

AN EFFICIENT SOLVENT FREE MICROWAVE ASSISTED MgFe_2O_4 MAGNETIC NANOPARTICLES CATALYZED GREEN PROTOCOL TOWARDS MICHAEL ADDITION

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Abstract. MgFe_2O_4 magnetic nanoparticles were used as an efficient catalyst for the synthesis of Michael products by treating substituted chalcones and β -nitro styrenes with electron donar species like malononitrile and ethyl cyanoacetate in solvent free microwave conditions. In this study, we report that MgFe_2O_4 magnetic nanoparticles were the best heterogeneous catalyst with 10 mol % loading for synthesis of Michael products as compared to several reported catalysts. The reusability of MgFe_2O_4 nanoparticles was checked for 5 times without appreciable loss of catalytic activity.

Keywords: MgFe_2O_4 MNP's, Michael addition, heterogeneous catalyst.

1. Introduction

Michael addition is one of the simple, efficient, atom economic classical and functional methodologies for C–C bond formation reaction [1-7]. Michael addition reaction can be used for synthesis of natural products like Culeatins [8] and HIV-1 drug like Calanolide A [9], (-)Epibatidine alkaloid [10] and also Culmorin as an antibacterial drug [11]. Generally Michael addition is performed in the presence of strong base or Lewis acid either at room temperature or at elevated temperature [12] in suitable organic solvents which usually result in undesirable side reactions such as multiple condensation, polymerization, rearrangements, retro-Michael addition, bis-addition and so on [13-16]. These undesirable side reactions lower the yields of targeted compounds and make the purification of products very cumbersome. An extensive study has been focused in the design and development of catalysts, which will result in high selectivity, mild reaction conditions and sufficient tolerance to a wide range of nucleophilic substrates. During the past decades more efficient and

milder catalysts including 1,5,7-triazabicyclo[4,4,0]dec-5-ene (TBD) [17], natural phosphate doped catalyst [18], SmI_3 [19], imidazolium ionic liquid [20], bifunctional organocatalyst [21] have been developed in this area of research. There have been few reports on Michael reaction catalyzed by K_2CO_3 in an organic solvent in the presence of water [22], surfactants [23] and under phase transfer catalyst conditions [24-26]. To some extent, these mild reaction conditions minimized the reversibility of Michael addition reaction [27] and side products, thus improved the yield of a product. In spite of the above newer developed protocols, there were still some disadvantages like long reaction time, tedious work up procedure and homogenous nature of the catalyst. Recently the microwave [28] and ultrasonic irradiation [29] have also been used to promote the Michael reaction. To circumvent the above problem, one of the best methodologies is to carry out the reaction under solvent free, milder reaction conditions with minimal or no side product formation, high atom economy, shorter reaction time and reusability of catalyst.

Aiming at the above target, and our keen interest in development of green methodologies [30-32] we herein report a simple, highly efficient microwave assisted green protocol for C–C bond formation *via* Michael addition reaction using magnetic MgFe_2O_4 nanoparticles as the reusable heterogeneous catalyst in the solvent free condition. The developed strategy acts as simple facile and environment friendly protocol for the conjugate addition of active methylene compounds to electron deficient alkenes under solvent free conditions, with shorter reaction time using a reusable heterogeneous catalyst.

2. Experimental

All solvents and reagents were used as supplied by commercial sources. The recorded melting points are uncorrected. IR spectra were recorded in KBr on a Shimadzu FTIR 8401 spectrometer and Perkin Elmer version 10.03.06 for the liquid samples. ^1H and ^{13}C spectra were recorded on a Bruker DRX 300

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spectrometer operating at 300 MHz for ¹H NMR and 75 MHz for ¹³C NMR as solutions in CDCl₃ and DMSO-d₆. The ESI mass spectra were measured by a Waters UPLC-TQD spectrometer. TLC was performed on a silica coated glass plate, spots were developed in I₂ chamber or visualized in UV chamber. A CEM Discover microwave was used for irradiation purposes.

2.1. Preparation of MgFe₂O₄ Magnetic Nanoparticles

Nanoparticles of MgFe₂O₄ were synthesized by combustion technique. 2.0 mmol of Fe(NO₃)₃·6H₂O and 1.0 mmol of MgCO₃ dissolved in HNO₃ were taken together. After uniform mixing, 1.0 mmol of monoethanolamine was added to the reaction mixture followed by 1.0 mmol of each of sucrose and excess of nitric acid, respectively. The resulting liquid reaction mixture was then put on a hot plate at 353 K till it completely dried to a black residue. This black residue was then kept in a muffle furnace at 1073 K for 4–6 h to obtain nanoparticles of MgFe₂O₄. MgFe₂O₄ nanoparticles were characterized by SEM, XRD and IR spectra and matched with JCPDS file no. 731960.

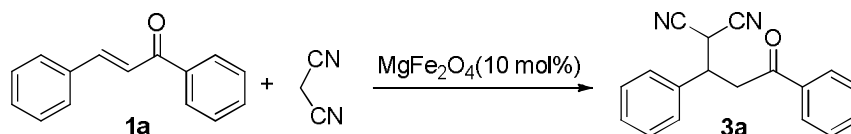
2.2. General Procedure for the Synthesis of Michael Product (3a-o and 5a-g)

Electron deficient alkenes (chalcone/nitrostyrene) (1.0 mol), malanonitrile/ethyl cyanoacetate (1.0 mol) and catalyst (10 mol %) were mixed thoroughly at room temperature and afterwards the mixture was intermittently irradiated in a microwave for the appropriate period of time. The reaction was monitored by TLC, after the completion of the reaction, the catalyst was removed by

using an external magnet and crude product obtained was purified by a column chromatography to afford the corresponding Michael product. All the synthesized compounds were fully characterized by FTIR, ¹H and ¹³C NMR, mass spectroscopy.

3. Results and Discussion

In our initial catalytic experiment, benzylidene acetophenone (**1a**), malanonitrile and MgFe₂O₄ nanoparticles as a catalyst were mixed thoroughly and irradiated in a microwave oven at 900 W for the certain time period as a model reaction (Scheme 1). To our delight, reaction took much less time for the completion as evident from the disappearance of a starting material on TLC plate which confirmed the completion of the reaction. Reaction mixture was then diluted with methanol, the heterogeneous catalyst was separated with an external magnet, the crude reaction mixture was concentrated on a rotatory evaporator and purified by a column chromatography to get 2-(3-oxo-1,3-diphenylpropyl)malanonitrile (**3a**) in appreciably good yields (Table 1, entry 4). To study the effect of the catalyst loading and wattage of a microwave on the model reaction, then we carried out the reaction in the presence and absence of the catalyst under microwave conditions. The results in Table 1 depict that in the absence of a catalyst, the reaction took longer reaction time with less yield of products (Table 1, entry 8), while under the optimized condition, the desired product was isolated in 89 % yield (Table 1, entry 4). However, the reaction at 600 W or less produced unsatisfactory results (Table 1, entries 6 and 7). The catalyst loading less than 10 mol % also gave unsatisfactory results (Table 1, entries 1-3).



Scheme 1. Synthesis of 2-(3-oxo-1,3-diphenylpropyl)malanonitrile under optimized condition (model reaction)

Table 1

Optimal conditions of catalyst loading and wattage used for microwave irradiations

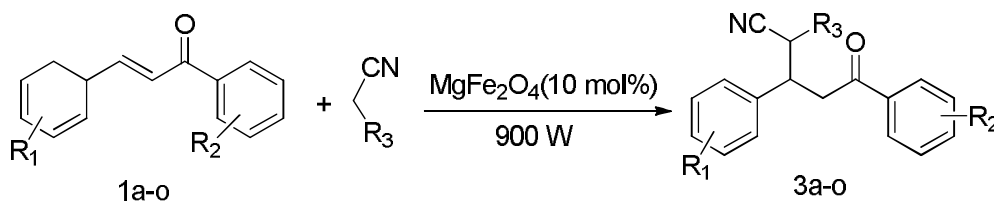
Entry	Power, W	Catalyst loading, mol % ^a	Time, s	Yield, % ^b
1	900	1	600	56
2	900	3	450	56
3	900	5	200	68
4	900	10	150	89
5	900	20	150	88
6	600	10	230	65
7	300	10	300	60
8	900	No catalyst	1 h	48

Notes: ^a reaction conditions: benzaldehyde (1.0 mol), malanonitrile (1.0 mol), MgFe₂O₄ catalyst, solvent free, microwave irradiation; ^b isolated yields

Table 2

Art protocol versus our methodology

Entry	Catalyst	Amount, mol %	Time	Solvent	Yield, %	Ref.
1	Guanidinium lactate Ionic liquid	–	3.2–24 h	DMF	25–95	[33]
2	No catalyst	–	5–60 min	[DBU][Lac]	46–95	[34]
3	Bifunctional amine thiourea	10	3–8 h	Toluene	70–83	[35]
4	KOH	1	1–5 min	–	57–82	[36]
5	LiClO ₄	5	5–1200 min	Et ₃ N	82–97	[37]
6	Quinine-Al(O ⁱ Pr) ₃ complex	10	180 h	Toluene	77–90	[38]
7	Hydrotalcite clay	200 mg	5–6 min	–	78–95	[39]
8	MgFe ₂ O ₄ catalyst	10	40–160 s	–	80–92	our work

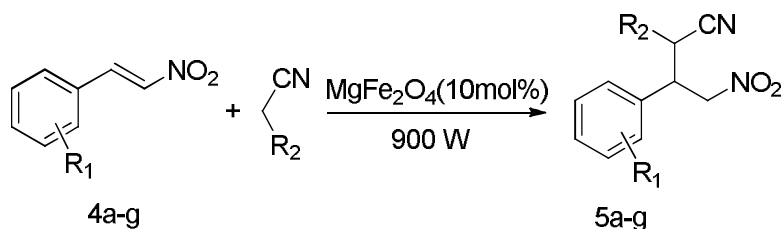


Scheme 2. Synthesis of Michael products by nucleophilic attack of active methylene compounds on substituted chalcones

Table 3

MgFe₂O₄ magnetic nanoparticles catalyzed Michael addition of chalcones with various active methylene compounds under microwave condition

Entry	R ₁	R ₂	R ₃	Product	Time, s	Yield, %
	1a-o					
1	H	H	CN	3a	150	89
2	4-Me	H	CN	3b	160	85
3	3-OMe	H	CN	3c	90	85
4	3,4-OMe	H	CN	3d	145	84
5	3,4-OMe	4-Me	CN	3e	145	84
6	3,4-OMe	H	CO ₂ Et	3f	80	82
7	2-OMe	H	CN	3g	70	82
8	3-Me	H	CN	3h	150	80
9	4-CN	H	CN	3i	60	92
10	2-Br	H	CN	3j	50	87
11	2,4-Cl	H	CN	3k	40	88
12	4-Br	H	CN	3l	90	90
13	4-Cl	H	CN	3m	160	86
14	3-NO ₂	H	CN	3n	70	76
15	4-Br	H	CO ₂ Et	3o	90	92



Scheme 3. Condensation of active methylene groups on substituted β -nitrostyrene

Michael addition of active methylene molecule to β -nitrostyrene catalysed by MgFe₂O₄ under microwave irradiation

Entry	R ₁	R ₂	Product	Time, s	Yield, %
1	H	CN	5a	130	85
2	H	CO ₂ Et	5b	90	85
3	4-OMe	CN	5c	90	90
4	4-Me	CN	5d	90	90
5	3,4-OMe	CO ₂ Et	5e	160	86
6	4-Cl	CN	5f	50	87
7	4-NO ₂	CN	5g	40	88

In comparison with the state of the art protocol, the results obtained by our methodology were very exciting and inspiring in terms of being solvent free, less reaction time, easy separation of the catalyst and a good yield of products as well (Table 2).

Using optimized reaction conditions, then we explored the scope and generality of Michael addition reaction (Scheme 2, Table 3). It was observed that the reaction of chalcone with various active methylene compounds proceeds smoothly under our developed protocol with an excellent yield of Michael product in shorter reaction time (Table 3, entries 1-15). Chalcones bearing electron withdrawing groups at *b* position of unsaturated chalcone took less reaction time with excellent yields (Table 3, entries 9-15) compared to aromatic ring having electron donating groups (Table 3, entries 1-8). Extending our work to other electron deficient alkenes like *b*-nitrostyrene, with dicyanomethane and ethyl cyanoacetate in the presence of MgFe₂O₄ as a catalyst. The results are presented in Scheme 3 and Table 4. In this protocol we got much more satisfactory and encouraging results. All the reactions were found to be very clean, fast and high yielding. Electron rich nitroalkenes yielded the products in 85–90 % (Table 4, entries 1-5), while the electron withdrawing nitroalkenes gave the Michael products in 87–88 % of yields (Table 4, entries 6-7).

It was noteworthy to examine the recovery and reuse of the catalyst on our model reaction for five consecutive cycles. Once the reaction was over, the catalyst was separated by the external magnet and washed several times with methanol and dried in the oven for 4 h and finally reused in the next cycle. The results summarized in Fig. 1 demonstrate the ability of the catalyst to retain its catalytic activity even after five cycles. Reusability is the main advantage of this cheaper, environment friendly heterogeneous catalyst.

The plausible mechanism for the formation of the products **3a-o** and **5a-g** are shown in Fig. 2. It is assumed that Mg NPs facilitate the Michael addition type coupling by coordinating to oxygen of chalcone groups. Also Mg

NPs can activate malononitrile or ethylcyanoacetate so that deprotonation occurs. As a result Michael Addition proceeds by activation of reactants by NPs.

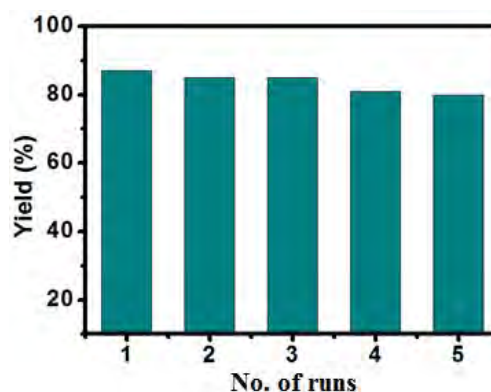


Fig. 1. Recyclability of heterogeneous nano MgFe₂O₄ catalyst

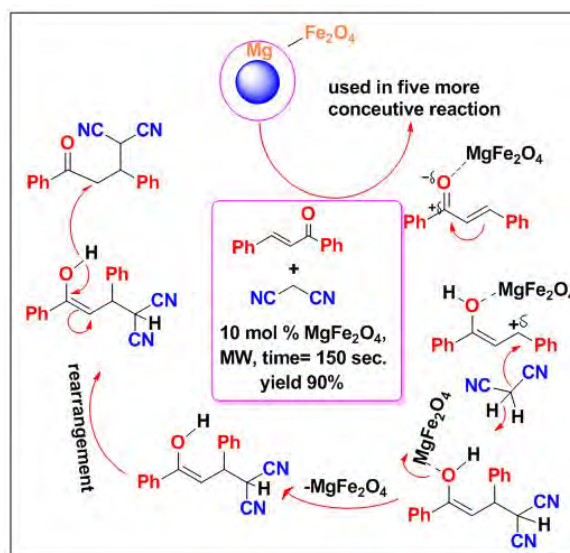


Fig. 2. Plausible mechanism of Michael addition reaction of activate chalcone and active methylene group by MgFe₂O₄ as a catalyst

4. Conclusions

In summary, we have developed a simple, efficient, solvent free, cleaner and high yielding microwave assisted protocol for carbon-carbon bond formation *via* Michael addition using $MgFe_2O_4$ magnetic nanoparticles as a heterogeneous reusable catalyst. The developed protocol in general involves shorter reaction time, no use of hazardous solvent, easy separation of the catalyst by the external magnet and reusability of the catalyst even after five runs thus making this methodology environmentally more acceptable and applicable in the field of green synthesis.

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ОБРОБЛЕНІ МІКРОХВИЛЯМИ У ВІДСУТНОСТІ РОЗЧИННИКА МАГНІТНІ НАНОЧАСТИНКИ $MgFe_2O_4$ ЯК ЕФЕКТИВНИЙ КАТАЛІЗАТОР РЕАКЦІЇ МІХАЕЛЯ

Анотація. Досліджено магнітні наночастинки $MgFe_2O_4$ як ефективний катализатор для синтезу продуктів за реакцією Міхаеля внаслідок оброблення мікрохвилями у відсутності розчинника заміщених халконів і β -нітро стиролів з електронними донорами, такими як малонітрил та етилцаноацетат. Показано, що магнітні наночастинки $MgFe_2O_4$ є кращими гетерогенними катализаторами (10 мол. %) у порівнянні з відомими катализаторами. Визначено, що за п'ять циклів роботи синтезований катализатор не втрачає каталітичної активності.

Ключові слова: магнітні наночастинки $MgFe_2O_4$, реакція Міхаеля, гетерогенний катализатор.