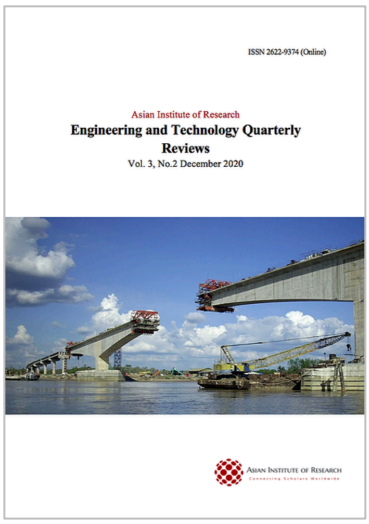

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One-pot Synthesis of Spirooxindole Derivatives Catalyzed by Bi2Fe4O9 Nanoparticles

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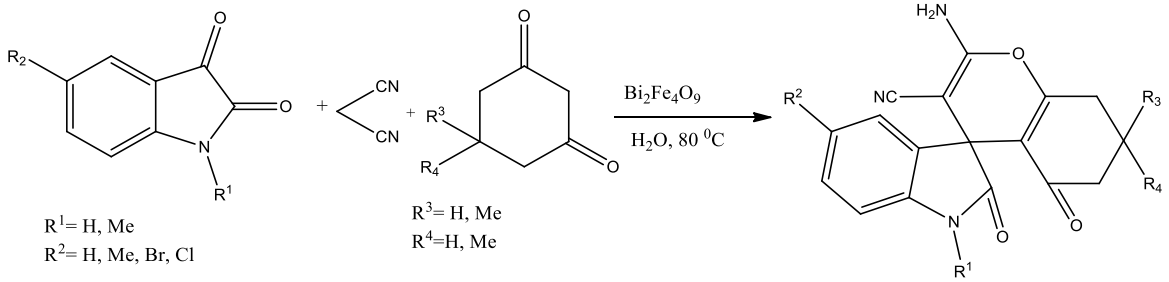
Abstract
In this study regarding the catalytic application of Bismuth Ferrite nanoparticles in the synthesis of heterocyclic compounds, we synthesized $Bi_2Fe_4O_9$ nanoparticles by sol-gel combustion method from bismuth nitrate pentahydrate [$Bi(NO_3)_3.5H_2O$] and iron nitrate nonahydrate [$Fe(NO_3)_3.9H_2O$] as starting materials. Structural and microstructural were characterized using X-ray diffraction (XRD), Field Emission Scanning Electron Microscopy(FESM), Vibrating-Visible Spectroscopy(VSM) and infrared spectroscopy (IR). The average size of nanoparticles was determined 36, 3 nm, by XRD and Scherer's equation. The results show that the pure phase of $Bi_2Fe_4O_9$ can be formed by this method. Then it is used in the one- pot synthesis of spirooxindole derivatives via three-component reaction of isatins, malononitrile and 1,3- dicarbonyl compounds in water as a green solvent in the temperature of 80℃. The reaction yields 88-98 percentages of the products. The catalyst was reused several times in the same reaction yielding unchanged products.

Keywords: Nanoparticles, Sol-gel, Bismuth Ferrite, Spirooxindole Derivatives, Malononitrile, Green Solvent



R^1= H, Me
R^2= H, Me, Br, Cl
R^3= H, Me
R^4=H, Me

1. Introduction

Multicomponent reactions are those in which three or more reactants take part as one-pot reactants in a chemical reaction and yield a product[Ugi,2001- Climent,2012]. This kind of reactions is one of the important reactions in Chemistry which has been known for 150 years; it also has been widely used and studied in Organic Chemistry recently. The first multicomponent reaction is the synthesis of strecker α-amino cyanide[Stercker,1882]. The overall properties of multicomponent reactions are; they are completed in one pot yielding high percentages of products, using accessible reactants, simple synthesis, needless to separate the intermediate substances and

environmental friendly. Multicomponent reaction is an important method for producing complex products like heterocyclic compounds[Bhaskar,2012- Dömling,2010]. Heterocyclic compounds generally, and spirooxinadoles -five membered nitrogen containing cyclic compounds especially have vital role in the chemistry of drugs. The synthesis of oxinadoles is still a challenge in Organic and Industrial Chemistry[Allahresani,2016-Bhaskar,2012]. The core of most drug factors and natural alkaloids is spirooxinadoles[Shanthi,2007]. Recently the spirooxinadole derivatives are synthesized by different methods utilizing various catalysts[Hassani,2018]. The usual synthesizing way of these compounds is condensation of tripartite isatine, 1,3-dicarbonyl and one part of active methylene[Hemmat,2019]. The spiroxinadole derivatives are having biological and pharmaceutical activites[Allahresani,2011] such as; anti-tumor[Yu,2013], anti-micro organs[Nandakumar,2010], anti-fungal, anti-malaria[Thangamani,2010-Yeung,2010], antibiotic[Ghahremanzadeh,2016] and anti HIV[KL,2006]. Therefore the synthesis of these compounds is important in Organic Chemistry and industry of drugs. This article explores the synthesis of spirooxinadoles derivatives from one-pot malononitrile, isatine, 1,3-dicarbonyl compounds and water as solvent with the existence of bismuth ferrate ($Bi_2Fe_4O_9$)

2. Experimental

2.1. Used chemicals

All the utilized chemicals and solvents including bismuth nitrate pentahydrated, iron nitrate nonahydrated, citric acid, nitric acid and ammonia are provided from Merck Company.

2.2. Procedure

Pour 1 mmole (0.148g) Isatine, 1 mmole (0.112g) cyclohexane-1,3-dione, 1 mmole (0.066g) malononitrile, catalyst $Bi_2Fe_4O_9$ and 6 mL of water in a round- based balloon with a magnetic stirrer at 80℃ stir it and watch the progress of the reaction by TLC for controlling.
Once the reaction is completed and the solvent is removed, solve the yielded mixture in acetone and draw out the catalyst by centrifuge from the mixture. Then crystalize it in Ethanol which yields 88 – 95% of the product.

3. Optimizing conditions of reaction in synthesis of spirooxinadole derivatives

3.1. Optimization of solvent

pour1 mmole (0.148g) Isatine, 1 mmole (0.112g) cyclohexane-1,3-dione, 1 mmole (0.066g) Malononitrile, catalyst $Bi_2Fe_4O_9$ and various solvents (water, solution of water and ethanol 1:1, solution of ethyl acetate and ethanol) in a round-based balloon and stir it at 80℃. Observe the progress of the reaction with TLC. After the completion of the reaction solve the mixture in acetone and draw out the catalyst with a centrifuge from the mixture. Then solve the mixture of the reaction in water and ethyl acetate, after that isolate the water and organic phases from each other with a decanter funnel. Once the solvent is removed from the mixture, the product is crystalized in Ethanol. The outcome of the test is illustrated in the table of 3-1.

Table 3-1: Optimization of solvent

No	Solvent	Temperature (℃)	Time (min)	Percentage of product
1	Water	80	10	95-98
2	Water and ethanol (1:1)	80	25	85-90
3	Ethyl acetate	Reflux	25	15-20
4	Ethanol	Reflux	20	80-85

3.2. Optimizing the amount of catalyst

pour1 mmole (0.148g) Isatine, 1 mmole (0.112g) cyclohexane-1,3-dione, 1 mmole (0.066g) Malononitrile, different amounts (0.05, 0.012, 0.08, and 0.04g) of catalyst $Bi_2Fe_4O_9$ in a round-based balloon and complete the reaction as before mentioned. Its outcome is entered in table 3-2, as you see the best result is obtained with 0.012g $Bi_2Fe_4O_9$.

Table 3-2: Optimization of the amount of catalyst

Number	Amount of catalyst (g)	Time (min)	Percentage of the product (%)
1	0.004	20	50-55
2	0.008	30	80-85

3	0.012	10	95-98
4	0.05	10	95-98

3.3. Optimizing the Temperature

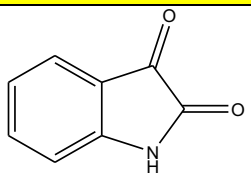
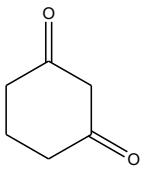
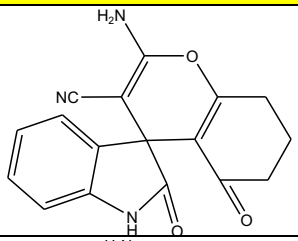
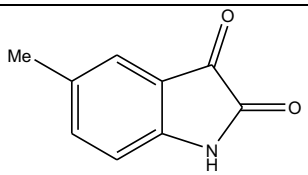
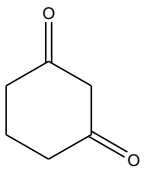
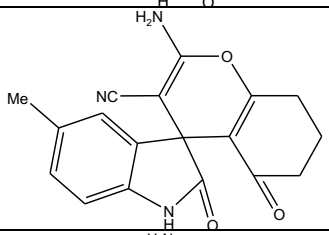
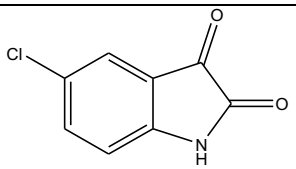
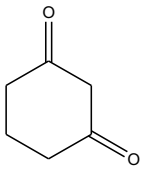
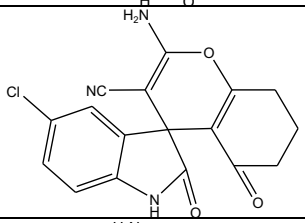
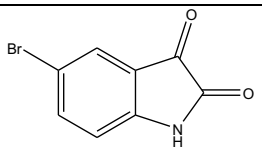
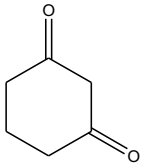
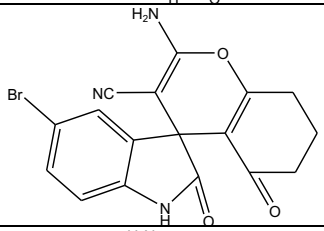
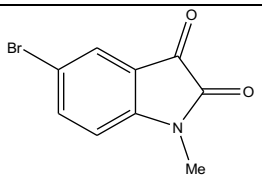
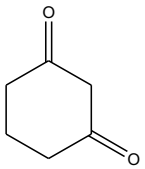
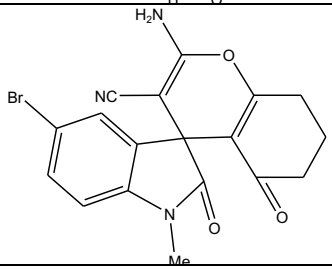
Pour1 mmole (0.148g) Isatine, 1 mmole (0.112g) cyclohexane-1,3-dione, 1 mmole (0.066g) Malononitrile, 5mL of water as solvent and 0.012g $Bi_2Fe_4O_9$ as catalyst in a round-based balloon and stir it with a magnetic stirrer in various temperature degrees (25, 80, and 100℃). Watch and control the progress of the reaction with the previously mentioned way. The data from the experiment is entered in the table 3-3 which shows the highest amount of yield is produced at 80℃.

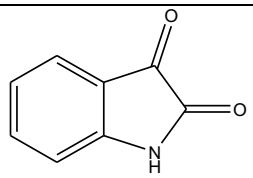
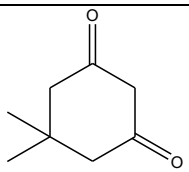
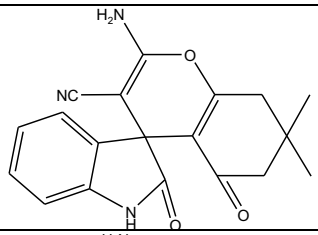
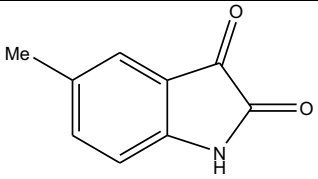
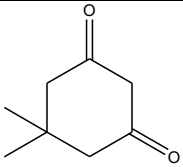
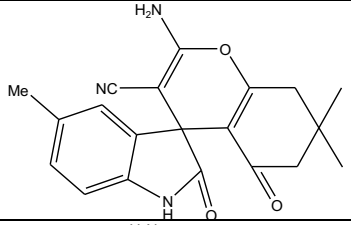
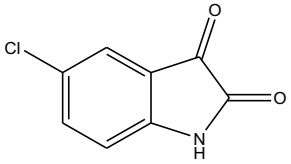
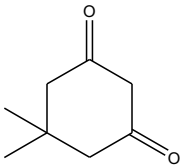
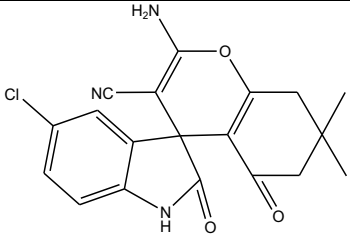
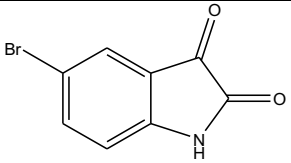
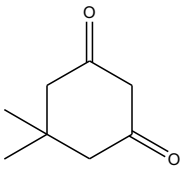
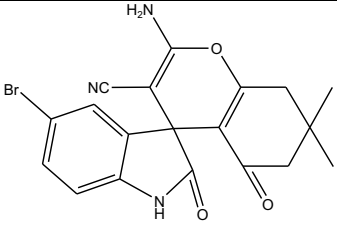
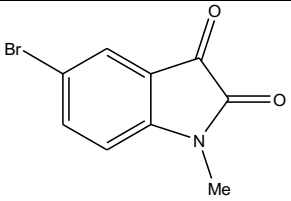
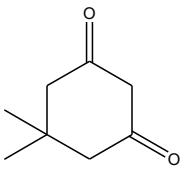
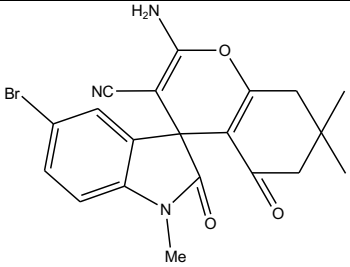
Table 3-3: Optimization of temperature

Number	Amount of catalyst (g)	Temperature (℃)	Time (min)	Percentage of the Product
1	0.012	25	30	30-40
2	0.012	80	10	95-98
3	0.012	100	10	95-98

The synthesis result of spirooxinadole derivatives from 1 mmole Isatine, 1 mmole diketone derivatives, 1 mmole Malononitrile in 6 mL of water and 0.012 g catalyst in 10 minutes are entered in table 3-4.

Table 3-4: synthesis of spirooxinadole derivatives with the existence of $Bi_2Fe_4O_9$ as catalyst and water as solvent.

Number	Reactants		Product	Percentage
1				98
2				93
3				95
4				95
5				90

6				97
7				93
8				95
9				95
10				88

3.4. Synthetic mechanism of spirooxinadole derivatives with the existence of $Bi_2Fe_4O_9$ nano-particles as catalyst

Figure 3-1 illustrates suggested mechanism for synthesis of spirooxinadole derivatives. Firstly the catalyst $Bi_2Fe_4O_9$ activates the carbonyl group of Isatine, then Malononitrile functions as nucleophile on the activated group of Isatine and forms the second intermediate state. The mentioned intermediate state makes the third intermediate state. Finally adding cyclohexane-1,3-dione on the yielded compound causes the target product to be produced.

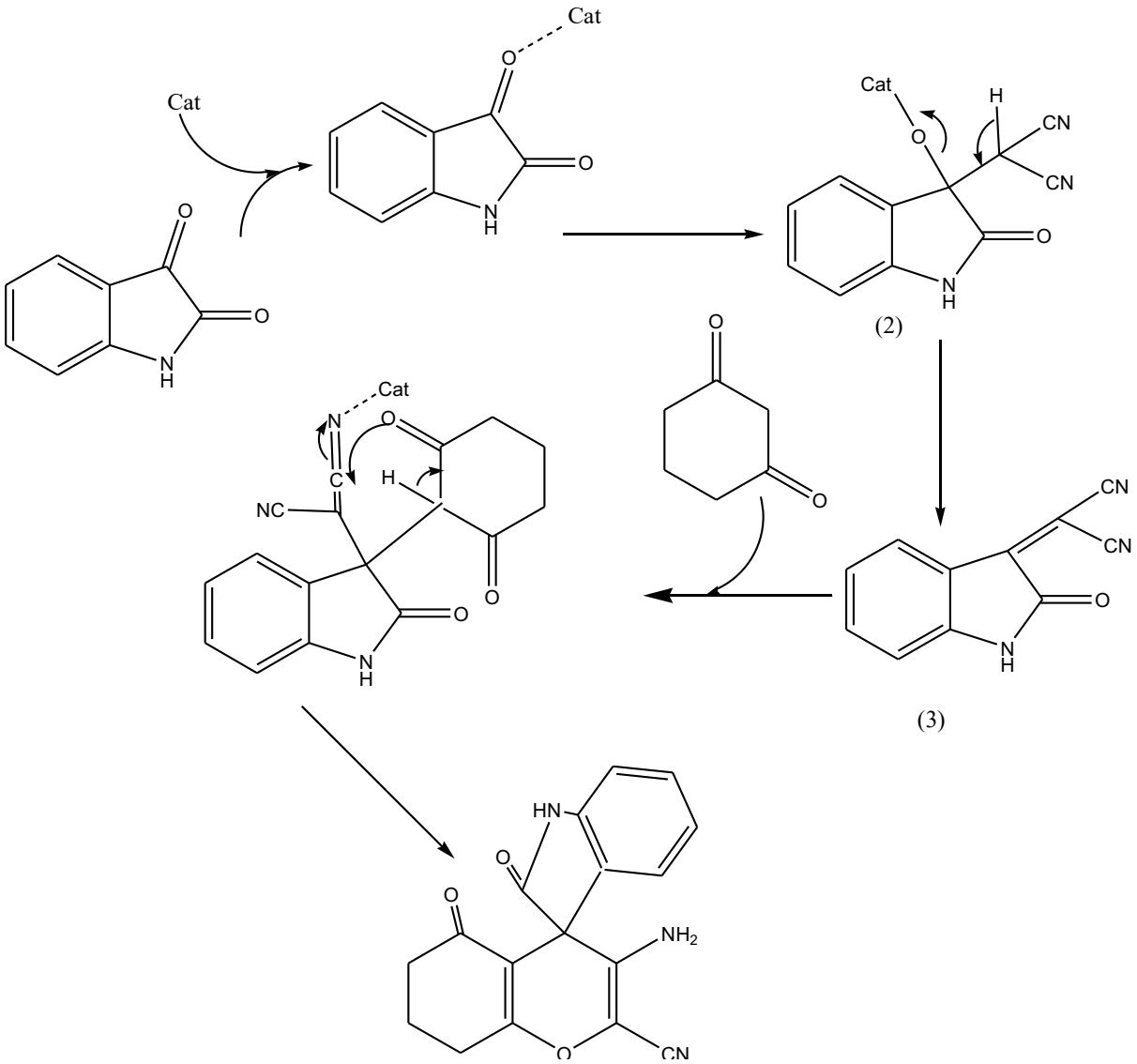


Figure 3.1: Synthetic mechanism of spirooxinadole derivatives with the existence of $Bi_2Fe_4O_9$.

Conclusion

As it is clear that catalysts play vital roles on chemical reactions rate, firstly $Bi_2Fe_4O_9$ as nano-catalyst has been synthesized for the first time by the sol-gel combustion method and has been signified by FESE, EDX, VSM and IR analysis. Then Malononitrile, Isatine, 1,3-dicabonyl compounds have been utilized in water as solvent in 80°C of temperature. The products of the reaction were produced with 88-98 %. finally, the catalyst has been recovered and used for similar reactions several time.

The applied method in this research for synthesis of spirooxinadole derivatives with the existence of $Bi_2Fe_4O_9$ as nano-catalyst in water as solvent has several advantages such as application of homogenous catalyst, its nontoxicity and stability against temperature, simple retrieval of the catalyst, high percentage and purity of the products, simple method and not producing additional products.

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