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Leila Moradi & Zeynab Ataei

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Efficient and green pathway for one-pot synthesis of spirooxindoles in the presence of CuO nanoparticles

Leila Moradi and Zeynab Ataei

Department of Organic Chemistry, Faculty of Chemistry, University of Kashan, Kashan, Iran

ABSTRACT

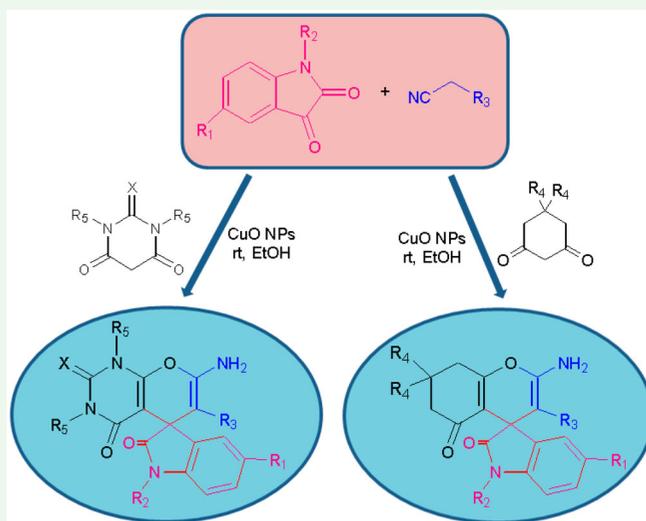
In this research, a new, green and eco-friendly method for the synthesis of spirooxindole derivatives was presented. The reaction was performed at room temperature in the presence of catalytic amounts (4 mol.%) of CuO nanoparticles and products were obtained in high to excellent yields. Low-cost high-efficiency reusable catalyst, short reaction times at room temperature, high to excellent yield and easy purification of products are the main advantages to this protocol. The pronounced advantages of catalyst are expected to create a new pathway for the synthesis of spirooxindoles.

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spirooxindoles; one-pot
synthesis; reusable catalyst;
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1. Introduction

Multicomponent reactions appear as a powerful synthetic strategy because of their productivity, simple procedures and facile execution. The flexibility of multicomponent reactions makes them an important type of reaction classes with short reaction times and high to excellent yields (1–4).

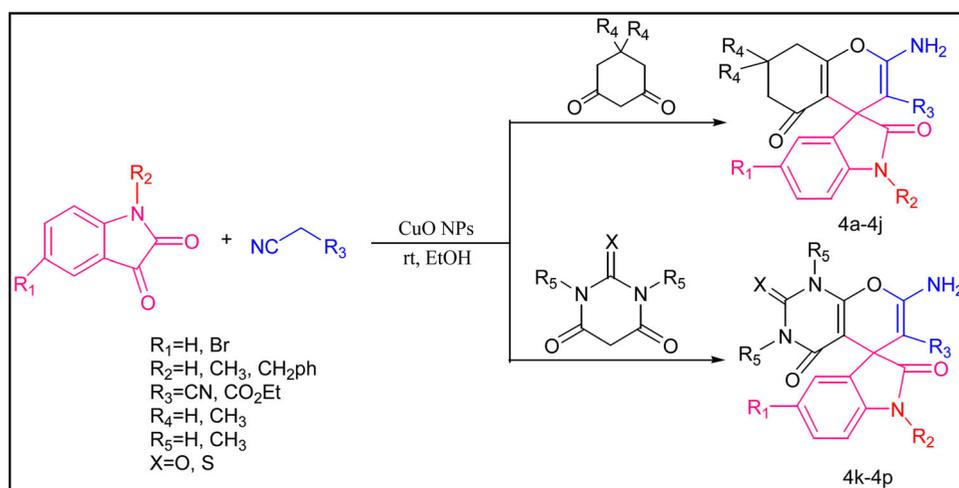
Isatin, as a key structure in the synthesis of heterocyclic compounds, has some biological activities (such as anticonvulsant, antidepressant, anti-inflammatory and antimicrobial activities) and effects on the central nervous system (CNS) (5–7). A variety of spirooxindoles containing isatin are important compounds with biological and medicinal properties (8–11). The need to develop synthetic methods for the preparation of these

heterocycles has attracted the attention of many scientists. Therefore, different catalysts have been used to synthesize these structures, such as guanidine-functionalized magnetic nanoparticles (12), MgO nanoparticles (13), nickel chloride (14), p-TSA (15, 16), H₂AuCl₄·3H₂O (17), cesium fluoride (18), L-proline (19), carbon-SO₃H (20), hexamethylenetetramine (21), glutathione@Fe₃O₄ nanoparticles (22) and triphenylphosphine (23).

Copper oxide nanoparticles (CuO NPs) have various applications, such as in gas sensing and field emission (24–26), in antibacterial (27) and antimicrobial activities (28, 29), and as reaction catalyst (30–33). Due to high surface area and high efficiency of CuO NPs, we presented a simple synthetic method for the synthesis of

CONTACT Leila Moradi  l_moradi@kashanu.ac.ir

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Scheme 1. Synthesis procedure of spirooxindole derivatives.

spirooxindole derivatives under room temperature, using catalytic amounts of CuO NPs (Scheme 1). Reusability of nanocatalyst, short reaction times and high yield of products under ambient conditions are other merits of this method.

2. Results and discussion

CuO NPs were synthesized using $\text{Cu}(\text{CH}_3\text{CO}_2)_2$, based on the Tetsuya Kida method (34). The obtained nanoparticles were characterized using FTIR, XRD and SEM techniques.

Figure 1 shows the FTIR of CuO NPs. In this spectrum, the peak at about 3429 cm^{-1} is related to the hydroxyl groups on CuO NPs and the water absorbed by KBr. The absorption peaks at 1576 and 1414 cm^{-1} are from

the bending vibrations of OH combined with copper atoms. Finally, the stretching modes of CuO appeared on 525 and 620 cm^{-1} .

Crystallinity of CuO NPs was evaluated by the XRD method. From the XRD pattern of CuO NPs in Figure 2, it is clear that main diffraction peaks can be indexed to a crystalline structure of CuO NPs. The size of synthesized nanoparticles calculated from the Debye–Scherrer equation based on the XRD pattern shows that the nano copper oxides have mean sizes of about 18.55 nm .

In addition, the morphology of CuO NPs was investigated by the SEM technique. Figure 3 shows that CuO NPs were prepared through the precipitation method and this result confirmed the particle size obtained from the XRD pattern.

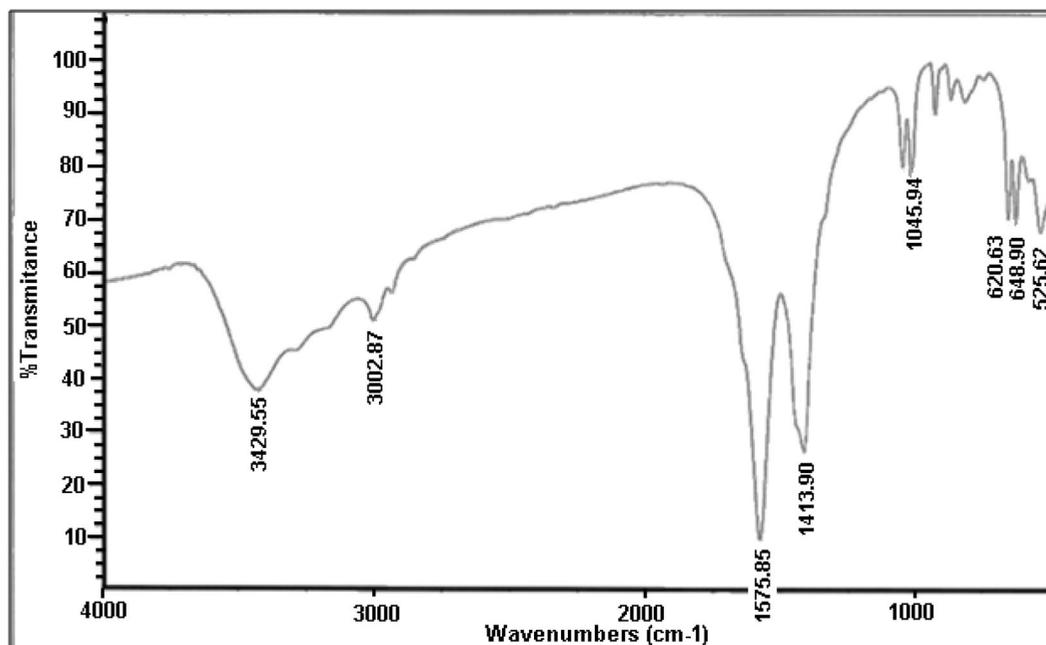


Figure 1. FTIR of CuO NPs.

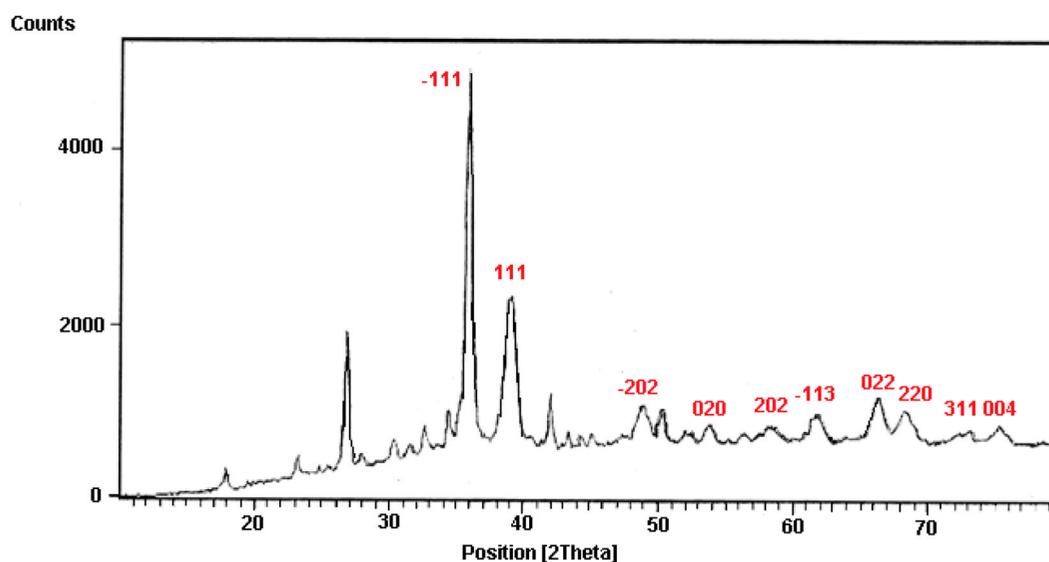


Figure 2. XRD pattern of CuO NPs.

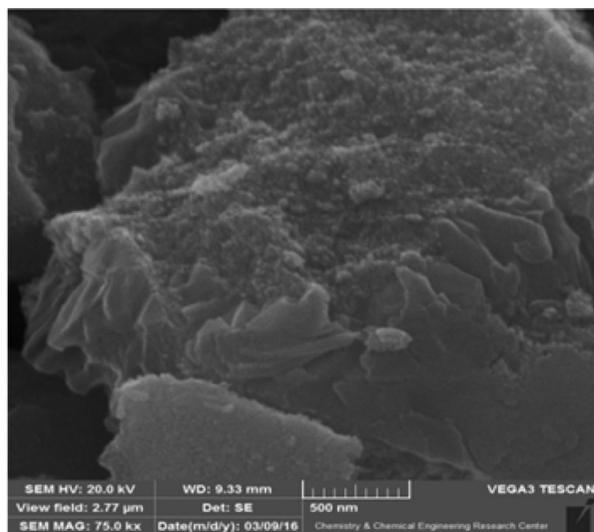


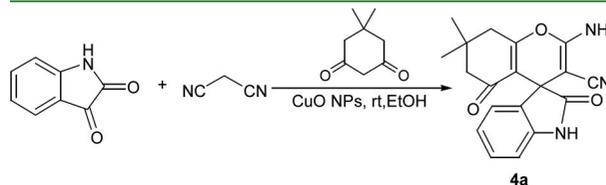
Figure 3. SEM images of CuO NPs.

After the preparation and characterization of nanocatalyst, the optimization of the reaction conditions (catalyst amounts and solvent) was investigated using a model reaction containing isatin (1 mmol), malononitrile (1 mmol) and dimedone (1 mmol) in the presence of CuO NPs at room temperature.

For evaluation of the effect of catalyst amounts on the yield of product, the model reaction was performed in the presence of a different quantity of catalyst. Based on the results obtained from Table 1, it is found that 4 mol.% of CuO NPs is the best quantity for obtaining the highest yield (entry 4).

Additionally, the solvent effect on the yield and time of reaction was studied using model reaction in the presence of 4 mol.% (0.003 g) of catalyst and different organic solvents. The obtained results showed that

Table 1. Optimization of the catalyst amount.



Entry	Nano CuO (mol.%)	Time (min)	Yield ^a (%)
1	1.5	10	32
2	2	10	45
3	2.5	8	65
4	4	8	98
5	5	8	93
6	4 ^b	40	27

^aIsolated yield of **4a**.

^b4 mol.% of bulk CuO.

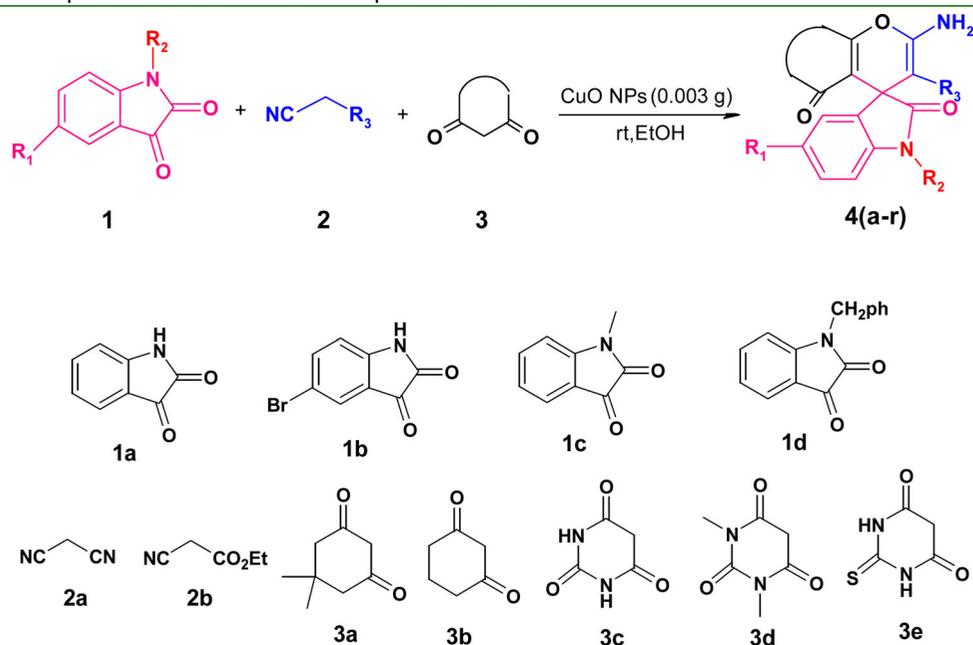
Table 2. Study of solvent effect on the yield of **4a**.

Entry	Solvent	Time (min)	Yield ^a (%)
1	CH ₃ OH	8	93
2	H ₂ O	8	85
3	C ₂ H ₅ OH	8	98
4	C ₂ H ₅ OH/H ₂ O (1:1)	20	65
5	CH ₃ CN	90	80
6	CH ₃ Cl	120	30

^aIsolated yield.

EtOH had more effect on the yield of reaction and can be used as efficient solvent (entry 3) (Table 2).

After the optimization of catalyst and solvent, for evaluation of nanocatalyst efficiency, a variety of spirooxindoles were synthesized at optimum conditions using malononitrile or ethylcyanoacetate, 1,3-diketones such as dimedone, barbituric acid, 1,3-dimethyl barbituric acid, 2-thiobarbituric acid and also 1,2-diketo compounds such as isatin and three of isatin derivatives as substrates. The results and details are summarized in

Table 3. Synthesis of spirooxindole derivatives in the presence of CuO NPs.

Product	Isatin	Alkyl malonate	Diketone	Time (min)	Yield ^a (%)	MP (°C) (reference)	TOF ^b (min ⁻¹)	TON ^c
4a	1a	2a	3a	8	98	267–269 (35)	3224	25,790
4b	1a	2a	3b	8	93	251–253 (35)	3059	24,474
4c	1a	2b	3a	20	86	259–261 (35)	1132	22,631
4d	1b	2a	3a	8	95	301–303 (36)	3125	25,000
4e	1b	2a	3b	8	97	280–282 (20)	3223	25,789
4f	1b	2b	3a	25	81	261–263 (36)	853	21,316
4g	1d	2a	3a	20	97	267–269 (37)	1276	25,526
4h	1c	2a	3b	8	94	247–249 (36)	3092	24,737
4i	1c	2a	3a	9	96	256–258 (21)	2807	25,263
4j	1a	2a	3c	9	96	300–302 (22)	2807	25,263
4k	1b	2a	3c	15	85	223–225 (39)	1491	22,368
4l	1a	2a	3e	8	96	244–246 (22)	3158	25,263
4m	1a	2a	3d	9	93	231–233 (22)	2719	24,474
4n	1b	2a	3d	20	80	295–297 (40)	1053	21,052
4o	1b	2a	3e	10	92	241–243 (39)	2421	24,211

^aIsolated yield.^bTOF = turn over frequency = mol of product/ mole of catalyst per min.^cTON = turn over number = mol of product/ mole of catalyst.

Table 3. As shown in this table, good to excellent yields were achieved at room temperature and short reaction times. Also, the yields of products from the reaction of ethylcyanoacetate gave corresponding spirooxindoles in lower yields and longer reaction times than malononitrile (**4c**, **4f**). This is due to less reactivity of ethylcyanoacetate. On the other hand, the low yield of **4k** product in longer time is from lower reactivity of 5-bromoisatin. Also, steric hindrance of *N,N*-dimethyl barbituric acid in

addition to low reactivity of 5-bromoisatin leads to low yield of **4n** after 20 min.

In addition, *turn over frequency* (TOF) and turnover number (TON) values were calculated and results are depicted in **Table 3**. Results exhibited high efficiency (due to high turnover frequencies) and greater stability (high turnover numbers) of catalyst.

Presented methodology is a chromatography free process. In fact, products were purified only with recrystallization from ethanol and this is the most important advantage of this process. All obtained pure products were characterized using physical and spectroscopic data and were consistent in comparison with authentic samples.

Finally, we studied the reusability of the CuO NPs in the reaction between isatin, malononitrile and dimedone to give **4a** product. After every cycle of reaction,

Table 4. Evaluation of reusability of CuO NPs.

Entry	Cycle	Time (min)	Yield ^a (%)
1	First time	8	98
2	1	8	97
3	2	8	95
4	3	8	92

^aIsolated yield.

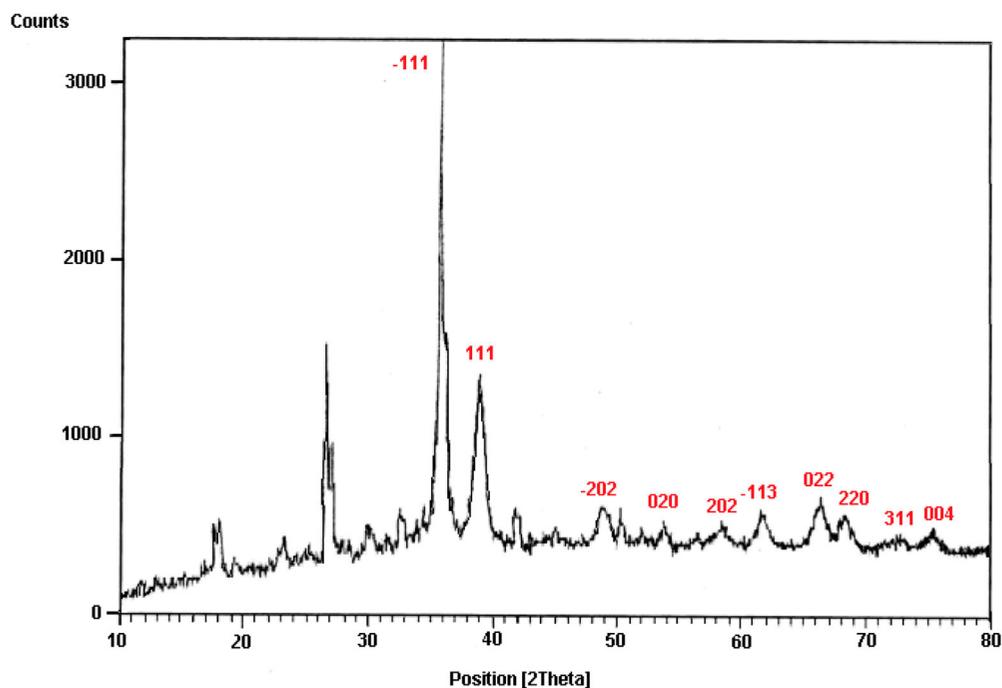
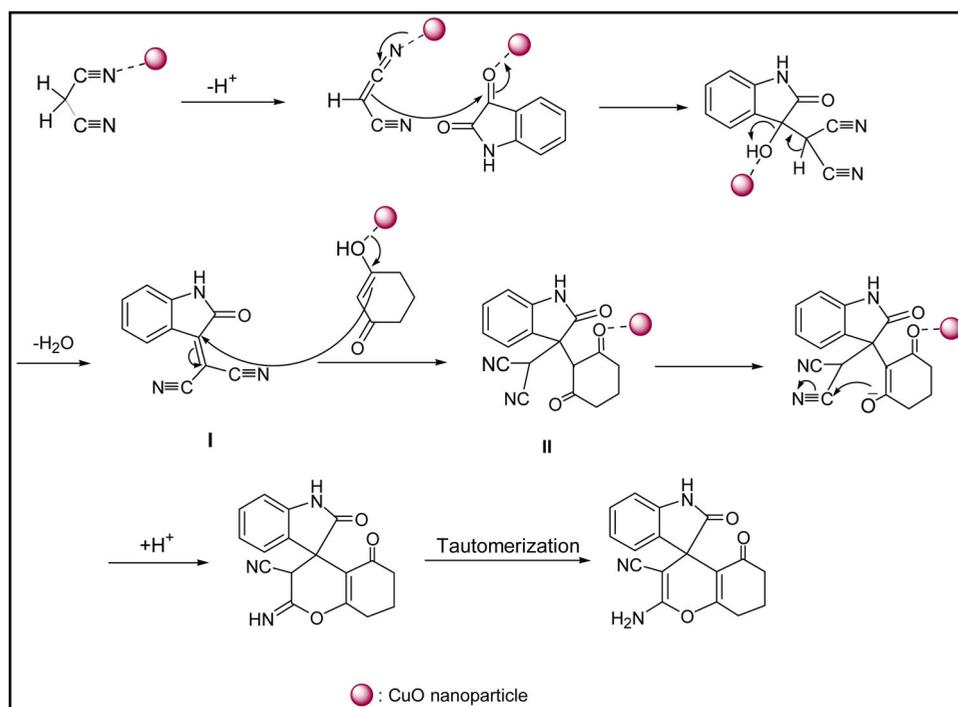


Figure 4. XRD pattern of reused catalyst.

nanocatalyst was separated, washed with EtOH and dried and then reused in new reaction. Results in Table 4 show that CuO NPs have high efficiency even after reused for three times. In addition, a slight, gradual decrease in the catalyst activity is observed because of the clogging of some catalyst active sites with organic reactants during the reaction process.

Reused catalyst was characterized using the XRD technique (Figure 4). As can be seen from Figure 4, the XRD pattern of recycled catalyst is the same as the initial nanocatalyst with no considerable changes. It is concluded that the structure and performance of catalyst is stable under reaction conditions after three times recycling.



Scheme 2. A schematically mechanism for the synthesis of spirooxindole derivatives using CuO NPs.

Table 5. Comparison of the efficiency of CuO NPs with other catalysts for the synthesis of **4a** and **4j**.

Entry	Catalyst	T (°C)	Time	Yield (%)	Reference
1	(HAuCl ₄ ·3H ₂ O)	70	30 min	96	17
2	Cesium fluoride	r.t.	5 min	82	18
3	Carbon-SO ₃ H	80	3 h	81	20
4	Hexamethylenetetramine	60	20 min	95	21
5	Glutathione@Fe ₃ O ₄ nanoparticles	80	15 min	94	22
6	Triphenylphosphine	78	30 min	94	23
7	Triethylbenzylammonium chloride	60	2 h	94	37
8	Triethanolamine ^a	MWI ^b	5 min	84	38
9	Oxalic acid dihydrate:proline (1:1)	r.t.	30 min.	94	39
10	Oxalic acid dihydrate:proline (1:1) ^a	r.t.	55 min.	90	39
11	L-Proline	80	20 min	92	40
12	Tetrabutyl ammonium bromide	100	40 min	90	41
13	CuO NPs	r.t.	8 min	98	This work
14	CuO NPs ^a	r.t.	9 min	96	This work

^aSynthesis of **4j**.^bMicrowave irradiation.

Additionally, we have carried out the leaching test through the filtration method. In this test, two experiments were designed. In first reaction, 4 mol.% of CuO NPs was added to a mixture of isatin (1 mmol), malononitrile (1 mmol) and dimedone (1 mmol) in EtOH (2 ml). The mixture was stirred for 4 min at room temperature. After that, reaction mixture was dissolved in acetone and the catalyst was separated. Isolated yield of reaction was about 50%. Another reaction was carried out in the same manner as that of the first one. In the second test, the catalyst was separated after 4 min and the reaction was continued with filtrate for another 4 min at room temperature. After the separation of product, isolated yield was 50% and no increasing was observed in the yield of product.

A proposed mechanism for the synthesis of spirooxindoles in the presence of CuO NPs is presented in Scheme 2. As can be seen in this scheme, in the first step, malononitrile was activated by CuO NPs and then attacked as a nucleophile to the carbonyl group of isatin (chelated to CuO NPs). After condensation reaction, resulted intermediate (**I**) was obtained and addition of 1,3-dicarbonyl compound to **I** through Michael addition reaction generated intermediate of **II**. In the last step, the cyclization and tautomerization leads to a spirooxindole derivative.

The efficiency of CuO NPs has been compared with some of the other catalysts applied for the synthesis of spirooxindole derivatives. Results were listed in Table 5. As can be seen from this table, reactions catalyzed with CuO NPs (as a high efficient eco-friendly catalyst) showed shorter reaction times along with higher yields of products.

3. Experimental section

3.1. Materials and methods

The products were isolated and characterized by physical and spectral data. The FTIR spectra were recorded on FTIR Magna 550 apparatus using KBr plates. ¹H NMR

and ¹³C NMR spectra were recorded with a Bruker Avance DRX-400 spectrometer at 400 and 100 MHz, respectively. Powder X-ray diffraction (XRD) was carried out on a Philips diffractometer of X'pert Company with monochromatized Cu K α radiation ($\lambda = 1.5406 \text{ \AA}$). The morphology of products was studied by electron scanning microscopy (SEM; model: LEO 1455VP).

3.2. Synthesis of CuO NPs

CuO NPs were prepared through a precipitation reaction between (25 mmol) Cu(CH₃COO)₂ in (100 mmol) NaOH dissolved in ethanol at 78°C for 1 h. The obtained brown nanoparticles were separated by filtration and washed with ethanol and finally dried at 100°C for 12 h (34).

3.3. General procedure for the synthesis of spirooxindoles

A mixture of isatin derivative (1 mmol), malononitrile or ethyl cyanoacetate (1 mmol) and 1,3-dicarbonyl compound (1 mmol) in the presence of 4 mol.% of CuO NPs was stirred in 2 ml ethanol at room temperature. The progress of the reaction was monitored by TLC (*n*-hexane/ethyl acetate, 2:1 ratio). After the completion of the reaction, resulted mixture was resolved in acetone and filtered for the separation of nanocatalyst. Then, the product was obtained by evaporation of solvent from filtrate and for further purification, was recrystallized from EtOH to obtain pure products.

4. Conclusion

In conclusion, a mild, safe and efficient method for the preparation of spirooxindoles was presented. The process has proved to be very effective, with a high-

performance catalyst and easy to operate. It is also very clean in that the products require no further purification and the scale up of this method is easy.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Notes on contributors

Leila Moradi was born in Qom, Iran. She received her M.Sc. degree in Organic Chemistry from the university of Kashan, Kashan Iran under the supervision of Professor Hossein Naeimi in 2004. She obtained her Ph.D. degree in the same University, under the supervision of Professor Hossein Naeimi and Professor Ali Mohajeri, in 2009. She is a Professor Assistant in department of organic chemistry, faculty of chemistry, of Kashan University. Her research interests include organic synthesis, carbon nanotubes, functionalization and application of carbon nanotubes, synthetic methodology and applications of nano-heterogeneous catalysts in multicomponent reactions.

Zeynab Ataei was born in Roudbar, Iran. She received her B.Sc. degree in pure Chemistry from Guilan University, Rasht, Iran (2012) and her M.Sc. degree in Organic Chemistry at University of Kashan, Kashan, Iran (2016) under supervision of Dr. Leila Moradi. Her research field was the synthesis of spirooxindoles through multicomponent reaction using nano-heterogeneous catalysts.

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