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SYNTHESIS OF SUBSTITUTED PYRROLIZIDINE ALKALOID DERIVATIVES USING MAGNETICALLY SEPARABLE $NiFe_2O_4$ NANOPARTICLES

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ABSTRACT:
A series of Pyrrolizidine alkaloid derivatives were synthesized by multicomponent reaction of Malononitrile, substituted aryl aldehydes and 2-Thiohydantoin/Hydantoin in the presence of magnetically Nickel-ferrites nanoparticles and Ethanol:Water(1:1) as a solvent under reflux condition. Nickel ferrite can be recovered easily using an external magnetic field and reused four times with unaltered catalytic activity, making them efficient. These catalysts can have a wide range of applications due to their efficiency, ease of handling, and cost effectiveness.

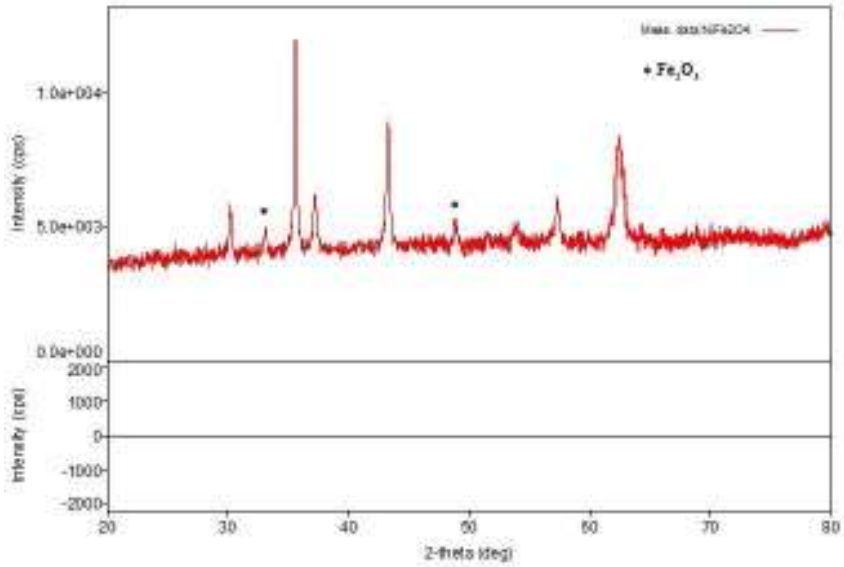
1.INTRODUCTION
The biological activity of hydantoin and 2-thiohydantoin derivatives has been known for a long time. Hydantoins and their bi- and tricyclic derivatives are reported[I-II] to be an important class of biologically active molecules with broad medicinal[III-IV] applications.Hydantoin nucleus containing an active urea moiety is responsible for several biological activities such as antiarrhythmic, antihypertensive, antiviral, antineoplastic, anticonvulsant, anti-micobacterial, antiulcer, anti-inflammatory agents, as well as pesticides[V]. Additionally, 2-Thiohydantoin derivatives have been identified as molecules which can have a wide range of applications as fungicides and herbicides[VI]. Pyrrolizidine alkaloids consist of a number of natural products which have been used in many studies. They have various biological applications in the treatment of cancer, diabetes, and viral infections such as HIV[VII]. The pyrrolizidine alkaloids (PAs) are regarded as typical secondary metabolites that illustrate the chemically mediated plant-herbivore interactions. Due to biological activities of PAs they have been a target molecule for synthesis over the last few decades.
In the light of the current paradigm shift to “Green Chemistry”,Nickel Nanoparticles provides a powerful way to do synthetic chemistry. It provides many chemical reactions with attributes, such as enhanced reaction rates, higher yields of pure products, and eco-friendly method of synthesis is an added advantage[VIII-XI].The conventional synthesis involves three component reaction between hydantoin, malononitrile and Aryl-aldehydes in water to obtain

(trans-7,7a)-5-amino-7-phenyl-1,3-dioxo-1H-pyrrolo[1,2-c]-imidazole-6-carbonitrile[XII] in the presence of piperidine as a base catalyst. This method suffers from the disadvantage of long reaction time. Thus using Nickel Ferrite is simple, clean, fast, efficient and economic for synthesis of organic molecules also Water:Ethanol mixture can be visualized as an elegant approach to achieve diverse molecular skeletons. The current work involves synthesis of 2-Azapyrrolizidine Alkaloid derivatives using Nanoparticles.

2. Results and Discussion

$NiFe_2O_4$ nanoparticles were synthesized by the citrate sol-gel method and the synthesized $NiFe_2O_4$ nanoparticles were characterized using powder X-ray diffraction (PXRD) and scanning electron microscopy (SEM).

X-Ray Diffraction



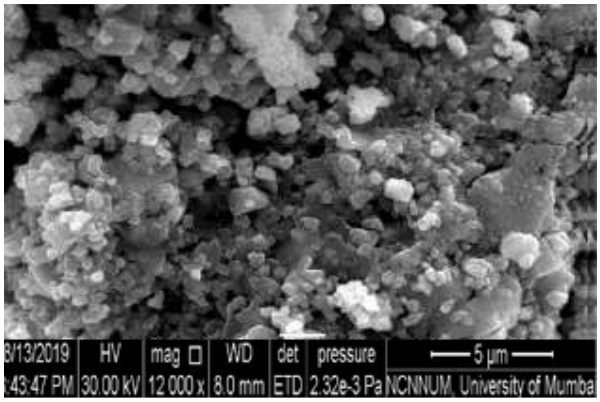
X-ray diffraction patterns of $NiFe_2O_4$ nanoparticles prepared by sol-gel method, calcined at 600 ºC

The sharp peaks appearing in the X-Ray diffractogram shows the fully crystalline phase of nickel ferrite ($NiFe_2O_4$) with well pronounced cubic spinel crystal structure. The main peak is centered at $2\theta = 35.6°$ and corresponds to the crystal plane with Miller indices (3,1,1) which is characteristic of $NiFe_2O_4$ cubic spinel. However, the sample showed some extra peaks. These peaks were indexed according to standard JCPDS Card No. 87-1166 and corresponded to the presence of hematite phase (α-Fe_2O_3).

The average crystallite size of the particles was calculated for $NiFe_2O_4$ sample using the high-intensity peak at $2\theta = 35.6°$ with the help of the Debye-Scherrer equation. The average crystallite size and the lattice strain were calculated to be 31.14 nm and 0.0038, respectively.

SEM

Scanning electron microscopy (SEM) was used to study the morphology of the synthesized $NiFe_2O_4$ samples. Fig. 2 shows SEM images of $NiFe_2O_4$ nanoparticles calcined at 600ºC



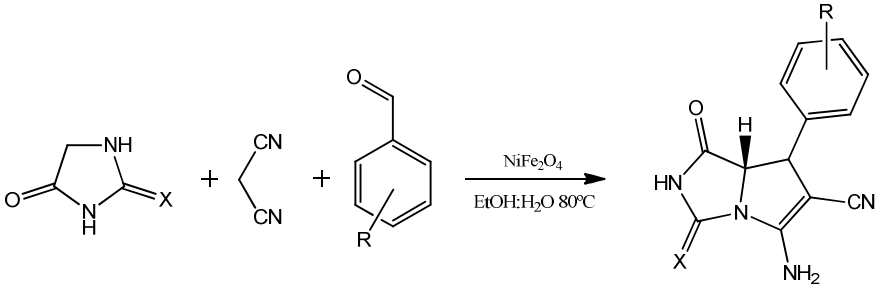
SEM image of $NiFe_2O_4$ nanoparticles prepared by sol-gel method, calcined at 600 ºC

The SEM image shows that the ferrite NPs consist almost uniform-sized particles and reveals that the particles are more or less spherical in shape. The particle size is in good agreement with the results obtained from X-ray analysis.

2.1. Project Strategy

A mixture of 2-Thiohydantoin/Hydantoin (6mmol)(**1**), substituted aldehyde (3 mmol) **(3)**, and malononitrile (3mmol) **(2)**, in Ethanol:Water(1:1)(10ml) aided by $NiFe_2O_4$(25mol%).

The reaction was monitored by TLC. Upon completion, catalyst was separated with the help of magnet, the reaction mass was cooled to room temperature. The solid thus obtained, was filtered, washed with hot water and ethanol, then recrystallized from alcohol to afford pure compound



1 **2** **3** **4**

Fig 5.1 *MCR for synthesis of Azapyrrolizidine Alkaloid*

2.2. Solvent Screening

The effect of several solvents on the yield of the reaction was studied (**Table 1**). The results showed that ethanol gave the best yield.

Table 1 *Effect of solvents on the yield of the reaction.*

Sr.No.	Solvent	Yield of product (%)	Time (min)
1	**EtOH:H_2O(1:1)**	**92***	**35**

2	EtOH	85	40
3	MeOH	82	70
4	DMF	63	180
5	DMSO	67	180

Reaction conditions: *Benzaldehyde (3mmol), and Malononitrile (3mmol)), imidazolidine-2,4-dione (6mmol) $NiFe_2O_4$ (20 mol%), Reflux condition.*

2.3. Catalyst Quantity

Quantity of $NiFe_2O_4$ catalyst was varied and it was found that 25 mol% of the catalyst gave the best yields. Further increase in concentration of catalyst did not show any improvement in the yield of the product. We also found that the catalyst could be reused multiple times after washing, without any loss in catalytic activity**.**

Table 2 *Optimization of catalyst quantity for the reaction*

Sr. No.	**Catalyst quantity (mol%)**	**Time (min)**	**Yield of product (%)**
1	Without catalyst	50	No reaction
2	05	50	66
3	10	50	72
4	15	50	80
5	20	50	86
6	**25**	**50**	**92***
7	30	50	92

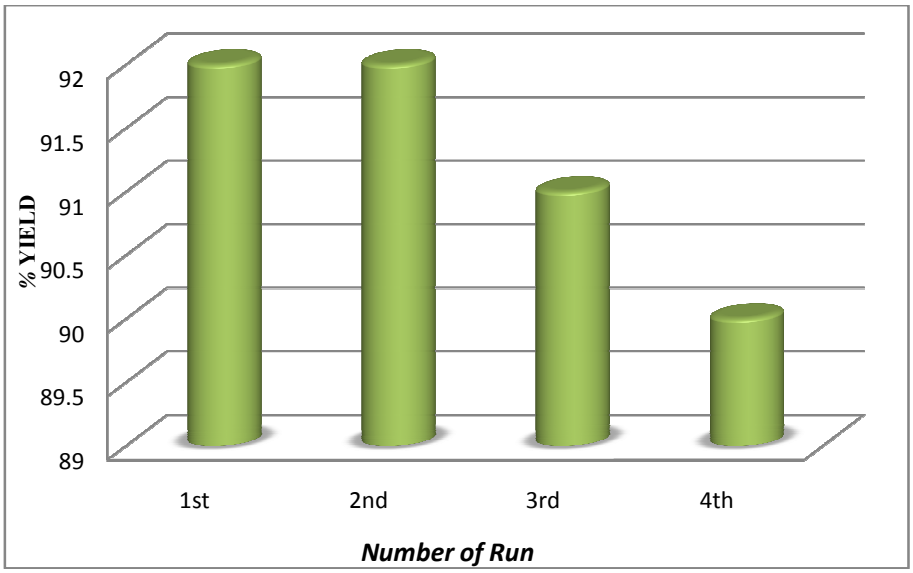
Reaction conditions: *Benzaldehyde (3mmol), Malononitrile (3mmol), imidazolidine-2,4-dione (6mmol) , solvent (10ml), under reflux condition 80℃.*

***** *The reaction gave 92% yield after 35 mins. However, the reaction time was extended to observe any significant increase in the yield.*

2.4. Reusability of Catalyst

After completion of the reaction, the catalyst was easily removed by using an external magnet, leaving the reaction mixture. After each run, the catalyst was washed with Hot ethanol, dried and used directly in the next cycle. The nano-sized $NiFe_2O_4$ catalyst could be reused at least 4 times without any considerable change in its activity. (**Table 4.3)**

Table 4.3 : *Reusability of catalyst*



2.5. Preparation of library of 2-Azapyrrolizidine Alkaloid derivatives

After optimizing the solvent and catalyst quantity, variety of aromatic aldehydes were allowed to react with malononitrile and imidazolidine-2,4-dione derivatives to check the viability of this protocol in obtaining a library of 2-Azapyrrolizidine Alkaloid (**Table 4.4**)

Table 4.4 *Synthesis 2-Azapyrrolizidine Alkaloid derivatives*

SR NO.	R	X	Product	Yield (%)	Time (min)	Melting Point (C°)
1	C_6H_5-	O	**4a**	92	35	267-269
2	2-ClC_6H_4-	O	**4b**	90	30	271-273
3	4-ClC_6H_4-	O	**4c**	89	30	276-279
4	4-$MeOC_6H_4$-	O	**4d**	90	35	257-259
5	3-$MeOC_6H_4$-	O	**4e**	87	30	256-258
6	3-$NO_2C_6H_4$-	O	**4f**	90	30	267-269
7	4-$MeOC_6H_4$-	S	**4g**	88	38	264-266
8	C_6H_5-	S	**4h**	89	37	242-246

3. Conclusion

From the above observations, it was concluded that, this three component reaction worked efficiently by adding 25 mol% $NiFe_2O_4$ catalyst with ethanol as the solvent under reflux conditions. After the optimization of the reaction conditions, the scope and efficacy of this reaction was studied by using other substituted aromatic aldehydes containing both electron-withdrawing (nitro, chloro) and electron-donating (methoxy) groups in ortho and para positions, and it was observed that all the compounds reacted effectively to give desired product of 2-Azapyrrolizidine Alkaloid in good to excellent yields.

4. Experimental section

4.1 Synthesis of 5-amino-7-(4-phenyl)-2-thioxo-1,2,3,7-tetrahydropyrano[2,3-d]imidazole-6-carbonitrile (4) :

In a 50 mL RB flask, a mixture of aromatic aldehyde (3 mmol) **(3)**, malononitrile (3 mmol) **(2)**, and catalytic amount of $NiFe_2O_4$ (25 mol%) in ethanol (10 mL) was allowed to stir for few minutes. To this, imidazolidine-2,4-dione derivatives (6 mmol) **(1)** was added and the resultant mixture was refluxed with stirring for the specific time for different aldehydes as mentioned in **Table 4.4** The progress of reaction was monitored by TLC. After completion of the reaction, the catalyst was easily removed by using an external magnet, the solid product obtained was washed with hot water ,then the reaction mixture was heated in order to dissolve the solid product formed and filtered. The catalyst was washed with hot water and ethanol. The filtrate was concentrated to obtain the solid product, which was filtered and recrystallized from hot ethanol. Purity of product was checked by TLC, M.P. and characterized by ^{1}H-NMR and ^{13}C-NMR.

(trans-7,7a)-5-amino-1,3-dioxo-7-phenyl-2,3,7,7a-tetrahydro-1H-pyrrolo[1,2-c]imidazole-6-carbonitrile 4a:

Molecular Wt: 254.54

Molecular Formula: $C_{13}H_{10}N_4O_2$

Description: White solid

IR (KBr) vmax : 3405, 3323, 3264, 2184, 1784, 1712, 1659, 1601 cm^{-1}

1H NMR (400 MHz, DMSO-d6): δ 4.35 (s, 2H), 7.31-7.39 (s, 2H), 7.41-7.62 (m,5H), 11.37 (s, 1H) ppm

13C NMR (100 MHz, DMSO-d6): δ = 48.5, 62.4, 71.4, 119.5, 127.7, 128.76, 129.2, 141.8, 155.5, 157.8, 174.9 ppm

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