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IN SITU RECRYSTALLIZED ECO-FRIENDLY MULTICOMPONENT SYNTHESIS OF BIOLOGICALLY ACTIVE TETRAHYDROBENZO [B] PYRAN DERIVATIVES USING NOVEL Ni-DOPED-Ag NANOCATALYST.

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ABSTRACT

An environmentally friendly, one-pot, in-situ recrystallized synthesis of tetrahydro benzo[b]pyran compounds was accomplished by reacting aromatic aldehydes, dimedone, and malononitrile with a new Ni-doped Ag nanocatalyst. Good to exceptional yields were obtained from the reaction, which took place in ethanol as the solvent under mild conditions. By eliminating the requirement for chromatographic purification of the products, in-situ recrystallization made workup easier.

KEY WORDS: Aldehyde, Malononitrile, Dimedone, Ni-doped-Ag Nano-catalyst, Tetrahydrobenzo[b]pyran derivatives, Multicomponent synthesis.

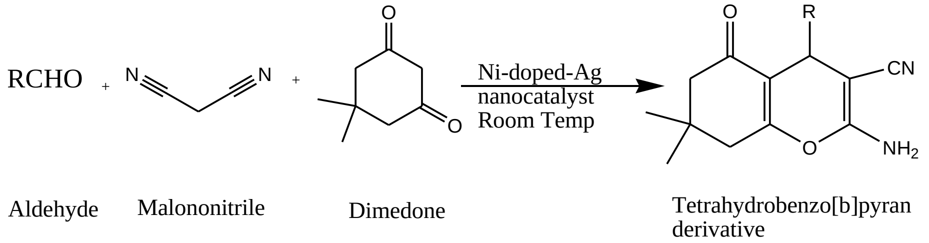
INTRODUCTION:

In recent years, multicomponent processes have drawn a lot of attention from researchers in the fields of organic substances, medicine, and related sciences. The advantages of carrying out these procedures in situ include reduced time, atom economy, improved product purity, operational flexibility, and adherence to green chemicals principles.[ii] The pharmacological and biological properties of tetrahydrobenzo[b]pyrans, which include diuretic, spasmolytic, anticoagulant, anticancer, and anti-anaphylactic effects, make them a significant class of organic chemicals. As cognitive stimulants, they have also demonstrated promise in the treatment of neurological and neurodegenerative conditions, including myoclonus, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, dementia associated with AIDS, Down syndrome, and schizophrenia.[ix]

Polysubstituted tetrahydrobenzo[b]pyrans constitute a key structural framework present in numerous natural products.[ix] Owing to the intrinsic reactivity of the pyran ring, these compounds serve as valuable intermediates in organic synthesis. [ix] Given their broad spectrum of biological and pharmacological activities, the synthesis of heterocyclic derivatives based on this scaffold holds considerable significance in both medicinal chemistry and synthetic organic chemistry. [ix] Several synthetic strategies have been reported, ranging from multi-step procedures to more efficient one-pot protocols. Among these, the one-pot, three-component condensation of malononitrile, an aldehyde, and dimedone under various conditions has emerged as a simple and widely used method. A variety of catalysts, including silica nanoparticles and 1,4-diazabicyclo[2.2.2]octane (DABCO)[ix], Sulfonic acid functionalized silica[xiii], trioctylmethylammonium chloride (Aliquat®336)[vii] , Co_3O_4 nano-flake[vi], Graphene Oxide Functionalized Organic-Inorganic Hybrid (GO–Si–NH_2–PMo)[i], $LaMnO_3$ Supported Ionic Liquid[viii] , Amines[xii] , Copper Doped Iron Tartarate [xi], Tetrabutylammonium Bromide[iv], iodine/DMSO system[iii], KF/Basic Al_2O_3 Under Ultrasound Irradiation[v], [(diacetoxyiodo)benzene] (DIB)[x] have been employed to promote this transformation effectively.

In this study, we investigated the role of a Ni-doped-Ag nanocatalyst in promoting the condensation reaction between aldehyde, malononitrile, and dimedone. The catalyst exhibited excellent compatibility with the reaction components, facilitating smooth progression to completion within a reasonable timeframe. Importantly, the reaction proceeds efficiently under mild conditions, without the need for chromatographic separation.

This study emphasizes the potential of Ni-doped Ag nanocatalysts in the efficient synthesis of tetrahydrobenzo[b]pyran derivatives, offering useful insights for researchers seeking novel synthetic strategies for these compounds.



Scheme 1: - Synthesis of Polysubstituted tetrahydrobenzo[b]pyrans

EXPERIMENTAL:

METHOD OF SYNTHESIS OF Ni-DOPED-Ag NANO-CATALYST:

The Ni-doped Ag nanocatalyst was synthesized by reacting 5.0 g of silver nitrate and 1.0 g of nickel nitrate with a calculated amount of glycine and L-ascorbic acid in a minimal volume of distilled water. In this process, silver nitrate serves as the source of silver ions, while nickel nitrate provides nickel ions. The resulting reaction mixture was heated on a hot plate at 80 °C. Continued heating led to the formation of a homogeneous gel as the excess water evaporated. Upon further heating, the gel swelled, and brownish gases were released within 2–3 seconds. The resulting powder was subsequently calcined at 500 °C in a muffle furnace for approximately 4 hours. The final crystalline powder obtained was the desired Ni-doped Ag nanocatalyst, with an average particle size of 33.08 nm. The synthesized nanocatalyst was characterized using XRD, SEM, TEM, EDAX and IR spectroscopy.

CHARACTERIZATION OF CATALYST:

The powder XRD pattern shown in figure 1 of the sol-gel generated by Ni-doped-Ag nano catalyst revealed that the product formed is single-phase and the crystallite sizes are calculated using Scherrer's equation from the broadening diffraction peak and is found to be 33.08 nm.

The Ni-doped-Ag Nano catalyst's FTIR spectra shown in figure 2 were in the range of 450–4000 cm^{-1}, and they revealed the formation of Ni–O and Ag–O stretching bands at 1400-1500 cm^{-1} and 600-700cm^{-1} respectively. The absence of broad peaks in the range 3200-3600 cm^{-1} indicates that the catalyst is stable to moisture.

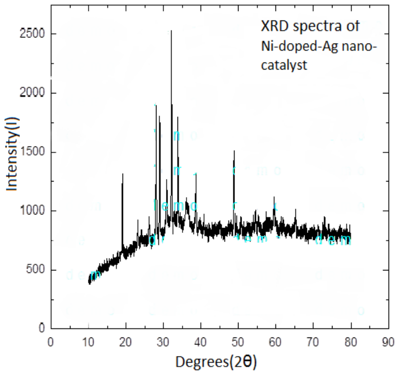


Figure 1: XRD spectra of Ni-doped-Ag nano-catalyst:

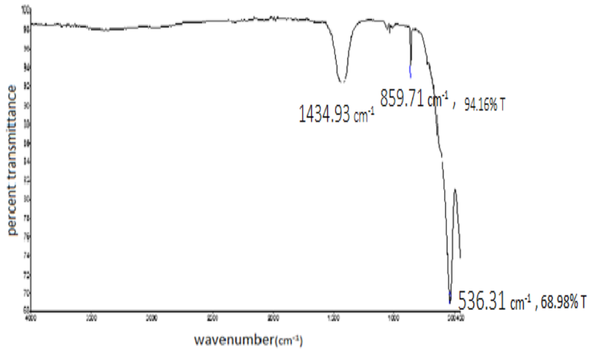
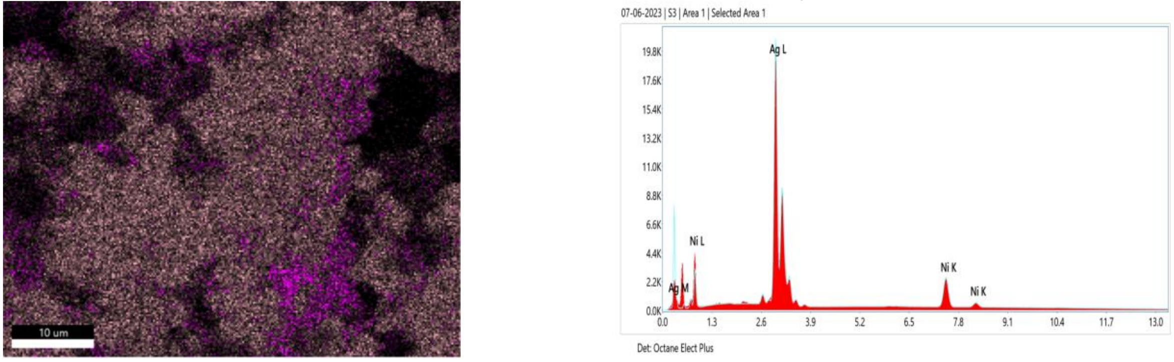


Figure 2: The Ni-doped-Ag Nano catalyst's FTIR spectra

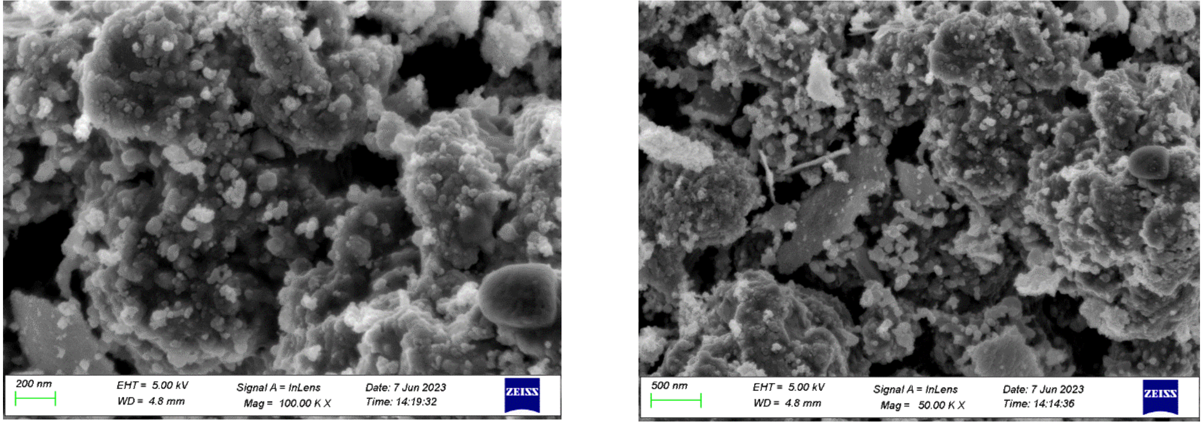
A uniform distribution of a nickel and silver nanoparticles in lattices, as well as nickel doping into silver lattice structures with a percentage composition of nickel 14% and silver 86%, are all visible in the Energy Dispersive X-ray (fig. 3) of the developed catalyst. Based on the charged quantities of iron nitrate (5 gm) and cadmium nitrate (1 gm), the expected results were 84% iron and 16% cadmium, which matched the EDAX analysis results.



A B

Fig. 3 EDAX of Ni-Doped-Ag MNPs

The field emission scanning electron microscopy technique was used to determine the particle patterns of distribution, surface morphology, and particle shape of manufactured Ni-Doped-Ag nanoparticles, as illustrated in fig. 4. The following doping was achieved using spherical deposition on silver cluster matter with a large surface area, as shown by the FE-SEM image. Nanoparticles in doped particles with sizes ranging from 10 to 60 nm are also visible in the FE-SEM image.



A B

Fig. 4 - FE-SEM of Ni-Doped-Ag MNPs at different magnificence

TEM pictures of doped materials are shown in Figure 5 displays the crystalline silver nanoparticles doped with nickel. It was discovered that nickel-doped silver nanoparticles had an average particle size of 10–50 nm. The average particle size as established by XRD and FE-SEM analysis is represented by this value.

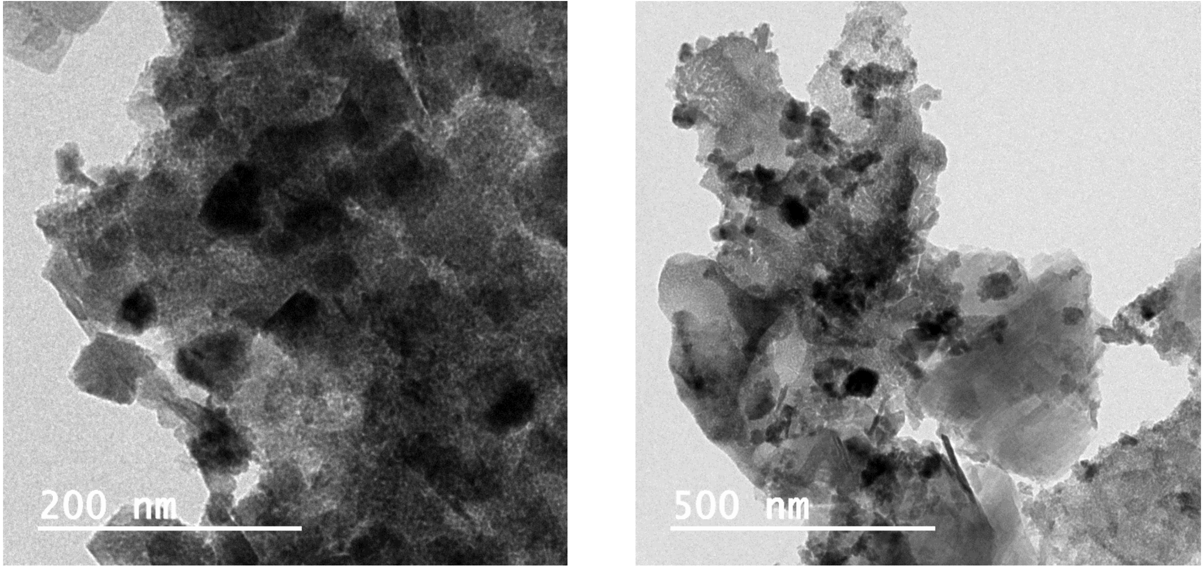


Fig. 5 - TEM of Ni-Doped-Ag MNPs at different magnificence

EXPERIMENTAL:

At the outset of our research, we selected benzaldehyde—a simple aromatic aldehyde—as the model substrate to monitor the progress of the reaction. The methodology employed is detailed below. In a round-bottom flask, a mixture containing benzaldehyde (0.0023 mol), malononitrile (0.0023 mol), and 5,5-dimethyl-1,3-cyclohexanedione (dimedone, 0.0023 mol) was combined with 0.025 g of Ag-doped Ni nanocatalyst (Scheme 1). To this mixture, 2 mL of ethanol was added as the solvent. The resulting reaction mixture was stirred magnetically at room temperature until the reaction reached completion, as monitored by thin-layer chromatography (TLC). After completion, the product dissolved in hot ethanol was filtered under hot conditions to separate the catalyst. The purity of the resulting compound was again confirmed via TLC. Evaporation of the solvent from the filtrate followed by cooling led to the isolation of the final product in solid form.

Following the successful reaction with benzaldehyde, various substituted benzaldehydes were subjected to the same reaction conditions. For each substrate, the reaction time and yield were recorded (Table 1). Notably, the nanocatalyst was successfully recovered and reused in subsequent reactions without significant loss of activity.

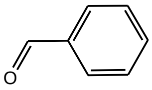
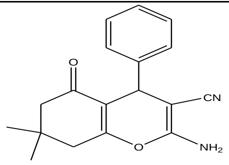
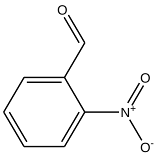
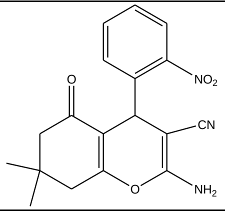
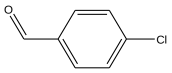
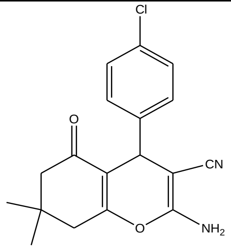
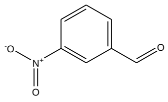
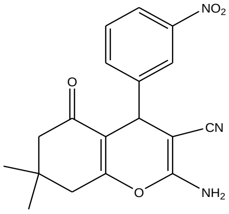
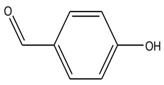
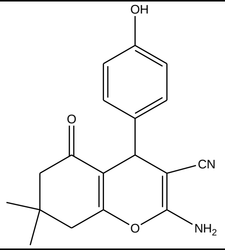
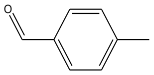
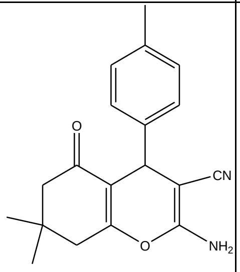
MATERIALS USED:

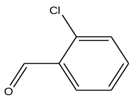
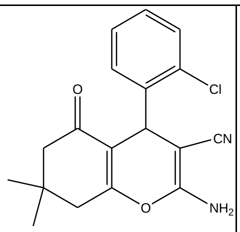
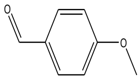
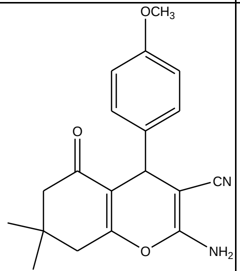
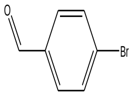
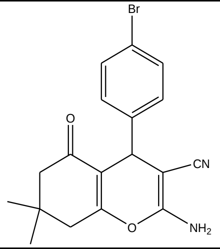
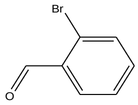
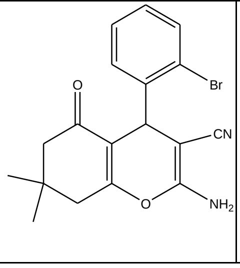
For the research work, different reagents and solvent used are all AR grade and they were made available by our institute K. L. E. College Kalamboli, Navi Mumbai.

Result and Discussions:

After completion of the experimental reactions outlined in Table 1, selected compounds were subjected to further structural analysis. The selected compounds from the prepared derivative were characterized by Infrared (IR) spectroscopy, proton nuclear magnetic resonance (^{1}H NMR), and carbon-13 nuclear magnetic resonance (^{13}C NMR) spectroscopy.

Table No. 1: - Preparation of Polysubstituted tetrahydrobenzo[b]pyrans derivatives

Sr. No.	Aldehyde	Product formed	Time (Min.)	Yield (%)	M. P. °C (observed)	M.P. °C (Reported)	References
1.			45	98.2	228-230	228-230	1
2.			30	94.5	214-216	212-214	6
3.			40	98	211-213	210-212	1
4.			35	95	178-179	177-178	1
5.			45	94	207-208	204-206	1
6.			50	96	221-223	220-222	7

7.			35	95	203-204	200-202	5
8.			45	98	197-199	198-200	1
9.			35	97	205-207	207-209	7
10.			30	98	233-235	-	-

The spectroscopic data obtained confirmed the successful formation of the desired products, consistent with the proposed reaction mechanism and expected structures. The IR spectra indicated the presence of characteristic functional groups, while the ^{1}H and ^{13}C NMR spectra provided detailed insights into the molecular framework of the synthesized compounds.
A summary of the key spectral data for selected compounds is presented below:

COMPOUND CHARACTERIZATION

1. 2-Amino-5, 6, 7, 8- tetrahydro-7, 7- dimethyl-5-oxo-4-phenyl-4H-chromene-3-carbonitrile

Molecular formula: ($C_{18}O_2N_2H_{18}$) (Table-1 Entry 1), Yield- g, (98.2%), M. P. (228-230), IR (KBr, cm^{-1}) : 3400, amine; 3200, methylene; 2900, methyl; 2250, nitrile; 1705, carbonyl; 1680, sp2 carbon; 1200 C-N; 1100, C-O-C; 750, monosubstituted benzene; ^{1}H NMR (500 MHz, DMSO) : δ [(S 3H 0.95), (S 3H 1.03), (S 2H 2.11), (S 2H 2.23),(S 2H 3.34),(S ^{1}H 4.17), (d 2H 6.97), (d ^{1}H 7.14), (t 2H 7.28)] ; ^{13}C NMR (500 MHz, DMSO): δ 27.25, 28.25, 32.25, 36.03, 40.30, 50.43, 58.78, 113.20, 120.16, 127.60, 128.77, 145.19, 158.95, 162.93, 196.08.

2. 2-Amino-5, 6, 7, 8-tetrahydro-4-(4-hydroxyphenyl)-7, 7-dimethyl-5-oxo-4H-chromene-3-carbonitrile

Molecular formula: ($C_{18}O_3N_2H_{18}$) (Table-1 Entry 5), Yield- g, (94%), M. P. (207-208), IR (KBr, cm^{-1}) : 3500, hydroxyl (broad); 3400, amine; 3200, methylene; 2900, methyl; 2250, nitrile; 1705, carbonyl; 1680, sp2 carbon; 1200 C-N; 1100, C-O-C; 750, p-substituted benzene; ^{1}H NMR (500 MHz, $CDCl_3$) : δ [(S 3H 0.94), (S 3H 1.02), (S 2H 2.07), (S 2H 2.25),(S 2H 3.44),(S 1H 4.07), (d 2H 6.94), (d 1H 6.98), (s 2H 9.27)] ; ^{13}C NMR (500 MHz, $CDCl_3$): δ 27.18, 28.88, 32.22, 35.14, 39.75, 50.47, 59.22, 117.12, 120.36, 132.55, 135.63, 156.42, 158.83, 163.76, 196.14.

3. 2-Amino-5, 6, 7, 8- tetrahydro-7, 7- dimethyl-4-(3-nitrophenyl)-5-oxo-4H-chromene-3-carbonitrile

Molecular formula: ($C_{18}O_5N_3H_{17}$) (Table-1 Entry 4), Yield- g, (95%), M. P. (178-179), IR (KBr, cm^{-1}) : 3400, amine; 3200, methylene; 2900, methyl; 2250, nitrile; 1705, carbonyl; 1680, sp2 carbon; 1550, nitro; 1200 C-N; 1100, C-O-C; 750, 680, m-substituted benzene; ^{1}H NMR (500 MHz, $CDCl_3$) : δ [(S 3H 1.08), (S 3H 1.11), (S 2H 2.25), (S 2H 2.47),(S 2H 2.52),(S 1H 4.53), (d 1H 7.25), (d 1H 7.45), 1H s 7.6 (s 2H 8.07)] ; ^{13}C NMR (500 MHz, $CDCl_3$): δ 27.61, 28.25, 32.25, 36.03, 40.30, 50.43, 61.67, 113.20, 117.32, 118.31, 122.35, 129.60, 134.63, 145.19, 148.25, 157.95, 162.40, 196.08.

4. 2-Amino-4-(4-chlorophenyl)-5, 6, 7, 8-tetrahydro-7,7-dimethyl-5-oxo-4H-chromene-3-carbonitrile

Molecular formula: ($C_{18}O_2N_2H_{17}Cl$) (Table-1 Entry 3), Yield- g, (98%), M. P. (211-213), IR (KBr, cm^{-1}) : 3400, amine; 3200, methylene; 2900, methyl; 2250, nitrile; 1705, carbonyl; 1680, sp2 carbon; 1550, nitro; 1200 C-N; 1100, C-O-C; 850-550, C-Cl; 750, p-substituted benzene; ^{1}H NMR (500 MHz,$CDCl_3$) : δ [(S 3H 1.02), (S 3H 1.14), (S 2H 1.70), (S 2H 2.20),(S 2H 2.26),(S 1H 4.38), (d 1H 7.16), (d 1H 7.26), (1H s 7.52) (s 2H 7.94)] ; ^{13}C NMR (500 MHz, $CDCl_3$): δ 27.62, 28.87, 32.20, 35.06, 40.64, 50.58, 63.03, 113.69, 130.06, 131.84, 132.99, 141.67, 158.26, 161.61, 195.03.

5. 2-Amino-5, 6, 7, 8-tetrahydro-7, 7-dimethyl-4-(2-nitrophenyl)-5-oxo-4H-chromene-3-carbonitrile

Molecular formula: ($C_{18}O_5N_3H_{17}$) (Table-1 Entry 2), Yield- g, (94.5%), M. P. (214-216), IR (KBr, cm^{-1}) : 3400, amine; 3200, methylene; 2900, methyl; 2250, nitrile; 1705, carbonyl; 1680, sp2 carbon; 1550, nitro; 1200 C-N; 1100, C-O-C; 700, o-substituted benzene; ^{1}H NMR (500 MHz, $CDCl_3$) : δ [(S 3H 0.97), (S 3H 1.07), (S 2H 2.09), (S 2H 2.17),(S 2H 2.44),(S 1H 4.82), (d 1H 7.25), (d 1H 7.31), (1H s 7.49), (s 2H 7,78)] ; ^{13}C NMR (500 MHz, $CDCl_3$): δ 27.58, 28.76, 30.62, 32.21, 40.46, 50.17, 61.21, 113.28, 118.21, 126.28, 127.92, 130.44, 132.77, 137.74,149.69, 154.31, 162.03, 195.85.

CONCLUSIONS:

The novel Ag-doped Ni nanocatalyst demonstrated excellent catalytic activity in the condensation reactions involving various substituted aromatic aldehydes, malononitrile, and dimedone, efficiently yielding tetrahydrobenzo[b]pyran derivatives. These heterocyclic compounds are known for their potential pharmacological applications, as discussed in the introduction. The reaction proceeded under mild conditions with a simple work-up protocol, offering high yields of pure products without the need for further purification. The catalyst showed broad compatibility with different aldehyde substituents and maintained its efficiency throughout the process. Given its effectiveness, reusability, and operational simplicity, the Ag-doped Ni nanocatalyst presents a promising option for green and sustainable synthesis of biologically significant compounds. Its applicability across a wide range of substituted aldehydes makes it a valuable tool in the development of diverse heterocyclic scaffolds.

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The author, Ms. Rupa Ranbahddur Bogati, gratefully acknowledges the invaluable guidance and continuous support of Assistant Professor Mr. Vaishnav throughout the course of this research work. Sincere thanks are also extended to the University of Mumbai for providing the opportunity and necessary resources to carry out this research.

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