Journal of Medicinal and Nanomaterials Chemistry 3 (2022) 225-233

Journal of Medicinal and Nanomaterials Chemistry

Journal homepage: https://jmnc.samipubco.com/

Original Research Article

One-Pot synthesis of oxindoles derivatives as effective antimicrobial agents by Nano-Magnesium aluminate as an effective aatalyst

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ARTICLE INFORMATION

Received: 5 May 2022
Received in revised: 11 September 2022
Accepted: 16 September 2022
Available online: 20 Octobr 2022

DOI: 10.48309/JMNC.2022.3.5

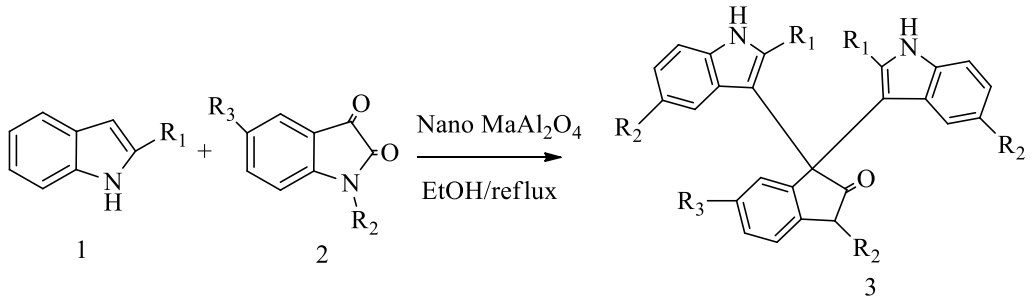
KEYWORDS

Multicomponent Reactions (MCRs)
Nano-Magnesium Aluminate
Oxindole Derivatives
One-Pot Synthesis
Antimicrobial Agents

ABSTRACT

A magnesium aluminate catalyzed environmentally benign strategy for the synthesis of oxindole derivatives via the one-pot reaction between indole and isatin is established under reflux conditions in excellent yields. The reaction was carried out in ethanol and in the catalyst presence to give the corresponding oxindoles derivatives in high yields. The low cost, availability of catalyst, and the novel and green procedure makes this strategy more useful for the preparation of xanthene derivatives.

Graphical Abstract



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Introduction

Oxindole derivatives are found as the main components in the structure of biologically active and natural compounds. Spirooxindoles received remarkable attention among oxindole systems due to their biological characteristics, including antibacterial, anti-cancer, and anti-inflammatory activities. They are also used as progesterone receptor (PR) agonists [1]. Clothamidine, a natural oxindole derivative, has an important role in the differentiation of human promyelocytic leukemia cells HL-60 [2]. Examples of these compounds include two natural alkaloids isolated from the fermentation of Aspergillus fumigatus, Spirotryprostatin A, B, and C, with which antibacterial activity that is known as the new inhibitors of microtubule assembly.

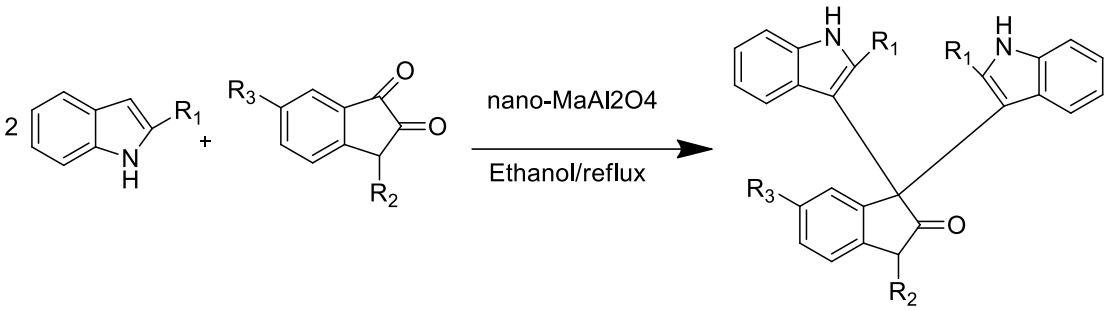
In addition to the aforementioned examples, other molecules in this group show potential biological effects such as (a) spermicide activity, (b) anti-cancer effect and inhibition of α-glucosidase, and (c) tris indoline which has a significant inhibitory effect against the mycobacterium tuberculosis, H37RV5, and cytotoxicity to drug-resistant cancer cells [3-5].

In this study, the preparation of oxindole derivatives through a one-pot three-component reaction by using magnesium aluminate catalyst in solvent-free conditions was investigated. We utilized the synthesis of oxindole derivatives with a nano-magnesium aluminate catalyst, which is a catalyst with a high melting point and corrosion-resistant. The lack of environmentally harmful solvents, high speed, short reaction time, high product efficiency, and recyclability of the catalyst are the advantages of this method. Even though these methods are unique, they sometimes utilize harmful solvents for the environment. Therefore, the development and introduction of efficient and environmentally friendly methods, without harmful or with low-risk solvents, as well as appropriate and economical catalysts in the oxindole synthesis is essential. Likewise, this component has other properties that make it suitable for application in various industries.

In recent years, nanomaterials have played an important role as powerful catalysts in organic transformations. Magnesium aluminate spinel has many applications as a catalyst due to its unique features such as chemical immobilization, high surface area, small crystal size, and a large number of active sites [6].

Magnesium aluminate ($MgAl_2O_4$) powder has a high melting point (2135 °C), low thermal conductivity at room temperature (RT), high temperatures, and corrosion resistance, making it a durable raw material, which acts as catalyst support in the petrochemical industry for dehydrogenation of alkanes and oxidation of methane [7]. This substrate is characterized by low dielectric constant, mechanical strength, high chemical resistance, and good optical properties. Therefore, it is used in various fields of engineering [8], metallurgy, electrochemical, radio technology, and industrial chemistry [9].

As a part of our work on one-pot multicomponent reactions (MCRs) and developing new selective and environmental friendly methodologies for the synthesis of various heterocyclic compounds, we describe the nano-magnesium aluminate-mediated pseudo-three component reaction of indoles and istains in ethanol under reflux condition to afford oxindole derivatives in excellent yields (Scheme 1).



Scheme 1. Synthesis of substituted oxindole

Experimental

Material and methods

The melting temperatures of the compounds were measured by using the KRUSs (KSP-IN 90-264). IR -spectrums of the compounds are measured by the spectrometer FT-IR Tensor 27. The ^{1}HNMR spectrum was recorded by the spectrometer AVANCE BRUKER DRX 400 MHZ. The solvents and chemicals used in this research are provided by the MERCK Company. The structure of the produced products is compared and affirmed by adapting the spectrum and physical data recorded in the references.

Preparation method of nano-magnesium aluminate catalyst

First, a stoichiometric amount of magnesium nitrate, aluminum nitrate, and some hexadecyl-trimethyl-ammonium bromide (CTAB) were dissolved in deionized water and stirred for 30 minutes, and then the ammonia solution was dropped into the mixture until it turns to a jelly-like substrate, with the pH about 9. After settling, it remained under reflux conditions for 24 hours at 80 °C. Next, the resulting mixture was cooled at room temperature, and then filtered. After that, it was dried at 100 °C for 24 hours, and then calcined at 700 °C.

General procedure for the synthesis of Oxindoles derivatives

A mixture of Isatin (1 mmol), indole (2 mmol), ethanol (5 mL) and nano-$MgAl_2O_4$ (0.05 g) was refluxed in a 25 mL balloon. The progression rate of reaction was monitored by using TLC in a mixture of ethyl acetate and n-hexane in a 1:1 ratio. After completion, methanol (10 mL) was added. Then, the solution was cooled at room temperature, the mixture was filtered, and the impurities were recrystallized by dissolving them in hot ethanol.

Melting points, IR spectra, and HNMR of the obtained crystals were measured and compared with the references. The interpretation of product spectral data is provided in the discussion and conclusion sections, and the spectra for some of them are represented in the attachments section.

*3,3-Di(1H-indol-3-yl)indolin-2-one (**3a**)*

IR (KBr) (ν_{max}/ cm^{-1}): 3429, 3327, 3068, 1709, 1612, 1539, 1474, 1338, 1243, 1175, 1106, and 739. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.77 (t, J = 7.8 Hz, 2H), 6.89 (s, 2H), 6.98 (t, J = 7.6 Hz, 1H), 6.69–7.08 (m, 3H), 7.23–7.26 (m, 4H), 7.38 (d, J = 8.2 Hz, 2H), 10.58 (s, 1H, NH), 10.99 (s, 2H, NH). Anal. Calcd for $C_{24}H_{17}N_3O$: C, 79.3 2; H, 4.72; N, 11.56. Found: C, 79.38; H, 4.69; N, 11.65. MS (EI, 70 ev): m=z 363.

*3,3-Di(1H-indol-3-yl)-5-bromo-indolin-2-one (**3d**)*

IR (KBr) (ν_{max}/ cm^{-1}): 3369, 3118, 3054, 1659, 1616, 1491,1425, 1338, 1245, 1173, 1105, and 745. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.84 (t, J = 6.8 Hz, 2H), 6.89 (s, 2H), 6.98 (d, J = 8.5 Hz, 1H), 7.05 (t, J = 7.5 Hz, 2H),7.27 (d, J = 6.8 Hz, 2H), 7.33 (s, 1H), 7.36 (d, J = 8.2 Hz,2H), 7.46 (d, J = 7.2 Hz, 1H), 10.78 (s, 1H, NH), and 11.09 (s, 2H, NH) ppm. Anal. Calcd for C_{24} $H_{16}BrN_3O$: C, 65.17; H, 3.65; N, 9.50. Found: C, 65.15; H, 3.48; N, 9.63. MS (EI, 70 ev): m=z 444.

Results and Discussion

The SEM and TEM spectrum is displayed in Figures 1 and 2 [10]. The nanoparticles dimensions were determined by TEM and it indicates that the catalyst dimensions are in nano-dimensions.

EDX in Figure 3 indicates that the catalyst mainly consisted of magnesium and aluminum. The weight percent of product confirms the molecular formula of $MgAl_2O_4$. Likewise, EDAX indicates that there are no impurities. The Au amount is negligible.

The morphology and phase identification of synthesized nanocatalyst were studied by using XRD pattern (Figure 4). Accordingly, the peak values were observed at the following scattering angles 22.38, 36.85, 43.37, 53.07, 70.82, and 78.29 (reported by using cobalt anode). These peaks correspond to 111, 220, 311, 400, 4 22, and 511 crystalline planes. The peaks show the $MgAl_2O_4$ nanocrystal with a spinel structure (according to JCPDS card No. 77-0435).

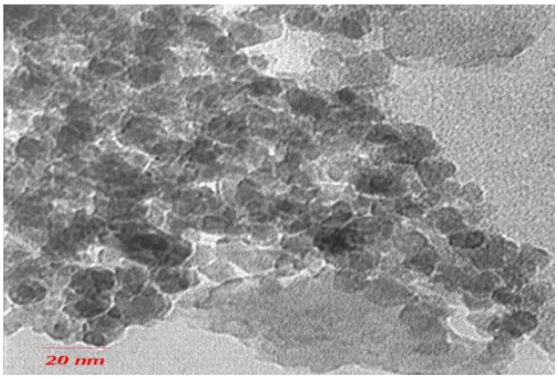


Figure 1. SEM spectra of nano $MgAl_2O_4$

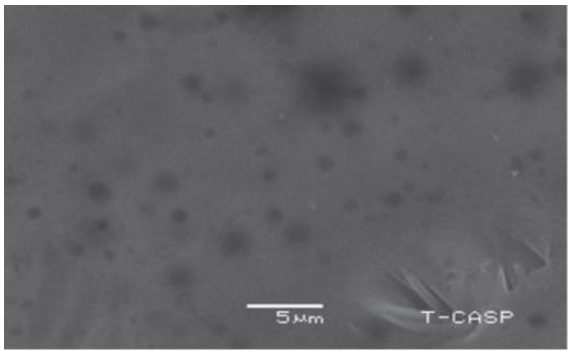


Figure 2. TEM spectra of nano $MgAl_2O_4$

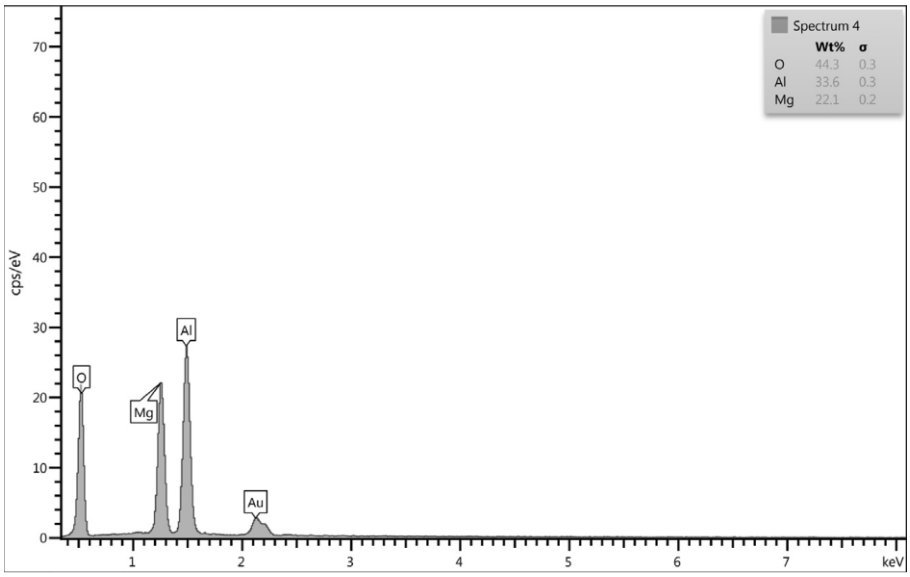


Figure 3. EDX spectra of nano $MgAl_2O_4$

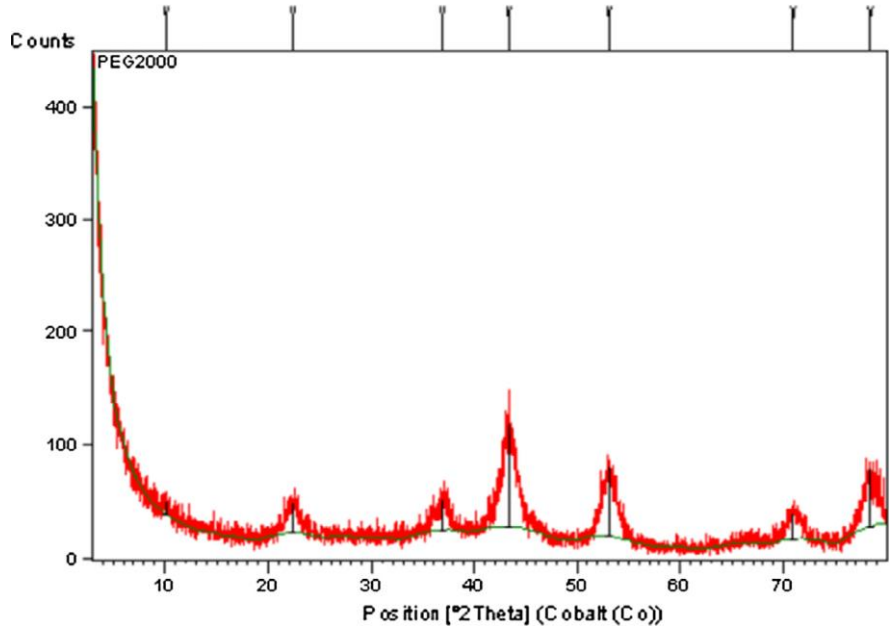


Figure 4. EDX spectra of nano $MgAl_2O_4$

To optimize the catalyst amount of for synthesis reaction, compound **3a** was selected as the sample. Table 1 presents the test results for optimizing the amount of catalyst in the presence of different amounts of nano-magnesium aluminate catalyst. Based on the table results, 0.05 g of magnesium aluminate catalyst exhibits the highest efficiency.

To optimize the reaction conditions, the condensation reaction of isatin and indole was performed in solvent-free conditions in different solvents. Ethanol was selected as the best solvent according to the best efficiency and suitable time. The experimental results are summarized in Table 2.

Table 1. Comparison of the amount of suitable catalyst for the **3a** preparation

Entry	Solvent	Yield (%)[a]
1	0.02g	80
2	0.03g	89
3	0.05g	99
4	0.07g	99

[a]Yields were analyzed by GC

Table 2. Synthesis of **3a** in the presence of nano-$MgAl_2O_4$ by using different solvents

Entry	Solvent	Yield (%)[a]
1	THF	68
2	C_2H_5OH	99
3	CH_3CN	85
4	$CHCl_3$	71
5	water	90
6	Solvent-free	92

[a]Yields were analyzed by GC

The results of the preparation of oxindole derivatives are indicated in Table 3. According to the Table 3, the selected method for the synthesis of derivatives oxindole and the selection of nano-magnesium aluminate catalyst for all the aromatic aldehyde derivatives with electron-donor and electron-withdrawing groups can be done with a high efficiency.

After comparing the results of the **3a** synthesis with other methods, it was found that the nano-magnesium aluminate catalyst performs the reaction faster and with higher efficiency (Table 4).

Table 3. Synthesis of the substituted oxindole catalyzed by nano-magnesium aluminate

Entry	R1	R2	R3	Product	Time (h)	Yield (%)	m.p. (°C) Observed	m.p. (°C) Reported [10]
1	H	H	H	3a	2	99	313-314	312-314
2	H	CH_3	H	3b	2	99	293-295	292-293
3	H	H	CH_3	3c	2	97	322-324	321-322
4	H	H	Br	3d	2	93	311-313	310-311
5	H	H	NO_2	3e	2	95	299-300	298-299
6	CH_3	H	H	3f	2	93	301-303	300-301
7	CH_3	CH_3	H	3g	2	93	273-275	272-273
8	CH_3	$PhCH_2$	H	3h	2	93	214-215	212-214
9	CH_3	H	CH_3	3d	2	93	239-300	238-239

Table 4. Comparison of various catalysts for the **3a** synthesis

Entry	Catalyst	Solvent	Yield (%)	Time (h)	Ref.
1	MCM-41	THF	31	3	[11]
2	PMOA	THF	39	3	[11]
3	PWA	THF	46	3	[11]
4	PWA/MCM-41	THF	99	3	[11]
5	$MgAl_2O_4$	EtOH	99	2	Present study

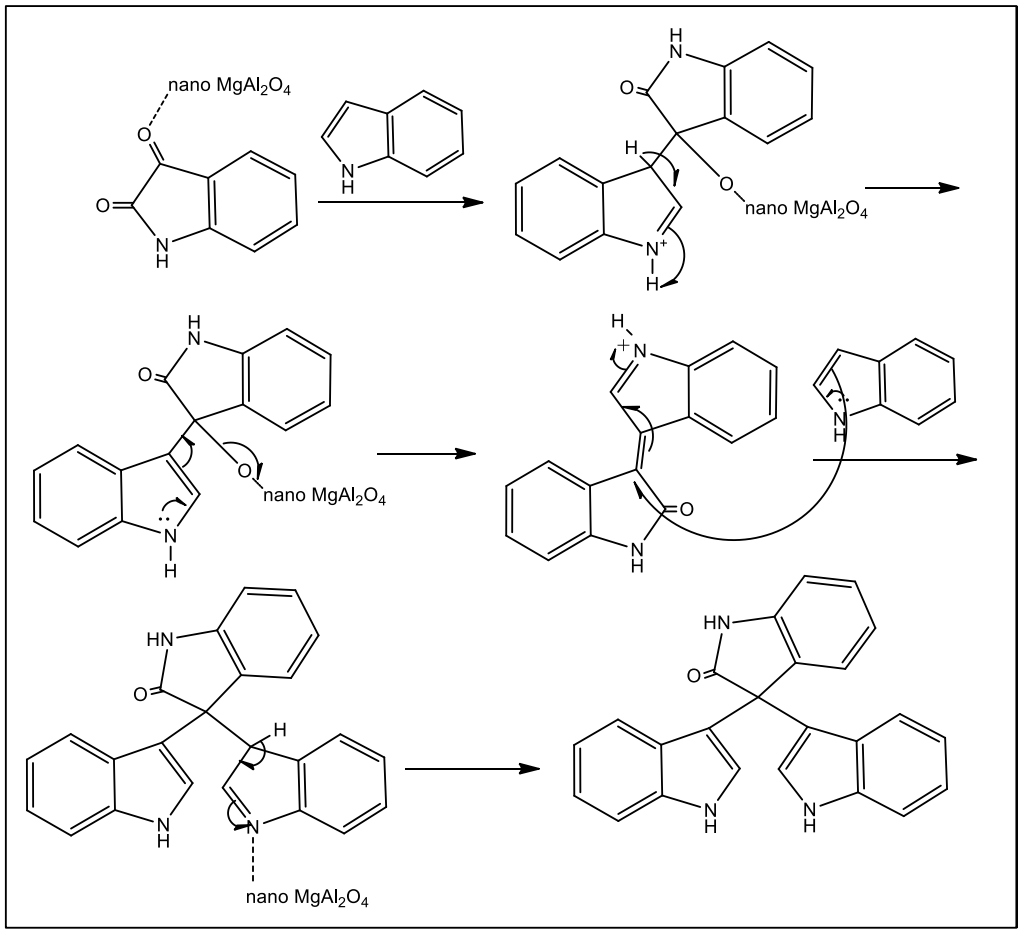
Reusability of nano $MgAl_2O_4$

Next, the reusability of $MgAl_2O_4$ nanocatalyst was investigated. At the end of the reaction, the catalyst was recovered by a simple filtration, washed with methanol, dried, and subjected to the second step of the reaction process. To ensure that the catalysts did not dissolve in methanol, they were weighed after filtration and before use and reuse for the next reaction.The comparison of the efficiency of nano-$MgAl_2O_4$ as a catalyst in the synthesis of **3a** after five times is reported in Table 5. Accordingly, the first reaction by using the recovered nano-$MgAl_2O_4$ achieved very similar yields to those obtained in the first round. In the second, third, fourth, and fifth rounds, the yield was gradually decreased.

Table 5. Reuse of the nano $MgAl_2O_4$ for the synthesis of **3a**

Entry	Run	Yield (%)[a]
1	First	99
2	Second	98
3	Third	95
4	Fourth	91
5	Fifth	88

Isolated yields



Scheme 2. A plausible mechanism for the reaction

Mechanism of reaction

A plausible mechanism for this reaction is proposed in Scheme 2. Due to its empty orbital, the catalyst plays the role of Lewis acid and attracts the oxygen electrons of carbonyl group, thus activating carbon of carbonyl group and being better attacked by the nucleophilic attack. Therefore, carbonyl group is activated in both dimedone and aromatic aldehyde reactors by a magnesium aluminate catalyst. Activated carbonyl aldehyde creates an intermediate element-A through a nucleophilic attack on the C1 component of 2-naphthol, which is now ready to attack the dimedone as an electrophile element, and then cycloaddition reaction takes place at the intermediate-C. Thereafter, a water molecule is removed and the desired products are created.

Conclusion

In this research, a very efficient green method was investigated for the preparation of oxindoles derivatives through the condensation reaction of indole and isatin derivatives in the presence of nano-magnesium aluminate as a catalyst. This method has many advantages, including operational simplicity, high efficiency, use of environmentally and friendly solvent, ease of catalyst recovery, ease of product separation, and low cost, which can make this reaction as a useful and interesting industrial process for the preparation of these compounds. In this research, nano-magnesium aluminate was used as an efficient and suitable catalyst for the preparation of oxindole compounds, and it was determined by SEM and TEM analysis. According to the data in this research, oxindoles in the presence of nano magnesium aluminate catalyst can prepare products with a high efficiency and in a shorter time than other catalysts.

Disclosure Statement

No potential conflict of interest was reported by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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How to cite this manuscript: Bita Baghernejad*, Atefe Zakariayi. One-Pot synthesis of oxindoles derivatives as effective antimicrobial agents by Nano-Magnesium aluminate as an effective aatalyst. *Journal of Medicinal and Nanomaterials Chemistry*, 4(3) 2022, 225-233. DOI: 10.48309/JMNC.2022.3.5