



AN ECO-FRIENDLY GREEN ONE-POT SYNTHESIS OF ACRIDINE DERIVATIVE USING MAGNETICALLY SEPARABLE Cd-DOPED-Fe NANO CATALYST

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ABSTRACT:

A cadmium-doped-iron magnetically separable nanocatalyst accelerated the four-component synthesis of Acridine derivatives. This catalyst was successfully used for sterically hindered substrate in the Hantzsch reaction with excellent yields of Acridine derivatives. A fascinating feature of this method is the affordable catalyst that is commercially available and has exceptional selectivity with neutral reaction conditions.

KEYWORDS: Tetrahydro Aryl Acridinone, Cd-doped-Fe, MNPs catalyst, N-heterocycle, eco-friendly.

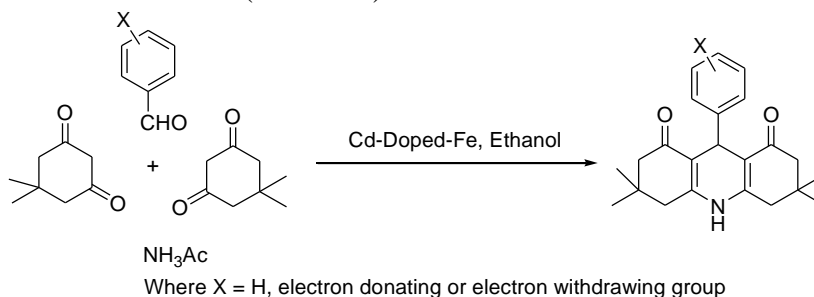
INTRODUCTION:

The N-heterocycle-containing substances exhibit a range of physiological and biological functions. Scientists have been giving close attention to it because of its use in biological studies over the past few yearsⁱⁱ, medicinal^{iii, iv} and pharmacological activities^v such as cyclooxygenase-2 inhibitors-2 inhibitors against a glucosidase^{vi}, and antihypertensive activity^{vii, viii}, anti-inflammatory activity^{ix}, myo relaxant activity of gastric fundus^x.

There have been findings of the numerous catalysts in the Hantzsch reaction such as chitosan nanoparticles^{xi}, Zn-VCO₃ hydrotalcite^{xii} La₂O₃^{xiii}, sodium perchlorate^{xiv}, Yb(OTf)₃^{xv}, Sc(OTf)₃^{xvi}, ceric ammonium nitrate (CAN)^{xvii}, bismuth nitrate^{xviii}, Triton X-100^{xix}, samarium chloride^{xx}, Zr(H₂PO₄)₂^{xxi}, ASA (alumina sulfuric acid)^{xxii}, PtNPs@GO^{xxiii}. SnCl₄ functionalized nano Fe as a heterogeneous catalyst with ultrasound^{xxiv}, and costly PdRuNi@GO^{xxv}.

Researchers are enthusiastic about the development of magnetic catalysts due to the fact that they can be effectively separated by magnetic decantation following the reaction, improving reusability^{xxvi-xxviii}. Therefore, this idea holds great potential for the creation of sophisticated catalysts with higher selectivity and activity. Consequently, a novel class of nanocatalysts known as MNPs has surfaced^{xxvii, xxix} in catalysis and medicine research areas, MNPs are among of the most promising materials. MNPs of Fe are a major and efficient substitute for traditional heterogeneous catalytic supports because of their magnetic properties. These

characteristics make it easier to separate the catalyst after the reaction is complete. Nano-Fe are inexpensive, easily prepared, readily available, chemically stable, and have low toxicity. We developed a low-cost, reliable, and effective heterogeneous cadmium-doped-iron magnetic nanocatalyst that has been used in multicomponent synthesis with excellent activity as part of our ongoing research into environmentally friendly chemical processes for the synthesis of acridine derivatives. (Scheme I)



Scheme I: General synthesis of tetra hydro aryl acridine

EXPERIMENTAL:

The experiment was conducted using only AR-Grade chemicals from SD Fine Ltd., loba, etc. Using CDCl₃ as the solvent, a 500 MHz machine was used to gather 1-H nuclear magnetic resonance (NMR) spectra. Chemical shifts were represented as parts per million (ppm) values in relation to the solvent. On silica-coated aluminum plates, thin layer chromatography (TLC) was carried out and observed through an ultraviolet chamber. All solvents were used without purification unless otherwise indicated in the techniques below, and no steps were taken to remove ambient moisture. Glassware was dried in an oven at 90 °C for at least one hour before use. With Shimadzu's muffle furnace, the catalyst was calcined at 500°C.

GENERAL PROCEDURE:

General Procedure for Synthesis of Acridinone Derivatives:

A mixture of Aromatic aldehyde (1 m mol), Dimedone (2 m mol), and ammonium acetate (1 m mol), Cd-Doped-Fe MNPs (1.5 mg 1 % w/w) catalyst with ethanol as solvent was stirred magnetically at reflux and Thin-layer chromatography (TLC) was used to track the reaction's progress (45 min). The reaction mixture was hot-filtered after 45 minutes and concentrated to ¼th volume followed by cooling to get tiny needle-shaped crystals which were collected by filtration. Following the standard workup, the product showed satisfactory spectral data such as IR, and ¹H-NMR.

Preparation of Cd-doped-Fe Nano Catalyst

Preparation of Cd-doped-Fe MNPs catalyst done with the help of Iron Nitrate (1.596 gm.) as a source of Fe ion with Cadmium nitrate (0.332 mg) as a source of Cd ion and calculated amount of glycine along with L-Ascorbic Acid has taken in a minimum amount of de-ionized water. It is heated on a hot plate at 80°C in order to get homogenized gel, after the removal of excess water and further heating gel gets swallowed and releases brownish gases within 2-3 seconds. Finally, the powder was calcined for four hours at 500°C in a muffle furnace. The resultant crystalline powder (1.43 gm.) of the Cd-doped-Fe MNPs catalyst has the average particle size (1.72 nm). Characterization of nanomaterial was done with FE-SEM, TEM, XRD, EDAX and IR.

ANALYTICAL DISCUSSION:

Entry 1: - **3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-9-(4-nitrophenyl) acridine 1,8(2H,5H,9H,10H)-dione**

• **IR (KBr) (cm⁻¹):** 1600(Ar-C=C), 1490(-NO₂), 1701(CO), 3200(-NH) singlet, 1195 (Ar C-N stretching)

- **$^1\text{H NMR}$** : (500MHz, CDCl_3): $\delta = 1.0$ (s, 12H, $-\text{CH}_3$), 1.9 (s, 4H, $-\text{CH}_2$) ; 2.4(s, 4H, $-\text{CH}_2\text{CO}$); 4.2((s, 1H, $-\text{CH}$); 5.1(s,-NH); 7.4(d,2H,Ar-H); 8.1 (d, 2H, Ar-H)

Entry 3 : 3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-9-(3-nitrophenyl)acridine-1,8(2H,5H,9H,10H)-dione

- **IR (KBr): (cm^{-1}):** 1614(Ar-C=C), 1486($-\text{NO}_2$), 1697 (CO), 3291(-NH) singlet, 1170 (Ar C-N stretching)

- **$^1\text{H NMR}$ (500MHz, CDCl_3):** $\delta = 1.0$ (s, 12H, $-\text{CH}_3$), 1.7 (s, 4H, $-\text{CH}_2$) ; 2.3(s, 4H, $-\text{CH}_2\text{CO}$); 4.0((s, 1H, $-\text{CH}$); 5.9(s,-NH); 7.2(dd,1H,Ar-H); 7.5(d,1H,Ar-H); 7.7 (d, 2H, Ar-H),

Entry 5 : 9-(4-chlorophenyl)-3,4,6,7-tetrahydro-3,3,6,6-tetramethylacridine-1,8(2H,5H,9H,10H)-dione

- **IR (KBr): (cm^{-1}):** 1608(Ar-C=C), 1489($-\text{NO}_2$), 1698(CO), 3278(-NH) singlet, 1168 (Ar C-N stretching)

- **$^1\text{H NMR}$: (500MHz, CDCl_3):** $\delta = 1.1$ (s, 12H, $-\text{CH}_3$), 2.0 (s, 4H, $-\text{CH}_2$) ; 2.8(s, 4H, $-\text{CH}_2\text{CO}$); 4.0((s, 1H, $-\text{NH}$); 5.4(s,-CH); 7.2(d,2H,Ar-H); 7.4 (d, 2H, Ar-H),

Characterization of Catalyst

The powder XRD patternv(fig.1) of the sol-gel-prepared Cd-doped-Fe Nanocatalyst showed that a single-phase product was produced and the crystallite size (1.72 nm) was determined from the broadening diffraction peak using Scherrer's equation.

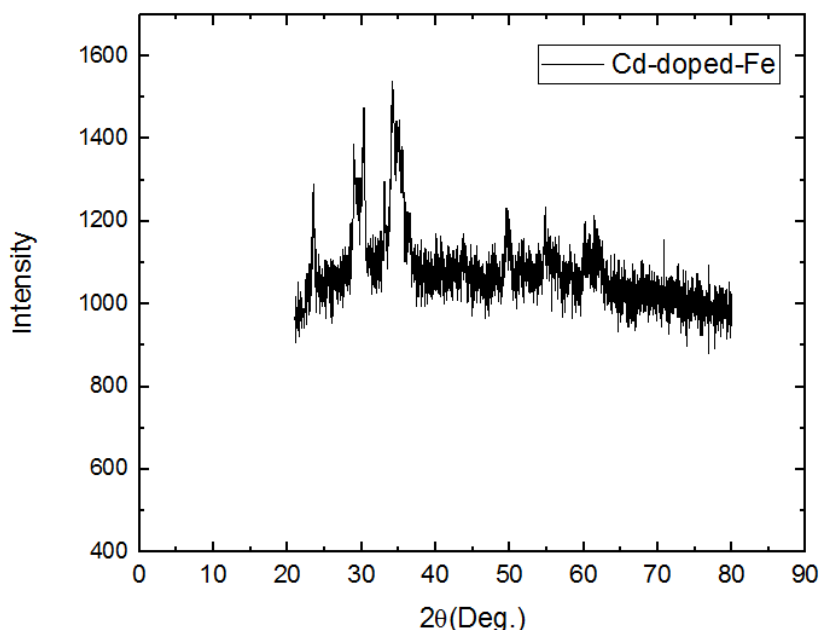


Fig.1 -XRD pattern Of Cd-Doped-Fe Nano Catalyst

FTIR spectra (fig.2) of Cd-doped-Fe Nano catalyst was in the range of $450\text{-}4000\text{ cm}^{-1}$ wave number which shows characteristic peak at 535 cm^{-1} described Fe-O stretching band which show the formation of Fe-O and peaks at 859 cm^{-1} revealed the formation of Cd-O with the peaks at 1434 cm^{-1} respect to asymmetric bending vibration of CO, absence of broad peak in the range of $3200\text{-}3600$ shows catalyst is stable to moisture.

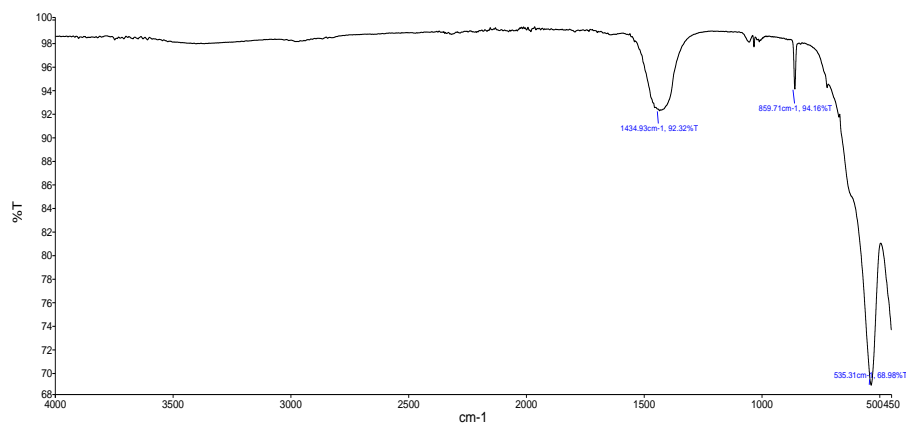
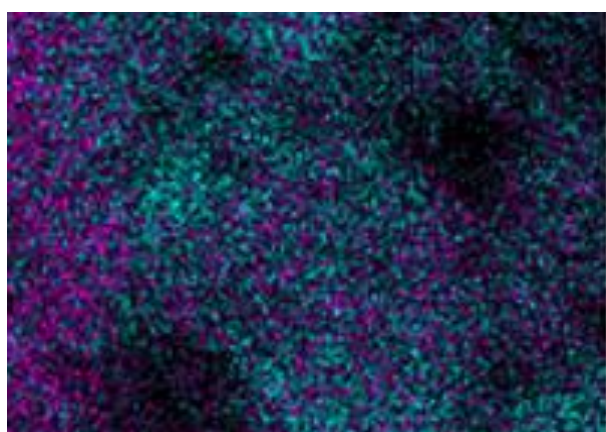
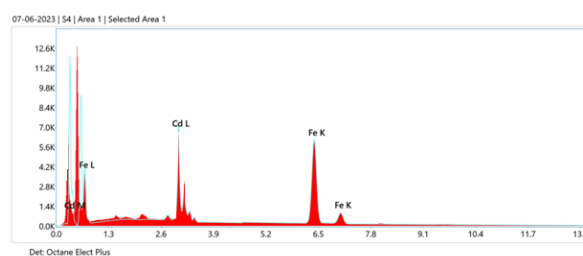


Fig.1 IR of Cd-Doped-Fe Nano Catalyst

The Energy Dispersive X-ray (Fig.3) of the developed catalyst reveals the existence of Cadmium, Iron, uniform distribution of cadmium and Iron nanoparticles in lattices, and Cadmium doping into Iron lattices with a percentage composition of Cadmium 16.8% and Iron 83.2. The expectation was 84% Iron and 16% Cadmium based on the charged quantity of Iron nitrate (5 gm) and Cadmium nitrate (1 gm), which matched the outcome of the EDAX analysis.



A



B

Fig.3 EDAX of Cd-Doped-Fe MNPs

As shown in Fig.4 the particle distributions, surface morphology, and particle shape of manufactured Cd-Doped-Fe nanoparticles were determined using the field emission scanning electron microscopy technique. According to the FE-SEM image, the following doping was accomplished with the porous fibrous material with a large surface area. This is because Cadmium (0.16 nm) is greater in size than Iron (0.126 nm). Doped nanoparticles have a smaller average size and a greater metal surface area. The FE-SEM image also depicts nanoparticles in doped particles ranging in size from 10 to 60 nm.

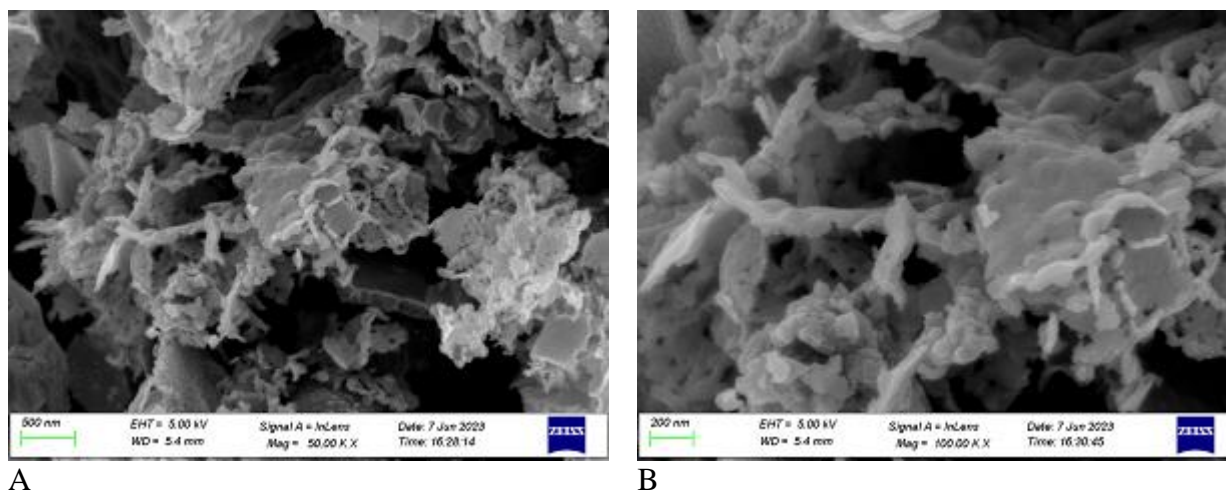


Fig.4- FE-SEM of Cd-Doped-Fe MNPs at different magnificence

Figure 5 depicts TEM images of doped materials. The crystalline Cd-doped-Fe nanoparticles are shown in Figure 5a. The average particle size of cadmium-doped-Fe nanoparticles was found to be 10-50 nm. This value corresponds to the average particle size determined by XRD and FE-SEM analysis. Because Cd doping reduces particle size while increasing particle surface area, more particles become involved in the chemical process. Figure 5b depicts the SAED pattern of cd-doped Fe nanoparticles. The SAED pattern with brilliant circular rings corresponds to the creation of the FCC structure of metallic Cd doped Fe with nanosize particles.

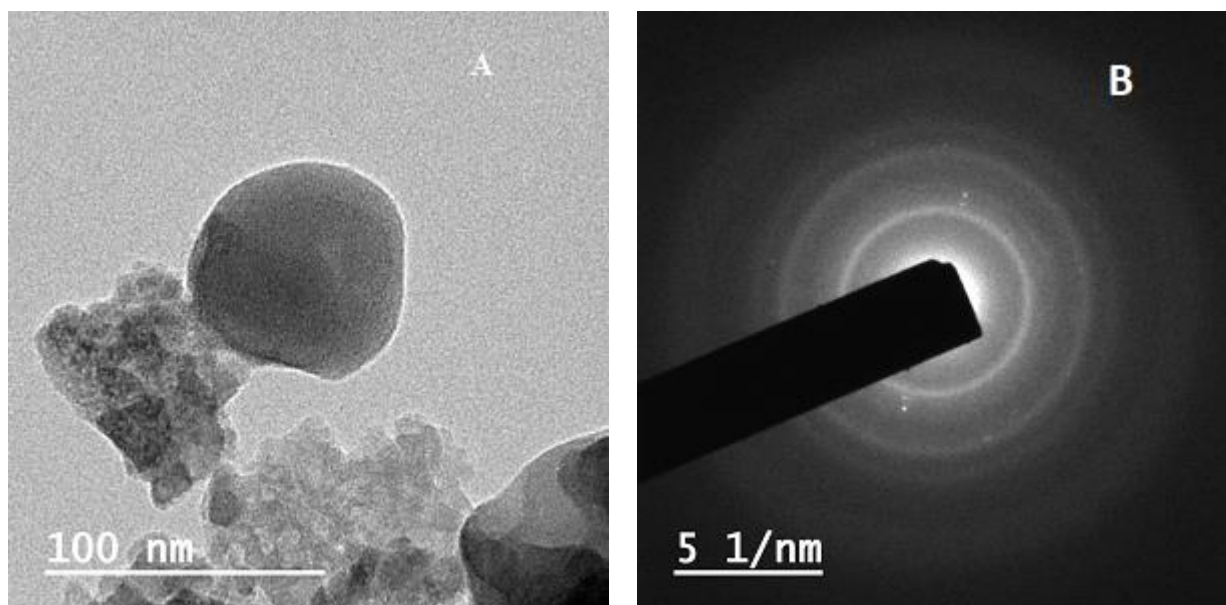


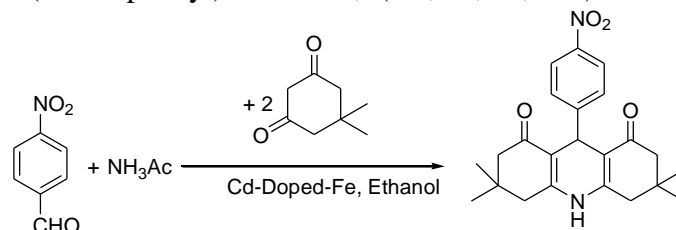
Fig.5- TEM of Cd-Doped-Fe MNPs at different magnificence

RESULTS AND DISCUSSION:

As a preliminary step towards optimizing the reaction conditions, we conducted a reaction involving para-nitrobenzaldehyde, 2-mole equivalent dimedone, and ammonium acetate (Scheme 1). On the model reaction, the impact on several reaction parameters

including catalyst dopant composition, catalyst loading, solvent, temperature, and time was examined.

Table -1 Screening the reaction parameters for the synthesis of diethyl 3,4,6,7-tetrahydro-3,3,6,6-tetramethyl-9-(4-nitrophenyl)acridine-1,8(2H,5H,9H,10H)-dione



The standard model reaction

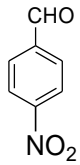
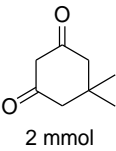
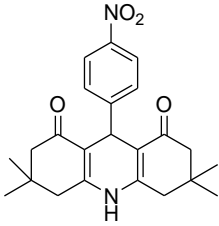
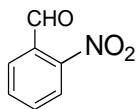
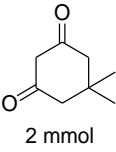
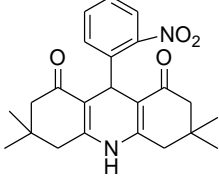
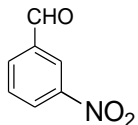
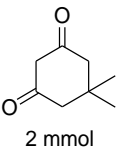
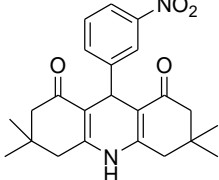
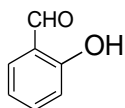
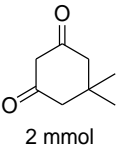
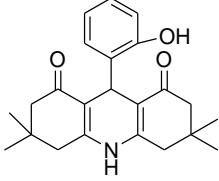
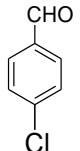
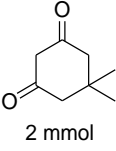
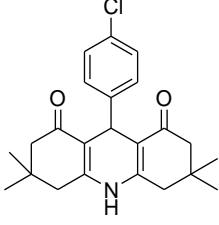
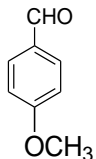
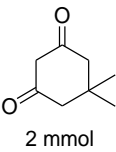
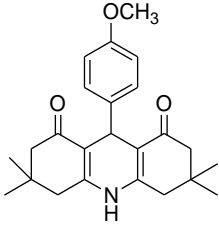
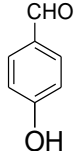
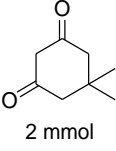
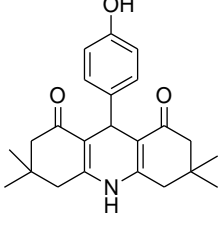
Entry	% of Cd (w/w)	Cd catalyst (mg)	solvent	Temp. °C	Time (min)	Yield ^b (%)
1	8	1.5	C ₂ H ₅ O H	Reflux	60	70
2	24	1.5	C ₂ H ₅ O H	Reflux	35	85
3	16	1	C ₂ H ₅ O H	Reflux	45	75
4	16	2	C ₂ H ₅ O H	Reflux	30	92
5	16	2.5	C ₂ H ₅ O H	Reflux	35	92
6	16	1.5	THf	65	60	60
7	16	1.5	CH ₂ Cl ₂	40	60	82
8	16	1.5	CHCl ₃	Reflux	60	75
9	16	1.5	Et ₂ O	Reflux	60	35
10	16	1.5	DMF	80	60	72
11	16	1.5	C₂H₅O H	Reflux	25	92
12	16	1.5	C ₂ H ₅ O H	25	120	55
13	00	1.5	C ₂ H ₅ O H	25	120	75

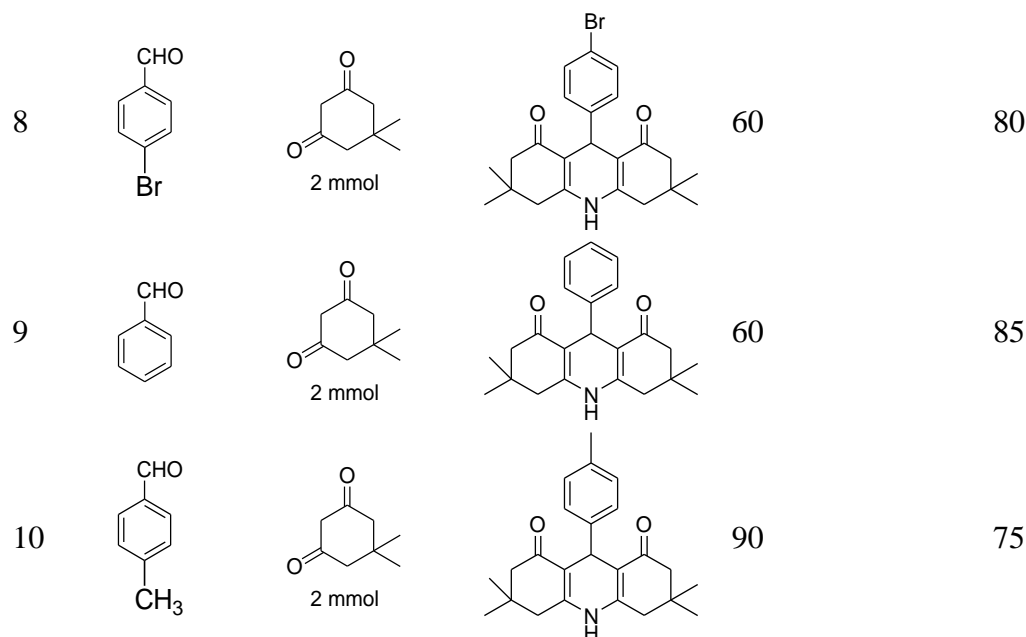
^a Condition; para nitro benzaldehyde (1 mmol), Ethyl aceto acetate (2 mmol), Solvent (2 ml), ammonium acetate (1.2 mmol)

^b Isolated pure yield

According to experimental results summarized in Table 1, the reaction was carried out in the presence of ethanol at reflux with a catalyst loading of 1.5 mg, and this combination produced the best results in terms of reaction time and yield of the product diethyl 1,4-dihydro-2,6-dimethyl-4-(4-nitrophenyl)pyridine-3,5-dicarboxylate (table 1, entry 11). The yield remained unchanged even after raising the catalyst concentration further. Furthermore, we performed the reaction with various dopant Cadmium composition percentages and found that a 16% w/w composition gave an outstanding yield. The reaction without dopant gives comparatively less yield (table 1, entry 13)

Table- 2. . Synthesis of Acridine derivatives in the presence of Cd-Doped-Fe MNPs catalyst with various aldehydes and 1,3-Dimidone^a

Entry	Aldehyde	1,3- diketone	product	Time (min)	m.p.	Yield ^c
1 ^c		 2 mmol		45		92
2		 2 mmol		90		80
3 ^c		 2 mmol		60		90
4		 2 mmol		90		75
5 ^c		 2 mmol		60		78
6		 2 mmol		90		75
7		 2 mmol		90		75



An aromatic aldehyde(1 mmol) and Ammonium acetate (1.1 mmol) reacted with dimedone (2 mol) in ethanol at reflux.

^b Isolated yields

^c All products were identified by their IR and ¹H NMR spectra

We prepared a wide range of Acridine derivatives by using a variety of aromatic aldehydes and using ideal reaction conditions. The results are summarized in Table 2. Aromatic aldehyde and ammonium acetate were treated with 2 mmol Dimedone (table -2 entry 1-10) in the presence of ethanol at reflux gives excellent yields. Sterically hindered reactants give considerable yield. (Table 2. Entry 2, 4)

CONCLUSION:

In conclusion, this paper presents an approach for synthesizing acridine derivatives using Cd-doped Fe MNPs as a powerful catalyst. The advantages include affordability, simplicity, catalyst recovery, and in-situ recrystallization of products without chromatographic purification in the reactions with high yields.

Recyclability of Catalyst

The easy recovery of the Cd-doped-Fe Nanocatalyst in model reaction, which results from its magnetically separable heterogeneity, has proven its recyclability. Up to eight cycles, the catalyst was shown to produce a product with a tiny reduction in catalytic activity (Figure 6).

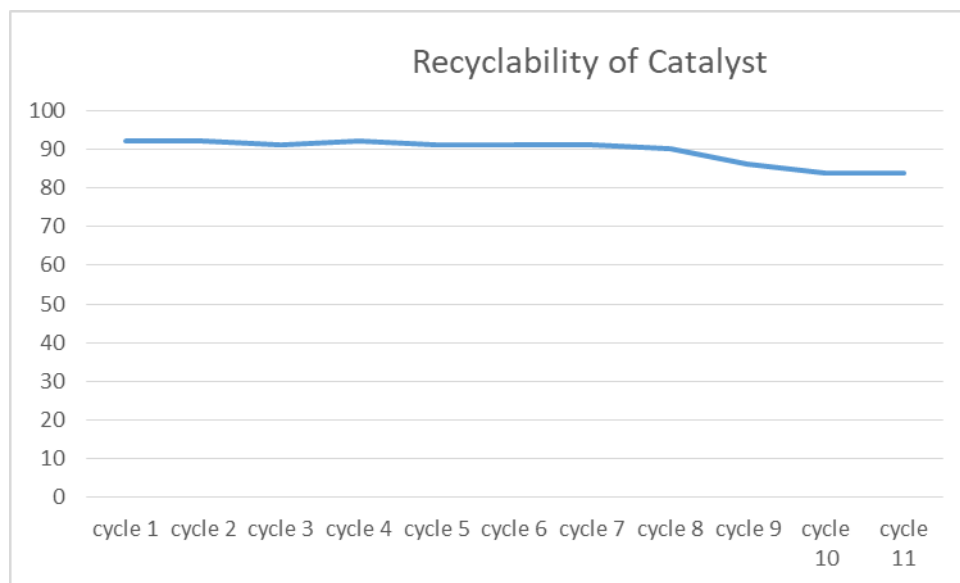


Fig. 6-Recyclability of catalyst

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