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Nano Nickel-Zinc Ferrites Catalysed One-Pot multicomponent Synthesis of B-Acetamidoketones Derivation Microwave Irradiation

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Abstract : Nano Nickel-Zinc Ferrite is a heterogeneous catalyst for the synthesis of one-pot multi component by a different aro β -acetamido ketones armatic aldehydes, acetophenone and acetyl chloride in acetonitrile under microwave conditions. The present methodology offers several advantages such as good yield, short time reaction, non toxic, environmentally benign, mild reaction conditions and recyclable catalyst.

Keywords : Multicomponent reaction, Nano Nickel-Zinc Ferrites, β -acetamidoketones , Microwave Irradiation, heterogeneous catalyst, Reusable.

1. Introduction

One-pot Multicomponent condensation reactions are the chemical reactions in which three or more components mixed together in a single reaction vessel to form a product, which retains majority of the atoms of all the reactants. These reactions provide rapid access to molecular diversity by combining several reactants into functionalized molecules. These reactions draw greater attention in generating structurally diverse chemical entities like heterocyclic compounds. These reactions are inherently more environmentally benign and provide atom economy.

One part transformations, particularly multi component reactions (MCR) are of current interest to organic chemists. Since the first Multicomponent reactions reported in 1850 by Strecker, they have emerged as efficient and powerful tools for the construction of complex molecule in organic synthesis [1-2]. In particular, MCRs are very useful to generate diverse combinatorial libraries for drug discovery [3-4].

The acetamido ketones are important building blocks in medicinal chemistry because of their wide biological and pharmaceutical properties [5-7]. These are valuable intermediates for preparation of β -amino acids and β -amino alcohols such as antibiotic Nikkomycins (nucleoside-peptide antibiotics) [8-9] and Neopolyoxines [10]. The best known and commonly used route for synthesis of these compounds is the Dakin-West reaction [11], which involves the condensation of an α -amino acid with acetic anhydride in presence of a base, providing α -acetamido ketones via azalactone intermediate [12].

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The general method for the synthesis of β -acetamidoketones by the condensation of enolizable Ketone with aldehydes, acetonitrile and acetyl chloride in presence of different Lewis-Bronsted acid catalysts such as CoCl₂ [13-15], SiO₂/H₂SO₄ [16], BiCl₃ [17-18], ZrOCl₂.8H₂O [16], Sc(OTf)₃ [19]. FeCl₃.6H₂O [19], ZnO [20], H₆P₂W₁₈O₆₂ [21], H₃PW₁₂O₄₀[22-27], Co(OAc)₂ [28], p-TSA [29], Cu(BF₄)₂ [30-32], SnCl₂.2H₂O [33-36], Fe(ClO₄)₃.6H₂O[37]. But many of these methods are suffering from some drawbacks such as prolonged reactions time, vigorous reaction conditions. Use of expensive catalyst and getting low yields. Therefore it is necessary to development of mild truly catalytic and environmental friendly protocol for the synthesis of β -Acetamidoketones. Hence, a new method in which, a reusable and magnetically separable [38] nanoNi_{0.5}Zn_{0.5}Fe₂O₄ ferrite catalysts for the preparation of β -Acetamidoketones under Microwave Irradiation inAcetonitrile which gives us high yield and shorter reaction times (6-7 min) is developed. The general synthetic scheme is presented in scheme 1.

Microwave assisted organic synthesis (MAOS) [3-4] has emerged as a new "lead" in organic synthesis. The technique offers simple, clean, fast, efficient, and economic for the synthesis of a large number of organic molecules. In the recent year microwave assisted organic reaction has emerged as new tool in organic synthesis. Important advantage of this technology include highly accelerated rate of the reaction, Reduction in reaction time with an improvement in the yield and quality of the product. Now a day's this technique is considered as an important approach toward green chemistry, because this technique is more environmentally friendly. This technology is still under-used in the laboratory and has the potential to have a large impact on the fields of screening, combinatorial chemistry, medicinal chemistry and drug development. Conventional method of organic synthesis usually needs longer heating time, tedious, work-up. Which result in higher cost of process and the excessive use of solvents/ reagents lead to environmental pollution. This growth of green chemistry holds significant potential for a reduction of the by product, a reduction in waste production and a lowering of the energy costs. Due to its ability to couple directly with the reaction molecule and by passing thermal conductivity leading to a rapid rise in the temperature, microwave irradiation has been used to improve much organic synthesis.

Microwave assisted synthesis has gained much attention in recent years. The application of microwave Irradiations are used for carrying out chemical transformations, which are solvent free, pollution free, eco-friendly, low cost and offer high yields together with simplicity in processing and handling [39-45].

In continuation to our efforts to explore the catalytic activity of magnetically separable substituted nanoferrites for various organic transformations, it is observed that the efficiency of Nickel substituted Zinc nano ferrite catalysts for the synthesis of β -acetamidoketones has not been explored before. Hence, a one-pot multi-component reaction of aldehydes, enolizable ketones or 1,3-dicarbonyls, acetonitrile/benzonitrile and acetyl chloride is described for the preparation of β -acetamido ketones using as Nickel substituted Zinc nano ferrite catalysts a mild, inexpensive, and highly efficient catalyst.

During last decade, synthetic chemists had make notable emphasize to develop economically viable processes for synthesis of biologically active compounds having medicinal and industrial applications using Green Chemistry approach. To achieve this, microwave assisted reactions in aqueous media is considered a promising alternative over conventional methods. Literature [46-50] reveals use of BF₃.Et₂O catalyst for the synthesis of β -Acetamido ketones. In view of these aspects, we have done efficient investigation and demonstration of BF₃.Et₂O catalyst for preparation of β -Acetamido ketones from microwave assisted reactions in solvent free conditions. An organized comparative study was performed for these methods and optimized conditions are employed for preparation of range of β -Acetamido ketones from aldehydes, acetophenone, acetonitrile in acetyl chloride solution. The key features of this methodology are operational simplicity, mild reaction conditions with good yields.

2. Materials and methods

2.1. Preparation of the Nickel-cobalt ferrite nano catalyst:

Nickel-Zinc Ferrites with formula $Ni_xZinc_{1-x}Fe_2O_4$ (x= 1, 0.75, 0.5, 0.25 and 0) have been chosen for the study and was synthesized by a chemical sol-gel co-precipitation method. Zinc (II) nitrate, Nickel (II) nitrate, iron (III) nitrate of Merck, AR grade were taken in a stiochiometric proportions they were separately dissolved in a little amount of deionised water and then citric acid solution was prepared in a stiochiometric proportion. These two solutions were added in a 1:1 molar ratio and P^{H} adjusted to 7 by the addition of ammonia. The aqueous mixture was heated to 60°C it converted to gel and then temperature increased to 200°C finally we got a powder. That powder was calcined to 600°C and then characterized by FT-IR XRD, SEM, TEM and particle size analysis as by us [37]

2.2. Experimental procedure for β-Acetamidoesters

some β -acetamido ketones have been synthesised under microwave irradiation and magnetically separable catalysts which are presented in **Table 1**. In this, 0.5g of nano Nickel-Zinc ferrites (Ni_{0.5}Zn_{0.5}Fe₂O₄) along with benzaldehyde (1mmol), acetophenone (1mmol), acetonitrile (1mmol) and acetyl chloride (1mmol) in stoichiometric portions and subjected to micro wave irradiation. The completion of reaction was monitored by thin layer chromatography technique using n-hexane and ethyl acetate as mobile phase elute (3:1 ratio).

After getting product the catalyst was separated out and was recovered by magnetization and washed with diethyl ether. The catalyst separated, washed with ethyl acetate and alcohol added until the product was dissolved. The products were isolated by removing the catalyst magnetically from the reaction mixture and the formed solid products were characterized and compared by IR, ¹H NMR and MASS spectral techniques .



R=(5a) H,(5b) p-OCH₃, (5c) p-Br, (5d)o-NO₂,(5e) p-Cl, (5f) 3-hydroxy,4-methoxy(-OCH₃) (5g) 3,4 di methoxy \bigcirc = Nano Nickel Zinc Ferrite

3. **Results and Discussion**

3.1 Catalytic Study

The working hypothesis that the reaction goes via an aldol reaction followed by acetylation and subsequent nucleophilic displacement by the alkyl/aryl nitrile to get the desired product as shown in **Scheme 5.2**. When aliphatic ketones or keto esters react with substituted aromatic aldehydes, the intermediate acetylated aldol products prefer a proton elimination to provide α,β -unsaturated ketones to the formation of desired acetamido Ketone by nucleophilic substitution by alkyl nitrile. This may be attributed to the electronic effect i.e., the electron withdrawing nature of the substituent as well as, the stability of the elimination products. Next to prove that acetyl chloride is not incorporated in the final product and acetonitrile itself is the N-donor and Nucleophile (i.e., it follows the Ritter reaction pathway), this reaction nitrile acts not only as a solvent but also as a nitrogen donor [37].



Scheme 3.2 Plausible mechanism for the formation of β -acetamido ketones

Table 1.1: Effect of the different catalysts on synthesis of β-acetamido ketones

| S.No | Catalyst | Time | Yield | |
|------|----------------------------------|-------|-------|--|
| • | | (min) | (%) | |
| 1 | ZnFe ₂ O ₄ | 5 | 80 | |
| 2 | $Ni_{0.25}Zn_{0.75}Fe_2O_4$ | 5 | 85 | |
| 3 | $Ni_{0.5}Zn_{0.5}Fe_2O_4$ | 5 | 90 | |
| 4 | $Ni_{0.75}Zn_{0.25}Fe_2O_4$ | 5 | 93 | |
| 5 | NiFe ₂ O ₄ | 5 | 95 | |

It is observed from **Table 1.1**, that Nickel substituted Zinc ferrites have shown effective yields under microwave irradiation. When these reactions have been conducted with $Fe(ClO_4)_3.6H_2O$ catalysts [37] the time of reaction was reported in the range of 3.5 to 4.5 hours. Where as in this case, a combined effect of both the catalyst and the microwave irradiation could drastically reduce the time of the reaction, which is an important contribution from this study.

1.2.2 Recycling of the catalyst

Catalyst reusability is of major concern in heterogeneous catalysis. The recovery and reusability of the catalyst was investigated. Catalyst recycling was achieved by fixing the catalyst magnetically at the bottom of the flask with a strong magnet, after which the solution was taken off with a pipette, the solid washed twice with acetone and ethyl alcohol and the fresh substrate dissolved in the same solvent was introduced into the flask, allowing the reaction to proceed for next run. The catalyst was consecutively reused five times without any noticeable loss of its catalytic activity. Therefore, they could be easily and almost completely separated by an external magnet which is of a great advantage for a heterogeneous catalyst.

catalyst and the recovered catalyst is reused for few more cycles. It is observed that there was no leaching of catalyst and the catalysts are reused after thorough washing, drying and pre-heating before the next cycle.

| S. | Aldehyde | Aceto-phenone | Aceto- | β-acetamido ketone | Time | Yield |
|----|-------------------------|------------------|-------------------------------------|--|-------|-------|
| Ν | Substrate | | nitrile | product | (min) | (%) |
| 0 | | | | | | |
| 1 | | H ₃ C | CH ₃ IC Ⅲ N | Sa NH O | 5 | 90 |
| 2 | H ₃ CO | H ₃ C | CH ₃ −C Ⅲ N | H O NH Sb | 7 | 84 |
| 3 | Br | H ₃ C | CH3 −C≡Z | Sc Briteria | 6 | 85 |
| 4 | NO ₂ O H | H ₃ C | CH₃ IC IIIN | Sd ZO NH O Sd | 7 | 85 |
| 5 | cl H | H ₃ C | CH ₃ I C Ⅲ N | Se Se | 7 | 84 |
| 6 | H ₃ CO OH | H ₃ C | CH ₃ −C EN | H, CO OH OH OH OH O Sf | 6 | 86 |

Table 1.2: Comparison of different β-Acetamido Ketone compounds prepared



1.3.1 Spectral Data of the β -Acetamido Ketone compounds

1a: N-(3-Oxo-1, 3-diphenylpropyl) acetamide

Colourless, Yield 96%, M.P.($152^{0}-154^{0}C$); FTIR: υ_{max} (KBr): 3422, 3062, 2855, 1682, 1602, 1525, 1492, 1450, 1216, 749, 707, 685 cm⁻¹; ¹H NMR (400 MHz, CDCl₃/TMS): δ (ppm)= 1.2(s, 3H), 2.0(d,2H), 5.1 (m,1H),8.3 (brs, N-H),7.05(d,2H),7.41(d,2H),7.90(t,1H), 7.45-7.59(m,4H), 8.1(m, 1H); LCMS: m/z: 267.3 (M)⁺ : Elemental analysis of C₁₇H₁₇O₂N [Found: C= 76.49%; H=6.39%; N= 5.19% O= 11.97%. C₁₇H₁₇O₂N requires C= 76.38%; H=6.34%; N= 5.24%; O=12.21%]

1b: N-(1-(4-methoxyphenyl)-3-Oxo-3-phenylpropyl) acetamide

Colourless, Yield 84%, M.P. $(103^{0}-105^{0}C)$; FTIR: υ_{max} (KBr): 3421, 3219, 2962, 1725, 1683, 1577, 1567, 1510, 1261, 121, 834, 633, 601 cm⁻¹; ¹H NMR (400 MHz, CDCl₃/TMS): δ (ppm) = 2.1 (s, 3H), 2.6 (d, 2H), 4.2 (s, 3H), 9.8(brs, NH), 7.984(d,2H),7.791(d,2H),7.529(d,2H),7.508(d,2H), 5.01(m, 1H) ; LCMS: m/z:283(M)⁺ Elemental analysis C₁₇H₁₇O₃N [Found: C= 76.49%; H= 6.39%; N= 5.19%; O=16.95%. C₁₇H₁₇O₃N requires C= 76.38%; H= 6.41%; N=5.24%; O= 17.23%]

1c: N-(1-(4Bromophenyl)-3-Oxo-3-phenylpropyl) acetamide

Colourless, Yield 85%, M.P. ($154^{0}-156^{0}$ C); FTIR: v_{max} (KBr): 3410, 3016, 2962, 1705, 1690, 1590, 1567, 1493, 1283, 1242, 835, 640, 605 cm⁻¹; ¹H NMR (400 MHz, CDCl₃/TMS): δ (ppm) = 3.3 (s, 3H), 2..5 (d, 2H), 2.4 (m, 1H), 9.9(brs, NH), 8.1(d,2H),7.791(d,2H),7.769(m,5H),2.5(d,2H); LCMS: m/z:345(M)⁺ Elemental analysis C₁₇H₁₆O₂NBr [Found: C= 76.49%; H= 6.39%; N= 5.19%; O=16.95%. C₁₇H₁₆O₂NBr requires C= 67.38% H= 5.21%; N=4.3%; O= 10.34%]

1d: N-(1-(2-nitrophenyl)-3-Oxo-3-phenylpropyl) acetamide

Colourless, Yield 85%, M.P. $(119^{0}-1121^{0}C)$; FTIR: v_{max} (KBr): 3424, , 2924, 2925, 1696, 1662, 1607, 1571, 1547,1530,1349, 1270, 742, 643, 615 cm⁻¹; ¹H NMR (400 MHz, CDCl₃/TMS): δ (ppm) = 3.3 (s, 3H), 2.5 (S, 2H), 5.6 (m, 1H), 10.2(brs, NH), 8.1(m,4H),7.9(s,5H); LCMS: m/z:314(M)⁺ Elemental analysis C₁₇H₁₇O₃N [Found: C= 76.49%; H= 6.39%; N= 5.19%; O=16.95%. C₁₇H₁₆O₄N₂ requires C= 76.38%; H= 6.64%; N=5.24%; O= 20.56%]

1e: N-(1-(4-chlorophenyl)-3-Oxo-3-phenylpropyl) acetamide

Colourless, Yield 84%, M.P. (146–148⁰C); FTIR: υ_{max} (KBr): 3441, 3219, 2926, 1682, 1591, 1597, 1573, 1491, 1282, 852, 681, 629 cm⁻¹; ¹H NMR (400 MHz, CDCl₃/TMS): δ (ppm) = 3.5(s,3H), 2.6(s,2H), 10.1(brs, NH), 7.984(d,2H), 7.791(d,2H),7.5(s,5H),7.529(d,2H),7.508(d,2H), 6.974(m, 1H) ; LCMS: m/z:301(M)⁺ Elemental analysis C₁₇H₁₆O₂NCl [Found: C= 76.49%; H= 5.21%; N= 4.34%; O=10.34%. C₁₇H₁₆O₂NCl requires C= 67.38%; H= 6.41%; N=5.24%; O= 17.23%]

1f: N-(1-(2-hydroxy4-methoxyphenyl)-3-Oxo-3-phenylpropyl) acetamide

Colourless, Yield 85%, M.P. $(103^{0}-105^{0}C)$; FTIR: υ_{max} (KBr): 3420, 3240, 2974, 1725,1673, 1664, 1578, 1511, 1277, 1215, 829, 731, 680 cm⁻¹; ¹H NMR (400 MHz, CDCl₃/TMS): δ (ppm) = 3.3 (s, 3H), 3.5(s, 3H), 2.2 (s, 2H), 7.1 (s, 5H), 9.7(brs, NH), 7.4(d, 2H), 7.4(d, 2H), 7.2(s, 1H), 5.5(s, OH), 7.508(d, 2H), 5.6 (m, 1H) ; LCMS: m/z:283(M)⁺ Elemental analysis C₁₇H₁₇O₃N [Found: C= 76.49%; H= 6.39%; N= 5.19%; O=16.95%. C₁₇H₁₇O₃N requires C= 76.38%; H= 6.41%; N=5.24%; O= 17.23%]

1g: N-(1-(3,4-dimethoxyphenyl)-3-Oxo-3-phenylpropyl) acetamide

Colourless, Yield 85%, M.P. $(103^{0}-105^{0}C)$; FTIR: v_{max} (KBr): 3378, 3004, 2962, 1725, 1681, 1597, 1567, 1513, 1283, 1216, 834, 639, 601 cm⁻¹; ¹H NMR (400 MHz, CDCl₃/TMS): δ (ppm) = 2.1 (s, 3H), 2.6 (d, 2H), 3.7 (s, 3H), 9.8(brs, NH), 7.584(d,2H), 7.691(d,2H), 7.769(m,1H), 7.129(s,5H), 7.508(d,2H), 3.6(s, 3H) ; LCMS: m/z:283(M)⁺ Elemental analysis C₁₇H₁₇O₃N [Found: C= 76.49%; H= 6.39%; N= 5.19%; O=16.95%. C₁₇H₁₇O₃N requires C= 76.38%; H= 6.41%; N=5.24%; O= 17.23%]

The reaction products of substituted β -acetamido ketones were characterized by IR-peaks at around 1695 cm⁻¹ indicating Ketone (C=O) functional group, 1682 cm⁻¹ indicating amide (C=O) functional group, 3451 cm⁻¹ indicating N-H group present in the compound.

The ¹H NMR spectra of the chemical shift at δ 8.1-9.1 as doublet confirms the presence of N-H proton. A singlet at δ 2.2-2.4 indicates methyl proton attached to carbonyl functional group, a multiplet at δ 6.4-8.4 confirms the presence of aromatic protons. The mass spectrum provides the molecular weight of the molecule along with M+1 peak, and the fragments give the information about the daughter ions.

1.4 Conclusion

An efficient method has been developed for the synthesis of β -acetamido ketones using Ni_{0.5}Zn_{0.5}Fe₂O₄ nano ferrites. This method offers several advantages including high yield, short reaction time, and ease of separation and recyclability of the magnetic catalyst.

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Figure 1: XRD SpectrumofNi_{0.5}Zinc_{0.5}Fe₂O₄ at 600°C.



Figure 2: SEM image of Ni_{0.5}Zinc_{0.5}Fe₂O₄.



Figure 3 :FTIR Spectrum of Ni_{0.5}Zinc_{0.5}Fe₂O₄





Figure 1.1: FTIR Spectrum of (1a)



Figure 1.2: Mass Spectrum of (1a)



Figure 1.3: ¹HNMR Spectrum of (1b)



Figure 1.4: FTIR spectrum of compound(1b)



Figure 1.5: Mass spectrum of compound(1b)



Figure 1.6: ¹HNMR Spectrum of (1b)



Figure 1.7: FTIR spectrum of compound(1c)



Figure 1.8: Mass spectrum of compound(1c)







Figure 5.10: FTIR spectrum of compound(5d)



Figure 1.11: Mass spectrum of compound(1d)



Figure1 .12: ¹HNMR Spectrum of (1d)



Figure 1.13:FTIR spectrum of compound(1e)



Figure 1.14: Mass spectrum of compound (1e)



Figure 1.15: ¹HNMR Spectrum of (e)



Figure 1.16:FTIR spectrum of the compound(1f)



Figure 1.17: Mass spectrum of compound(1f)



Figure 1.18: ¹HNMR Spectrum of (1f)



Figure 1.19: FTIR spectrum of compound(1g)



Figure 5.20: MASS Spectrum of (5g)



Figure 1.21: ¹HNMR Spectrum of (1g)

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