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Application of a biological-based nanomagnetic catalyst in the synthesis of bis-pyrazols and pyrano[3,2-*c*]pyrazoles

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{Fe_3O_4@SiO_2@$(CH_2)_3$-thiourea dioxide-SO_3H/HCl}, a newly reported nanomagnetic core–shell supported solid acid catalyst, was successfully employed in the preparation of 4,4′-(arylmethylene)bis(1*H*–pyrazol-5-ol) and pyrano[3,2-*c*]pyrazole derivatives. The presented methods are very efficient and high-yielding. Also, the catalyst exhibited powerful potential for reusability in both types of reactions.

KEYWORDS

4,4′-(arylmethylene)bis(1*H*–pyrazol-5-ol), nanomagnetic catalyst, pyrano[3,2-c] pyrazole, solvent-free condition

1 | INTRODUCTION

Nowadays, knowledge-based design, synthesis and applications of nanomagnetic particles are in great demand, and a wide variety of nanostructured magnetic catalysts have been used because of their recyclability and reusability, high activity and selectivity in chemical processes. Application of recyclable and reusable catalysts or catalytic systems in chemical processes is in close accord with green chemistry disciplines because their use will decrease activation energy, waste of reactions and energy consumption. The development of nanomagnetic catalysts and their roles in pollution prevention in the environment at the past, present and future have been extensively reviewed.[1–3] To the best of our knowledge, employing nanomagnetic core–shell catalysts as heterogeneous promoters for various organic transformations is preferred over the use of homogeneous catalytic systems due to countless merits such as the recyclability and reusability. Furthermore, this influential and persuasive alternative for ordinary homogeneous catalysts is compatible with green chemistry protocols.[2,3]

Green chemistry principles emphasize the design and use of safe procedures in order to increase efficiency and productivity, reduce the steps of synthetic pathways, use less toxic solvents and minimize waste production as much as possible.[4] One of the main areas in the field of practical green chemistry is the replacement of unsafe volatile organic solvent with eco-friendly gentle ones or accomplishment of reactions under solvent-free conditions. It is demonstrable that the solvent-free types of reactions are emerging as a great tool for various organic interconversions in the absence of any harmful organic solvents. Also, solvent-free conditions present various advantages such as marked reduction in reaction times and lead to an increase of desired product yields and facile work-up.[5–7]

The construction of pharmaceutically and medicinally active heterocyclic compounds, using one-pot multicomponent strategies, has attracted much attention due to excellent merits such as enhancement of atom- and step-economy and improvement of efficiency for the synthesis of complex scaffolds. Also, this technique offers meaningful benefits over conventional linear-type synthesis protocols such as productivity, ease of execution and high yields.[8–12]

Molecules containing heterocyclic rings are ubiquitous in nature and are fundamental to life. Among such heterocyclic compounds, pyrazole derivatives are influential structural motifs as they exhibit various therapeutic and pharmaceutical applicabilities.[13–16] More specifically, among them, bis(pyrazolyl)methane derivatives like 4,4′-(arylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) derivatives have an extensive domain of pharmacological applications.[17–20] Also, they can be utilized as fungicides,[21] pesticides,[22] insecticides,[23] dyestuffs, and chelating and extracting agents for metal ions.[24] In addition, a survey of the literatures discloses that pyrano[2,3-*c*]pyrazole derivatives are established as significant precursor materials for the synthesis of promising drugs in the medicinal chemistry field and have a wide variety of biological and pharmaceutical

applications such as potential inhibitors of human Chk1 kinase,[25] and anti-inflammatory,[26] anticancer,[27] analgesic,[28] molluscicidal[29] and antimicrobial[30] activities have been reported for these versatile heterocyclic compounds.

Hence, owing to the varied practical beneficial properties as therapeutic and curative agents in clinical applications, a great deal of attention of synthetic and medicinal chemists has been focused on the topic of the preparation of 4,4′-(arylmethylene)bis(1*H*–pyrazol-5-ol) derivatives and pyrano[3,2-*c*]pyrazoles.[31–47] Although a number of procedures have been reported for the synthesis of 4,4′-(arylmethylene)bis(1*H*–pyrazol-5-ol) derivatives and pyrano[3,2-*c*]pyrazoles, all of the investigated methods suffer from one or more defects, including difficult-to-prepare catalysts, prolonged reaction times with low or moderate yields, employing toxic and hazardous organic solvents, harsh reaction conditions and tedious work-up protocols. Therefore, the development of a cost-effective and eco-friendly catalyst and procedure for the preparation of these valuable heterocyclic molecules is highly desirable.

In continuation of our efforts for the development of knowledge-based design and construction of applicable solid acids,[48,49] inorganic acidic salts,[50] nanomagnetic catalysts with a tag of ionic liquid[51] and novel nanostructured ionic liquids and molten salt catalyst[52] for organic functional group interconversion, herein we explore the catalytic performance of {Fe_3O_4@SiO_2@$(CH_2)_3$-thiourea dioxide-SO_3H/HCl} as a newly reported nanomagnetic core–shell supported solid acid catalyst in the synthesis of 4,4′-(arylmethylene)bis(1*H*–pyrazol-5-ol) derivatives and pyrano[3,2-*c*]pyrazoles under mild and solvent-free conditions (Scheme 1).

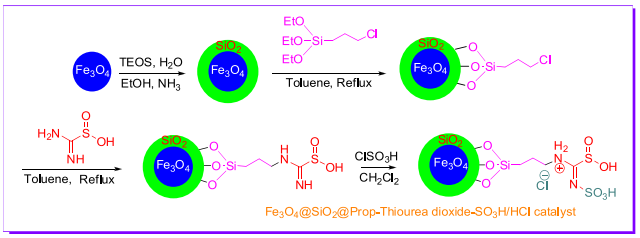
2 | RESULTS AND DISCUSSION

A catalytic reaction is a cyclic system and separation of a heterogeneous catalyst from a reaction mixture should be easier than that of a homogeneous one. Usual heterogeneous nanomagnetic solid acid catalysts are hybrids of organic and inorganic materials with suitable tags. Solid acid catalysts should have a great many pores, many active acidic sites, high stability with good selectivity, recyclability and reusability, high turnover number and turnover frquency and also should be economically and environmentally sustainable.[53] In this regard, we decided to apply a new biological-based nanomagnetic solid acid with sulfonic acid tag, namely {Fe_3O_4@SiO_2@$(CH_2)_3$-thiourea dioxide-SO_3H/HCl},[54] in the synthesis of 4,4′-(arylmethylene)bis(1*H*–pyrazol-5-ol) derivatives and pyrano[3,2-*c*]pyrazoles under mild and solvent-free conditions (Scheme 2).

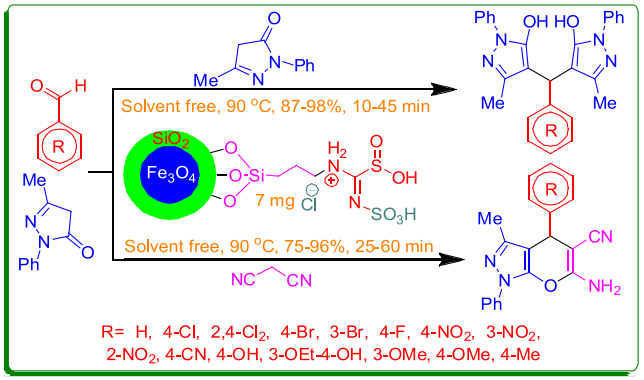
In the first place, in attempting to find the best operational experimental reaction conditions for the synthesis of 4,4′-(arylmethylene)bis(1*H*–pyrazol-5-ol) derivatives, we investigated the optimal reaction temperature, the amount of catalyst that was required and also the solvent for the reaction of 4-chlorobenzaldehyde and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (Scheme 3). The data obtained, as summarized in Table 1, reveal that the best results are achieved with 7 mg of nanomagnetic catalyst at 90°C under solvent-free conditions (Table 1, entry 4).

After determination of the optimal reaction conditions for the synthesis of 4,4′-(arylmethylene)bis(1*H*–pyrazol-5-ol) derivatives, to confirm the generality, scope and limitations of the presented protocol, different arylaldehydes (bearing electron-withdrawing and electron-donating groups and halogens) were subjected to reaction with 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one, to afford the corresponding desired compounds in relatively short reaction times with good to high yields. The obtained data are summarized in Table 2.

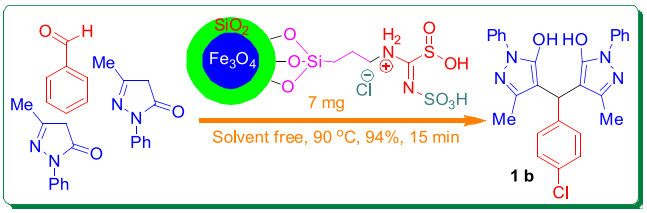
In another assay, the applicability of the nanomagnetic core–shell catalyst was explored for the synthetic reaction of pyrano[3,2-*c*]pyrazole derivatives. Initially, to find the



SCHEME 2 Stepwise synthesis pathway of {Fe3O4@SiO2@(CH2)3-thiourea dioxide-SO3H/HCl}as a nanomagnetic core–shell supported solid acid catalyst.



SCHEME 1 Synthesis of 4,4′-(arylmethylene)bis(1H–pyrazol-5-ol) derivatives and pyrano[3,2-c]pyrazoles under mild and solvent-free conditions.



SCHEME 3 Optimized reaction conditions for the synthesis of 4,4′-(arylmethylene)bis(1H–pyrazol-5-ol) derivatives.

TABLE 1 Optimization of reaction conditions for synthesis of 4,4′-(arylmethylene)bis(1*H*–pyrazol-5-ol) derivatives[a]

Entry	Solvent	Load of catalyst (mg)	Temperature (°C)	Time (min)	Yield (%)[b]
1	—	7	r.t.	135	30
2	—	7	50	70	55
3	—	7	70	60	74
4	**—**	**7**	**90**	**15**	**94**
5	—	7	110	15	88
6	**—**	**3**	**90**	**30**	**72**
7	—	5	90	30	78
8	—	10	90	19	90
9	—	—	90	70	33
10	H_2O	7		120	85
11	EtOH	7		60	88
12	CH_3CN	7		160	87
13	*n*-Hexane	7		100	76

[a]Reaction conditions: 4-chlorobenzaldehyde (1 mmol, 0.144), 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (2 mmol, 0.348).

[b]Isolated yield.

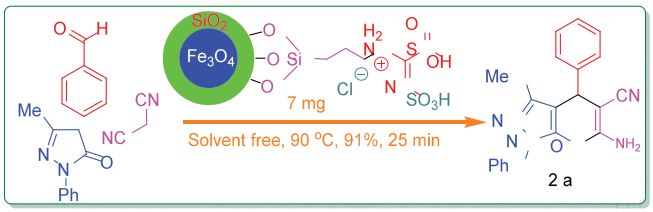
TABLE 2 Synthesis of 4,4′-(arylmethylene)bis(1*H*–pyrazol-5-ol) derivatives under solvent-free conditions in the presence of {Fe_3O_4@SiO_2@$(CH_2)_3$-thiourea dioxide-SO_3H/HCl} at 90°C[a]

Entry	R	Product	Time (min)	Yield (%)[b]	M.p. (°C): found (lit.)
1	H	**1a**	25	93	169–171 (168–170)[34]
2	4-Cl	**1b**	15	94	213–215 (213–215)[34]
3	4-NO_2	**1c**	10	95	224–226 (229–231)[34]
4	4-F	**1d**	20	91	186–188 (180–182)[40]
5	4-OH	**1e**	28	87	214–217(156–158)[40]
6	4-Me	**1f**	25	90	193–196 (201–203)[34]
7	4-$N(Me)_2$	**1 g**	45	89	154–156 (172–173)[41]
8	3-NO_2	**1 h**	40	92	193–196 (145–147)[34]
9	2,4-Cl_2	**1i**	10	87	229–232 (229–230)[41]
10	2-Cl	**1j**	17	89	235–237 (235–236)[34]
11	4-OMe	**1 k**	25	90	174–176 (173–175)[40]
12	4-Br	**1 l**	20	92	213–216 (212–214)[40]
13	3-OEt-4-OH	**1 m**	15	98	207–209 (205–207)[41]
14	3-Br	**1n**	40	98	157–158 (173–175)[34]
15	2-Thienyl	**1o**	25	89	187–190 (189–190)[34]
16	3-OMe	**1p**	15	94	184–186 (192–194)[40]

[a]Reaction conditions: arylaldehyde (1 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (2 mmol, 0.348 g), catalyst (7 mg).

[b]Isolated yield.

optimal reaction conditions for the synthesis, the reaction of 4-chlorobenzaldehyde, malononitrile and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one was chosen as a test reaction (Scheme 4). The related data obtained for the screening of different temperatures, loads of catalyst and solvents are summarized in Table 3. The resulting data demonstrate that the best conditions are when the reaction is performed under solvent-free conditions in the presence of



SCHEME 4 Optimized reaction conditions for the preparation of pyrano[3,2-c]pyrazole derivatives.

TABLE 3 Optimization of reaction conditions for synthesis of pyrano[3,2-*c*]pyrazole derivatives[a]

Entry	Solvent	Load of catalyst (mg)	Temperature (°C)	Time (min)	Yield (%)[b]
1	**—**	**7**	**90**	**25**	**91**
2	—	7	70	40	85
3	—	7	110	25	90
4	—	3	90	30	85
5	—	5	90	90	87
6	—	10	90	30	72
7	—	—	90	140	58
8	EtOAc	7		75	33
9	H_2O	7	Reflux	90	66
10	EtOH	7	Reflux	60	68
11	CH_3CN	7	Reflux	65	70
12	*n*-Hexane	7	Reflux	70	25

[a]Reaction conditions: 4-chlorobenzaldehyde (1 mmol, 0.144), 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (1 mmol, 0.174), malononitrile (1 mmol, 0.066).

[b]Isolated yield.

7 mg of the nanomagnetic core–shell supported solid acid catalyst at 90°C (Table 3, entry 1).

Afterwards, as in the case of the synthesis of 4,4′-(arylmethylene)bis(1*H*–pyrazol-5-ol) derivatives, the versatility and the generality of the optimized reaction conditions were checked for the preparation of various pyrano[3,2-*c*]pyrazoles. From the data obtained (Table 4), it can be inferred that the desired products are obtained in relatively short reaction times with good to high isolated yields.

Besides the easy separation of the catalyst after the completion of the reaction, as an additional merit of {Fe_3O_4@SiO_2@$(CH_2)_3$-thiourea dioxide-SO_3H/HCl} as a magnetic solid acid supported catalyst, the recycling possibility was investigated for both of the presented methods for eight times. After accomplishment of each run, in order to dissolve the crude product and separate the catalyst, 10 ml of acetone was added to the reaction mixture and stirred for 5 min. Afterwards, the core–shell catalyst was easily separated through applying a simple external magnet. The separated nanomagnetic catalyst washed repeatedly with ethanol, weighed and recovered for the next run. The crude products were purified by recrystallization from ethanol. In the case of preparation of 4,4′-(arylmethylene)bis(1*H*–pyrazol-5-ol) derivatives, the reaction of benzaldehyde and

TABLE 4 Synthesis of pyrano[3,2-*c*]pyrazole derivatives under solvent-free conditions in the presence of {Fe_3O_4@SiO_2@$(CH_2)_3$-thiourea dioxide-SO_3H/HCl} at 90°C[a]

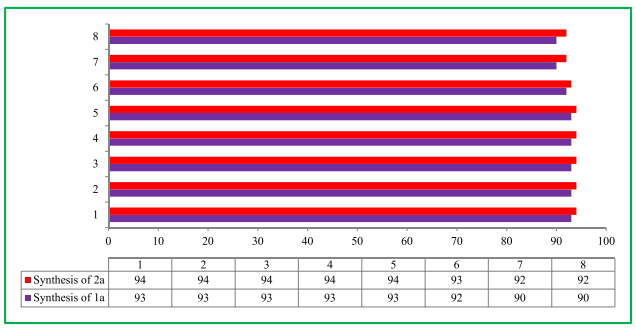
Entry	R	Product	Time (min)	Yield (%)[b]	M.p. (°C): found (lit.)
1	H	**2a**	25	91	178 (161–163)[43]
2	4-Cl	**2b**	25	95	179–182 (172–174)[43]
3	4-NO_2	**2c**	37	96	193–195 (187–188)[43]
4	4-F	**2d**	30	96	163–165 (170–171)[45]
5	4-OH	**2e**	45	86	215–216(206–207)[43]
6	4-Me	**2f**	30	82	177–178 (174–175)[43]
7	2-NO_2	**2 g**	35	93	174–177 (new)
8	3-NO_2	**2 h**	30	95	207 (193–194)[43]
9	2,4-Cl_2	**2i**	45	89	189–194 (182–184)[43]
10	2-Cl	**2j**	30	90	164–167 (144–146)[43]
11	4-OMe	**2 k**	33	88	204–206 (171–173)[43]
12	3-OEt-4-OH	**2 l**	35	91	178 (169–171)[41]
13	3-Br	**2 m**	25	89	156–158 (new)
14	2-OH	**2n**	30	82	216–217 (not reported)[55]
15	4-CN	**2o**	35	95	212–214 (not reported)[55]

[a]Reaction conditions: arylaldehyde (1 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (1 mmol, 0.174 g), malononitrile (1 mmol, 0.066 g), catalyst (7 mg).

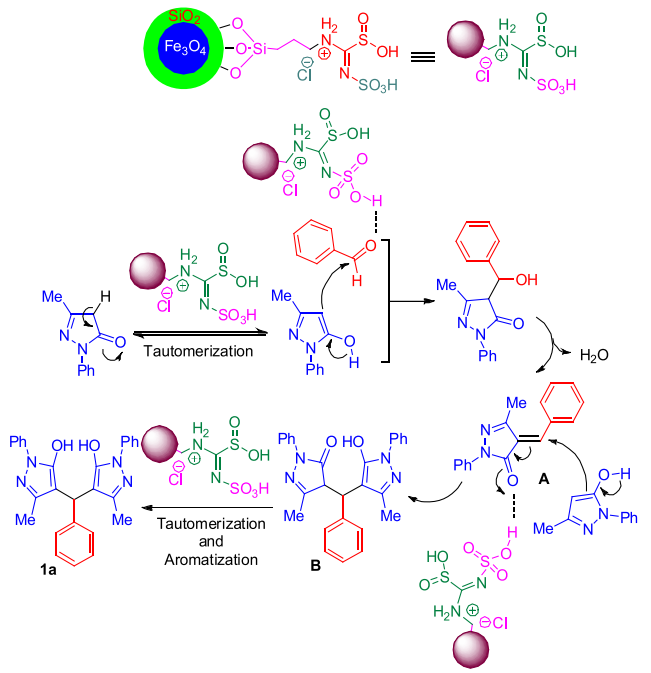
[b]Isolated yield.

3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one in 25 min was selected as a model reaction, and for the synthesis of pyrano[3,2-*c*]pyrazoles the reusability of the catalyst was examined in the reaction of benzaldehyde, 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one and malononitrile in 35 min. The resulting data reveal that regardless of the type of multicomponent reaction, the catalyst can be used for several runs (up to eight runs) without any discernible reduction of its initial catalytic performance. The achieved results are described in Scheme 5.

For a plausible mechanistic pathway for the synthesis of 4,4′-(arylmethylene)bis(1*H*–pyrazol-5-ol) derivatives, the preparation of the target molecule **1a** in the presence of the nanomagnetic catalyst was chosen as a model (Scheme 6). At first, 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one converts to its enol form through interaction with the nanomagnetic catalyst and attacks the activated benzaldehyde to yield the



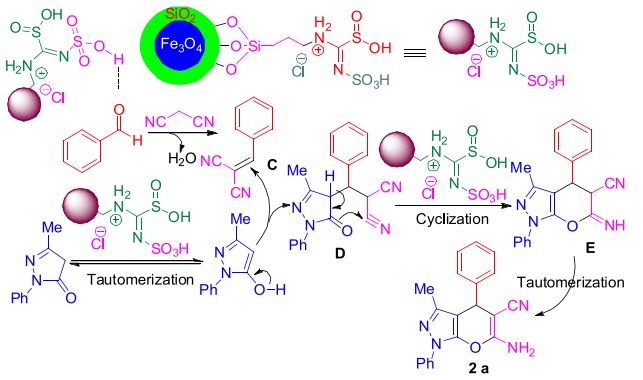
SCHEME 5 Reusability of the nanomagnetic solid acid supported catalyst in both multicomponent reactions.



SCHEME 6 Suggested mechanism for the synthesis of compound 1a in the presence of the described nanomagnetic catalyst.

corresponding intermediate **A** via dehydration. Subsequently, a second molecule of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one in its tautomer form attacks the intermediate **A** to give the intermediate **B**. Finally, through the tautomerization and aromatization of the intermediate **B** the desired product **1a** is obtained.

In the case of compound **2a** as a model for the synthesis of pyrano[3,2-*c*]pyrazoles, the suggested mechanism is as follows. Initially, the Knoevenagel adduct **C** generated from the reaction of benzaldehyde and malononitrile is subjected to reaction with the enol form of 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one to produce the related intermediate **D**. The cyclization of intermediate **D** in the presence of the nanomagnetic catalyst yields the intermediate **E** which could be tautomerized to compound **2a** as a desired product through the interaction with the catalyst (Scheme 7).



SCHEME 7 Plausible mechanism for the synthesis of compound 2a in the presence of the described nanomagnetic catalyst.

3 | CONCLUSIONS

In this presentation, the catalytic applicability of {Fe_3O_4@SiO_2@$(CH_2)_3$-thiourea dioxide-SO_3H/HCl} as a nanomagnetic core–shell supported solid acid catalyst was successfully examined in the synthetic reactions for the preparation of 4,4′-(arylmethylene)bis(1*H*–pyrazol-5-ol) derivatives and pyrano[3,2-*c*]pyrazoles. The catalyst shows excellent catalytic activity and the presented protocols are efficient and high-yielding. Also, the catalyst exhibited reusability in both the multicomponent reactions investigated.

4 | EXPERIMENTAL

4.1 | General

All chemicals were purchased from Merck. The structural confirmation of the known products was made by comparison of their physical properties and spectral data with those of authentic samples reported in the literature. The reaction progress and purity of the compounds were determined using TLC performed with silica gel SIL G/UV 254 plates. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded with a Bruker spectrometer. Melting points were recorded with a Buchi B-545 apparatus in open capillary tubes.

4.2 | General procedure for synthesis of 4,4′-(Arylmethylene)bis(1*H*–pyrazol-5-ol) derivatives in the presence of {Fe_3O_4@SiO_2@$(CH_2)_3$-thiourea dioxide-SO_3H/HCl} as reusable catalyst

To a test tube containing a mixture of aromatic aldehydes (1 mmol) and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (2 mmol, 0.384 g) was added 7 mg of {Fe_3O_4@SiO_2@$(CH_2)_3$-thiourea dioxide-SO_3H/HCl} which was heated in an oil bath at 90°C. The resulting mixture was stirred vigorously under solvent-free conditions for the required time (Table 2). After completion of the reaction as determined by TLC monitoring (using *n*-hexane and EtOAc as solvent system), the mixture was cooled to room temperature. Afterwards, in order to separate the catalyst, 10 ml of acetone was added to the reaction mixture and the crude products were extracted. The acetone was evaporated and the pure products were obtained via recrystallized from ethanol with good to excellent yields (Scheme 1 and Table 2).

4.3 | General procedure for synthesis of pyrano[3,2-*c*]pyrazoles in the presence of {Fe_3O_4@SiO_2@$(CH_2)_3$-thiourea dioxide-SO_3H/HCl} as reusable catalyst

To a mixture of aromatic aldehydes (1 mmol), 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (1 mmol, 0.174 g) and malononitrile (1 mmol, 0.066 g), according to the optimized reaction conditions, was added 7 mg of {Fe_3O_4@SiO_2@$(CH_2)_3$-thiourea dioxide-SO_3H/HCl} as a nanomagnetic core–shell supported solid acid catalyst. The resulting mixture was heated in an oil bath at 90°C under solvent-free conditions. The mixture was stirred vigorously for the required time (Table 4). After completion of the reaction as monitored by TLC (using *n*-hexane and EtOAc as solvent system), the mixture was cooled to room temperature. Then, in order to separate the nanomagnetic catalyst, boiling ethanol was added to the reaction mixture and the catalyst was isolated using an external magnet. Finally, the pure products were obtained via recrystallization from ethanol with good to excellent yields (Scheme 1 and Table 4).

4.4 | Selected spectral data of 4,4′-(Arylmethylene)bis(1*H*–pyrazol-5-ol) derivatives (Table 2)

4,4′-(Phenylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (**1a**). Melting point: 169–171°C. FT-IR (KBr, ν, cm^{-1}): 3443, 3067, 1601, 1580, 1501, 1488, 1298, 1015, 748. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 13.87 (s, 2H, OH), 7.71 (s, 5H, aromatic), 7.45–7.27 (m, 11H, aromatic), 4.97 (s, 1H, CH), 2.33 (s, 6H, 2 × CH_3). ^{13}C NMR (101 MHz, DMSO, δ, ppm): 146.22, 141.14, 130.52, 129.11, 128.89, 127.98, 125.59, 120.53, 32.53, 11.51.

4,4′-(*p*-Tolylmethylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (**1f**). Melting point: 193–196°C. FT-IR (KBr, ν, cm^{-1}): 3443, 3050, 1601, 1580, 1505, 1407, 1025, 749. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 13.93 (s, 2H, OH), 7.71 (brs, 4H, aromatic), 7.45 (brs, 4H, aromatic), 7.25 (s, 2H, aromatic), 7.14–7.09 (m, 4H, aromatic), 4.91 (s, 1H, CH), 2.32 (s, 6H, 2 × CH_3), 2.26 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO, δ, ppm): 146.20, 139.13, 134.78, 128.88, 128.65, 127.04, 125.48, 120.47, 32.73, 20.49, 11.61.

4,4′-((3-Ethoxy-4-hydroxyphenyl)methylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (**1 m**). Melting point: 207–209°C. FT-IR (KBr, ν, cm^{-1}): 3217, 2988, 1599, 1578, 1498, 1486, 1276, 1127, 753. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 14.06 (s, 2H, OH), 8.73 (s, 1H, OH), 7.77 (brs, 4H, aromatic), 7.51 (brs, 4H, aromatic), 7.32 (s, 2H, aromatic), 6.91 (s, 1H, aromatic), 6.75 (s, 2H, aromatic), 4.90 (s, 1H, CH), 3.99 (brs, 2H, —O—CH_2), 2.38 (s, 6H, 2 × CH_3), 1.34 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO, δ, ppm): 146.13, 145.17, 133.22, 128.88, 125.60, 120.52, 119.69, 115.25, 113.47, 63.95, 32.77, 14.69.

4,4′-((3-Bromophenyl)methylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (**1n**). Melting point: 157–158°C. FT-IR (KBr, ν, cm^{-1}): 3136, 3081, 1605, 1596, 1501, 1473, 1300, 1055, 763. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 13.98 (s, 2H, OH), 7.75 (d, 4H, J = 8 Hz, aromatic), 7.49 (t, 4H, J = 8 Hz, aromatic), 7.44 (s, 2H, aromatic), 7.32–7.28 (m, 4H, aromatic), 5.04 (s, 1H, CH), 2.37 (s, 6H, 2 × CH_3). ^{13}C NMR (101 MHz, DMSO, δ, ppm): 146.32, 146.25,

145.12, 130.32, 129.83, 128.93, 128.87, 126.45, 125.70, 121.54, 120.57, 118.45, 32.79, 11.51.

4,4′-((3-Methoxyphenyl)methylene)bis(3-methyl-1-phenyl-1*H*-pyrazol-5-ol) (**1p**). Melting point: 184–186°C. FT-IR (KBr, ν, cm^{-1}): 3512, 2972, 1604, 1582, 1503, 1486, 1275, 1043, 752. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 14.01 (s, 2H, OH), 7.72 (d, 4H, J = 8 Hz, aromatic) 7.45 (t, 4H, J = 8 Hz, aromatic), 7.27–7.19 (m, 3H, aromatic), 6.87–6.76 (m, 3H, aromatic), 4.92 (s, 1H, CH), 3.70 (s, 3H, ─O&─CH_3) , 2.33 (s, 6H, 2 × CH_3). ^{13}C NMR (101 MHz, DMSO, δ, ppm): 159.15, 146.27, 143.96, 129.15, 128.90, 125.56, 120.54, 119.61, 113.77, 110.40, 54.83, 33.15, 11.61.

4.5 | Selected spectral data of pyrano[3,2-*c*]pyrazole derivatives (Table 4)

6-Amino-3-methyl-4-(2-nitrophenyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**2 g**). Melting point: 174–177°C. FT-IR (KBr, ν, cm^{-1}): 3486, 3337, 2197, 1655, 1520, 1402, 1129, 750. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 7.99 (d, 1H, J = 8 Hz, aromatic), 7.89 (d, 2H, J = 8 Hz, aromatic), 7.79 (t, 1H, J = 8 Hz, aromatic), 7.65–7.58 (m, 4H, aromatic), 7.45–7.42 (m, 3H, NH_2 and aromatic), 5.30 (s, 1H, CH), 1.85 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO, δ, ppm): 159.7, 149.3, 144.9, 144.3, 137.4, 136.7, 133.4, 131.6, 129.3, 128.6, 126.3, 123.7, 120.1, 119.4, 97.3, 56.8, 31.9, 12.2.

6-Amino-4-(3-ethoxy-4-hydroxyphenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**2 l**). Melting point: 178°C. FT-IR (KBr, ν, cm^{-1}): 3503, 3420, 3328, 2196, 1660, 1596, 1514, 1398, 1126, 755. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 8.86 (s, 1H. OH), 7.84–7.82 (brs, 2H, aromatic), 7.53 (brs, 2H, aromatic), 7.35 (brs, 1H, aromatic), 7.16 (s, 2H, NH_2), 6.84–6.78 (m, 2H, aromatic), 6.67–6.65 (brs, 2H, aromatic), 4.60 (s, 1H, CH), 4.03–4.02 (brs, 2H, ─O─CH_2), 1.86 (s, 3H, ─O─CH_2─CH_3), 1.35 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO, δ, ppm): 159.18, 146.40, 145.80, 145.37, 143.73, 137.58, 134.47, 129.28, 126.03, 120.16, 120.06, 119.82, 115.59, 113.48, 98.86, 63.94, 58.67, 36.29, 14.68, 12.62.

6-Amino-4-(3-bromophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**2 m**). Melting point: 156–158°C. FT-IR (KBr, ν, cm^{-1}): 3454, 3338, 2195, 1656, 1591, 1519, 1390, 1127, 753. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 7.90 (d, 2H, J = 8 Hz, aromatic), 7.62–7.58 (m, 4H, aromatic), 7.46–7.41 (m, 3H, aromatic), 7.39 (s, 2H, NH_2), 4.85 (s, 1H, CH), 1.91 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO, δ, ppm): 159.6, 146.4, 145.1, 137.5, 130.8, 130.4, 130.0, 129.3, 127.0, 126.2, 121.8, 120.1, 119.8, 98.0, 57.5, 36.3, 12.6.

6-Amino-4-(4-cyanophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (**2o**). Melting point: 212–214°C. FT-IR (KBr, ν, cm^{-1}): 3400, 3112, 2236, 2192, 1653, 1593, 1516, 1388, 1124, 759. ^{1}H NMR (400 MHz, DMSO, δ, ppm): 7.84–7.79 (m, 4H, aromatic), 7.51–7.48 (m, 4H, aromatic), 7.35–7.31 (m, 3H, NH_2 and aromatic), 4.84 (s, 1H, CH), 1.79 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO, δ, ppm): 159.7, 149.1, 145.1, 144.0, 137.4, 132.6, 129.3, 128.9, 126.2, 120.1, 119.7, 118.7, 110.0, 97.6, 57.1, 36.7, 12.5.

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