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ORIGINAL PAPER

Synthesis of spiro[pyrazoloquinoline-oxindoles] and spiro[chromenopyrazolo-oxindoles] promoted by guanidine-functionalized magnetic Fe_3O_4 nanoparticles

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Abstract
Magnetic nanoparticles (MNPs) Fe_3O_4-immobilized guanidine (Fe_3O_4 MNPs-guanidine) have been used as an efficient catalyst for the preparation of spiro[pyrazoloquinoline-oxindoles] and spiro[chromenopyrazolo-oxindoles] by four-component reactions of phenylhydrazine or hydrazine hydrate, isatins, ketoesters and naphthylamine or 2-naphthol under reflux condition in ethanol. This method provides several advantages including mild reaction conditions, the applicability to a wide range of substrates, the reusability of the catalyst and low catalyst loading.

Keywords Fe_3O_4 nanoparticles · Heterogeneous catalyst · Spirooxindoles · One pot reaction

Introduction

Spirooxindoles have emerged as a group of important heterocycles due to their presence in a broad spectrum of natural and synthetic organic compounds [1–3], with diverse biological properties such as antimicrobial [4–6], antitumor [7, 8], antidiabetic [9] and can also serve as synthetic intermediates for diverse kinds of pharmaceuticals or drug precursors [10]. These activities make spirooxindoles attractive targets in organic synthesis. Recently, multicomponent reactions performed with a heterogeneous catalyst under moderate conditions have attracted much attention [11–13]. Magnetic materials have emerged as a particularly useful group of heterogeneous catalysts due to their diverse applications in synthesis and catalysis [14, 15]. The surface of MNPs can be functionalized simply through suitable surface modifications to provide the attachment of a variety of favorable functionalities. Recently, MNPs have been successfully used to immobilize enzymes, polymers, transition metal catalysts and organocatalysts [16, 17]. The expansion of surface modification of magnetic nanoparticles as significant candidates in the search for supporting catalysts is presently a subject of increasing interest [18, 19].

Herein, we report the use of magnetic nanoparticles Fe_3O_4-immobilized guanidine as an efficient catalyst for the preparation of spirooxindoles (Scheme 1). The synthesis of spirooxindoles has been reported in the presence of diverse catalysts such as *p*-TSA [20, 21], piperidine [22], alum ($KAl(SO_4)_2{\cdot}12H_2O$) [23], amino-functionalized SBA-15 (SBA-Pr-NH_2) [24], nanocrystalline MgO [25] and L-Proline [26]. However, some of the reported methods tolerate disadvantages including long reaction times and harsh reaction conditions. Therefore, to avoid these limitations, the exploration of an efficient, easily available catalyst with high catalytic activity and short reaction time for the preparation of spirooxindoles is still favored.

Experimental

Chemicals and apparatus

Reagent grade chemicals were purchased from Sigma-Aldrich or Merck and were used without further purification. All melting points are uncorrected and were determined in a capillary tube on Boetius melting point microscope. NMR spectra were obtained on a Bruker 400 MHz spectrometer

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13738-018-1361-8) contains supplementary material, which is available to authorized users.

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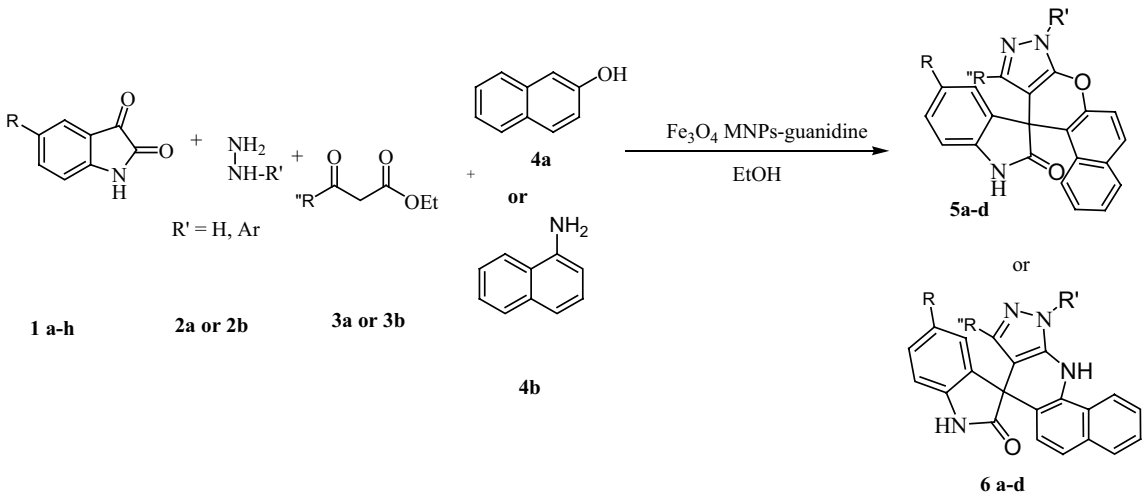


Scheme 1 Synthesis of spirooxindoles using MNPs-guanidine

(^{1}H NMR at 400 Hz, ^{13}C NMR at 100 Hz) in DMSO-d_6 using TMS as an internal standard. Chemical shifts (δ) are given in ppm, and coupling constants (J) are given in Hz. FT-IR spectra were obtained by WQF-510, spectrometer 550 Nicolet in KBr in the range of 400–4000 cm^{-1}. The energy-dispersive X-ray spectroscopy (EDS) measurement was carried out with the SAMX analyzer. X-ray photoelectron spectroscopy (XPS) spectra were measured on an ESCA-3000 electron spectrometer. DLS was performed using a Malvern apparatus. Magnetic properties were measured by a vibrating sample magnetometer (Meghnatis Daghigh Kavir Co.; Kashan Kavir; Iran) at room temperature in an applied magnetic field sweeping between ± 10,000 Oe). Powder XRD was performed on a Philips diffractometers X'pert with monochromatized Cu Kα radiation ($\lambda = 1.54056$ Å). The SEM images were prepared by MIRA3-TESCAN. A TGAQ5 thermogravimetric analyzer was used to study the thermal characteristics of the nanoparticles under heating at a rate of 10 °C min^{-1} and an inert N_2 atmosphere at 20 mL min^{-1}.

General procedure for the preparation of spirooxindoles

A mixture of isatin derivatives (1 mmol), phenylhydrazine or hydrazine hydrate (1 mmol), alkyl acetoacetate (1 mmol) and naphthalene amine or 2-naphthol (1 mmol) and MNPs-guanidine (20 mg) were heated in EtOH (10 mL) under reflux conditions. The completion of the mixture was monitored by TLC, and the catalyst was separated from reaction before work up by an external magnet field. Then, the mixture was poured into cold water, and the precipitate obtained was filtered and recrystallized twice by (EtOAc/*n*-hexane 3:1). Afterward, the products were characterized by ^{1}H NMR, FT-IR and ^{13}C NMR spectroscopy.

Spectral data of new products

5′-Chloro-10-methyl-8*H*-spiro[benzo-[5, 6]-chromeno-[2, 3-c]-pyrazole-11, 3′-indolin]-2′-one (5a)

Yellow solid; yield: 87%; M. p. 196–198 °C,—IR (KBr): $\nu = 3321$, 3201, 3071, 1689, 1618, 1433 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.86 (s, 3H, CH_3), 6.90–6.95 (m, 2H, ArH), 7.10–7.15 (m, 6 H, ArH), 7.70 (s, 1H, ArH), 10.24 (s, 1H, NH–CO), 11.25 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 10.13 (CH_3), 48.80 (C), 108.70 (C), 111.09 (C), 117.51 (CH), 120.28 (2CH), 123.20 (CH) 124.51 (C), 125.90 (2CH), 125.99 (2C), 128.35 (C), 130.74 (CH), 133.93 (C–Cl), 133.98 (C), 136.70 (CH), 137.92 (C), 142.56 (CH–C–Cl), 156.70 (CH–C–O), 163.74 (C=O). Analysis for $C_{22}H_{14}ClN_3O_2$: calcd. C 68.13, H 3.64, N 10.83; Found C 68.08; H 3.57, N, 10.73.

10-Methyl-8*H*-spiro[benzo-[5, 6]-chromeno-[2, 3-c]-pyrazole-11, 3′-indolin]-2′-one (5b)

Yellow solid; yield: 85%; M. p. 185–187 °C,—IR (KBr): $\nu = 3332$, 3202, 3071, 1680, 1616, 1435 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.92 (s, 3H, CH_3), 6.45 (m, 2H, ArH), 6.75 (m, 2H, ArH), 6.86 (m, 2H, ArH), 6.96–7.21 (m, 4H, ArH), 10.18 (s, 1H, NH-CO), 11.20 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 10.10 (CH_3), 49.07 (C), 106.72 (C), 111.07 (C), 112.09 (CH), 117.34 (2CH), 120.13 (CH), 123.20 (2CH), 124.37 (CH), 125.99 (CH), 126.90 (CH), 128.63 (C), 128.82 (CH), 130.66 (C), 133.92 (C), 135.90 (C), 137.00

(C), 141.33 (C), 156.60 (CH–C–O), 165.07 (C=O). Analysis for $C_{22}H_{15}N_3O_2$: calcd. C 74.78, H 4.28, N 11.89; Found C 74.69, H 4.21, N 11.76.

5′-Methyl-10-methyl-8*H*-spiro[benzo-[5, 6]-chromeno-[2, 3-c]-pyrazole-11, 3′-indolin]-2′-one (5c)

Yellow solid; yield: 82%; M. p. 171–173 °C,—IR (KBr): $\nu = 3330$, 3209, 3075, 1682, 1613, 1433 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.90 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 6.50–6.80 (m, 4H, ArH), 6.82–6.87 (m, 2H, ArH), 7.16–7.35 (m, 3H, ArH), 10.18 (s, 1H, NH–CO), 11.20 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 10.19 ($\underline{C}H_3$), 23.45 ($\underline{C}H_3$), 49.10 (C), 107.75 (C), 112.04 (C), 112.18 (CH), 117.44 (2CH), 120.22 (CH), 123.25 (2 CH), 124.41 (C), 125.90 (C), 126.84 (CH), 128.74 (CH), 128.84 (C), 130.72 (CH), 133.94 (C), 135.96 (C), 137.21 (C), 141.43 (C), 156.64 (CH–C–O), 165.12 (C=O). Analysis for $C_{23}H_{17}N_3O_2$: calcd. C 75.19, H 4.66, N 11.44; Found C 75.25, H 4.59, N 11.40.

5′-Nitro-10-methyl-8*H*-spiro[benzo-[5, 6]-chromeno-[2, 3-c]-pyrazole-11, 3′-indolin]-2′-one (5d)

Yellow solid; yield: 87%; M. p. 190–192 °C,—IR (KBr): $\nu = 3335$, 3223, 3087, 1692, 1627, 1437, cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) = 1.88 (s, 3H, CH_3), 6.92–6.98 (m, 2H, ArH), 7.14–7.18 (m, 6H, ArH), 7.92 (s, 1H, ArH), 10.24 (s, 1H, NH–CO), 11.25 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 10.18 ($\underline{C}H_3$), 48.78 (C), 107.78 (C), 111.29 (C), 117.63 (2CH), 120.38 (CH), 124.22 (2CH), 124.55 (CH), 125.93 (C), 126.80 (CH), 128.10 (CH), 128.25 (CH), 130.87 (C), 133.76 (C), 134.57 (C), 137.88 (C), 139.62 (C), 143.42 (C–NO_2), 156.62 (CH–C–O), 163.95 (C=O). Analysis for $C_{22}H_{14}N_4O_4$: calcd. C 66.33, H 3.54, N 14.06; Found C 66.25, H 3.44, N 14.12.

Results and discussion

Initially, we explored and optimized different reaction parameters for the synthesis of spirooxindoles by the condensation reaction of hydrazine hydrate, 5-chloro-isatin, ethyl acetoacetate and 2-naphthol as a model reaction. The model reaction was carried out in the presence of various catalysts including CAN NPs, $NaHSO_4$ NPs, Et_3N, Fe_3O_4 NPs and MNPs-guanidine. Several reactions were scrutinized using various solvents such as EtOH, CH_3CN, water or DMF. The best results were obtained in ethanol, and we found that the reaction gave satisfying results in the presence of MNPs-guanidine which gave excellent yields of products (Table 1). The catalyst showed best activity in ethanol compared to other organic solvents such as DMF, CH_3CN and H_2O.

To investigate the scope and limitation of this catalytic process, phenylhydrazine or hydrazine hydrate, isatins, ketoesters and naphthylamine or 2-naphthol were chosen as substrates. The above results obviously show the present catalytic procedure is extendable to a wide variety of substrates to construct a diversity-oriented library of spirooxindoles. Investigations of the reaction scope revealed that various isatins (bearing electron-withdrawing and electron-donating groups) can be utilized in this protocol (Table 2).

The reusability is one of the significant properties of this catalyst. The reusability of MNPs-guanidine was studied for the reaction of hydrazine hydrate, 5-chloro-isatin, ethyl acetoacetate and 2-naphthol, and it was found that product yields decreased to a small extent on each reuse (run 1, 87%;

Table 1 Optimization of reaction conditions using different catalysts

Entry	Solvent (reflux)	Catalyst	Time (min)	Yield (%)[a]
1	EtOH	–	200	Trace
2	EtOH	CAN (5 mol%)	120	17
3	EtOH	$NaHSO_4$ (10 mol)	120	32
4	EtOH	Et_3N (10 mol%)	120	38
5	EtOH	Fe_3O_4 NP (50 mg)	120	22
6	EtOH	TsOH (20 mol%)	120	51
7	H_2O	MNPs-guanidine (20 mg)	25	58
8	DMF	MNPs-guanidine (20 mg)	25	62
9	CH_3CN	MNPs-guanidine (20 mg)	25	80
10	EtOH	MNPs-guanidine (10 mg)	25	84
11	EtOH	MNPs-guanidine (20 mg)	25	87
12	EtOH	MNPs-guanidine (30 mg)	25	87

Hydrazine hydrate (1 mmol), 5-chloro-isatin (1 mmol), ethyl acetoacetate (1 mmol) and 2-naphthol (1 mmol)

[a]Isolated yield

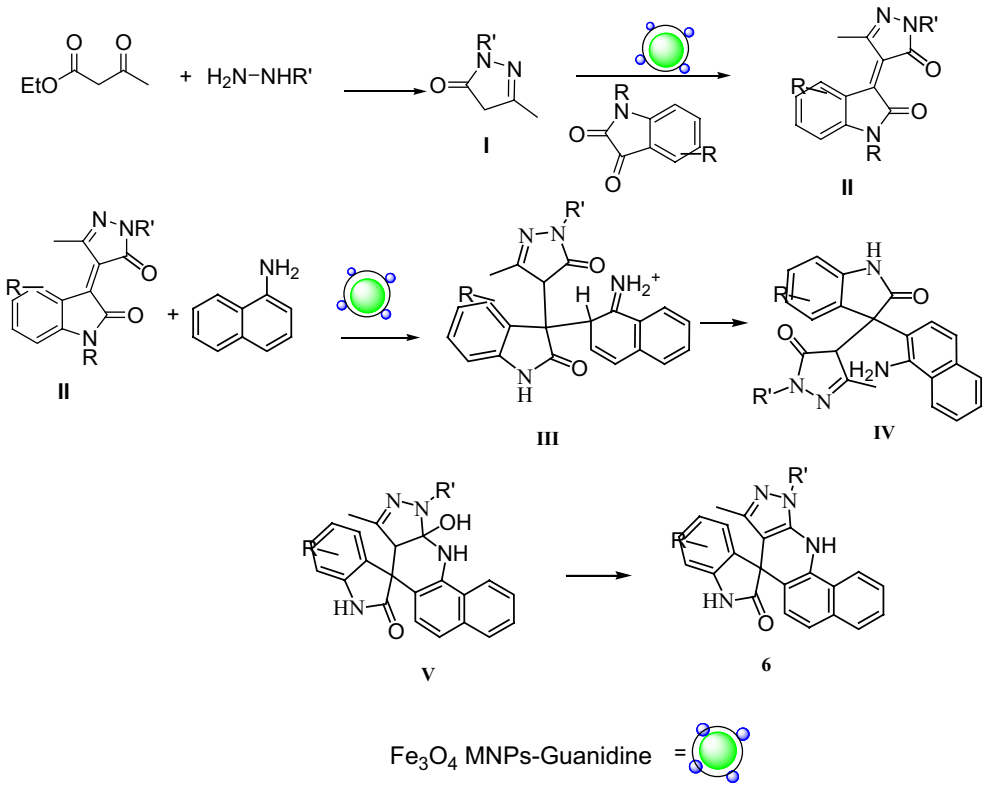
Table 2 Synthesis of spirooxindoles by MNPs-guanidine

Entry	Isatins *R*	*R′*	*R″*	**4a** or **4b**	Product	Time (min)	Yield (%)[a]	M.p. (°C) found	M.p. (°C) literature [Refs.]
1	Cl	H	Me	**4a**	**5a**	25	87	196–198	–
2	H	H	Me	**4a**	**5b**	25	85	185–187	–
3	Me	H	Me	**4a**	**5c**	30	82	171–173	–
4	NO_2	H	Me	**4a**	**5d**	23	87	190–192	–
5	H	Ar	Me	**4b**	**6a**	35	81	255–258	255–258 [20]
6	Cl	Ar	Me	**4b**	**6b**	30	84	262–264	264–267 [20]
7	H	Ar	*n*-Pr	**4b**	**6c**	35	79	300–302	304–307 [20]
8	Cl	Ar	*n*-Pr	**4b**	**6d**	33	82	295–297	298–301 [20]

[a]Isolated yield

run 2, 87%; run 3, 86%; run 4, 86%; run 5, 85%; run 6, 85%;). After completion of the reaction, the nanocatalyst was easily separated using an external magnet. The recovered magnetite nanoparticles were washed several times with acetone and then dried at room temperature.

A reasonable mechanism for the synthesis of spirooxindoles using MNPs-guanidine is shown in Scheme 2. The mechanism involves the initial nucleophilic attack of hydrazine on the alkyl acetoacetate to form the intermediate (I) and then, the reaction of isatin with intermediate (I) to give intermediate II. In the next step, the reaction can be followed by attack of the naphthylamine or 2-naphthol that leads to the formation of III and IV. The final product is formed by the intramolecular cyclization reaction. This mechanism has been supported by literature [20].



Scheme 2 Proposed reaction pathway for the synthesis of spirooxindoles using Fe_3O_4 MNPs-guanidine as catalyst

Conclusion

In conclusion, we have developed a straightforward and efficient method for the synthesis of spirooxindoles using magnetic nanoparticles Fe_3O_4-immobilized guanidine (MNPs-guanidine). The method offers several advantages including cleaner reaction profiles, easy availability, high yields, shorter reaction times, reusability of the catalyst and low catalyst loading.

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