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Ultrasound assisted synthesis of enaminones using Nickel oxide

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ABSTRACT

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An efficient and simple protocol of β -enaminones and β -enamino esters synthesis using nickel oxide under ultrasound sonication has been developed. Ultrasound sonication triggers the formation of enaminones under the mild reaction conditions. Nickel oxide was found to be efficient, heterogeneous, moisture stable, robust and recyclable catalyst.

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1. Introduction

β -Enaminones and β -Enamino esters are important classes of organic compounds having multiple applications because of their adaptable dual behavior as electrophiles and nucleophiles¹. Enaminones are widely used as versatile building blocks for synthesis of important heterocyclic compounds, nitrogen-containing compounds, naturally occurring alkaloids and pharmaceuticals with antiepileptic, anticonvulsant and antitumor properties^{2,3}. Condensation of carbonyl compounds and amines mediated by acid catalysts is a simple methodology for synthesis of enamino esters. Diversified acid catalysts such as metal triflates⁴, perchlorates⁵, InBr⁶, CoCl₂⁷, silica supported mineral acid⁸, BF₃*Et₂O⁹, silver nanoparticles¹⁰, copper nanoparticles¹¹, gold salts¹² and Zn(OAc)₂¹³ have been used in the synthesis of β -enaminones and enamino esters. The above catalysts are either expensive or moisture sensitive or nonrecyclable or require harsh reaction conditions. Hence new protocol development with elimination of above drawbacks was the driving force for present research work. In the last few years, ultrasound irradiation has played a significant role in the development of synthetic protocols for organic reactions¹⁴, while metal oxide catalyzed organic transformations have attracted

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considerable attention in last few decades^{15,16}. Few reports have highlighted the catalytic activity of NiO in different chemical transformations¹⁷⁻¹⁹. Yet, a little attention has been given to the catalytic activity of NiO as compared to other metal oxides in organic synthesis.

Hence, exploring the new catalytic properties of NiO for different chemical transformations was of interest in the field of catalysis. We herein report an efficient and mild protocol for the synthesis of enamines and enamino esters using NiO as a heterogeneous, moisture stable, robust and recyclable catalyst under ultrasonication.

2. Results and Discussion

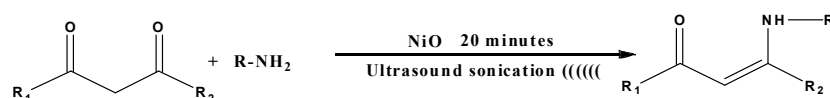
The condensation of aniline and acetyl acetone was selected as a model reaction. The influence of various reaction parameters such as solvent, catalyst loading and time was examined (**Table 1** entries, 1-15). Initially we have screened various metal oxides such as Co₃O₄, ZnO, CuO, and NiO as catalyst for the condensation reaction. NiO was found to be the most effective catalyst among the above metal oxides providing an excellent yield of 92 % (**Table 1**, entries 1-4). The control experiment was carried out in the absence of catalyst. However reaction did not proceed in the absence of catalyst and sonication even after prolonged stirring (12h) (**Table 1**, entry 5). The reaction was also studied under sonication in the absence of catalyst, which resulted in very low product yield (**Table 1**, entry 6). We have also studied the effect of various solvents on the condensation reaction to find out the most suitable solvent for Sonication. However, it was observed that the reaction proceeded very well in the absence of solvent and under neat conditions (**Table 1**, entries 7-11). The catalyst loading was optimized by increasing the amount of NiO from 0.05 mmol to 0.2 mmol for 1 mmol scale reaction. The yield increased with the increase in catalyst loading (**Table 1**, entries 12-15). Nevertheless, there was a very marginal increase in the yield when the catalyst loading is increased to 0.2 mmol (**Table 1**, entries, 14 and 15). Hence 0.15 mmol of catalyst was chosen as an optimal amount. Thus, the optimized reaction conditions for 1 mmol enamines synthesis were as follows: catalyst-NiO, catalyst loading - 0.15 mmol, time - 20 minutes and solvent free condition.

Table 1 Optimization of reaction conditions.

Entry	Solvents	Effect of catalyst		
		Catalyst	Catalyst loading, mmole	Yield, %
1	none	NiO	0.2	92
2	none	CuO	0.2	60
3	none	ZnO	0.2	50
4	none	Co ₃ O ₄	0.2	trace
5	none	none	none	No reaction ^a
6	none	none	none	trace
Effect of solvent				
7	Methanol	NiO	0.2	20
8	Water	NiO	0.2	trace
9	Ethyl acetate	NiO	0.2	trace
10	Toluene	NiO	0.2	10
11	none	NiO	0.2	92
Effect of catalyst loading				
12	none	NiO	0.05	68
13	none	NiO	0.1	78
14	none	NiO	0.15	90
15	none	NiO	0.2	92

Conditions: acetyl acetone (1.2 mmole), aniline (1 mmole), 30 °C, sonication 20 min. ^aWithout sonication.

In order to investigate the general applicability of protocol, various dicarbonyl and amines were condensed to give respective enaminones. The desired products were obtained in excellent yields (**Table 2**, entries 1-8). Aromatic amines containing electron withdrawing group such as nitro and chloro groups having strong deactivating effect were converted into corresponding products in lower yield (**Table 2**, entries 2 and 3). It also indicates that the catalyst shows good activity in case of liquid and semisolid compounds. However substituted aromatic amine having electron donating substituent were more reactive and afforded better yield of the corresponding product (**Table 2**, entries 1, and 4-7). The condensation of amines with different dicarbonyl compounds such as ethyl acetoacetate, methyl acetoacetate and benzoylacetone was also studied (**Table 2**, entries 5–8). Methyl and ethyl acetoacetate produced excellent yield of desired products (**Table 2**, entries 5-7). Benzoylacetone (more bulky diketone) also reacted efficiently with butyl amine to deliver a product with 90% yield (**Table 2**, entry 8).



Scheme 1. Condensation of di-carbonyl compounds with amines under sonication.

Table 2. Condensation of dicarbonyl compounds with amine.

Entry	R ₁	R ₂	R	Product	m. p., °C (lit.)	Yield, % (lit.)	Ref.
1	CH ₃	CH ₃	Ph		46-48 (45-47)	90 (89)	20
2	CH ₃	CH ₃	4-NO ₂ Ph		142-143 (142-143)	88 (65)	6
3	CH ₃	CH ₃	4-ClPh		60-61 (59-60)	90 (85)	20
4	CH ₃	CH ₃	4-CH ₃ Ph		64-65 (63-65)	94 (90)	20
5	CH ₃	OCH ₃	Ph		46-47 (46-47)	92 (91)	6
6	CH ₃	-OC ₂ H ₅	4-OCH ₃ Ph		43-44 (43-44)	94 (93)	6
7	CH ₃	-OC ₂ H ₅	Ph		oil	91 (87)	21
8	CH ₃	Ph	-CH ₂ -CH ₂ -C ₂ H ₅		oil	90 (99)	4

Conditions: dicarbonyl compound (1.2 mmol), amine (1 mmol), catalyst (0.15 mmol), 30 °C, sonication 20 min.

In order to make the protocol more economical, the recyclability of NiO was studied. The series of model reaction of acetyl acetone and aniline were carried out consecutively for 5 times by using recycled NiO catalyst under identical conditions. It was observed that reused up to three cycles catalyst allow obtaining products with marginal decrease in the yields (**Table 3**). During each cycle

the NiO was separated by centrifugation and then used for the next run after washing with distilled water and ethanol.

Table 3. Recycle run study

Entry	Run	Yield, %
1	1 st	90
2	2 nd	89
3	3 rd	88
4	4 th	85
5	5 th	82

Reaction Conditions: Acetyl acetone (1.2mmol), aniline (1mmol), NiO (0.15 mmol), sonication for 20 min at 30 °C.

3. Conclusions

To conclude, we have developed a new and efficient procedure for the synthesis of β -enaminones and β - enaminone esters catalysed by NiO under ultrasonication at 30 °C. Economically affordable, easy to handle, recyclable and robust nature are the advantages of NiO catalyst for the synthesis of β -enaminones and β -enamino esters. The protocol offers high yield of desired product with different amines and dicarbonyl compounds under solvent free ultrasonication. The other remarkable features of this protocol are simplicity, shorter reaction time and ease of separation of catalyst which make this protocol novel convenient and effective.

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4. Experimental

4.1. Materials and Methods

All reagents and chemicals were procured from BDH chemicals Ltd, Mumbai, India and were used without further purifications

4.2. General procedures

Synthesis of nickel oxide (NiO)

NiO was prepared by hydrothermal synthesis as mentioned below. In typical procedure, 1g nickel nitrate hexahydrate and 2g urea were dissolved in 30 mL distilled water in a 100 mL round bottom flask. The mixture was refluxed for 6h and allowed to cool at room temperature. The resultant blue green nickel hydroxide obtained was washed with small aliquots of water and ethanol for several times and dried at 110 °C for 12h. It was then further subjected to calcination at 500 °C for 5h to get NiO powder.

Synthesis of Enaminones

In a 10 mL round bottom flask, dicarbonyl compound (1.1 mmol), amine (1 mmol) and NiO (0.15 mmol) were added and sonicated in an ultrasonic bath (30 kHz) for 20 min.

Progress of the reaction was monitored by TLC and Gas chromatography. On completion of reaction, 5 mL of ethyl acetate were added to the reaction mixture and centrifuged at 5000 rpm for 20 minutes

to separate the catalyst. The supernatant was slowly decanted and used for product recovery. The NiO was allowed to air dry and reused for further recycle run study. The crude product was extracted with ethyl acetate (5 mL×3) and purified using column chromatography by n-hexane. In order to study general applicability of this protocol, different dicarbonyl and amines were condensed to give different enaminones and were characterized by using GC-MS (Shimadzu Q P 2010), ^1H NMR (Mercury Plus 300 MHz NMR spectrometer) and IR spectroscopy (FTIR Perkin Elmer). The m.p. of the products were determined and compared with reported methods (**Table 2**).

4.3 Physical and Spectral Data

Characterization of NiO

The formation of NiO was confirmed by analytical techniques using SEM-EDAX analysis (Quanta -200 at 20Kv as an operating voltage) and XRD (Rigaku Miniflex model by using $\text{CuK}\alpha = 1.54 \text{ \AA}$ with scanning range 0° to 80° with scanning rate 2 degree per minute).

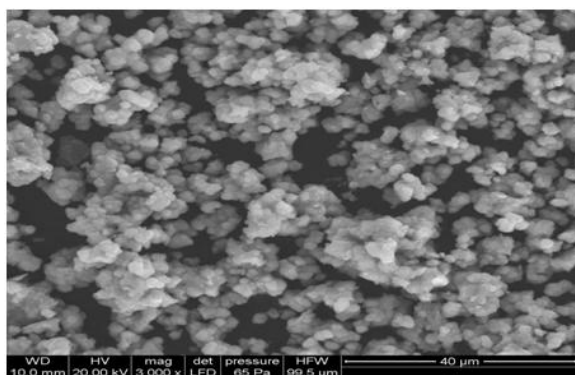


Fig. 1. SEM image of NiO

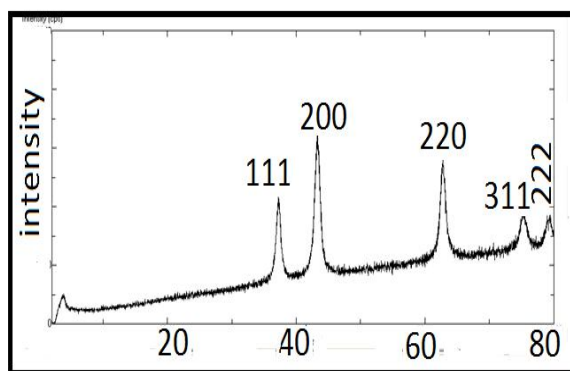


Fig. 2. XRD pattern of synthesized NiO

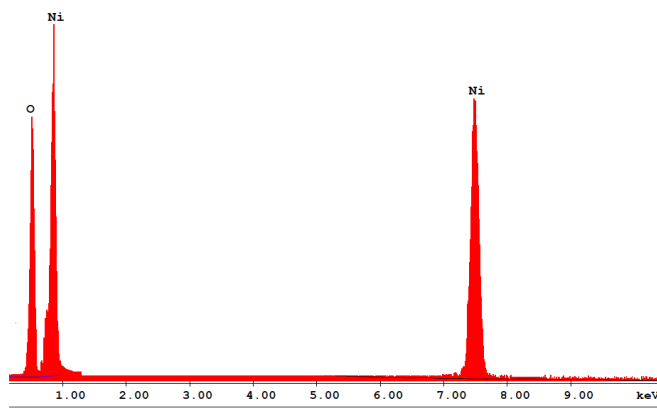


Fig. 3. EDAX analysis of NiO

SEM image of NiO showed that Particles were nearly of spherical shape (**Fig. 1**). X-ray diffractogram of NiO indicates that particles exhibit good crystallinity and FCC crystal pattern with peaks at 37° , 43° , 63° , 75° , and 79° indices for (111), (200), (220), (311), (222) planes respectively (**Fig. 2**). The EDAX spectrum (**Fig. 3**) showed peaks correspond to nickel and oxygen only which confirmed purity of nickel oxide.

Spectral data of compounds

4-(Phenylamino)pent-3-en-2-one (Table 2, entry 1). Pale yellow solid IR (KBr): $\nu = 3400, 3000, 1580, 1600 \text{ cm}^{-1}$. $^1\text{H NMR}$ (CDCl_3 , 300 MHz): $\delta = 1.99$ (s, 3H), 2.10 (s, 3H), 5.19 (s, 1H), 7.09-7.21 (m, 3H), 7.31-7.37 (m, 2H), 12.49 (br s, 1H, NH). M/z: 174.78. mp 46-47 °C (lit. 45-47 °C).

4-(4-nitrophenylamino)pent-3-en-2-one (Table 2, entry 2). Yellow solid IR (KBr): $\nu = 3410, 3090, 2972, 1639, 1581 \text{ cm}^{-1}$. $^1\text{H NMR}$ (CDCl_3 , 300 MHz): $\delta = 2.07$ (s, 3H), 2.2 (s, 3H), 5.23 (s, 1H), 7.2 (d, $J = 9.0$ Hz, 2H), 7.93 (d, $J = 9.0$ Hz, 2H), 12.68 (br s, 1H, NH). M/z: 220.10. mp 142-143.5 °C (lit. 142-143 °C).

4-(4-Chlorophenylamino)pent-3-en-2-one (Table 2, entry 3). Pale yellow solid IR (KBr): $\nu = 3466, 3032, 1643, 1560 \text{ cm}^{-1}$. $^1\text{H NMR}$ (CDCl_3 , 300 MHz): $\delta = 2.01$ (s, 3H), 2.13 (s, 3H), 4.98 (s, 1H), 7.05 (d, $J = 8.6$ Hz, 2H), 7.208 (d, $J = 8.6$ Hz, 2H), 12.43 (br s, 1H, NH). M/z: 209.07. mp 60-61 °C (lit. 59-60 °C).

4-(p-Tolylamino)pent-3-en-2-one (Table 2, entry 4). Pale yellow solid IR (KBr): $\nu = 3424, 3036, 1600, 1555, 1529 \text{ cm}^{-1}$. $^1\text{H NMR}$ (CDCl_3 , 300 MHz): $\delta = 1.99$ (s, 3H), 2.10 (s, 3H), 2.34 (s, 3H), 5.2 (s, 1H), 7.0 (d, $J = 8.7$ Hz, 2H), 7.24 (d, $J = 8.7$ Hz, 2H), 12.40 (br s, 1H, NH). M/z: 189.11. mp 64-65 °C (lit. 63-65 °C).

Methyl 3-(phenylamino)but-2-enoate (Table 2, entry 5). Pale yellow solid IR (KBr): $\nu = 3257, 2982, 1641, 1576, 1493 \text{ cm}^{-1}$. $^1\text{H NMR}$ (CDCl_3 , 300 MHz): $\delta = 1.98$ (s, 3H), 3.78 (s, 3H), 4.59 (s, 1H), 7.18 (m, 3H), 7.20-7.30 (m, 2H), 10.46 (br s, 1H, NH). M/z: 191.10. mp 46-47 °C (lit. 46-47 °C).

Ethyl 3-(4-methoxyphenylamino)but-2-enoate (Table 2, entry 6). Pale yellow solid IR (KBr): $\nu = 3246, 2835, 1710, 1640, 1619 \text{ cm}^{-1}$. $^1\text{H NMR}$ (CDCl_3 , 300 MHz): $\delta = 1.30$ (t, $J = 6.8$ Hz, 3H), 1.90 (s, 3H), 3.82 (s, 3H), 4.15 (q, $J = 6.8$ Hz, 2H), 4.63 (s, 1H), 6.75 (d, $J = 8.7$ Hz, 2H), 7.02 (d, $J = 8.7$ Hz, 2H), 10.18 (br s, 1H, NH). M/z: 235.12. mp 43-44 °C (lit. 43-44 °C).

Ethyl 3-(phenylamino)but-2-enoate (Table 2, entry 7). Yellowish oil IR (KBr): $\nu = 3266, 2978, 1663, 1586 \text{ cm}^{-1}$. $^1\text{H NMR}$ (CDCl_3 , 300 MHz): $\delta = 1.32$ (t, $J = 7.3$ Hz, 3H), 2.00 (s, 3H), 4.20 (q, $J = 7.3$ Hz, 2H), 4.69 (s, 1H), 7.17 (m, 3H), 7.30 (m, 2H), 10.48 (br s, 1H, NH). M/z: 205.16.

3-(butylamino)-1-phenylbut-2-en-1-one (Table 2, entry 8). Yellow oil IR (KBr): $\nu = 3420, 3025, 1590, 1550, 1520 \text{ cm}^{-1}$. $^1\text{H NMR}$ (CDCl_3 , 300 MHz): $\delta = 1.0$ (t, 3H), 1.31 (m, 2H), 1.52 (m, 2H), 2.89 (t, 2H), 2.26 (s, 3H), 6.95 (s, 1H), 7.89 (d, $J = 8.7$ Hz, 2H), 7.60-7.73 (d, 3H), 12.0 (br s, 1H, NH). M/z: 217.10

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