

# Nano *n*-propylsulphonated $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>: A novel magnetically recyclable heterogeneous catalyst for the efficient synthesis of *bis*(pyrazolyl)methanes in water

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MS received 19 February 2013; accepted 8 July 2013

**Abstract.** Nano *n*-propylsulphonated  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> (NPS- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>) was applied as a new magnetically recyclable heterogeneous catalyst for the efficient one-pot synthesis of *bis*(pyrazolyl)methanes in water. The catalyst was easily isolated from the reaction mixture by a magnetic bar and reused at least five times without significant degradation in activity.

**Keywords.** Nanomagnetic iron oxide; heterogeneous catalyst; *bis*(pyrazolyl)methanes; 1,3-propanesultone.

## 1. Introduction

Pyrazoles are an important class of bio-active drug targets in pharmaceutical industry. They are the core structure of numerous biologically active compounds.<sup>1</sup> For example, 2,4-dihydro-3*H*-pyrazol-3-one derivatives including 4,4'-(arylmethylene)-*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) are being used as antiinflammatory, antipyretic, gastric secretion stimulatory, antidepressant, antibacterial and antifilarial agents.<sup>2</sup> Moreover, the corresponding 4,4'-(arylmethylene) *bis*(1*H*-pyrazol-5-ols) are applied as fungicides, pesticides and insecticides.<sup>3</sup> They also play an important role in analytical chemistry as chelating and extracting reagents for different metal ions, catalysis, dye and extraction metallurgy.<sup>4</sup>

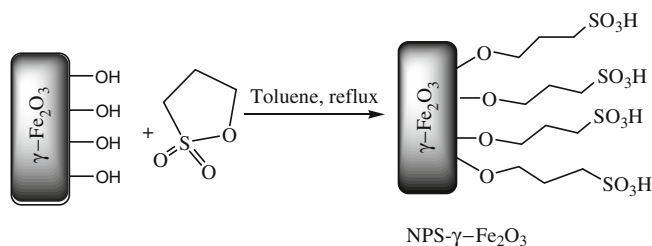
The conventional chemical approach to 4,4'-(arylmethylene)-*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) involves the successive Knoevenagel synthesis of the corresponding arylidenepyrazolones and its base promoted Michael reaction.<sup>3,5</sup> One-pot tandem Knoevenagel–Michael reaction of aldehydes with two equivalents of 5-methyl-2-phenyl-2, 4-dihydro-3*H*-pyrazol-3-one which can be performed under a variety of reactions is another approach for achieving these important scaffolds.<sup>6</sup> Even though, 4,4'-(arylmethylene)-*bis*(3-methyl-1-phenyl-1*H*-pyrazol-5-ols) could be synthesized by these methods, most of the methods suffer from limitations such as low yields, long reaction times, tedious work-up procedures and using hazardous solvents or unrecyclable catalysts. Therefore,

the development of a new method to overcome these shortcomings still remains an ongoing challenge for the synthesis of these significant scaffolds.

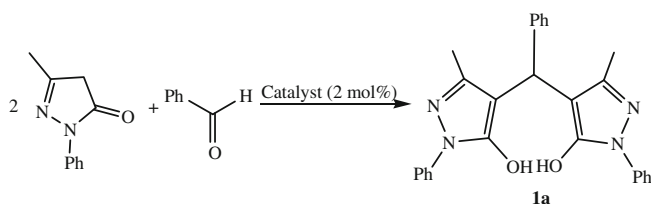
*n*-Propylsulphonated surface materials are one of the organic–inorganic hybrid materials that have been applied as effective heterogeneous acid catalysts in organic transformations.<sup>7</sup> In these types of acid catalysts, the reactive centres are highly mobile similar to that of homogeneous catalysts and at the same time these compounds have the advantage of being recyclable in the same fashion as heterogeneous catalysts. In general, synthesis of *n*-propylsulphonated surface materials with propanesulphonate moieties was conducted by SH oxidation of supported mercaptopropyl<sup>7a–e</sup> or directly through ring opening reaction of 1,3-propanesultone with hydroxyl groups on the surfaces such as SiO<sub>2</sub> and diamond.<sup>7f,g</sup> In both cases, sulphonic acid groups are introduced on the surface *via* covalently bonds through a 3-carbons chain. However, in SH oxidation method, imperfect oxidation of SH groups decreases the efficiency of the catalyst. On the other hand, these heterogeneous catalysts are recovered by time consuming methods such as filtration or centrifugation that may cause loss of the catalyst. Moreover, a substantial decrease in the activity and selectivity of these immobilized sulphonic acid catalysts is frequently observed due to the heterogeneous nature of supporting materials in reaction media, steric and diffusion factors.

In recent years, magnetic nanoparticles are receiving increasing interest as supporting material for the synthesis of heterogeneous catalysts.<sup>8</sup> The magnetic nature

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**Scheme 1.** Synthesis of NPS- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>.



**Scheme 2.** The reaction of benzaldehyde with 1-phenyl-3-methyl-5-pyrazolone.

of these particles allows the ease of recovery and recycling of the catalysts by an external magnetic field, which may optimize operational cost and enhance product's purity. Moreover, because of the available surface area of the nanoporous MNPs is external, their catalytic performance is enhanced and the internal diffusion is practically avoided.

As part of our ongoing program directed toward the development of new methods using heterogeneous catalysts for organic transformations<sup>9a-g</sup> and due to the importance of the using magnetic nanoparticles as support material, recently, we have synthesized heterogeneous catalysts based on functionalization of magnetic nanoparticles.<sup>9h-j</sup> Along this line, *n*-propylsulphonated  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> (NPS- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>) was synthesized directly

through ring opening reaction of 1,3-propanesultone by nano magnetic  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub><sup>9h,i</sup> (scheme 1) and applied as a heterogeneous catalyst for the synthesis of  $\beta$ -phosphonomalonates, 2-indolyl-1-nitroalkenes and bis(indolyl)methanes. Here, in this report, in order to explore the applicability of NPS- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> in other organic reactions, the efficiency of this catalyst was investigated for the one-pot synthesis of bis(pyrazolyl)methanes.

## 2. Experimental

### 2.1 General procedure for the synthesis of bis(pyrazolyl)methanes

NPS- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> (2 mol%) was added to a mixture of aldehyde (5 mmol) and 1-phenyl-3-methyl-5-pyrazolone (10 mmol) in water (5 mL). The mixture was stirred at room temperature for the appropriate time. The reaction was monitored by TLC. After completion, the catalyst was separated by a magnetic bar from the cooled mixture, washed with EtOH, dried for 30 min at 110°C and re-used for a consecutive run under the same reaction conditions. The crude product was isolated after centrifugation and decantation of the remaining solution. The pure product was obtained by flash chromatography on silica gel eluted with *n*-hexane:EtOAc (2:1).

## 3. Results and discussion

At first, in order to optimize the reaction conditions such as solvent, the reaction of two equivalents of 1-phenyl-3-methyl-5-pyrazolone with benzaldehyde was studied (scheme 2, table 1) in different solvents in the

**Table 1.** Reaction of 1-phenyl-3-methyl-5-pyrazolone with benzaldehyde under different reaction conditions.

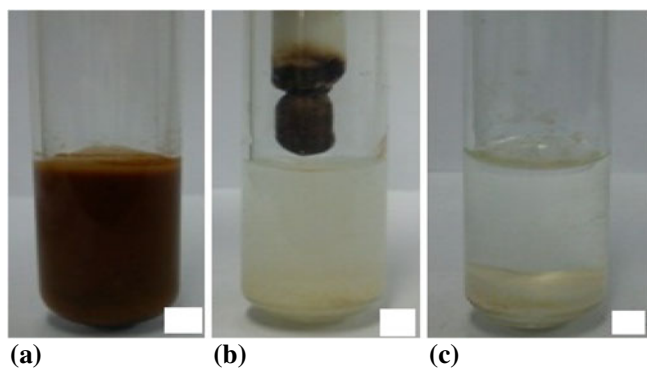
Entry	Catalyst	Solvent	Time (h)	Yield <sup>a</sup> (%)
1	NPS- $\gamma$ -Fe <sub>2</sub> O <sub>3</sub>	H <sub>2</sub> O	3	93
2	NPS- $\gamma$ -Fe <sub>2</sub> O <sub>3</sub>	Toluene	4	54
3	NPS- $\gamma$ -Fe <sub>2</sub> O <sub>3</sub>	Petroleum ether	4	43
4	NPS- $\gamma$ -Fe <sub>2</sub> O <sub>3</sub>	CH <sub>3</sub> CN	3	67
5	NPS- $\gamma$ -Fe <sub>2</sub> O <sub>3</sub>	EtOH	3	58
6	NPS- $\gamma$ -Fe <sub>2</sub> O <sub>3</sub>	-	3	66
7	NPS- $\gamma$ -Fe <sub>2</sub> O <sub>3</sub>	H <sub>2</sub> O	3	71 <sup>b</sup>
8	- <sup>c</sup>	H <sub>2</sub> O	24	31
9	$\gamma$ -Fe <sub>2</sub> O <sub>3</sub> <sup>d</sup>	H <sub>2</sub> O	24	65

<sup>a</sup>Isolated yield, conditions: benzaldehyde (1 mmol), 1-phenyl-3-methyl-5-pyrazolone (2 mmol), catalyst (2 mol%, except for entries 7 and 9), room temperature.

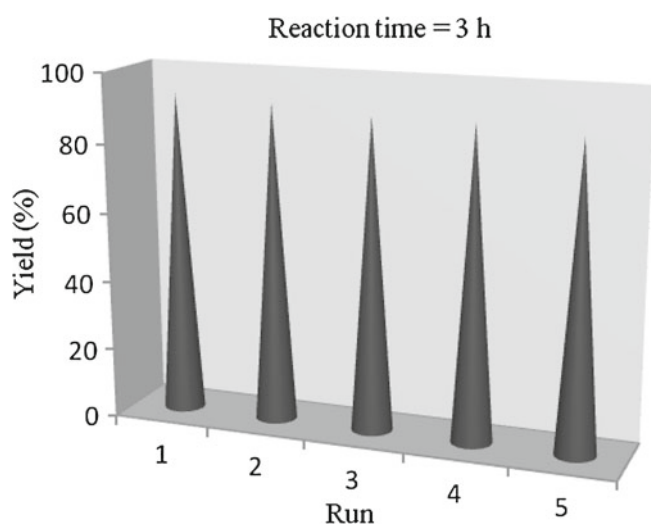
<sup>b</sup>Catalyst = 1 mol%.

<sup>c</sup>No catalyst.

<sup>d</sup>Catalyst = 0.088 g.



**Figure 1.** (a) Reaction mixture, (b) separation of NPS- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> from the reaction mixture by a magnetic bar, and (c) remaining solution after centrifugation.



**Figure 2.** Reusability of NPS- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> for the synthesis of bis(pyrazolyl)methane **1a**.

presence of NPS- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> (2 mol%) at room temperature (table 1, entries 1–5). We found that in the presence of NPS- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>, the desired product was obtained with good yield in water as the reaction solvent (entry 1). Under the same reaction conditions, when 1 mol% of the catalyst was used, the desired product was obtained in lower yield (entry 7). In order to show the role of the catalyst, similar reactions in the absence of the catalyst or in the presence of nanomagnetic  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> were also examined. Under these conditions, the reactions led to the formation of the desired product in lower yields after a long reaction time (entries 8 and 9).

Importantly, note that the magnetic property of NPS- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> facilitates efficient recovery of the catalyst from the reaction mixture during work-up procedure. The catalyst was separated by a magnetic bar from the reaction mixture (figure 1a, b), washed with EtOH, dried 30 min at 110°C and re-used for five runs without any significant deactivation. In each run, the desired pure product (**1a**) was obtained after centrifugation (figure 1c) and decantation of the remaining solution following by flash chromatography. The average isolated yield of the product for five consecutive runs was 90.6%, which clearly demonstrates the practical recyclability of this catalyst (figure 2).

To demonstrate that the synthesis of bis(pyrazolyl)methanes catalysed by NPS- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> is a heterogeneous process, the reaction of benzaldehyde with 1-phenyl-3-methyl-5-pyrazolone was carried out in water in which the nanocatalyst was separated by a magnetic bar at 50% conversion and the resulting clear solution stirred for an additional 2 h in the absence

**Table 2.** Synthesis of bis(pyrazolyl)methanes **1a–n** catalysed by NPS- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub>.

Entry	Aldehyde	Product	Time (h)	Yield <sup>a</sup> (%)
1	Benzaldehyde	<b>1a</b>	3	93
2	3-Methylbenzaldehyde	<b>1b</b>	4	82
3	4-Methoxybenzaldehyde	<b>1c</b>	1	85
4	4-Chlorobenzaldehyde	<b>1d</b>	3	81
5	4-Bromobenzaldehyde	<b>1e</b>	1	87
6	4-Nitrobenzaldehyde	<b>1f</b>	2	94
7	4-Cyanobenzaldehyde	<b>1g</b>	4	90
8	4-Hydroxybenzaldehyde	<b>1h</b>	4	82 <sup>b</sup>
9	2-Hydroxybenzaldehyde	<b>1i</b>	4	81 <sup>b</sup>
10	2-Naphthaldehyde	<b>1j</b>	4	83
11	Furfural	<b>1k</b>	1	85
12	Thiophene-2-carbaldehyde	<b>1l</b>	2	86
13	<i>iso</i> -Butyraldehyde	<b>1m</b>	4	85
14	Pentanal	<b>1n</b>	4	91

<sup>a</sup>Isolated yield, conditions: catalyst (2 mol% except for entries 8 and 9). All the products are known compounds in the literature.<sup>6c–k</sup> The products were characterized by spectroscopic methods (see supplementary data).

<sup>b</sup>Catalyst = 3 mol%.

**Table 3.** Comparison of the catalytic efficiency of NPS- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> with various catalysts for the synthesis of bis(pyrazolyl)methane **1a**.

Entry	Catalyst	Time (h)	Yield <sup>a</sup> (%)
1	NPS- $\gamma$ -Fe <sub>2</sub> O <sub>3</sub>	3	93
2	CdO	24	41
3	CuO	24	36
4	HgO	24	38
5	MgO	24	40
6	Al <sub>2</sub> O <sub>3</sub>	24	35
7	MoO <sub>3</sub>	24	36
8	CaO	24	39
9	RuO <sub>2</sub>	24	32
10	ZrO <sub>2</sub>	24	34
11	HClO <sub>4</sub> -SiO <sub>2</sub>	3	84
12	H <sub>3</sub> [P(W <sub>3</sub> O <sub>10</sub> ) <sub>4</sub> ]	3	92
13	Aminopropylated silica	24	84

<sup>a</sup>Isolated yield, conditions: benzaldehyde (1 mmol), 1-phenyl-3-methyl-5-pyrazolone (2 mmol), catalyst (2 mol%), H<sub>2</sub>O (1 mL), room temperature.

of the catalyst. No significant increase in the yield occurred after removal of the catalyst. A similar reaction in the presence of the isolated catalyst proceeded well to produce the desired product in 93% yield after 3 h. These observations indicate that the solution did not contain any active species leached from the catalyst.

The reaction of a variety of aldehydes with 1-phenyl-3-methyl-5-pyrazolone was then investigated to confirm the generality of the present method. The results of this study are depicted in table 2.

As shown in table 2, different aromatic, heteroaromatic and aliphatic aldehydes reacted with 1-phenyl-3-methyl-5-pyrazolone in the presence of NPS- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> to afford bis(pyrazolyl)methanes (**1a–n**) in good to high yields.

We have also performed the reaction of 1-phenyl-3-methyl-5-pyrazolone with benzaldehyde in the presence of a catalytic amount of metal oxides [e.g. CdO, CuO, HgO, MgO, Al<sub>2</sub>O<sub>3</sub>, MoO<sub>3</sub>, CaO, RuO<sub>2</sub>, ZrO<sub>2</sub>], Brønsted acids {e.g. HClO<sub>4</sub>-SiO<sub>2</sub> and H<sub>3</sub>[P(W<sub>3</sub>O<sub>10</sub>)<sub>4</sub>]} and aminopropylated silica as a base (table 3). As evident from table 3, NPS- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> is the most effective catalyst for this purpose leading to the formation of bis(pyrazolyl)methane (**1a**) in high yield in a short reaction time.

#### 4. Conclusions

In summary, we have found that NPS- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> can be used as a new, re-usable and efficient catalyst for the synthesis of a variety of bis(pyrazolyl)methanes via one-pot tandem Knoevenagel–Michael reaction of

different types of aldehydes (aryl, heteroaryl, alkyl aldehydes) with two equivalents of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one in water. NPS- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> was easily isolated from the reaction mixture by a magnetic bar and reused at least five times without significant degradation in its activity. This reaction system not only provides a novel method for the synthesis of bis(pyrazolyl)methanes, but also extends the applicability of NPS- $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> in organic synthesis.

#### Supplementary information

The electronic supporting information can be seen in [www.ias.ac.in/chemsci](http://www.ias.ac.in/chemsci).

#### Acknowledgements

We are thankful to the University of Birjand Research Council for the support to carry out this work.

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