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Magnetic Nanoparticle Immobilized *N*-Propylsulfamic Acid as a Recyclable and Efficient Nanocatalyst for the Synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones in Solvent-Free Conditions: Comparison with Sulfamic Acid

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N-Propylsulfamic acid supported onto magnetic Fe_3O_4 nanoparticles (MNPs-PSA) was used as an efficient and magnetically recoverable catalyst for synthesis of 2*H*-Indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives from the three-component, one-pot condensation reaction of phthalhydrazide, aromatic aldehydes and cyclic 1,3-diones, in good to excellent yields at 100 °C under solvent-free conditions. The catalyst was easily separated with the assistance of an external magnetic field from the reaction mixture and reused for several consecutive runs without significant loss of its catalytic efficiency. In order to compare, the synthesis of 2*H*-Indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives in the presence of catalytic amount of sulfamic acid (SA) under same reaction condition was also reported.

Key Words : Magnetic nanoparticle, Nanocatalyst, *N*-Propylsulfamic acid, Condensation reaction, 2*H*-Indazolo[2,1-*b*]phthalazine-triones

Introduction

Environmentally benign, economical, practical, and efficient processes for catalyst separation and reuse have been increasingly important goals in the chemical community from economic, safety, and environmental points of view.[1]

Nanoparticles have recently emerged as efficient alternatives for the immobilization of homogeneous catalysts and as catalysts themselves.[2,3] However, particles with diameters of less than 100 nm are difficult to separate by filtration techniques.

Magnetic separation of the magnetic nanoparticles is simple, economical and promising for industrial applications.[4] Among the various magnetic nanoparticles under investigation, Fe_3O_4 nanoparticles are arguably the most extensively studied as the core magnetic support because of their simple synthesis, low cost, and relatively large magnetic susceptibility Fe_3O_4 SPNs.[5] There are several protocols reported in the literature for preparing a wide variety of catalytic magnetic materials.[6]

Sulfamic acid (SA) is environmentally compatible, stable and commercially available catalyst. More important, its water resistance and incapability for formation of complexes make it an outstanding alternative to metal catalysts, in different areas of organic synthesis, as an efficient and green catalyst.[7,8] However the major disadvantage of this catalyst is its separation from products, which needs Solid-liquid or Liquid-liquid techniques in many reactions. This drawback can be overcome by immobilizing this catalyst on magnetic nanoparticles (MNPs), which can be easily removed from the reaction mixture by magnetic separation.

Fused phthalazines have been found effective for the inhibition of p38 MAP kinase,[9] for selective binding of GABA receptor,[10] and as *anti*-anxiety drug,[11] antitumor agent,[12] and high-affinity ligand to the a2d1 subunit of calcium channel.[13] Fused phthalazine derivatives also possess some biological activities such as anticonvulsant,[14] cardiotonic,[15] and vasorelaxant.[16] Although several reports on the synthesis of phthalazines fused with indazole have been published.[17-26] However, the development of an efficient and versatile method for the preparation of fused phthalazine with indazole is an active ongoing research area, and there is a potential for further improvement toward green chemistry.

Experimental

General Procedure for Synthesis of 1*H*-indazolo[1,2-*b*]phthalazine-triones catalyzed by MNPs-PSA. To a mixture of aromatic aldehyde (1.1 mmol), phthalhydrazide (1 mmol) and cyclic 1,3-diones compound (1 mmol), MNPs-PSA (30 mg) was added and the mixture was stirred and heated in an oil bath at 100 °C for appropriate time. Completion of the reaction was indicated by TLC (*n*-hexane/ethylacetate 60:40). After the indicated reaction time, the reaction mixture was cooled to room temperature. Et_2O (25 mL) was added and the catalyst was separated by an external magnet. The resulting solution was concentrated under reduced pressure to afford the essentially pure products. In some cases, for further purication, the product was recrystallized from ethanol.

General Procedure for Synthesis of 1*H*-indazolo[1,2-*b*]phthalazine-triones Catalyzed by SA. To a mixture of aromatic aldehyde (1.1 mmol), phthalhydrazide (1 mmol)

and cyclic 1,3-diones compound (1 mmol), SA (10 mg, 0.1 mmol) was added and the mixture was stirred and heated in an oil bath at 100 °C for appropriate time. Completion of the reaction was indicated by TLC (stationary phase: silica gel polygram SIL G/UV 254 plates and mobile phase: *n*-hexane/ethylacetate 60:40). After the reaction was completed, the reaction mixture was cooled to room temperature, and then the solid residue was washed by H_2O:EtOH (90:10). The solid product was purified by recrystallization procedure from ethanol (85%).

Spectral Data of Unknown Products are Given Below (see the supplementary materials):

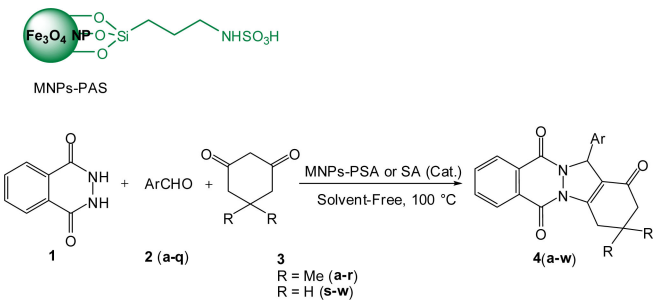
3,4-Dihydro-3,3-dimethyl-13-(3-methoxyphenyl)-2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione (4d): Green crystal, mp 206-208 °C; IR (KBr): 1659, 1625, 1354, 1310, 1273 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$) δ 1.21 (s, 6H), 2.34 (s, 2H), 3.22 and 3.40 (AB system, $^2J_{HH}$ = 19.0 Hz, 2H), 3.78 (s, 3H), 6.42 (s, 1H), 6.73-6.83 (m, 1H), 6.90-7.02 (m, 2H); 7.19-7.29 (m, 1H) 7.84-7.87 (2H, m), 8.26-8.37 (2H, m). ^{13}C NMR: (62.9 MHz, $CDCl_3$) δ 28.5, 28.7, 34.7, 38.0, 50.9, 55.2, 64.8, 113.1, 113.8, 118.5, 119.4, 127.7, 128.0, 129.0, 129.7, 133.5, 134.5, 138.0, 150.8, 154.3, 156,0, 159.7, 192.2; MS (EI, 70 eV, *m/z* %): 402 (M^+, 15), 380 (11), 295 (100), 273 (14), 104 (6), 76 (6).

3,4-Dihydro-3,3-dimethyl-13-(2-nitrophenyl)-2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione (4l): Yellow crystal, mp 236-238 °C; IR (KBr): 1679, 1648, 1500, 1530, 1352, 1305, 1262 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.21 (s, 3H), 2.32 (s, 2H), 3.25 and 3.39 (AB system, $^2J_{HH}$ = 19.1 Hz, 2H), 7.33-7.58 (m, 4H), 7.85-7.95 (m, 3H), 8.24-8.38 (m, 2H). ^{13}C NMR: (62.9 MHz, $CDCl_3$) δ 28.5, 28.6, 34.7, 38.1, 50.8, 60.6, 116.9, 125.2, 127.8, 128.2, 128.6, 129.0, 129.5, 130.7, 133.1, 133.8, 134.7, 149.3, 152.0, 154,4, 156.0, 191.9; MS (EI, 70 eV, *m/z* %): 417 (M^+, 15), 400 (100), 370 (37), 299 (75), 104 (55), 76 (60).

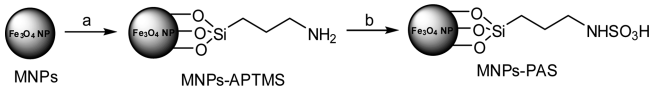
13-(3-(2,2-Dimethyl-1,6,11-trioxo-2,3,4,6,11,13-hexahydro-1*H*-indazolo[1,2-*b*]phthalazin-13-yl)phenyl)-2,2-dimethyl-2,3-dihydro-1*H*-indazolo[1,2-*b*]phthalazine-4,6,11(13*H*)-trione: Yellow powder, mp 284-286 °C; IR (KBr): 1663, 1628, 1602, 1359, 1308, 1264 cm^{-1}; ^1H NMR (250.1 MHz, $CDCl_3$) δ 1.15 (s, 6H), 1.20 (s, 6H), 2.18 and 2.37 (AB system, $^2J_{HH}$ = 16.2 Hz, 4H), 3.20 and 3.33 (AB system, $^2J_{HH}$ = 18.8 Hz, 4H), 6.42 (s, 2H), 7.26-7.46 (m, 4H), 7.65-7.80 (m, 4H), 8.17-8.29 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 28.4, 28.8, 34.6, 37.9, 50.9, 64.2, 118.0, 125.9, 127.6, 127.9, 129.0, 133.4, 134.3, 136.5, 151.1, 156.0, 192.0; MS (EI, 70 eV, *m/z* %): 666 (M^+, 15), 664 (15), 295 (100), 279 (20), 239 (10).

Results and Discussion

In continuation our study about application of sulfamic acid (SA) as a green catalyst in organic synthesis[27,28] herein we report catalytic application of MNPs-PSA as magnetically heterogeneous nanocatalyst or SA for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives from one-pot, three-component condensation of phthalhydrazide, aromatic aldehydes, and cyclic 1,3-diones compounds under solvent-free conditions at 100 °C (Scheme 1).



Scheme 1. The synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives by MNPs-SA or SA.



Schem 2. Synthesis of supported *N*-propylsulfamic acid on magnetic nanoparticles; (a) (3-aminopropyl)-triethoxysilane, ethanol/water, rt, 8 h; (b) chlorosulfuric acid, dichloromethane, 2 h, rt (see the supplementary materials for detailed experimental procedure).

First, the MNPs-PSA was prepared according to the very recently reported method[29] with some modifications as shown in scheme 2 (see the supplementary materials for detailed experimental procedure).

The catalyst has been characterized by scanning electron microscopy (SEM), X-ray diraction (XRD), fourier transform infrared spectroscopy (FT-IR) and by their comparisons with that of authentic sample (see the supplementary materials for figures). XRD pattern of MNPs-PSA is shown in Fig. S1 (supplementary materials). The position and relative intensities of all peaks confirm well. A SEM image of MNPs-PSA is shown in Fig. S2 (supplementary materials). It was confirmed that the catalyst was made up of nanometer-sized particles. The IR spectrum of MNPs-PSA shows peaks that are characteristic of a functionalized SA group, which clearly differs from that of the unfunctionalized Fe_3O_4 nanomagnets and aminopropyl-functionalized magnetic nanoparticles (supplementary materials, Fig. S3).

To determine the acid amount on the surface, the prepared catalyst (100 mg) was added to an aqueous NaCl solution (1 M, 10 mL) with an initial pH = 5.93. The mixture stirred for 0.5 h after which the pH of solution decreased to 1.72, indicating an ion exchange between sulfamic acid protons and sodium ions, this is equal to a loading of 1.9 mmol/g of sulfamic acid group. This result confirmed by back-titration of the catalyst.

Next, we evaluated the effect of different amounts of MNPs-PSA or SA on the three-component reaction of phthalhydrazide, benzaldehyde, and dimedone as a model reaction, in terms of time and product yield under solvent-free conditions at 100 °C. As shown in Table 1, when the amount of catalyst was added, the times were reduced; however 30 mg of MNPs-SA or 10 mol % of SA were chosen for the desired reaction.

With the above conditions, the generality and the appli-

Table 1. Effect of catalysts evaluation in synthesis of 2,2-dimethyl-13-phenyl-2,3-dihydro-1*H*-indazolo[2,1-*b*]phthalazine-4,6,11(13*H*)-triones at 100 °C under solvent-free conditions

Entry	Catalyst	Amount of catalyst	Time (min)	Yield (%)
1	none	-	60	no reaction
2	SA	5 mol %	32	89
3	SA	10 mol %	19	90
4	SA	20 mol %	16	90
5	SA	30 mol %	15	89
6	MNPs-SA	10 mg	55	88
7	MNPs-SA	20 mg	40	90
8	MNPs-SA	30 mg	35	93
9	MNPs-SA	40 mg	30	94
10	MNPs-SA	50 mg	25	93

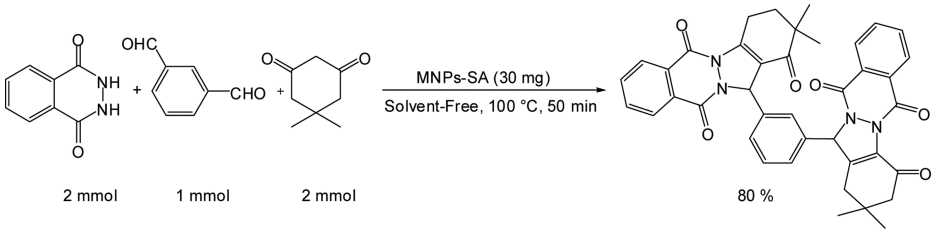
cability of these methods were further examined for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives from condensation of phthalhydrazide **1**, structurally diverse of aromatic aldehydes **2** and cyclic 1,3-diones **3**, in the presence of a catalytic amount of MNPs-PSA or SA at 100 °C under solvent-free conditions (Table 2). In all cases, the reactions gave the corresponding products in short reaction time and good to excellent yield. It was observed that the reaction proceed more rapidly with SA than MNPs-SA, instead, the higher has been obtained by MNPs-SA, suggesting the importance of magnetic separation. We have developed this synthetic method for the preparation of bis-2*H*-indazolo[2,1-*b*]phthalazine-trione derivative in a 2:1.1:2 molar ratio of phthalhydrazide to isophthaladehyde and dimedone as depicted in Scheme 3.

We examined the recycling of MNPs-PSA for the synthesis of 2,2-dimethyl-13-(4-methylphenyl)-2,3-dihydro-1*H*-indazolo[2,1-*b*]phthalazine-4,6,11(13*H*)-trione. After the completion of the reaction, the mixture was dark brown in color; the catalyst was separated easily and rapidly from the product by exposure to an external magnet (within 5 seconds), the solution became very clear (Fig. 1). The reaction solution was decanted and the remaining magnetic nanoparticles were further washed with the Et_2O, to remove residual product and dried under vacuum and subjected to the next run. The efficient separation using this method minimizes the loss of catalyst during separation. The SEM images of reused catalyst indicated that no detectable

Table 2. Synthesis of 1*H*-indazolo[1,2-*b*]phthalazine-triones[a] catalyzed by MNPs-PSA or SA

Entry	ArCHO	R	Product	MNPs-PSA		SA		mp/°C
				Yield (%)[b]	Time (min)	Yield (%)[b]	Time (min)	Lit.[c]
1	C_6H_5CHO	Me	4a	93	35	90	19	206-207[12,20]
2	2-$CH_3C_6H_4CHO$	Me	4b	91	35	89	17	242-244[13]
3	4-$CH_3C_6H_4CHO$	Me	4c	90	30	89	16	228-230[17]
4	3-$CH_3OC_6H_4CHO$	Me	4d	87	40	84	19	206-208
5	4-$CH_3OC_6H_4CHO$	Me	4e	89	35	88	19	220-222[14]
6	3,4-$(CH_3O)_2C_6H_4CHO$	Me	4f	88	30	82	14	186-188[14]
7	3-Br C_6H_4CHO	Me	4g	85	35	85	20	224-226[17]
8	2-Cl C_6H_4CHO	Me	4h	87	30	90	15	263-265[12]
9	4-Cl C_6H_4CHO	Me	4i	93	25	82	13	261-263[12,20]
10	2,4-$(Cl)_2C_6H_4CHO$	Me	4j	91	35	80	22	220-221[15,20]
11	4-FC_6H_4CHO	Me	4k	90	30	88	12	219-221[18]
12	2-$NO_2C_6H_4CHO$	Me	4l	82	45	85	26	236-238
13	3-$NO_2C_6H_4CHO$	Me	4m	86	40	83	24	270-272[12,20]
14	4-$NO_2C_6H_4CHO$	Me	4n	83	50	82	25	222-224[12,20]
15	2-naphtaldehyde	Me	4o	84	45	84	21	251-253[14,20]
16	C_6H_5CHO	H	4p	86	45	85	20	223-224[14]
17	4-$CH_3C_6H_4CHO$	H	4q	88	45	87	21	244-246[14]
18	4-$CH_3OC_6H_4CHO$	H	4r	90	40	90	20	251-253[14]
19	4-$NO_2C_6H_4CHO$	H	4s	83	50	82	25	252-254[18]
20	4-FC_6H_4CHO	H	4t	89	40	87	14	259-261[14]

[a]Reaction conditions: aromatic aldehydes (1.1 mmol), phthalhydrazide (1 mmol), cyclic 1,3-diones (1 mmol) and MNPs-PSA (30 mg) or SA (10 mol %), 100 °C, solvent-free. [b]Isolated yields. [c]References for spectroscopic data and melting point of products.



Scheme 3. Synthesis of bis-2*H*-indazolo[2,1-*b*]phthalazine-trione derivative catalyzed by MNPs-PSA.

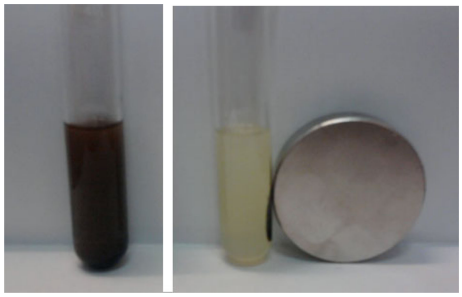


Figure 1. Image showing MNPs-PSA can be separated by applied magnetic eld. A reaction mixture in the absence (left) or presence of a magnetic eld (right).

Table 3. Recycling of MNPs-PSA for condensation reaction of phthalhydrazide, 4-methylbenzaldehyde and dimedone at 100 °C under solvent-free conditions

Entry	Recycle	Recovered catalyst (%)	Yield (%)
1	1st	100	90
2	2nd	100	90
3	3rd	100	88
4	4th	100	88
5	5th	100	88
6	6th	100	85
7	7th	100	82

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changes of the catalyst occurred during the reaction and the recycling stages (supplementary materials, Fig. S2). The recycled cata-lyst was used for up to seven runs without any significant loss of activity (Table 3).

Conclusion

In conclusion, we have developed efficient and eco-friendly protocols for the synthesis of 2*H*-indazolo[1,2-*b*]phthalazine-triones *via* one-pot, three-component condensation reaction of aromatic aldehydes, phthalhydrazide, and cyclic 1,3-diones, catalyzed by MNPs-SA or SA under solvent-free conditions at 100 °C. The MNPs-SA is easily synthesized and can catalyze the synthesis of 2*H*-indazolo[1,2-*b*]phthalazine-triones with comparable activity as SA. The product separation and catalyst (MNPs-SA) recycling are easier and simpler with the assistance of an external magnet. The catalyst can be recycled and reused for 7 times with little loss of activity. The MNPs-PSA couples the advantages of heterogeneous and homogeneous SA-based systems, which make it as a promising material for industrial applications.

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