An efficient one-pot, four-component synthesis of a series of pyrazolo [3,4-b]pyridines in the presence of magnetic LDH as a nanocatalyst.

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Abstract

One-pot, four-component reaction of 3-aryl-3-oxopropanenitriles, 1-aryl-3-methyl-1H-pyrazol-5(4H) one, arylglyoxals and ammonium acetate using green solvent systems and different catalysts under reflux conditions afforded a series of the corresponding 4-aroyl-3-methyl-1,6-diaryl-1H-pyrazolo pyridine-5-carbonitrile derivatives. The best yields (70-85%) were obtained using magnetic LDH as a nanocatalyst in EtOH/H_2O (1:1) under reflux conditions. This protocol provides mild reaction conditions, good yields, simple workup procedure, easy preparation of nanocatalyst and, products to structurally diverse bicyclic pyrazolo pyridines, which may have biological and pharmacological activities.

Keywords: Nanocatalyst, Pyrazolo pyridines, Arylglyoxals, 1-aryl-3-methyl-1H- pyrazol-5(4H) one, One-pot.

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Introduction

The green synthesis of nitrogen-containing heterocycles *via* environmentally friendly procedures has attracted much attention due to their various biological and pharmaceutical activities have increased in organic and pharmaceutical chemistry. Among these heterocycles, polycyclic heterocycles have received considerable attention because of various applications. Fused heterocyclic compounds such as pyrazolopyridines have biological and pharmacological activities such as antibacterial, antimicrobial, antileishmanial, antiproliferative agents, cytotoxicity and anti-biofilm, antioxidant, antimalarial, and anticancer, have classified as an important and vital structures.

Multicomponent reactions by multiple bond-making in green solvents in the presence of green catalysts would be a powerful tool in organic synthesis. MCRs offer benefits such as short time, with high atom-economy, high selectivity and environmentally friendly chemical process [1].

In continuation of our interests in the development of synthetic strategies to obtain new heterocyclic compounds, we have very recently reported the one-pot, three-component synthesis of a new series of pyrazolo pyridines in the presence of Al_2O_3 as a nanocatalyst.

Herein, we report the one-pot four-component synthesis of a series of 4-aroyl-3-methyl-1,6-diaryl-1H-pyrazlo pyridine-5-carbonitriles in the presence of different catalysts under reflux conditions [2].

Materials and Methods

The chemicals used in this work were obtained from Acros and Merck companies and used without purification. Melting points were measured on a Philip Harris C4954718 apparatus and are uncorrected. Infrared spectra were recorded on a Thermo-Nicolet Nexus 670-FT-IR instrument using KBr discs. 1_H and 13_C NMR spectra were recorded on a Bruker Avance AQS 300 MHz spectrometer at 300 and 75.5 MHz, respectively. Chemical shifts were measured in CDCl3 using TMS as the internal standard. The reaction monitoring was accomplished *via* TLC on silica gel PolyGram SILG/UV254 plates. The Scanning Electron Microscopy (SEM) image was obtained from JEOL JXA-840 Electron Microscopy Ltd. Japan [3]. Mass spectra were recorded on a varian Matt 311 spectrometer and relative abundance of fragments are quoted in parentheses after the m/z values.

Preparation of starting materials

The preparation of starting materials including 3-oxo-3-phenylpropanenitriles (2a,b), and arylglyoxal monohydrates (3a-d), along with reaction conditions are shown in (Figure 1).

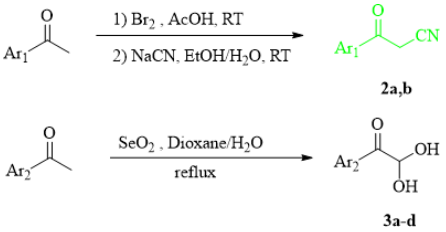

***Figure 1**. 3-oxo-3-phenylpropanenitriles (2a,b), and arylglyoxal monohydrates (3a-d), along with reaction conditions.*

Preparation of starting materials

Preparation of nanomagnetic Fe_3O_4: The Fe_3O_4 nanoparticles were prepared according to a previously reported method by chemical co-precipitation of chloride salts of Fe^{2+} and Fe^{3+}. Typically, $FeCl_2$•$4H_2O$ (2.147 g, 0.0108 mol) and $FeCl_3$•$6H_2O$ (5.838 g, 0.0216 mol) were dissolved in distilled water (100 ml).

The solution was stirred at 85˚C under N_2 atmosphere for 10 min. Then, aqueous ammonia (25 wt%, 10 mL) was added to the prepared solution at 85˚C and a black precipitate was immediately formed [4]. The resulting mixture was heated at 85˚C for 30 min with stirring under N_2 atmosphere followed by cooling to the room temperature. The precipitate was magnetically separated from the reaction mixture and washed twice with distilled water and solution of NaCl (0.02 M).

Preparation of nano-Fe_3O_4@SiO_2

The silica was covered on the Fe_3O_4 core according to the reported method. Magnetite (1.5 g) was dissolved in distilled water (20 ml) and it was added to 2-propanol (200 ml) and homogenized by ultrasonic (30 min). Under continuous mechanical stirring, PEG (5.36 g), distilled water (20 ml), aqueous O_H (28 wt%, 10 ml) and TEO_S (2 ml) were respectively added into the suspension and stirring was continued for 24h at room temperature. After the reaction was completed, the product was collected by an external magnet and washed twice with ethanol and distilled water [5].

Preparation of Fe_3O_4@SiO2@Ni-Zn-Fe LDH

The in situ growth of mesoporous Ni-Zn-Fe LDH on the surface of Fe_3O_4@SiO_2 nanoparticles was carried out. Typically, Fe_3O_4@SiO_2 (0.25 g), NaOH (0.160 g, 0.004 mol) and Na_2CO_3 (1.060 g, 0.01 mol) were dissolved in distilled. 0.009 mol), Zn $(NO_3)2•6H_2O$ (1.785 g, 0.006 mol) and this

as an eluent [7]. The precipitate was filtered, washed with

$FeCl_3•6H_2O$ (1.352 g, 0.005 mol) was prepared in distilled water (30 mL). Both of them were sonicated for 30 min. These two solutions were added drop-wise with stirring to distilled water (30 mL), during the reaction process, the solution pH was kept at 11 by addition of appropriate amounts of HCl and NaO_H solutions. The resulting slurry was stirred at room temperature for an additional 30 min and then it was aged for 20 h at 80˚C. Subsequently, the acquired sample was cooled to room temperature and filtered. The solid product was dried at 150˚C and the obtained catalyst was named as Fe_3O_4@SiO_2@Ni-Zn-Fe LDH.

The morphology and size distribution of the synthesized materials was analyzed by SEM. The SEM images indicate that the catalyst is roughly spherical and granule nanoparticles. The size distribution of Fe_3O_4@SiO_2@Ni-Zn-Fe LDH ranged from 17 to 36. The SEM approved the nanostructure of the catalyst [6].

General procedure for the synthesis of new pyrazolopyridine derivatives

The 3-oxo-3-phenylpropanenitrile (1 mmol) was dissolved in H_2O/EtOH (1:1) (5 mL) and arylglyoxal hydrate (1 mmol), 1-aryl-3-methyl-1H-pyrazol-5(4H) one (1 mmol), ammonium acetate with nanomagnetic catalyst (10% mol) was then added to the reaction mixture. The reaction mixture was refluxed for an appropriate time (approximately 2h). The reaction completion was monitored by TLC using (EtOAc/Hexane, 2:3) water and dried. Recrystallization from ethanol gave the desired product (5a-p) as white to yellow needles 70-85% yields as shown in (Figure 1).

Results and Discussion

In our initial studies the reaction of 1-(3-chlorophenyl)-3-methyl-1H-pyrazol-5(4h)-one (1b), 3-(4-chlorophenyl)-3-oxo propanenitrile (2a), phenylglyoxal hydrate (3a) and ammonium acetate (4) was chosen as a trial reaction in Table 1 [8]. Refluxing the reaction mixture using various catalysts and two different green solvent systems as mentioned in Table 1, a solid precipitate was separated in 40-84% yields, which was characterized by its spectral data to be the desired substituted 1-H-pyrazolo[3,4-b] pyridine (5i). The best result was obtained in terms of yield (84%) and reaction time (1h) when the reaction was performed using 10%mol of magnetic LDH as a nanocatalyst in H_2O/EtOH (1:1) (Table 1, entry 8). To study the effect of the amount of catalyst, the reaction was carried out in the presence of various amounts of nano LDH ranging from 5 to 15 % mol and the best condition was using 10% mol of catalyst in H_2O/EtOH (1:1). [9]. To find the best solvent for this reaction, we carried out the trial reaction using various green solvent systems such as EtOH, EtOH/H_2O (1:1), and H_2O as shown in Table 1 [10]. Among all these solvents, EtOH/H_2O (1:1) was proved to be the best solvent for this reaction in terms of yield (Table 1, entry 8). The catalyst with acidic nature such as p-TSA, and L-proline as an amino acid provided in (Table 1).

Table 1. *Optimization of the reaction conditions.*

Entry	Solvents	Temp(oC)	Catalyst[%mol]	Time(h)	Yields (%)
1	EtOH	Reflux	$NH_4CH_3CO_2$(20)	7	43
2	EtOH/H_2O (1:1)	Reflux	$NH_4CH_3CO_2$(20)	7	40
3	EtOH/H_2O (1:1)	Reflux	L-proline (20)	7	52
4	EtOH	Reflux	L-proline (20)	7	58
5	EtOH	Reflux	p-TSA (20)	7	50
6	EtOH/H_2O (1:1)	Reflux	p-TSA (20)	7	47
7	EtOH/H_2O (1:1)	Reflux	Nano LDH(5)	2	71
8	EtOH/H_2O 1:1)	Reflux	Nano LDH(10)	2	84
9	EtOH/H_2O (1:1)	Reflux	Nano LDH(15)	2	82
10	EtOH	Reflux	Nano LDH(10)	2	80
11	EtOH/H_2O (1:2)	Reflux	Nano LDH(10)	2	79
12	H_2O	Reflux	Nano LDH(10)	24	-

13	EtOH/H_2O (1:1)	Reflux	Nano Al_2O_3(10)	7	89

After optimizing the reaction condition (Figure 2), we next verify the scope of this reaction with different [11] arylglyoxals and ammonium acetate (4), to obtain our desired pyrazolopyridine derivatives(5a-p) (Table 2).

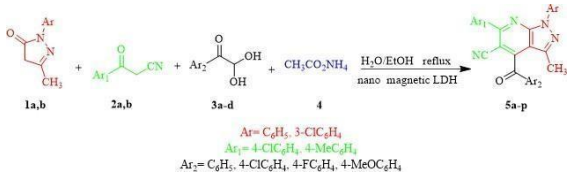

Figure 2. *Arylglyoxals (3a-d).*

Table 2. *Substituted 1H-pyrazolo[3,4-b]pyridines.*

Entry	Product	Ar	Ar1	Ar2	Time(h)	Yield (%)*	Mp(obsd) (oC)	Mp(Lit.) (oC)22
1	5a	C_6H_5	4-ClC_6H_4	C_6H_5	1	85	170-171	171-173
2	5b	C_6H_5	4-ClC_6H_4	4-FC_6H_4	1	81	176-178	178-179
3	5c	C_6H_5	4-ClC_6H_4	4-$MeOC_6H_4$	2	70	207-208	206-207
4	5d	C_6H_5	4-ClC_6H_4	4-ClC_6H_4	2	76	170-172	170-172
5	5e	C_6H_5	4-MeC_6H_4	C_6H_5	2	79	174-175	175-176
6	5f	C_6H_5	4-MeC_6H_4	4-FC_6H_4	2	75	204-206	204-205
7	5g	C_6H_5	4-MeC_6H_4	4-$MeOC_6H_4$	3	71	183-184	184-186
8	5h	C_6H_5	4-MeC_6H_4	4-ClC_6H_4	2	72	170-171	169-170
9	5i	3-ClC_6H_4	4-ClC6H4	C_6H_5	1	84	178-179	178-179
10	5j	3-ClC_6H_4	4-ClC_6H_4	4-FC_6H_4	2	74	207-209	208-209
11	5k	3-ClC_6H_4	4-ClC_6H_4	4-$MeOC_6H_4$	2	72	177-178	176-178
12	5l	3-ClC_6H_4	4-ClC_6H_4	4-ClC_6H_4	1	81	192-194	191-193
13	5m	3-ClC_6H_4	4-MeC_6H_4	C_6H_5	2	78	200-202	201-202
14	5n	3-ClC_6H_4	4-MeC_6H_4	4-FC_6H_4	2	79	184-185	185-187
15	5o	3-ClC_6H_4	4-MeC_6H_4	4-$MeOC_6H_4$	2	72	204-205	205-206
16	5p	3-ClC_6H_4	4-MeC_6H_4	4-ClC_6H_4	2	78	194-195	193-195
Isolated yield								

Reusability of Fe3O4@SiO2@Ni-Zn-Fe LDH

After completion of the reaction, the catalyst was separated by a permanent magnetic field, washed with $CHCl_3$, dried at room temperature and reused for six consecutive runs without considerable loss of activity Figure 3.

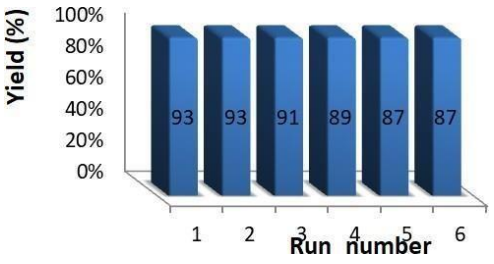

Figure 3. *Fe_3O_4@SiO_2@Ni-Zn-Fe LDH.*

Mechanistically, the formation of products (5a–p) was achieved by a sequence of reactions involving activation of carbonyl group (arylglyoxal) with nanocatalyst as a Brønsted acidic catalyst the initial condensation [12] of arylglyoxals with 5-amino-1-aryl-3-methylpyrazoles, followed by second condensation of the intermediate with 3-aryl-3-oxopropanenitriles, providing the corresponding dihydro-1H-pyrazolo [3,4-b]pyridines through intramolecular heterocyclization and subsequent tautomerization [13], which was finally dehydrogenated to the desired 4-aroyl-1,6-diaryl-3-methyl-1H-pyrazolo[3,4-b]-pyridine-5-carbonitriles *via* autoxidation (Figure 4) [14,15].

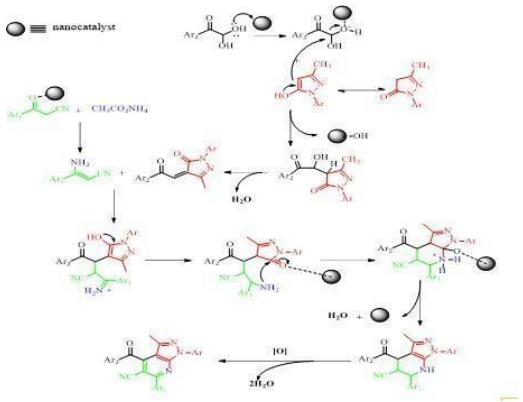

***Figure 4**. pyridine-5-carbonitriles via autoxidation.*

Conclusion

We have reported, one-pot, four-component synthesis of a series of pyrazolopyridine derivatives in the presence of Fe_3O_4@SiO_2@Ni-Zn-Fe LDH as a nanocatalyst. This new pyrazolo [3,4-b]pyridine which may have biological and pharmaceutical applications and they could also serve as intermediates for new planar polycyclic heterocycles. The simplicity, ease of product and catalyst isolations, mild reaction conditions, using green solvents and good yields are the main advantages of this method.

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