michael addition of 2 to 5 to form product 8.

3.6. Biological evaluation

Antimicrobial Activity

All the newly synthesized compounds were evaluated for *in vitro* antimicrobial activity against gram-positive bacteria (*B. subtilis, S. mutans and M. luteus*) and gram negative bacteria (*P. aeruginosa, S. typhi and S. paratyphi*) along with two fungal strains (*C. albicans and T. viride*). Streptomycin sulphate and ketoconazole were used as standard drug, respectively for antibacterial and antifungal activity evaluation. It was noticed that all tested compounds (except 8l) showed promising antibacterial activity with either of the tested bacterial strains. However, the antibacterial activity profile differed with type of bacterial strain and nature of compounds. For example compounds 8d, 8e displayed superior inhibitory activity on gram-positive bacteria *Bacillus subtilis, Streptococcus mutans* and *Micrococcus luteus* respectively. In case of gram negative bacteria the 8e, 8g, 8i and 8k compounds showed significant activity. The synthesized compounds showed good anti-bacterial activity ranging from 10.5–27.5 mm zone (Table 3). Critical evaluation of antibacterial profile of the synthesized compounds further indicated that all halogen and nitro substituted pyrazolone derivatives showed considerably better antibacterial activity while tri substituted pyrazolone derivative (8l) showed little or no biological activity with all test bacterial strains. In addition, pyrazolone derivative (8m) revealed better activity profile compared to compound

8l but not similar to that of halogen and nitro substituted compounds. Further, inter species difference in antibacterial activity for synthesized compounds also varied. For example compound 8k (dinitro substituted pyrazolone derivative) denoted better antibacterial activity with *B. subtilis, M. luteus, S. typhi and S. paratyphi* compared to *S. mutans* and *P. aeruginosa* suggesting a bacterial strain specificity towards these synthesized compounds. The compounds were also evaluated for antifungal activity (Table 3) and among the newly synthesized compounds seven compounds (8d, 8e, 8g, 8i-8k and 8o) showed activity against *Candida albicans* and three compounds (8e, 8i and 8k) showed activity against *Trichoderma viride.* The antifungal profile of these synthesized compounds further suggested that compound 8k (dinitro substituted pyrazolone derivative) has commercial importance as this compound showed better activity than standard i.e., ketoconazole at similar concentration (100 μg).

4. Conclusions

A new ceria–SiO_2 composite prepared through the sol–gel method was successfully applied as a heterogeneous Lewis acid catalyst in the synthesis of a series of 2-aryl-5-methyl-1H-pyrazol-3(2H)-ones in good yields. All the newly synthesized compounds were assessed for anti- microbial activity and showed promising activity against few of the bacterial and fungal strains. Herein, we have demonstrated a greener approach for the multi-component reaction using heterogeneous catalysis to prepare small molecules of biological interest.

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Figure captions

Fig. 1. N_2 adsorption–desorption isotherms of the Ce-SiO_2 composite; inset: BJH pore size distribution curve.

Fig. 2. The EDX spectra of the Ce-SiO_2 composite.

Fig. 3. Powder XRD patterns of (a) fresh and (b) used Ce-SiO_2 catalyst.

Fig. 4. XPS analysis showing (a) Ce 3d and (b) Si 2p core level spectra of the Ce-SiO_2 composite.

Fig. 5. UV-DRS spectra of the Ce-SiO_2 catalyst.

Fig. 6. SEM (a) fresh & (b) used and TEM (c) fresh & (d) used pictures of theCe-SiO_2 catalyst.

Fig. 7. Recycling experiment of Ce-SiO_2.

Fig. 8. Schematic representation of the characteristic ^{1}H-^{13}C HMBC correlations (shown as red arrows) of the compound 8o.

Fig. 9. Tautomeric forms of pyrazolone 8.

Fig. 10. Expanded region of (a) ^{1}H-^{15}N HSQC (Heteronuclear Single-Quantum Correlation) and (b) ^{1}H-^{1}H ROESY (Rotating frame Over Hauser Effect Spectroscopy) spectrum of compound 8o(Avance 700 MHz, DMSO-d_6, 25 °C).

Figure 1

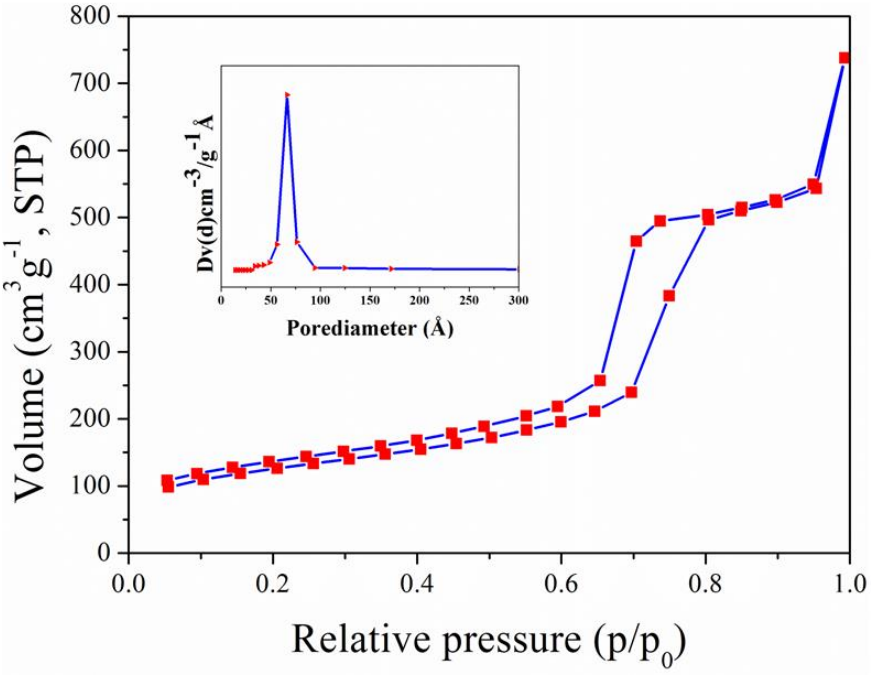


Figure 2

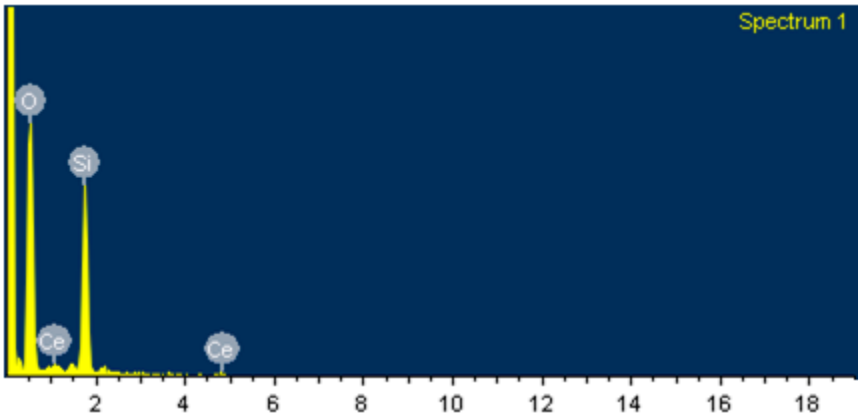
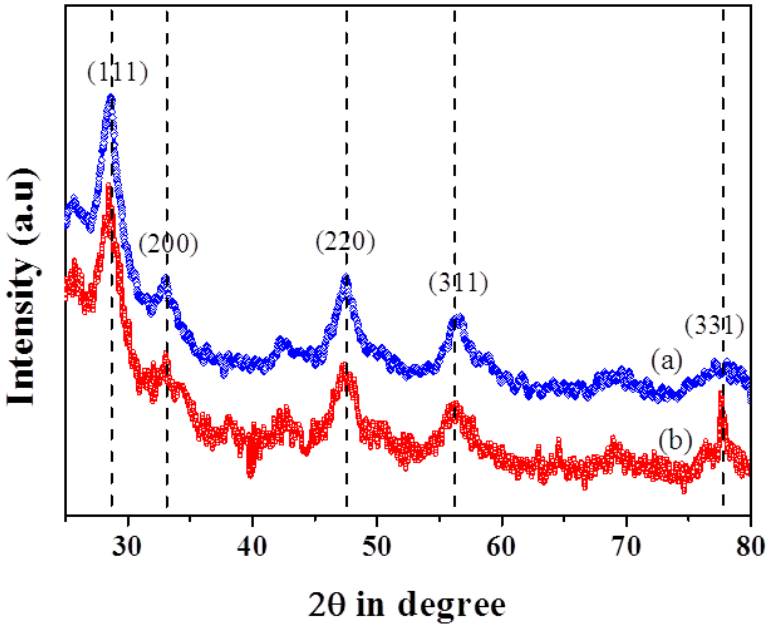


Figure 3



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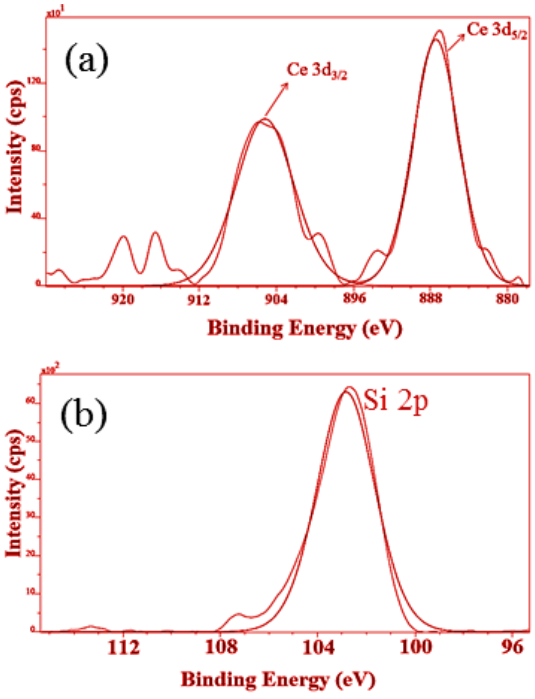

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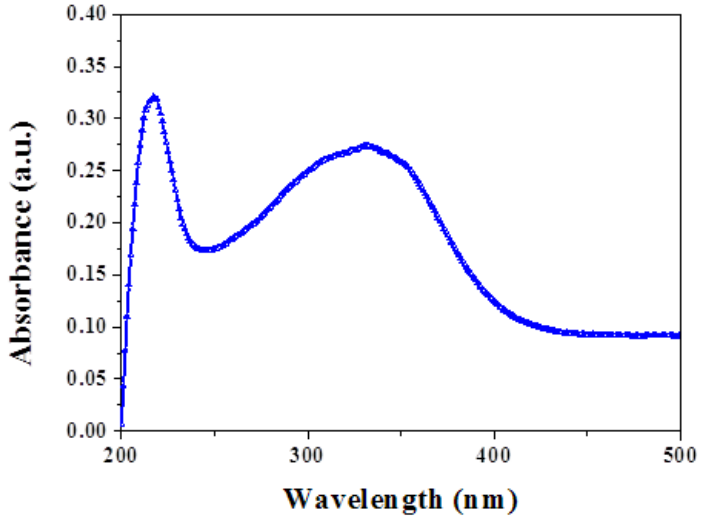

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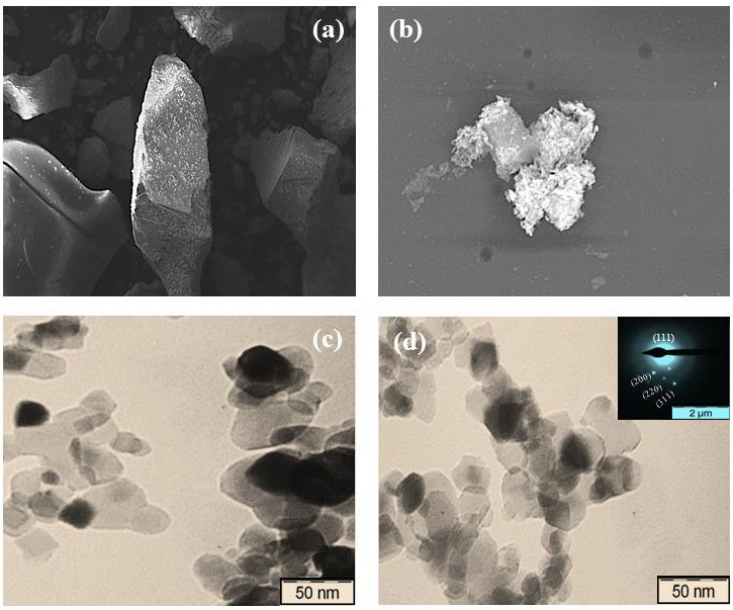


Figure 7

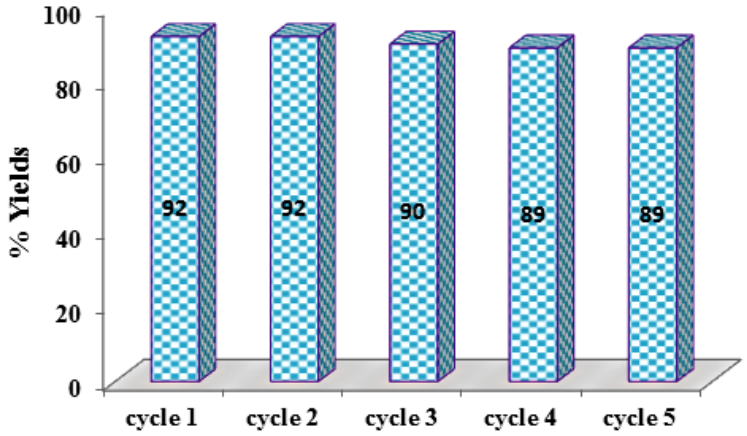


Figure 8

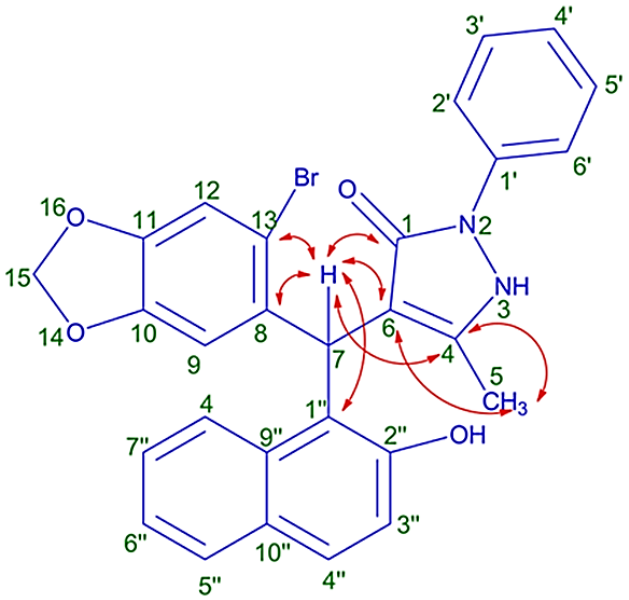
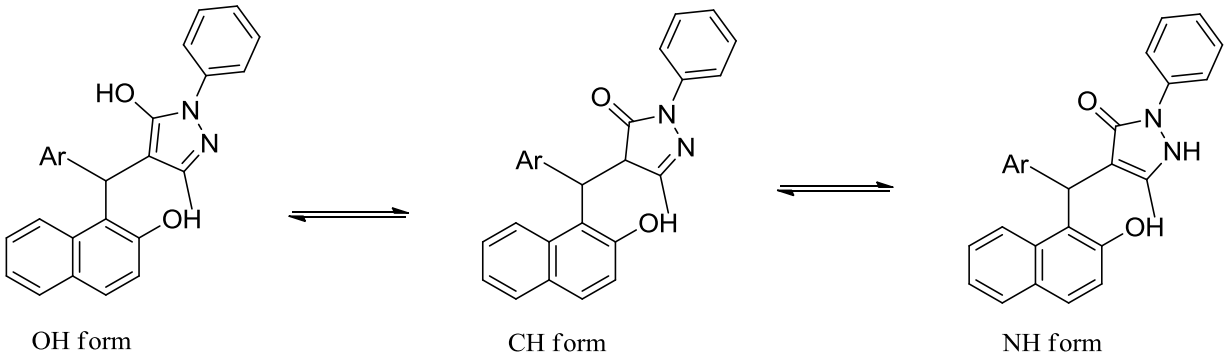
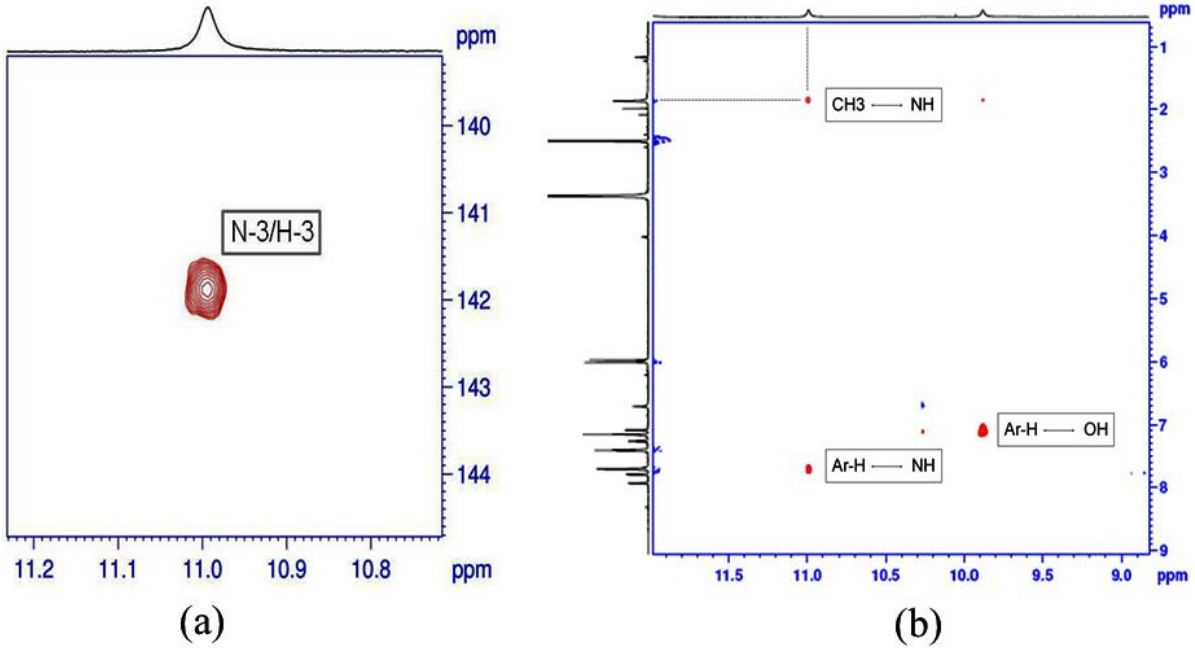


Figure 9

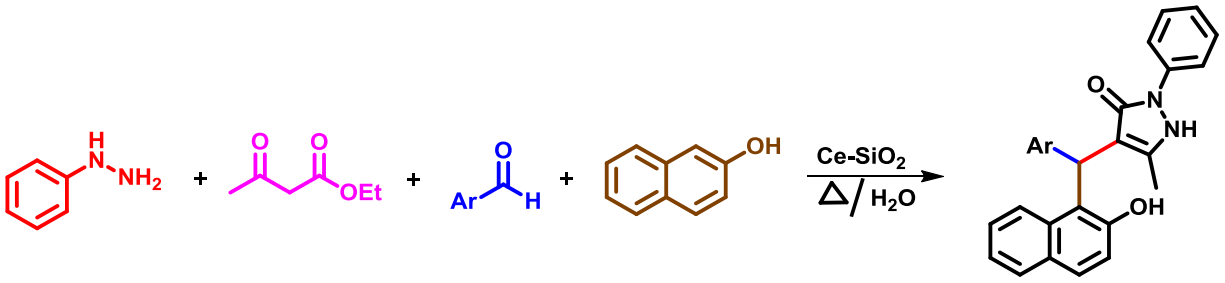


OH form CH form NH form

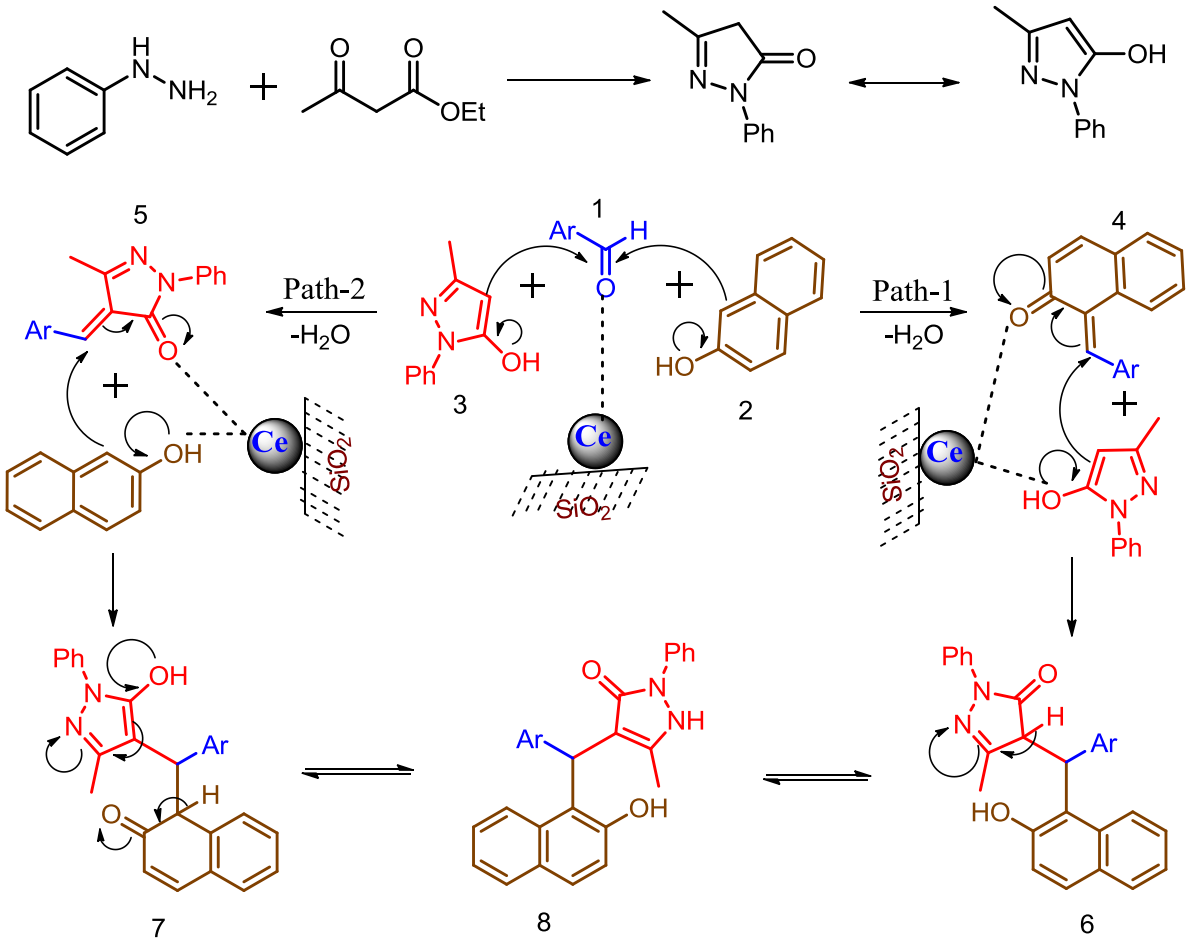
Figure 10



Schemes

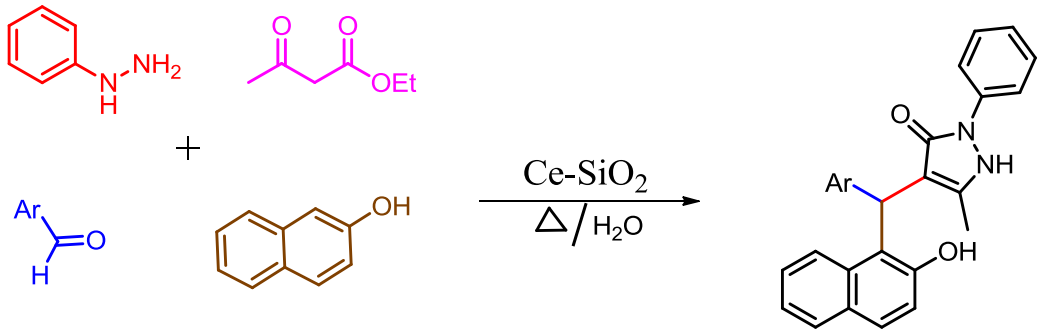


Scheme 1. General synthesis of 1H-3-pyrazolones



Scheme 2. Mechanistic considerations

Table 1. Screening of reaction parameters[a]

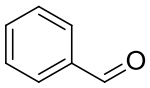
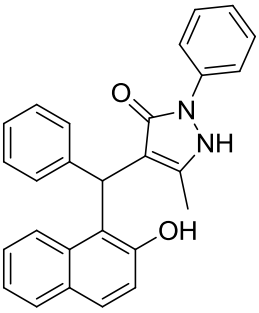
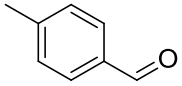
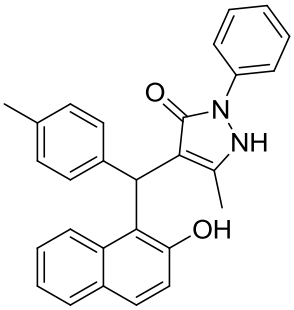
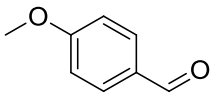
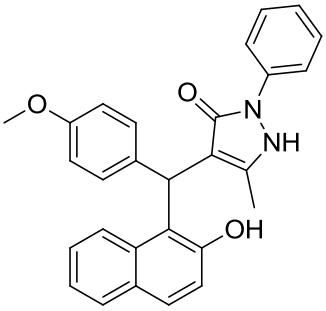
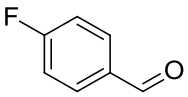
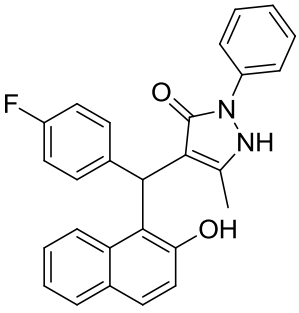
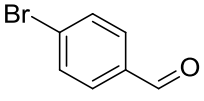
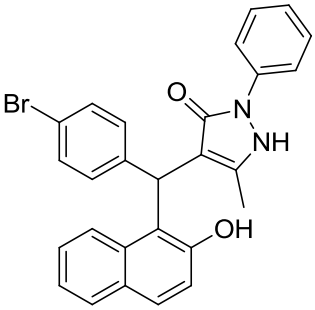


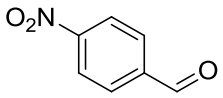
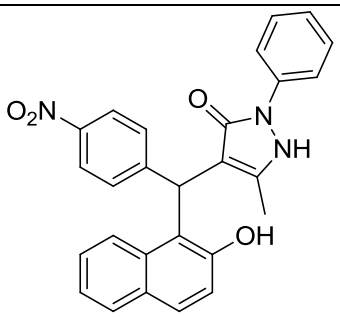
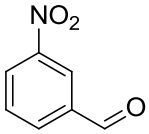
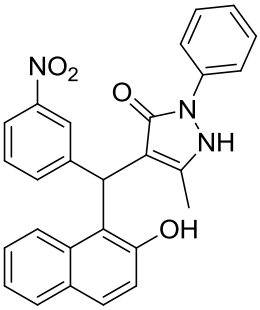
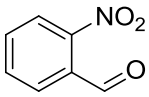
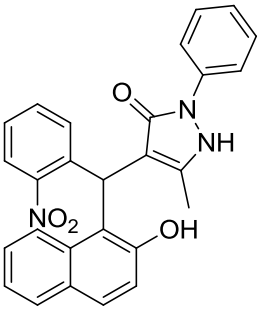
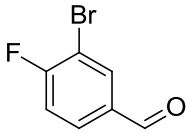
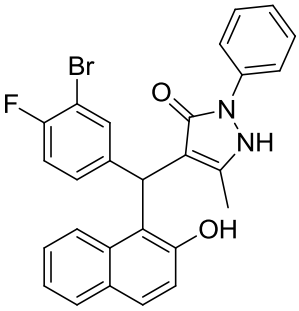
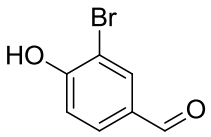
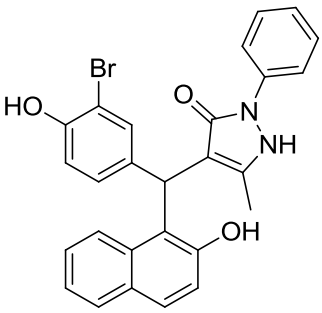
Entry	Catalyst	loading	Solvent	Temp (°C)	Time (min)	Yield (%)[b]
1.	-	-	H_2O	Reflux	120	Traces
2.	$CeCl_3$	5 mol%	H_2O	Reflux	120	54
3.	$Ce(SO_4)_2$	5 mol%	H_2O	Reflux	120	60
4.	CeO_2	5 mol%	H_2O	Reflux	120	61
5.	Ce-SiO_2	0.3 mol%	H_2O	Reflux	120	62
6.	Ce-SiO_2	0.6 mol%	H_2O	Reflux	80	86
7.	Ce-SiO_2	0.9 mol%	H_2O	60	100	74
8.	Ce-SiO_2	0.9 mol%	H_2O	80	80	90
9.	Ce-SiO_2	0.9 mol%	H_2O	Reflux	35	92
10.	Ce-SiO_2	1.2 mol%	H_2O	Reflux	35	91
11.	Ce-SiO_2	0.9 mol%	CH_3CN	Reflux	90	58
12.	Ce-SiO_2	0.9 mol%	MeOH	Reflux	90	55
13.	Ce-SiO_2	0.9 mol%	EtOH	Reflux	90	60
14.	Ce-SiO_2	0.9 mol%	Toluene	Reflux	90	53
15.	SiO_2	5 mol%	H_2O	Reflux	100	Traces

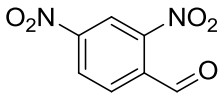
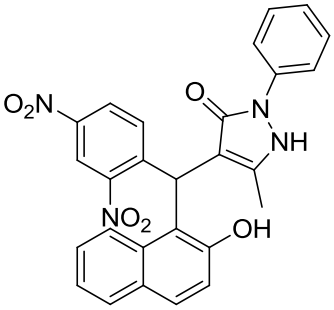
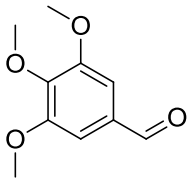
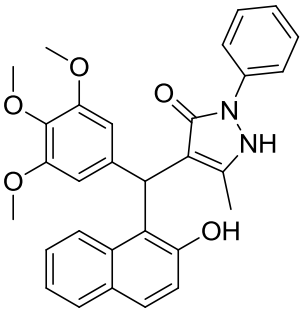
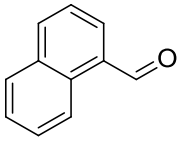
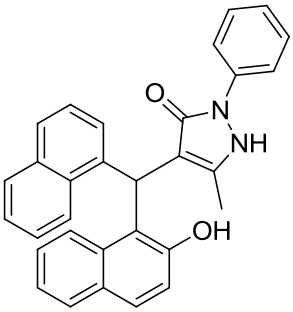
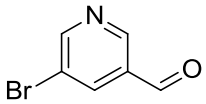
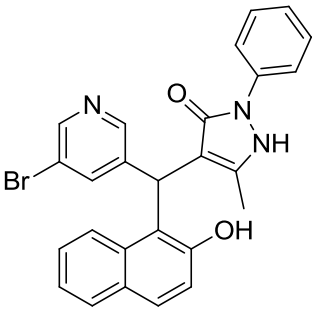
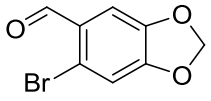
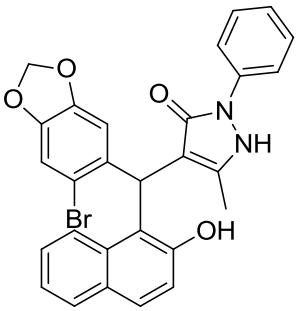
[a]Reactions were performed using benzaldehyde, 2-naphthol, phenyl hydrazine and ethyl acetoacetate in 1mmol scale.

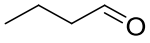
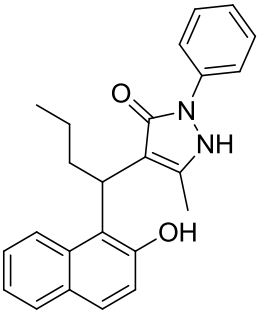
[b]isolated yields after column chromatography.

Table 2. Synthesis of 1H-3-pyrazolones via Ce-SiO_2 catalyst in H_2O[a]

Entry	Aldehyde	Product[b]		Time (min)	Yield (%)[c]	TOF[e] (min^{-1})
1.			8a	40	92,92,90,89,89[d]	2.56
2.			8b	50	86	1.91
3.			8c	40	88	2.44
4.			8d	55	83	1.67
5.			8e	55	84	1.69

6.			8f	30	87	3.22
7.			8g	35	92	2.92
8.			8h	35	90	2.85
9.			8i	35	93	2.95
10.			8j	55	85	1.72

11.			8k	45	90	2.22
12.			8l	60	92	1.70
13.			8 m	55	87	1.75
14.			8n	35	92	2.92
15.			8o	35	91	2.89

16.			8p	40	92	2.56

[a]Reaction conditions: aldehyde (1 mmol), 2-naphthol (1 mmol), phenylhydrazine (1mmol) and ethylacetoacetate (1 mmol), Ce-SiO_2 (0.9 mol%), Reflux, 35–60 min.

[b]All products are characterized by NMR and mass spectroscopy.

[c]Isolated yields after column chromatography.

[d]Yields from first to fifth cycle.

[e]TOF = TON/reaction time

Table 3. Anti-microbial activity[a]

	Compound	*B. subtilis*	*S. mutans*	*M. luteus*	*P. aeruginosa*	*S. typhi*	*S. paratyphi*		C. albicans	T. viride
Anti-bacterial activity	8d	18.5±0.71	27.5±0.71	13.5±0.71	13.5±0.71	19.5±0.71	19.5±0.71	Anti-fungal activity	14±0.00	0
	8e	18.5±0.71	29.5±0.71	18.5±0.71	14.5±0.71	19.5±0.71	19.5±0.71		15.5±0.71	13.5±0.71
	8g	19.5±0.71	19±0.141	14.5±0.71	10.5±0.71	19.5±0.71	20.5±0.71		13.5±0.71	0
	8i	19.5±0.71	18±0.00	16.5±0.71	14.5±0.71	20.5±0.71	19.5±0.71		18.5±0.71	10.5±0.71
	8j	17±0.00	12.5±0.71	15.5±0.71	13.5±0.71	16±0.00	20.5±0.71		12.5±0.71	0
	8k	22.5±0.71	14.5±0.71	21.5±0.71	13.5±0.71	20±0.00	20±0.00		28.5±0.71	21.5±0.71
	8l	13.5±0.71	0.00	0.00	0.00	10.5±0.71	12.5±0.71		0	0
	8m	12±0.00	10.5±0.71	19.5±0.71	11.5±0.71	12.5±0.71	15±0.00		0	0
	8n	20.5±0.71	14.5±0.71	18.5±0.71	12±0.00	16.5±0.71	20±0.00		0	0
	8o	16.5±0.71	13±0.00	15.5±0.71	11.5±0.71	15.5±0.71	16.5±0.71		13±0.00	0
	8p	15.5±0.71	16.5±0.71	13.5±0.71	12.5±0.71	14.5±0.71	16±0.00		0	0
	Std[b]	25±0.00	26±0.00	21.5±0.71	25.5±0.71	22.5±0.71	21.5±0.71		24.5±0.71	25±0.00

[a]zone of inhibition by compounds against selected test organisms.

[b]Streptomycin sulphate and ketoconazole were used as standard drug, respectively for antibacterial and antifungal activity evaluation.