

Green synthesis of 2,4-dinitro-substituted bischalcones using bifunctional magnetic nanocatalyst

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Abstract. Flavonoids have many biological properties, such as anticancer activity. Chalcones, one of their subunits, attribute their biological activity to their enone part. The presence of dinitrophenyl group in bischalcone because of its radiosensitivity property is important. Radiosensitivity property reduces radiation time in cancer patients and reduces damage to their healthy tissues. In this regard, 2,4-dinitrophenyl bischalcones were synthesized. The presence of 2,4-dinitrobenzaldehyde as a fixed component in synthesis pathway, leads to a reduction in yield of synthesis by common catalysts. Therefore, in this study, for bis-chalone synthesis, we used Graphene Oxide/Fe₃O₄/L-Proline nanocomposite as a green recoverable bifunctional organocatalyst. This catalyst was recovered simply by applying an external magnet and reused for eight runs. In this research, chalcones and asymmetric bis-chalcones have been synthesized with diverse substitutes in high yields (78–97%). Also, short reaction times (10–82 min), and simple experimental procedures with easy work-up are advantages of the introduced procedure. The synthesized compounds were characterized by melting point and analytical techniques. The chemical structures of synthesized compounds were confirmed by means of IR, ¹HNMR, and ¹³CNMR.

Keywords: Magnetic Catalyst, α , β -unsaturated ketones, asymmetric bischalcones, 2, 4-dinitrobenzaldehyde, Claisen-Schmidt condensation, radiosensitivity

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1. Introduction

Several patients with many types of cancer have been distinguished over the last few decades, and without new effective treatments, their number will be increased. Cancer is a group of diseases that results in abnormal cell growth as one of the principal causes of death worldwide. There are many ways to treat cancer, depending on the type of cancer, its location, and its degree. One of the ways to treat cancer is radiation therapy, which involves ionizing radiation, which damages the cancerous tissue DNA and destroys it [1]. Radio sensitizers increase the effect of radiation therapy and reduce damage to healthy and adjacent tissues. These compounds are molecules or fragments that increase the sensitivity of cancerous cells to radiation and have led to a reduction in radiotherapy time; and, as a result, the patient receives less radiation, and the damage to adjacent healthy tissues decreases [2]. In this regard, researchers have discovered several chalcones as strategic compounds with good antitumor activity *in vivo* and *in vitro*, such as xanthohumol, isoliquiritigenin, and lutein [3]. These α,β -unsaturated ketones, are essential in cancer research because they act as Michael receptors, especially with thiol groups such as amino acids and cysteine residues in proteins [4]. Nitro compounds have been exploited for radio-sensitization [5].

Chalcones, as α,β -unsaturated ketones, are extracted from natural sources widely used to promote potent and effective drugs in the treatment of diseases such as cancer, diabetes, tuberculosis, HIV, and malaria [6]. The presence of chalcone derivatives as a critical component or side chain in various active biological compounds encourages organic chemists to synthesize new chalcone derivatives [7]. Chalcones are synthesized in the presence of base catalysts through dehydration in an enolate mechanism, while in the presence of acid catalysts; they are through an enolytic mechanism. The main problem with this reaction is its very gradual speed. Also, the reaction mixture can include the expected product, byproduct, and sometimes raw material. Therefore, its efficiency can differ depending on the case, reactants, and used catalysts, yielding less than 10% to close to 100%. Despite its variable efficiencies, the reaction is used due to its easy application in the laboratory and the formation of a dual C-C bond with minor molecular complexity [8]. Another method for synthesizing these compounds is via Claisen-Schmidt condensation, in which aromatic aldehydes and ketones react together [9]. Although both acid and base catalysts are used for these reactions, the base catalyst plays a higher efficiency than acidic catalysts [10]. As mentioned above, because of several biological activities of chalcones, new techniques with different conditions and catalysts for their synthesis are in progress [11]. Szell and colleagues created a series of nitro-chalcones. They demonstrated the presence of electron-releasing substituents and electron-withdrawing substituents in aldehyde preferable aldol condensation by acids and bases, respectively, through two mechanisms of catalytic nucleophilic addition reactions. The activation of nucleophile precursors by basic catalyst to abstract their acidic parts, such as acyl groups and α -hydrogen atoms, and lowering the LUMO levels of electrophiles by interaction with Brønsted or Lewis acidic catalysts [12]. The base catalysts used in this concentration include Potassium tert-butoxide, sodium hydroxide, or potassium methanolic or ethanolic hydroxides [8]. Although Bronsted–Lowry acids [13], Lewis acids [14], and solid acids [14], are commonly used as catalyst for chalcones synthesis, most common acid catalyst is dry HCl gas for the reaction because this gas acts not only as a catalyst but also as a water absorber [8].

On the other hand, it's notable that one of the significant sources of waste in chemical industries is derived from the widespread use of liquid mineral acids and Lewis acids. They cannot easily be recycled and generally end up, via a hydrolytic workup, as waste streams containing large amounts of inorganic salts. Their widespread replacement by recyclable catalysts would afford a dramatic waste reduction. In this respect, heterogeneous catalysts [15], magnetic catalysts [16], ionic liquids [17], and other green catalysts have many advantages in chemical synthesis in avoid the generation of waste [15].

More recently, there has been a growing trend in applying proline, graphene, and Fe_3O_4 in composite catalysis. L-proline natural amino acid is a bifunctional organocatalyst that acts as Lewis base through the secondary amine group while acting as Bronsted acid catalyst through the carboxylic acid group [18]. Graphene is a good choice for use as safe and excellent catalyst support. Because of graphene's unique structure, it has many unmatched characteristics of other materials, including two-dimensional planar structure, single-atom thickness, large surface area, excellent electrical, thermal, and mechanical properties [19]. In order to make composites easy to separate, magnetic nanoparticles were added to Graphene oxide [20]. Balasubramanian et al. show that the catalytic activity of Fe_3O_4 increases significantly with the addition of graphene [21].

Based on our research, previously prepared and characterized nanocomposite magnetically by our research team [22], is a suitable choice for the synthesis of 2,4-dinitro-substituted bischalcones as radiosensitizer compounds; they can play a substantial role in cancer treatment.

2. Material and methods

2.1. Materials and reagents

All chemicals were prepared from Sigma-Aldrich Company, and the solvents were high purity. The reaction follow-up was performed using the TLC technique, and the IA9100 melting point device of the United Kingdom electrothermal fabrication measured melting points of solid compounds. The IR spectra of the compounds were recorded using KBr on a Bruker Vertex 70 Fourier-Transform Infrared Spectrometer (FTIR) in the range of $400\text{--}4000\text{ cm}^{-1}$. The $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were measured using chloroform deuterium solvent (CDCl_3) on a Bruker AVANCE spectrometer (400 MHz). The Vario El CHNS (made in Germany) was used for elemental analysis. Scanning electron micrographs (SEM) were obtained using a Cambridge S-360 instrument with an accelerating voltage of 20 kV (Cambridge, Austin, TX, USA). The powder X-ray diffraction (XRD) pattern was obtained by a Bruker AXS (D8, Avance) (Avance, San Antonio, TX, USA) instrument employing the reflection Bragg–Brentano geometry with CuK α radiation. A continuous scan mode was used to collect 2θ from 5°C to 40°C . The thermogravimetric and differential thermogravimetric (TG–DTG) analysis was performed on Netzsch STA449c (Kimia Sanat Ara, Tehran, Iran). The sample weight was ca. 10 mg and was heated from room temperature up to 600°C with $10^\circ\text{C}/\text{min}$ using alumina sample holders.

2.2. Methodology

2.2.1. Catalyst preparation

GO and $\text{GO}/\text{Fe}_3\text{O}_4$ were prepared according to the modified Hummer's [16, 17], and Song's methods [22], respectively. The mixture of the dried $\text{GO}/\text{Fe}_3\text{O}_4$ nanohybrid (0.2 g) and L-proline (0.5 g) was sonicated in deionized water (40 ml) in an ultrasonic bath at 28 kHz frequency (amplitude 70%) for 30 minutes, and the mixture was further stirred on round-bottom flask for 24 h at room temperature. The catalyst has been characterized by Fourier transform infrared (FT-IR), XRD, TGA, DTG, TEM, SEM, and elemental analysis [23].

2.2.2. Optimization of Claisen-Schmidt condensation using $\text{GO}/\text{Fe}_3\text{O}_4/\text{L-Proline}$

A mixture of benzaldehyde (1 mmol) and acetone (14 mmol) was placed together in a round-bottom flask, and subsequently, $\text{GO}/\text{Fe}_3\text{O}_4/\text{L-proline}$, according to Table 1, was added to the mixture. The suspension was then stirred at reflux condition for sufficient time based on TLC (*n*-hexane: ethyl acetate; 3:1) detection (Table 1). After completing the reaction, followed by TLC, the catalyst was separated by a permanent external magnet. The recovered catalyst was washed with acetone, dried, and

Table 1
Optimization of benzal acetone synthesis using GO/Fe₃O₄/L-proline the catalyst

Entry	mmol ratio benzaldehyde:Acetone	GO/Fe ₃ O ₄ /L-proline (g)	Temperature (°C)	Time (min)	Yield (%) ^a
1	1:14	0.1	40	360	44
2	1:14	0.1	30	360	41
3	1:14	0.04	30	300	21
4	1:14	0.06	30	300	29
5	1:14	0.04	Reflux	20	89
6	1:14	0.06	Reflux	10	98
7	1:14	0.08	Reflux	20	97
8	1:14	0	Reflux	600	15
9	1:10	0.04	Reflux	20	90
10	1:10	0.06	Reflux	10	94
11	1:10	0.08	Reflux	20	94
12	1:18	0.04	Reflux	20	86
13	1:18	0.06	Reflux	10	91
14	1:18	0.08	Reflux	20	90

^aYields refer to isolated and pure products.

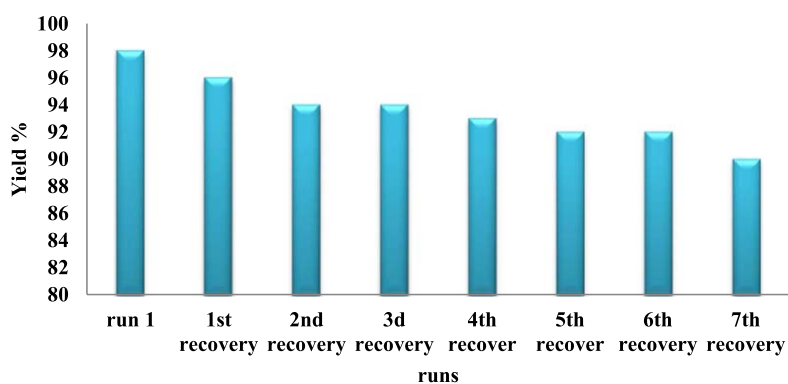


Fig. 1. Reusability study of GO/Fe₃O₄/L-proline.

stored for similar repeated runs. A simple consecutive work-up (concentration of the reaction mixture and addition of 25 cm³ of water) affords the crude oil. The product was extracted with AcOEt (3 × 25 cm³). The organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to afford benzalacetone.

2.2.3. Reusability study of GO/Fe₃O₄/L-Proline

The recovered catalyst of above optimized reaction (Table 1, raw 6) was weighed and reused for subsequent reaction under the optimized reaction conditions (reactants were added an appropriate amount to the catalyst). The reusability of the catalyst was investigated in different runs (Fig. 1).

2.2.4. Catalytic synthesis of 2,4-dinitro-substituted bischalcones

2.2.4.1. Benzal acetone derivatives synthesis using GO/Fe₃O₄/L-proline the catalyst. The optimized condition of condensation reaction using GO/Fe₃O₄/L-proline for benzalacetone synthesis (Table 1, raw 6) expanded to other benzaldehydes to synthesize other monochalcones (Table 2).

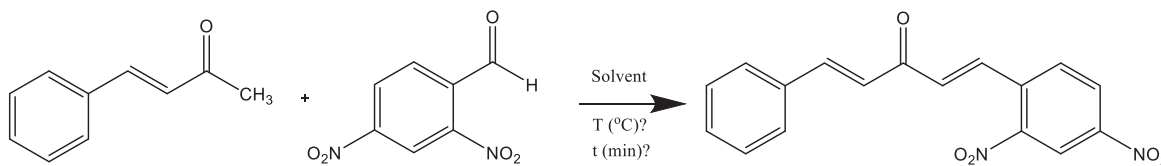
Table 3
 Compression of reported banzalacetone synthesis method by previously reported methods

Row	Cat. (mol %)	solvent	t (min)	Yield (%)	T (°C)	Ref	Run of reusability
1	GO/Fe ₃ O ₄ /L-Proline Nanocomposite	acetone	10	98		Current study	8
2	NaOH (20)	H ₂ O	420	99		[24]	–
3	NaOH (20)	Acetone/H ₂ O	360	99	20	[25]	–
4	Organobismuth Perfluorooctanesulfonate	H ₂ O	180	96	20	[26]	7
5	morpholin-4-ium 2,2,2-trifluoroacetate	acetone	1200	96	75	[27]	–
6	catalyst A-2XMP	–	60	94	RT	[28]	–
7	barium dihydroxide	ethanol	60	93	reflux	[29]	–
8	NaOH (10)	H ₂ O	135	65–78		[30]	–
9	Mg(Al)O(2,3,4)	H ₂ O	3*	–		[31]	–
10	Ionic liquid	H ₂ O	30	98		[32]	5
11	NaOH(20)	mortar and pestle	1.8	42		[33]	–
12	Ca(OH) ₂ (10)	EtOH/H ₂ O	600	85	50	[34]	–

*The scale of these times is hour.

Table 4

Optimization of (1E,4E)-1-(2,4-dinitrophenyl)-5-(phenyl)penta-1,4-dien-3-one synthesis using GO/Fe₃O₄/L-proline as catalyst



Row	Solvent	GO/Fe ₃ O ₄ /L-proline (g)	Temperature (°C)	Time (min)	Yield (%)
1	neat	0.06	100	300	20
2	CH ₂ Cl ₂	0.06	Reflux	100	26
3	CH ₃ CN	0.06	Reflux	140	32
4	THF	0.06	70	120	50
5	DMF	0.06	90	150	72
6	H ₂ O	0.06	Reflux	100	44
7	H ₂ O/DMF	0.06	Reflux	100	61
8	CH ₃ CH ₂ OH	0.05	Reflux	60	92
9	CH ₃ CH ₂ OH	0.07	Reflux	35	97
10	CH ₃ CH ₂ OH	0.09	Reflux	50	90

3. Results and discussion

As part of our studies on the synthesis of radiosensitivity compounds, structurally related to the bischalcone skeleton, we have recently focused on synthesizing α,β -unsaturated ketones known as benzal acetones, which possess exciting properties for organic synthesis [7]. In this regard, the GO/Fe₃O₄/L-proline catalyst, prepared and characterized by our research group, investigated the synthesis of benzal acetone based on its ability, the acidic and basic catalyst. Hydrogen-bonding interaction between hydroxyl, epoxy, and carboxyl groups on the GO sheet in GO/Fe₃O₄ nanohybrid with carboxyl and

secondary amine groups of L-proline is the driving force for L-proline binding to the GO/Fe₃O₄ nano hybrid.

The condensation reaction of benzaldehyde and acetone was selected as the model reaction (Table 1). The best result was achieved by carrying out the reaction in the presence of 0.06 g of GO/Fe₃O₄/L-proline under the reflux condition (Table 1, entry 6). Using more significant amounts of the catalyst (0.08 g, entry 7) did not improve the yield, while decreasing its amount led to decreased yield (0.04 g, entry 5). The addition of a suitable amount of catalyst enabled the reaction to achieve the optimum yield, but the addition of catalyst beyond a specific amount decreased the activity. This decrease can be attributed to catalyst agglomeration and the formation of bulk particles leading to a decrease in the number of active sites. The purity of the final products was controlled by NMR. The product is a known compound, and its IR and NMR spectroscopy data are compared with the reported values.

The recovery of a catalyst is highly preferred for a greener process. Fe₃O₄ nanoparticles were found suitable as catalyst carriers to realize long-term catalyst recycling [23]. Before the separation of the product, the catalyst was quickly recovered by the magnet. The reusability of GO/Fe₃O₄/L-proline was studied for eight consecutive cycles (fresh + seven cycles) to synthesize benzal acetone. From Fig. 1 shows, that GO/Fe₃O₄/L-proline catalyst can be reused for up to eight runs without reloading. The yield difference between the first and eighth runs is only 8%, indicating catalyst efficiency was maintained during eight consecutive runs. The nitrogen content of the fresh and reused catalyst was measured using the elemental analysis. The comparison of the nitrogen contents suggested that the catalyst lost only 6% of its nitrogen content after eight runs. This is solid proof of the meager leaching account of L-proline organocatalyst [23] from GO/Fe₃O₄/L-proline catalyst into the reaction mixture during eight runs, and also, confirms that the catalytic ability of GO/Fe₃O₄/L-proline has almost entirely remained stable after eight runs, which is in agreement with the recyclability study. The TEM image of the recovered catalyst after eight runs did not reveal any significant change in the morphology of the reused catalyst, which proved its robustness while maintaining catalytic activity. GO/Fe₃O₄/L-proline catalyst recovered from the reaction mixture simply by applying an external magnet, and its superparamagnetic properties remained constant even after eight runs. The results illustrated that the catalyst samples have the appropriate properties for magnetic actuation. However, there were some decreases in the magnetization after eight consecutive runs, which possibly originated from the decreases in the Fe₃O₄ nanoparticles loading on the GO surface during eight-repeated conditions.

The efficiency of this approach was explored for the synthesis of a wide variety of Benzal acetone derivatives, using the optimized reaction conditions. All the reactions delivered excellent product yields and accommodated a wide range of aromatic aldehydes bearing electron-donating and electron-withdrawing substituents (Table 2).

According to Table 3, many researchers have tried synthesizing monochalcone compounds with many methods and different catalysts. These methods can be used to synthesize these compounds, however, in some cases, we were faced with a small quantity of efficiency, and due to the undesirability of the abovementioned methods, and we have tried to use the reusable magnetic catalyst that has acidic and basic sites simultaneously (Fig. 2).

In addition, the catalyst used is effective for both steps of asymmetric bischalcones synthesis. In two steps, synthesis of asymmetric bis chalcone compounds, at the first mono-chalcones compounds which have the site for coupling by 2,4-dinitrobenzaldehyde synthesized. For this purpose, in this study, the used ketone in the first step reaction for synthesizing mono-chalcone compounds is acetone (Scheme 1).

The synthesis of 2,4-dinitro-substituted bischalcones, optimization of benzal acetone, and the 2,4-dinitrobenzaldehyde reaction were carried out (Table 4). In the second step, synthesized benzal acetone derivatives (Table 2) reacted with 2,4-dinitro benzaldehyde by optimized condition (Table 4, row 9) to produce 2,4-dinitro-substituted bischalcones (Table 5).

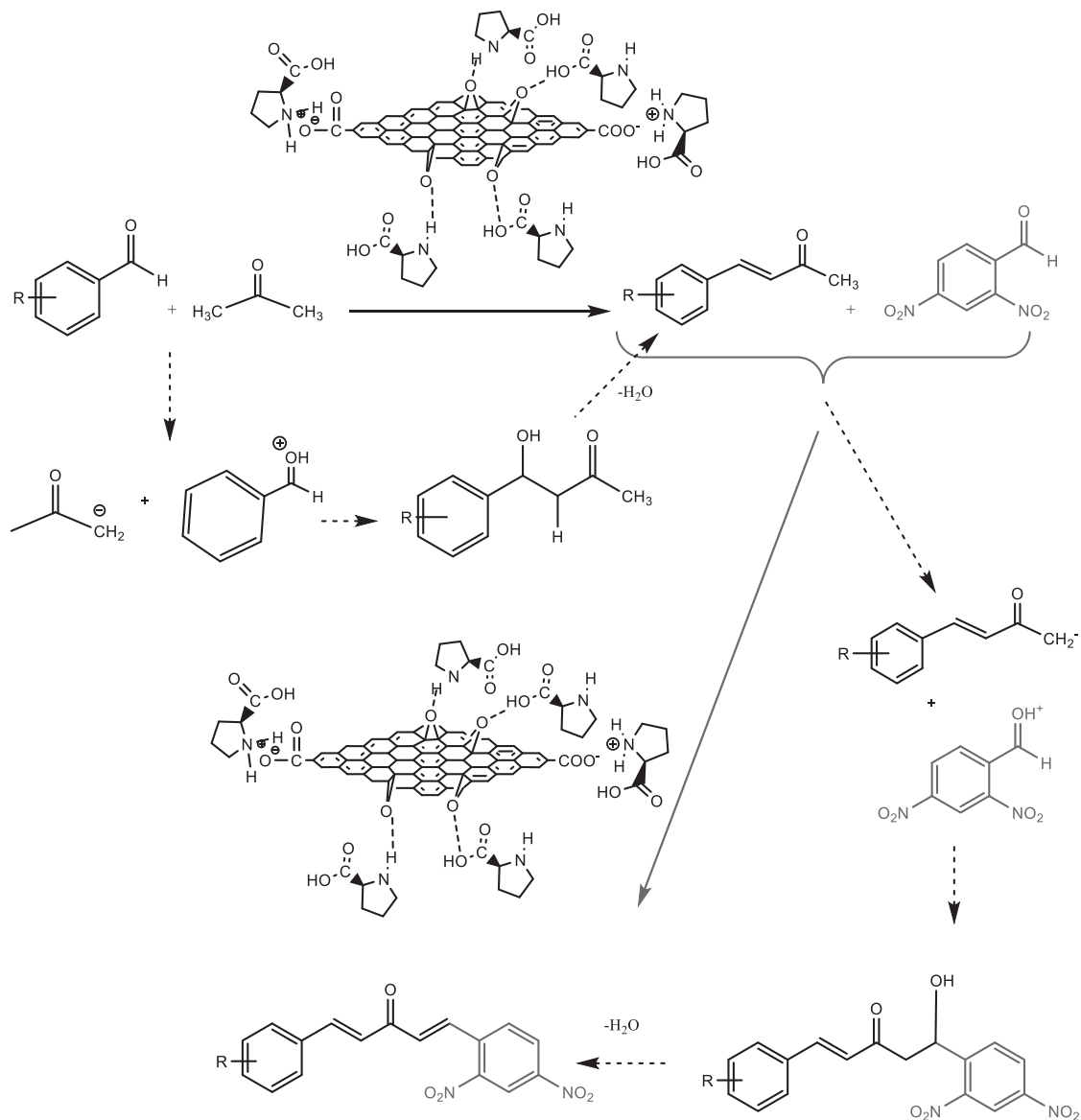
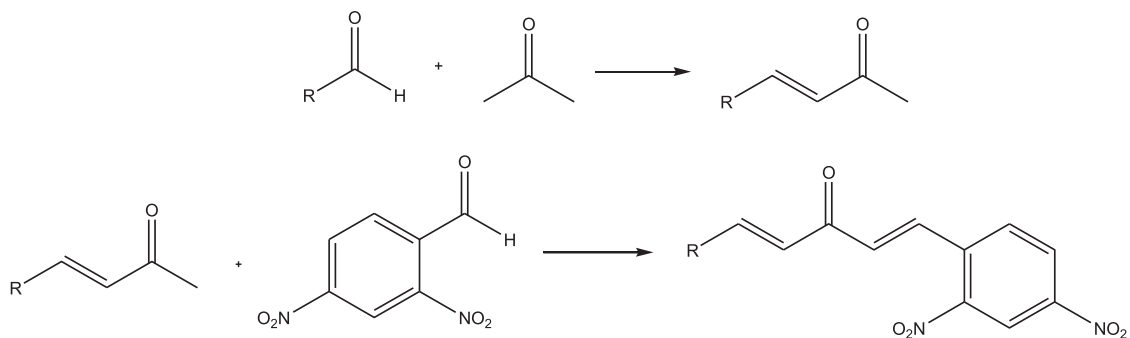
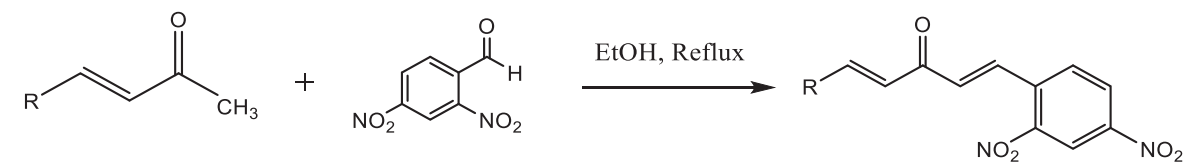


Fig. 2. Propose mechanism of bischalcone synthesis using the bifunctional catalyst.



Scheme 1. Two steps synthesis of asymmetric bischalcones.

Table 5
Synthesis of asymmetrically bischalcones



Entry	2:R	T (min)	product	Yield (%)
1	2a: Ph	55		90
2	2b: 4-ClC ₆ H ₄	65		88
3	2c: 4-MeOC ₆ H ₄	70		80
4	2d: 2,4-dinitroC ₆ H ₃	60		78
5	2e: 4-NO ₂ C ₆ H ₄	80		86
6	2f: 4-HOC ₆ H ₄	76		89
7	2g: 4-dimethylNC ₆ H ₄	69		83
8	2h: 2-C ₄ H ₃ S	82		84

A few studies have been done to synthesize asymmetric bis-chalcones, but they did not specifically synthesize the reported asymmetric chalcones. According to our study, the synthesis of new asymmetric bis-chalcone compounds improved using a magnetic catalyst prepared by our research group (Table 3).

While, the combination of 2,4-dinitrobenzaldehyde with monochalcone in previous reported works has a meager output [12], and also 4-nitrobenzaldehyde reaction with acetone has very low efficiency [34], we were able to synthesize it using the method outlined in this article (Table 2).

4. Conclusion

2,4-dinitrophenyl-substituted bischalcones were synthesized as a very significant class of compounds using GO/Fe₃O₄/L-proline nanocomposite. This green bifunctional organocatalyst has better catalytic activity than previously reported catalysts introduced for bischalcones synthesis. L-proline on the GO/Fe₃O₄ nanocomposite through the non-covalent immobilization via hydrogen bonding interaction between the L-proline and the GO/Fe₃O₄ gives a robustness catalytic system, and, at the same time, lets the L-proline organocatalyst to be flexible, mobile, and accessible on the surface of the GO/Fe₃O₄ support. Moreover, this method can enhance the thermal stability of the L-proline. Finally, this catalyst can be recovered simply by applying an external magnet and reusing at least eight runs to synthesize chalcone. Such advantages are characteristic properties of homogeneous and heterogeneous catalysts, which have been included in the GO/Fe₃O₄/L-proline hybrid. All the reactions delivered excellent product yields and accommodated a wide range of aromatic aldehydes bearing electron-donating and electron-withdrawing substituents.

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Supplementary material

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