NiO Nanoparticles: A Highly Efficient Catalyst For One-Pot Three-Component Synthesis of Pyrano[2, 3-d]Pyrimidine Derivatives in Green Media

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Original Research

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Abstract

In this paper NiO nanoparticles are utilized for effective strengthening of annulated pyrano [2, 3- d] pyrimidine synthesis through primary Knoevenagel, the following Micheal and ultimate heterocyclization reactions of aldehyde, malononitrile and barbituric acid. The NiO nanoparticles characteristics are identified through using advanced techniques like IR, UV, EDX, XRD, SEM and TEM. The nano-NiO particles are mostly of below < 100 nm sizes with uniform sphere shapes. The adopted approach is advantages due to its simple processing, relatively short reaction time, often good to high average yields, convenient workability, and environmental friendliness.

Introduction

The Nitrogen and Oxygen containing synthetic compounds like heterocyclic rings are very interesting because of possessing a wide spectrum of useful biological and pharmaceutical characteristic and activities [1-12]. Pyrano [2, 3-d] pyrimidines as an example, are structural motifs contained in synthetic and natural compounds that are biologically active. These heterocyclic rings exhibit invaluable biological healing activities, as they perform antitumor [13], hepatoprotective [14], antibronchitic [15] and anti-AIDS behaviours [16]. Accordingly, the efficient synthetization of such compounds and the relevant derivatives entail a motivating challenge for the organic chemistry researchers.

Fortunately, Multicomponent reactions (MCRs) in modern organic synthetic chemistry are regarded highly applicable tools owing to having almost all necessary features to take part in ideal syntheses; features like high atom performance, fast and easy put up with highly time and energy-cost savings, environmentally friendliness as well as providing targeted and diversity-oriented syntheses [17]. Hence, currently devising new multicomponent reactions to produce biomedical and industrial synthetic scaffolds is indispensable.

Numerous regular yet useful producers exist for producing the above compounds. From the above-mentioned techniques, the aromatic aldehydes, barbituric acid derivatives and malononitrile with their particular multi-component condensation reactions have been the focal of considerable focus and various bases have proved to be enduring catalysts for such reactions. Its noteworthy however that such protocols have their own drawbacks like corrosion, problematic catalyst recycling and waste generation issues [18-24]. Apparently, a potential of NPs application is using them as catalyst to develop new synthetic methods qualified for transformations in organic settings of environmentally friendly producers. According to some researchers, a number of nano-materials such as the metals metal oxides and NPs with semi-conductor properties could be utilized in organic chemistry as catalysts [25, 26].

Hence the development of new synthetic methods, facilitating the provision of organic compounds is most welcomed. Condensation reaction is among those chemical activities for which devising a new environmentally friendly catalyst could potentially provide an approach for dealing with the aforementioned challenges. Upon our previous study on synthesis of organic compounds by
nanoparticles [26-29], the scope of the present work was to achieve the multi-component pyraño [2, 3-d] pyrimidines by using NiO nano powders as a green, environmentally friendly catalyst (Scheme 1).

**Experimental**

**2.1 Materials**

All the chemical materials were supplied from Merck or Sigma Aldrich Co. and were used with no further treatment. We also used distilled water in this paper.

**2.2 Material characterization**

The characterization of supplied materials was performed in terms of physical constants against authentic samples and FT-IR spectroscopy. Thin layer chromatography (TLC) on Merck pre-coated silica gel 60 F254 aluminum sheets as well as UV light visualization technique was used to monitor the products purity and the reactions’ progress. A BUCHI 510 melting point device was utilized for determining the material melting points. To record Fourier, transform infrared (FT-IR) spectroscopy a JASCO FT-IR-4000 spectrophotometer was used while the samples were dispersed on KBr pellets across 4000–400 cm\(^{-1}\) (Bruker, Germany) wavelength range. Also, a Bruker Advance DPX 400 MHz equipment was utilized for recording nuclear magnetic resonance (NMR) spectra, measured on DMSO-d\(_6\) relative to tetramethylsilane as an internal standard. Scanning of the X-ray diffraction (XRD) fresh patterns was performed in reflection mode through the use of a powder X-ray diffractometer (X’ Pert MPD, PAN analytical) equipped with Cu-Ka source of radiation (\(\lambda = 0.154 \) nm) between 10° and 90° (2-Theta) having a stage width of 0.010") using a Philips XPERT PRO (Bruker, model D8 Advance). The NiO nanoparticles morphology was examined via scanning electron microscopy (SEM) (Nano SEM 450) (FEI, U.S.). To perform Transmission electron microscope (TEM) measurements, a HITACHI H-7650 electron microscope was used. To measure the UV–VIS spectra a USB-2000 UV–Vis spectrophotometer was used.

**2.3 General process of the NiO nanoparticles synthesis**

Nickel oxide nanoparticles underwent synthetization in free standing powder form using wet chemical synthesis technique. In this study a dissolution of 1 mmol of Nickel (II) nitrate hexahydrate [Ni(NO\(_3\))\(_2\)·6H\(_2\)O, Merck] was prepared in 10 mL of polyethylene glycol [H(OCH\(_2\)CH\(_2\))\(_n\) OH], Merck]. A magnetic stirrer was then used to stir the solutions for 1 h at 60°C. Additionally, separate solutions of 2 mmol NaOH and 4 mmol sodium dodecyl sulfate were prepared through dissolution in 10 mL polyethylene glycol, each stirred for 1 h using a magnetic stirrer at 60°C; the prepared solution were then both added to Nickel (II) nitrate solution and stirred using magnetic stirrer for 2 h. at 60°C. The mixture so prepared underwent 450, 650 and 750 w irradiation for a 4 min time span then left to cool down to reach ambient temperature. Afterwards the centrifugation method was used to form the precipitates; they were then rinsed frequently by ethanol and dried in vacuum oven apparatus at 60°C to finally accumulate the nickel oxide nanoparticles.
2.4 General preparation process of benzopyrano [2,3-d] pyrimidinones

Aromatic aldehydes 1 (1.9 mmol), malononitrile 2 (2.2), barbituric acid or 2-thiobarbiturate 3 (2 mmol) and NiO nanoparticles (0.04 g) were taken in an RB flask with 10 mL H₂O as solvent and stirred for appropriate time at reflux condition. Thin layer chromatography was used to monitor the reactions, after the completion of which 5 mL of DMSO was introduced into the reaction mixture. Afterwards the solid compound (catalyst) was separated through filtration, and water was added to the remaining solution so as to form precipitates. The precipitates were filtered and washed by ethanol to acquire the derivatives of pure product benzopyrano [2, 3-d] pyrimidine derivatives. Spectral data of the selected compound is given below:

7-Amino-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-2,4-dioxo-1H-pyrano [2, 3-d] pyrimidine-6-carbonitrile (4a): M. P.: 260- 265 °C, IR (KBr, Cm⁻¹): 1679, 2200, 3314. ¹H NMR (400 MHZ, DMSO-d₆) δ: 4.51 (s, 1H, CH), 7.32 (2H, brs- NH₂), 7.61 (1H, t, J = 8.0H, H-Ar), 8.10- 8.11 (m, 2H, H- Ar), 11.72 (s, 1H, NH), 12.47 (s,1H, NH). ¹³C NMR (100 MHz, DMSO-d₆) δ: 35.4, 58.3, 88.3, 119.6, 122.8, 122.9, 130.6, 135.3, 147.2, 148.5, 150.4, 153.2, 158.9, 163.2 ppm.

Results And Discussion

3.1 Characterization of nickel oxide nanoparticles

To investigate the impacts of microwave on the nickel oxide nanoparticles’ synthesis, the nickel oxide nanoparticles were prepared by applying microwave various power levels (450, 650 and 750 W). Figs. (1a, 1b and 1c) respectively illustrate the NiO nanoparticles scanning electron microscope images. The SEM image represented a spherical structure of the NiO nanoparticles, revealing that they were distributed widely under the effect of agglomeration, probably due to the presence of sodium dodecyl sulfate. The below fig. (1a) SEM image of NiO nanoparticles demonstrates an area of narrow distribution of 50-60 nm particle size, suggesting that 450 w is providing the suitable radiation power condition.

As can be seen from the obtained TEM images, the NiO nanoparticles are spherical in shape. The TEM image Fig. (2) shows that NiO mostly spherical nanoparticle sizes lie somewhere between 40-50 nm, while heavy agglomeration can be spotted in some areas. In this study the TEM and SEM imaging systems measurements confirmed the average particle size obtained from Debye-Scherer formula through XRD patterns.

Infrared spectrometer (IR) measuring NiO nanoparticles exhibited some absorption bonds at 1409 cm⁻¹ and 11590 cm⁻¹ relative to NiO spinal structure. Also 600-1200 cm⁻¹(Ni-O), 2850 and 2918 (CH₂-SDS) and 1082, 1362 (S=O-SDS) adsorption bonds were consistent with the SDS-based synthesized NiO nanoparticles.

The following main elements were obtained from the energy dispersive X-ray (EDX) spectroscopy results: Ni (34%), O (28%), C (24%) and Na (18%). The NiO nanonoparticles’ XRD spectrum, synthesized under
microwave optimal irradiations condition has been illustrated in Fig. (3). According to the Xpert high score software data, the synthesized sample XRD pattern with its JCPD card No. 47-1049 acknowledges the fruitful synthesis of NiO nanoparticles at 0.058 S\(^{-1}\) scanning rate across 10\(^\circ\) to 80\(^\circ\) in spinal phase spectrum. The below XRD pattern also contains –in addition to the NO diffusers–the Ni (OH)\(_2\) and SDS diffractions. A significant absorption peak of about 260 nm can be seen in the UV-VIS spectra of NiO nanoparticles.

3.2. Synthesis of pyrano [2, 3-d] pyrimidine derivatives by using NiO nanoparticles

To extend the present study to experimental research, so that high performance MCRs are developed for the provision of annulated bioactive molecules of pyrimidine [29, 31], here we claim that in aqueous media, through one-pot three-component domino Knoevenagel- Michael addition reactions, the NiO nanoparticles led to catalysis of fast, efficient, and simple synthesis of pyrano[2,3-d]pyrimidine derivatives (Scheme 1).

Initially, as a model reaction, the three-component reaction of 3-nitrobenzaldehyde 1a, barbituric acid 2a, and malononitrile 3 was employed to examine different solvents including: MeOH, EtOH, H\(_2\)O, CHCl\(_3\) and CH\(_2\)Cl\(_2\) (Table 1) in the presence of NiO nanoparticles (0.04 g). The appropriate chosen solvent for utilization in the reaction was H\(_2\)O. Consequently, as Table 1 shows, the three-component model reaction was conducted while various amounts of catalysts were available. In order to come upon the optimal amount of catalyst for accessing pyrano [2, 3-d] pyrimidine 4a, the above investigation was conducted. According to the results, H\(_2\)O with 0.04 g of NiO nanoparticles as the catalyst was the optimal reaction media for the formation of the products 4a.

Once the reaction conditions were optimized, the suitability and effectiveness of the same procedure were surveyed by conducting the reaction through various readily accessible and simple substrates under the optimum conditions. Thus, under the optimum conditions, different aromatic aldehydes containing electron-donating and electron-withdrawing groups, namely, NO\(_2\), N, N-dimethyl and OCH\(_3\) in the para and ortho positions of the benzene ring were came into reaction with malononitrile and barbituric or thiobarbituric acid. As entries 1–12 in Table 4 show, within short reaction times, the concerned products were achieved in moderate-good isolated yields. Also, as entries 8-12 in Table 2 suggest, under the optimum conditions, thiobarbiturate acid was employed, giving high yields of the desired products.

The proposed mechanism of the one-pot reaction between benzaldehyde derivatives, malononitrile and barbituric acid was described in Scheme 2. The acidic surface probably coordinates with the nitrogen and oxygen of the carbonyl carbon on which a partial positive charge appears. Based on this proposed mechanism, NiO nanoparticles are capable of activating aldehyde carbonyl group whilst accelerating barbituric acid enolization. The higher reactivity of the iminium group is utilized to facilitate Knoevenagel condensation between benzaldehyde 1 and malononitrile 2, which produce intermediate 6 that is attacked by the enolized barbituric acid 5 for generation of product 4 after proton transfer and tautomerization of intermediate 7 (Scheme 2).
In summary, by employing the multi-component reaction of malononitrile, barbituric acid, and aromatic aldehydes, in the presence of nanoparticles of NiO as a catalyst, an efficient and rapid synthesis route was developed for pyrano [2,3-d] pyrimidine derivatives in this study resulting in good yields. One can cite several advantages for the same synthesis: it is simple to prepare NiO nanoparticle as the catalyst, the easy accessibility to the starting materials, high reaction times, the clean reaction profile, the easy workup and green media.

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**Tables**

**Table. 1** Optimization of reaction condition for the yield of 7-amino-2,3,4,5-tetrahydro-5-(3-nitrophenyl)-2,4-dioxo-1H-pyran[2,3-d]pyrimidine-6-carbonitrile (4a)
Table. 2 Pyrano[2,3-d]pyrimidine derivatives obtained by the reaction of aromatic aldehydes, malononitrile with barbituric and thiobarbituric acid using NiO nanoparticles as catalyst

| Entry | Nanocatalyst | Solvent  | Temperature | Time (min) | Yield (%)<sup>a</sup> |
|-------|--------------|----------|-------------|------------|------------------------|
| 1     | catalyst free| H₂O      | r.t.        | 24 h       | No reaction            |
| 2     | catalyst free| H₂O      | 100 °C      | 24 h       | trace                  |
| 3     | NiO (0.03g)  | H₂O      | 100 °C      | 5 min      | 75                     |
| 4     | NiO (0.04g)  | H₂O      | 100 °C      | 4 min      | 78                     |
| 5     | NiO (0.05g)  | H₂O      | 100 °C      | 120 min    | 55                     |
| 6     | NiO (0.06g)  | H₂O      | 100 °C      | 130 min    | 50                     |
| 8     | NiO (0.04g)  | MeOH     | 70 °C       | 40 min     | 50                     |
| 9     | NiO (0.04g)  | EtOH     | 80 °C       | 24 h       | 25                     |
| 10    | NiO (0.04g)  | CHCl₃    | 60 °C       | 24 h       | trace                  |
| 11    | NiO (0.04g)  | CH₂Cl₂   | 40 °C       | 24 h       | trace                  |

Table. 2 Pyrano[2,3-d]pyrimidine derivatives obtained by the reaction of aromatic aldehydes, malononitrile with barbituric and thiobarbituric acid using NiO nanoparticles as catalyst

| Entry | Ar              | X  | Product | Time (min) | Yield (%)<sup>a</sup> | Mp (°C)   |
|-------|-----------------|----|---------|------------|------------------------|-----------|
| 1     | 3-NO₂C₆H₄      | O  | 4a      | 4          | 78                     | 260-265   |
| 2     | C₆H₄            | O  | 4b      | 45         | 71                     | 200-210   |
| 3     | 4-(Me₂N)C₆H₄   | O  | 4e      | 5          | 77                     | 252-258   |
| 4     | 4-MeOC₆H₄      | O  | 4d      | 15         | 64                     | 310-315   |
| 5     | 2,4-(MeO)₂C₆H₄ | O  | 4e      | 10         | 76                     | 262-268   |
| 6     | 3,4,5-(MeO)₃C₆H₃- | O  | 4f      | 5          | 75                     | 222-227   |
| 7     | 3-OHC₆H₄       | O  | 4g      | 10         | 37                     | 172-179   |
| 8     | 4-(Me₂N)C₆H₄   | S  | 4h      | 5          | 74                     | 265-270   |
| 9     | 3-NO₂C₆H₄      | S  | 4i      | 10         | 41                     | 192-196   |
| 10    | 2,4-(MeO)₂C₆H₄ | S  | 4j      | 20         | 74                     | 312-318   |
| 11    | 3,4,5-(MeO)₃C₆H₃- | S  | 4k      | 5          | 95                     | 290-295   |
| 12    | C₆H₄            | S  | 4l      | 20         | 17                     | 234-238   |