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Solvent-Free Synthesis of Dihydropyrazolo [4',3':5,6] Pyrano [2,3-d] Pyrimidine-5,7-Diones Derivatives by using Magnetic Hf- UiO-66 MOFs

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Abstract: *In this study, we successfully synthesized Fe3O4@SiO2@UiO-66-Hf and Fe3O4@SiO2@UiO-66-Hf (Hl) by microwave assisted solvothermal method and applied for the synthesise of dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7-diones via one-pot four-component reaction of hydrazine hydrate, ethyl acetoacetate aldehydes and barbituric acid/ dimethyl barbituric acid under solvent-free conditions. After completion of the reaction, the catalyst was separated by external magnet and reused. So, recycling system, simple work-up, excellent yields and short reaction times makes our research green and convenient for preparation of these classes of organic compounds. In this study we are also observe Fe3O4@SiO2@UiO-66-Hf (Hl) than Fe3O4@SiO2@UiO-66-Hf that is more Effective catalyst for synthesis.*

Keywords: MOFs, Heterocyclic compounds, Uio-66, solvent free, Multicomponent reaction

I. INTRODUCTION

Metal-organic frameworks (MOFs) are crystalline solids that are built by metal ions or inorganic clusters linked by bi-or multifunctional organic ligands. The unique characteristics of Metal organic frameworks (MOFs) such as high surface area, considerable and tunable porosity, tunable pore size and shape, high physical and chemical stability, the presence of active binding sites within the framework,diverse structures, large pore size, nanometer-scale size, and biodegradability[1–2] have caused their importance and application in various industrial and biomedical fields, in which the following can be mentioned: generation of MOF-based metal and metal oxide nanocomposites as heterogeneous catalysts or as catalyst supports/precursors in organic reactions, catalyze a vast range of transformations from organic reaction to photocatalysis[3].,as stationary phases for liquid and gas chromatographies and as the efficient adsorption materials in sample pretreatment5, application as agents' gas and energy storage, heat transformation, imaging, molecular separation, sensing, biosensors, contrast agents for magnetic resonance imaging [4,5].

Multi component reactions (MCRs) become powerful tools in organic reactions to form more than one carbon–carbon or carbon–heteroatom bond in one-pot procedures. However, not all multi-component reactions are actually greenif one or more of the twelve green chemistry principles are violated, such as utilization of non-recoverable catalysts, poisonous solvents, pollutants chemical reagents etc.The organic chemists are designing new synthetic methods in organic synthesis that they are environmentally and economically useful in compare with multi-step reactions which produce large amounts of waste after each step [6]. The development of simple, efficient, environmentally benign and economically profitable process in organic synthesis is in great demand.Inregards the view of green approach multicomponent reactions (MCRs) have been refined as powerful and useful tool for the synthesis of novel organic molecules from readily available starting material. This reaction reduces the consumption of solvent, catalyst, time, energy, minimizing waste, cost compared to the corresponding series of individual reactions.[6-7].

Recently, heterocyclic compounds (e.g.pyrazolopyranopyrimidine) have attracted the attention of researchers world-wide due to their unique pharmaceutical-biomedical properties [7,8]. Thepyranopyrazoles have their unique characterizations such as anti-cancer [9], anti-bacterial [10], anti-depressant [11], and anti-inflammatory [12], but also are known as biodegradable agrochemicals [13]. In addition, Pyranopyrimidines, which can be found in natural

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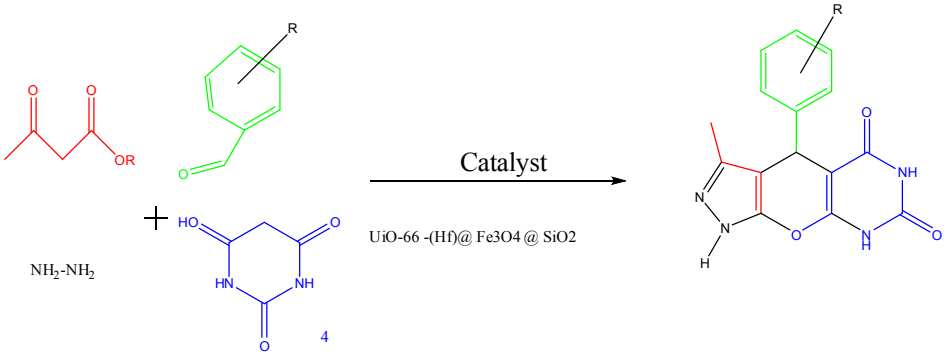
products [14], are well-known components due to their hepatoprotective, anti-tubercular, anti-microbial [15,16], anti-tumor [17], and antibronchitis [18].

Some MCRs have been reported for the synthetic of heterocyclic compounds such aspyranopyrimidines., We intend to develop an efficient, green, inexpensive, environmentally friendly and economical approach for the synthesis of different heterocyclic compounds. The proposed method employs magnetic Hf-UiO-66 as a novel, highly efficient and reusable catalyst to synthesize a series of pyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine derivatives through reaction of barbituric acid derivatives, hydrazine hydrate, ethyl acetoacetate and aromatic benzaldehyde withoutsolvent-free conditions in presence and under microwave assisted (Scheme 1).



Scheme 1. Four-component synthesis of dihydropyrazolo[4', 3':5, 6]pyrano[2, 3-d]pyrimidines by Magneteic Hf@UiO-66 catalysts.

II. MATERIAL AND METHODS

Commercial reagent (A.R grade) of the chemicals used in this research were purchased from Loba, Sigma- Aldrich and Merck and were used without any further purification. Melting points were uncorrected and determined in capillary tube on melting point microscope.^{1}H NMR and ^{13}C NMR spectra were obtained through Bruker 400 MHz spectrometer with CDCl3 as solvent using TMS as an internal standard. FT-IR spectrawere derived by Magna-IR, spectrometer 550. The elemental analyses (C, H, and N) were carried out using a Carlo ERBA Model EA 1108 analyzer. Powder X-ray diffraction (PXRD) was performed on a Philips diffractometer of X'pert Company with mono chromatized Cu Kα radiation (λ = 1.5406^{0}A)

2.1 Preparation of Fe_3O_4@SiO_2@UiO-66-Hf ;

Fe3O4@SiO2@UiO-66- Hf was synthesized by a lightly modifying microwave assisted solvothermal method according to the previous report [20] using the following procedure: 1.0 g Fe3O4 @ SiO2 was suspended in 60 mL of DMF through sonication for 20 Min. 2 mmole $HfCl_4$,and 2mmole 1,4- benzene dicarboxylic acid was dissolved in 30 mL N, N-dimethyl formamide (DMF) containing 0.9 mL HCl by sonication for 10 Min. Then above mixture of metal alt and ligands were added to the suspension of Magnetic nanoparticles and flask was placed in microwave oven and irradiate at 120 0C, 700 W Power at the atmospheric pressure for 10 Min. The solids were separated by external magnet and washed with DMF and chloroform several times.

2.2. General procedure for the preparation of pyrano[2,3- d]pyrimidinones-

Aromatic aldehydes (1), active methylene compound (2), barbituricacid (3) , and hydrazine hydrate (4) (2 mmol each) and 10 mol% catalyst were taken in an RB flask with5 ml solvent dry ethanol mixture and stirredfor 20 min at room temperature. The reaction mixture was stirred well, dried in air and subjected to microwave irradiation (700W, 90 ^{0} C) for 3 minutes. The reaction was monitoredby thin layer chromatography using eluent petroleumether and ethyl acetate 7:3. The solid compound was filtered,washed with cold water and recrystallization from ethanol toobtain pure product pyrano[2,3-d]pyrimidine derivatives.At the next step, theproduct was dispersed in 20 mL of anhydrous dicholro methane and magnetic catalyst was separated by external magnet. The final solid was collected by evaporation and dried under vacuum at110 °C for 2 hrs.

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III. RESULTS AND DISCUSSION

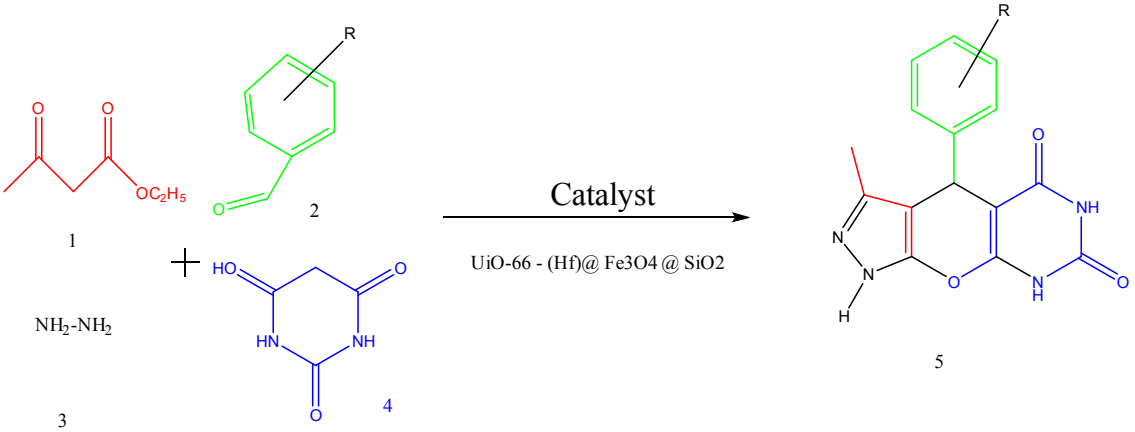
First, we studied the reaction of hydrazine hydrate (1 mmol) andethyl acetoacetate (1 mmol), barbituric acid (1 mmol), benzaldehyde(1 mmol) as a model reaction under solvent-free conditions in differenttemperatures and variety of amount of catalyst-Fe3O4@SiO2@UiO-66- Hfto choose theoptimum conditions which is described in Table 1. As shown from Table 1,the optimum condition was obtained at 100 ^{0}C and 0.1 g of the catalyst.

Sr. No.	Catalyst (in g)	Temp. in ^{0} C	Yield (%)
1	0.08	90	85
2	0.08	100	88
3	0.08	110	90
4	0.10	90	90
5	0.10	10	92
6	0.10	110	91

Table 1. Optimization of the reaction conditions for the synthesis ofdihydropyrazolo [4',3':5,6] pyrano [2,3-d] pyrimidine-5,7-diones underthermal and solvent-free conditions.

In order to generalize the optimum conditions; different derivativesof substituted dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7-dioneswere prepared under solvent-free condition at 100 ^{0}C (Table 2). Aromaticaldehydes carrying both electron-donating and electron-withdrawing groupswere used and desired products were obtained in high yields and shortreaction times (Table 2, Entry 1 -10).Entry Substrate Product

Table 2 Synthesis of substituted dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7-dionescatalyzed by of Fe_3O_4@SiO_2@UiO-66- Hf shown as follows.



Entry	Substrate (Aromatic aldehyde)	R	Product	Yield (%)	M.P.^{0}C [find] M.P. ^{0}C [literature][c]
1	C_6H_5-CHO	H	5a	94	210-212 206-210[21]
2	3-NO_2-C_6H_4-CHO	-NO_2	5b	89	236 238-240[22]
3	4-NO_2-C_6H_4-CHO	-NO_2	5c	87	290 289-291[21]
4	4-CH_3-C_6H_4-CHO	-CH_3	5d	92	300 296-298[21]
5	2-OCH_3-C_6H_4-CHO	-OCH_3	5e	94	292 290-293[23]
6	4-OCH_3-C_6H_4-CHO	-OCH_3	5f	95	304 303-306[21]
7	2-Cl-C_6H_4-CHO	-Cl	5g	85	222

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					223-225[24]
8	4-Cl-C_6H_4-CHO	-Cl	5h	86	298 295-300[21]
9	4-Br-C_6H_4-CHO	-Br	5i	89	214 211-212[24]
10	4-F-C_6H_4-CHO	-F	5j	90	240 237-238[24]

Table 2 Synthesis of substituted dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7-dionescatalyzed by of Fe_3O_4@SiO_2@UiO-66- Hf

IV. SELECTED SPECTRAL ANALYSIS

4-(4-Fluorophenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7(1H,4H)-dione (5j).
White solid; IR (KBr): 3171, 3052, 1705, 1634, 1508, 1464, 1375 cm-1;1H NMR (DMSO-d6,500 MHz) δ ppm: 2.34 (s, 3H, CH3), 5.43 (s, 1H, CH), 7.08-7.10 (m, 4H, HAr), 10.33 (s, 2H, NH); 13CNMR (DMSO-d6, 125 MHz) δ ppm: 10.4, 30.6, 91.8, 106.2, 114.9 (d, 2JFC =20.8 Hz), 128.9 (d, 3JFC =7.5Hz), 138.8, 138.8, 144.1, 151.4, 159.9, 160.9 (d, 1JFC =234.6 Hz), 160.3; Anal. Calcd for C15H11FN4O3: C,57.33; H, 3.53; N, 17.83. Found: C, 57.52; H, 336; N, 18.00.

4-(2-Chlorophenyl)-3-methyl-6,8-dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7(1H,4H)-dione (5g).
White solid; IR (KBr): 3410, 3167, 1714, 1604, 1528, 1468, 1381 cm-1; 1H NMR (DMSO-d6,500 MHz) δ ppm: 2.24 (s, 3H, CH3), 5.53 (s, 1H, CH), 7.18 (t, J = 7.5 Hz, 1H, HAr), 7.23 (t, J = 7.5 Hz,1H, HAr), 7.32 (d, J = 7.5 Hz, 1H, HAr), 7.49 (d, J = 6.5 Hz, 1H, HAr), 10.19 (s, 2H, NH), 13.23 (br s, 1H,NH); 13C NMR (DMSO-d6, 125 MHz) δ ppm: 10.8, 30.5, 91.1, 126.7, 128.0, 129.9, 130.7, 133.0, 140.2,143.7, 151.1, 161.3, 165.0; Anal. Calcd for C15H11ClN4O3: C, 54.47; H, 3.35; N, 16.94. Found: C, 54.66; H,3.19; N, 17.11.

V. CONCLUSION

The present study is an efficient synthetic route to achieve various substituted dihydropyrazolo[4',3':5,6]pyrano[2,3-d]pyrimidine-5,7-dionederivatives by using magnetic catalyst Fe_3O_4@SiO_2@UiO-66- Hf as an inexpensive, convenient , magnetically separable and recoverable catalyst. Moreover, this method has another advantage like short reaction times, recycling system, simple work-up, non-toxic materials, excellent yields, and solvent-free conditions.

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