

Research Article

Catalytic Synthesis of Pyrazolo[3,4-*d*]pyrimidin-6-ol and Pyrazolo[3,4-*d*]pyrimidine-6-thiol Derivatives Using Nanoparticles of NaX Zeolite as Green Catalyst

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An efficient and environmental benign method is reported for the synthesis of some pyrazolopyrimidine derivatives using 3-methyl-1-phenyl-5-pyrazolone with carbonyl compounds in the presence of nanozeolite NaX catalysts, solvent-free and at reflux conditions. It is noteworthy to mention that this method of the synthesis requires less time, less temperature, and better yield.

1. Introduction

Pyrazolopyrimidine derivatives have received a great deal of attention due to their pharmacological activities. Pyrazolopyrimidine derivatives have demonstrated promising antimicrobial activity against gram-positive bacteria [1]. Synthesis of such biologically important compounds assumes great importance. Pyrazolopyrimidine derivatives are purine analogues, and as such they have useful properties as antimetabolites in purine biochemical reaction [2]. Moreover, these compounds also display marked antitumor and antileukemic activities [3]. Pyrazolopyrimidine derivatives have received a great deal of attention due to their pharmacological activity [4], such as allopurino [5], which is still the drug of choice for the treatment of hyperuricemia and gouty arthritis [6]. 1-Phenyl-3-methyl-4-arylmethylene-5-pyrazolones are very useful intermediates in the synthesis of substituted pyrazolones, generally, which were prepared by the condensation of 3-methyl-1-phenyl-5-pyrazolone with aromatic aldehydes [7]. The incorporation of another heterocyclic moiety in pyrans either in the form of a substituent or as a fused component changes its properties and converts it into an altogether new and important heterocyclic derivative. Pyrazoles have attracted particular interest over the last few decades

due to the use of such ring system as the core nucleus in various drugs. They are well known for their popular pharmacological activities. Considering the importance of pyrazolone derivatives, it was thought worthwhile to synthesize new compounds incorporating both these moieties. All the compounds synthesized in the present study were screened for their antibacterial activity against some bacteria (both gram-negative and gram-positive) namely, *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis*, and *C. albicans* by filter paper disc technique. Zeolite X is a highly versatile molecular sieve from the faujasite family of zeolites whose 7.4 Å, three-dimensional pore structure and solid acidity make it useful as a catalyst, adsorbent, membrane, and others [8–10]. This type of zeolite is used for heavy metal adsorption [11], aromatics from aromatic/alkane mixtures [12], and para-xylene [13] separation, as well as natural gas desulfurization [14]. The powerful catalytic properties of X zeolite due to its use in the reaction between MeOH and PhNH₂ [15], hydrocarbons cracking [16], chlorination of toluene [17], and the ammonia synthesis [18]. In this paper, nanozeolite NaX was synthesized via hydrothermal methods with agitation and temperature controlling. We did not use the addition of organic templates, directing agent, seeding crystals, and other additives in this synthesis.

TABLE 1: Synthesis of several pyrazolone-pyrimidine derivatives using urea and nanoparticles of NaX zeolite catalyst.

Entry	Product	Time (h)	^a Yield (%)	MP (°C)
1	4a , -H	1	90	185
2	4b , 4-OH	1.5	95.5	171
3	4c , 3-OH	1.5	93.5	156
4	4d , 2-OH	1.5	91	166
5	4e , 4-Cl	2.5	84	154
6	4f , 3-Cl	2.5	80	150
7	4g , 4-CH ₃	1	92	138
8	4h , 4-OCH ₃	1	94	145
9	4i , 3-NO ₂	3	77	188
10	4j , 4-NO ₂	3	81	183
11	4k , 4-F	3.5	71	124

^aIsolated yield.

2. Experimental

2.1. Chemicals and Apparatus. All melting points are uncorrected. IR spectra were recorded in KBr discs using a Shimadzu IR-740 spectrophotometer. ¹H- and ¹³C-NMR spectra were recorded on a Bruker DPX 400 MHz super-conducting NMR spectrometer with CDCl₃ as a solvent and TMS as an internal standard; chemical shifts are reported in δ units (ppm). Mass spectra were measured on FAB/MS INCOS XL Finnigan MAT. Microanalyses were performed on a LECO-CHNS-932 elemental analyzer.

2.2. Nanozeolite NaX Synthesis. The chemical reagents such as fumed silica (7 nm, Sigma-Aldrich), NaOH (Merck, Darmstadt, Germany), and NaAlO₂ (Sigma-Aldrich) were used for zeolite synthesis. The nanometer-sized faujasite-X zeolite was synthesized by hydrothermal crystallization in a temperature-controlled shaker. Aluminosilicate gel was prepared by mixing freshly prepared aluminate and silicate solutions together in the molar ratio 5.5 Na₂O : 1.0 Al₂O₃ : 4.0 SiO₂ : 190 H₂O. Typically, an aluminosilicate gel containing 5.34 g of NaOH, 2.42 g of NaAlO₂, 3.43 g of SiO₂, and 50.0 g of H₂O was adopted. First, a 250 mL plastic bottle containing freshly prepared sodium aluminate solution and SM-30 and fumed silica, the silicate sources were directly mixed with freshly prepared aluminate solution at room temperature and then immediately moved to a shaker at the desired temperature for hydrothermal crystallization. Hydrothermal crystallization was conducted at 60°C for 4 days in a shaker with a rotation rate of 250 rpm. The powdered products were recovered with centrifugation, washed with DI water until pH < 8, and then dried at room temperature for 24 h for further characterization.

2.3. Nanozeolite Characterization. The X-ray powder diffraction (XRD) patterns were recorded at 25°C on a Philips instrument (X'pert diffractometer using CuK α radiation) with a scanning speed of 0.03° (2θ) min⁻¹. The crystallinity of sample was determined from the peak areas of 6° [18], 16° [10], and 27° [13], and the average crystal dimension was

calculated using Scherrer's equation [12, 13]. Also, the particle size distribution was measured by the Mastersizer 2000 (Malvern instrument). The SEM (Hitachi, model S-4160) was used to particle size distribution of nanozeolite crystals, and the Si/Al ratio, elemental compositions of nanoparticles was determined by XRF (Philips instrument).

2.4. Synthesis of Pyrazolone-Pyrimidine Derivatives. Urea/thiourea (0.01 mol), 3-methyl-1-phenyl-5-pyrazolone (0.01 mol) and various substituted aldehydes (0.01 mol) were added nano zeolite NaX (0.02 mol). The reaction mixture was refluxed for appropriate time; the reaction was monitored by thin liquid chromatography. Upon completion of the reaction the clear solution thus obtained was treated with crushed ice to give the solid product which was filtered and dried. The crude product was purified by recrystallization from ethanol (absolute ethanol).

2.5. Selected Spectra Data

Compound (4a). IR (KBr, cm⁻¹): 3505, 3422, 3005, 1634, 1573. ¹H-NMR (400 MHz, CDCl₃, δ /ppm): 8.53 (s, 1H), 4.88 (s, 1H), 3.74 (m, 8H), 2.28 (m, 8H), 2.45 (s, 3H), 7.48 (m, 9H). ¹³C-NMR (400 MHz, CDCl₃, δ /ppm): 163.1, 155.7, 143.7, 136.5, 129.6, 128.7, 128.2, 126.1, 120.7, 116.6, 26.8. HRMS (EI) Calcd. for C₁₈H₁₇N₄O [M]⁺, 305.1003, Found 305.1006; Anal Calcd for C₁₈H₁₇N₄O: C 70.82, H 5.60, N 18.36. Found: C 70.88, H 5.52, N 18.39%.

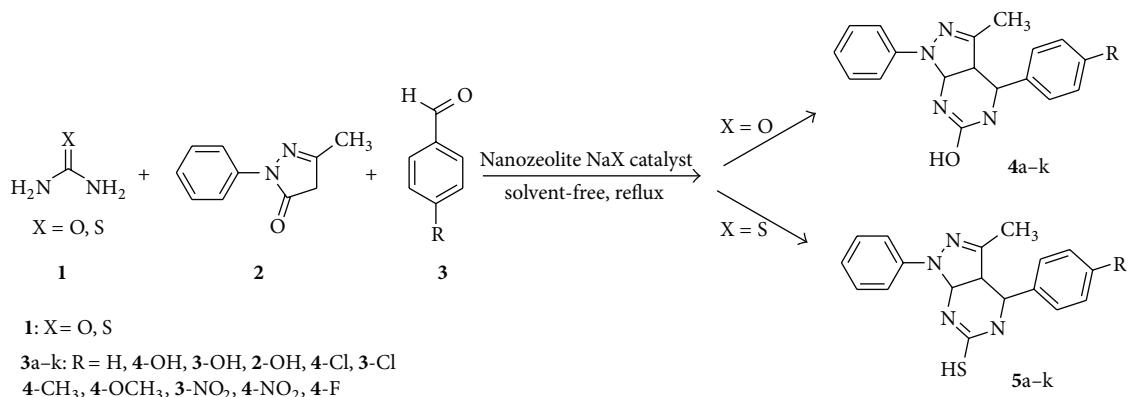
Compound (5a). IR (KBr, cm⁻¹): 2552, 3427, 3005, 1636, 1575, 662. ¹H-NMR (400 MHz, CDCl₃, δ /ppm): 8.54 (s, 1H), 1.26 (m, 1H), 3.73 (m, 8H), 2.27 (m, 8H), 2.36 (s, 3H), 7.54 (m, 9H). ¹³C-NMR (400 MHz, CDCl₃, δ /ppm): 163.2, 155.7, 143.7, 136.5, 129.6, 128.9, 128.2, 126.1, 116.5, 62.6, 52.2, 43.9, 26.6. HRMS (EI) Calcd. for C₁₈H₁₇N₄S [M]⁺, 321.1001, Found 321.1008; Anal Calcd for C₁₈H₁₇N₄S: C 67.25, H 5.37, N 17.45. Found: C 67.29, H 5.41, N 17.54%.

3. Results and Discussion

The preparation of the pyrazolone-pyrimidine derivatives involved the reaction of the respective urea/thiourea, 3-methyl-1-phenyl-5-pyrazolone with aromatic aldehydes by using nanoparticles of NaX zeolite catalyst under solvent-free and at reflux conditions (Scheme 1).

All the tested aromatic aldehydes bearing various substituents such as chloro, nitro, methoxyl, and other substituents could successfully react with 3-methyl-1-phenyl-5-pyrazolone within 60–90 minutes with high yields. The results were summarized in Tables 1 and 2.

Interestingly, we have not obtained the side products which were usually accompanied with the target compounds when the reaction was carried out in solvent-free. The formation of the pyrazolopyrimidine system was unequivocally established after analysis of NMR data of the products. The chemical shifts and multiplicity of the protons were in consonance with the expected values, for example, the proton at position 3 of all the compounds was found between 8.50 and 9.07 ppm as a sharp singlet. The XRD pattern matches



SCHEME 1: Synthesis of pyrazolone-pyrimidine derivatives by using nanoparticles of NaX Zeolite catalysts.

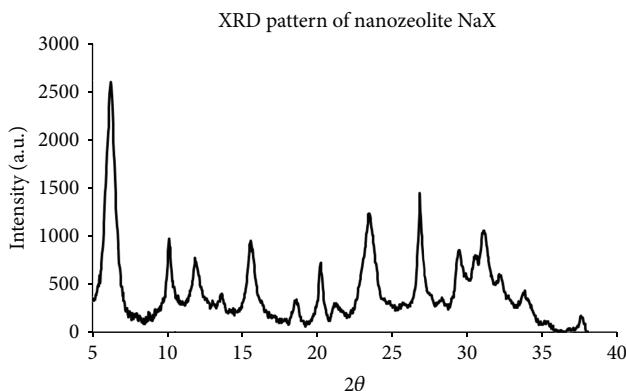


FIGURE 1: XRD pattern of as-synthesized sample crystallized.

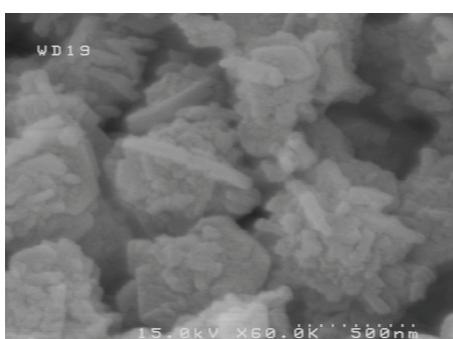


FIGURE 2: The FESEM image of nanozeolite NaX.

very well with the simulated XRD powder pattern for FAU zeolite [12–16] indicating that the synthesized crystal is pure FAU zeolite and shows that nanozeolite NaX sample has more than 95% crystalline (Figure 1).

The crystalline phase of aluminosilicate could be produced NaX hydrate zeolite phase after left it in the suitable temperature and time. From the experimental results, it can be explained that the silica content in fly ash is not enough to form NaX hydrate zeolite phase after incubated

TABLE 2: Synthesis of several pyrazolone-pyrimidine derivatives using thiourea and nanoparticles of NaX zeolite catalyst.

Entry	Product	Time (min)	^a Yield (%)	MP (°C)
1	4a , -H	1	91	186
2	4b , 4-OH	1.5	96.5	180
3	4c , 3-OH	1.5	93	176
4	4d , 2-OH	1.5	91.5	184
5	4e , 4-Cl	2.5	84	181
6	4f , 3-Cl	2.5	80	185
7	4g , 4-CH ₃	1	92.5	182
8	4h , 4-OCH ₃	1	95	285
9	4i , 3-NO ₂	3	76	216
10	4j , 4-NO ₂	3	81.5	224
11	4k , 4-F	3.5	72	151

^aIsolated yield.

at 60°C for 4 × 24 h. Figure 1 showed that strong broad peaks of pure silica are centered range on ≈22–23° (2θ), which are in keeping with the strong broad peak of a characteristic of amorphous SiO₂ [19]. The result showed that pure silica is in an amorphous state.

The nanozeolite NaX is very hydrophilic with entrance pores of approximately 7.4 Å. The particle size distributions of nanozeolite crystal from dynamic light scattering (DLS) are shown in Figure 2 results indicated a narrow distribution of particle size, with an average crystal size of 112 nm. The average crystal dimension of 105 ± 9 nm was calculated by Scherrer's equation from the diffraction peaks at 2θ values of 6° [18], 16° [10], and 27° [13]. The average particle size (Å) was calculated by (1).

Scherrer's equation is

$$r = \frac{k\lambda}{\beta \cos \theta} \quad (1)$$

where *k* is the shape factor, *λ* is the X-ray wavelength, typically 1.54 Å, *β* is the line broadening at half the maximum intensity (FWHM) in radians, and *θ* is the Bragg angle.

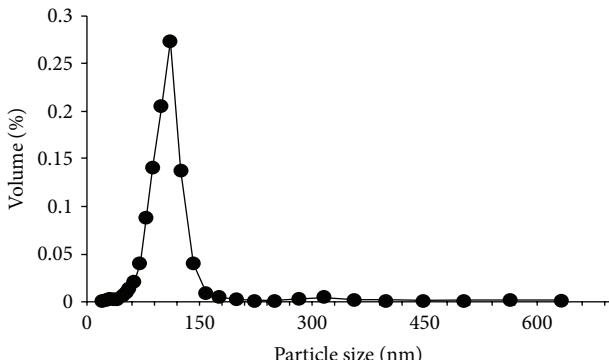


FIGURE 3: Distribution of particle size of nanozeolite NaX.

The result of DLS is more important than XRD methods because the DLS calculates the particle distribution, but the Scherrer's equation measures an average particle size. The SEM image recorded for the as-synthesized nanozeolite sample is shown in Figure 2. The Field-Emission Scanning Electron Microscope (FESEM) image recorded for the as-synthesized nanozeolite sample is shown in Figure 2 which clearly indicates that the particle size of nano-NaX is ultrafine and within a range of 40–150 nm which is consistent with the results calculated from the XRD pattern and dynamic light scattering (Figure 3).

The particle size distributions of nanozeolite crystal from dynamic light scattering (DLS) are shown in Figure 3; results indicated a narrow distribution of particle size, with an average crystal size of 112 nm.

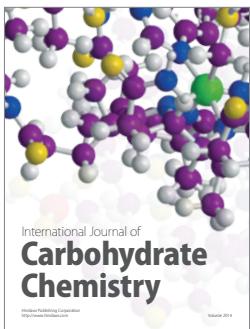
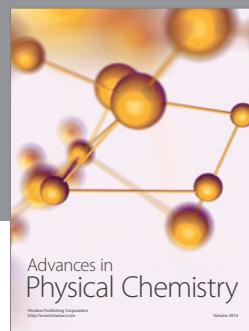
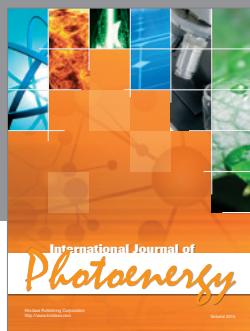
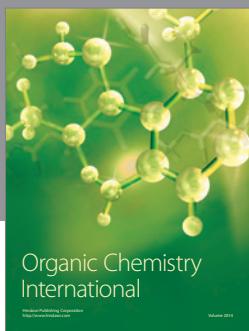
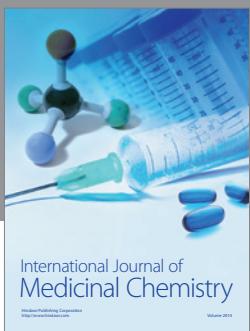
Also, the Si/Al ratio of the nanoozeolite NaX was calculated 1.25 through XRF analysis. The unit cell mass of NaY zeolite was calculated using the composition provided by XRF test: $\text{Na}_{106}[(\text{Al}_{106}\text{Si}_{86}\text{O}_{384})]$.

4. Conclusion

We have demonstrated that the reaction between 3-methyl-1-phenyl-5-pyrazolone with aldehydes and urea/thiourea could be effectively performed in the presence of nanozeolite NaX catalyst at reflux and solvent-free conditions. The present method has many obvious advantages over classical procedures, including being environmentally more benign, simple, the ease of product isolation, higher yield, shorter reaction times, and the potential for recycling ionic liquid and catalyst. The recyclability and reusability of the catalyst have been tested. The new catalyst was inexpensive, easy to prepare, and stable. It maintained its original activity during a period of more than a year that constituted this study.

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