

Multi-Doped ZrO₂ Nanomaterial Assisted Mechanochemical Synthesis Of Indole Derivatives

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We have successfully synthesized a series of substituted 2-phenylindole derivatives using Ni multi-doped ZrO₂ nanomaterials as an efficient heterogeneous catalyst. The target compounds were obtained by the condensation of acetophenone derivatives with phenylhydrazine under environmentally friendly, solvent-free conditions. These reactions were carried out using two approaches: conventional methods employing ethanol as a green solvent and a mechanochemical solvent-free grinding technique. Moreover, the Ni multi-doped ZrO₂ nanomaterials exhibited excellent stability and reusability, maintaining high catalytic efficiency over multiple reaction cycles. These findings confirm the catalyst's remarkable performance and its potential for sustainable and scalable synthesis of substituted indole derivatives.

Keyword: - mechanochemical, green method, nanomaterials.

Introduction:-

Indole and its derivatives are an important class of heterocyclic molecules in organic chemistry and the pharmaceutical sector.[1] Substituted indole derivatives, as a class of heterocyclic compounds, have been extensively investigated in organic synthesis because of their valuable biological and medicinal properties. Particular compounds have been shown to have antibacterial,[2] anti-inflammatory,[3, 4] anticoagulant, antifungal, and antiviral, and antitubercular, anticancer,[5] antimalarial, and anti-diabetic properties.[6] Thus, a recent area of particular interest is developing of new method for the synthesis of indole derivations.[7] Grinding has been recognized as an innovative green approach for performing chemical reactions, enabling high product yields without the need for solvents.[8]

Chemical reactions can be facilitated by crushing the reactant materials with a high-speed vibrating mill or by manual grinding with a mortar and pestle.[9] For case, ball milling procedure is regarded as one of the mechanical druthers of mortar and pestle. As a versatile technique for conducting rapid, secure, and environmentally friendly synthesis without the use of dangerous chemical solvents, mechanochemistry has attracted a lot of interest from organic chemistry

experts.[10] This approach relies on mechanical forces, grinding, and milling, to promote chemical reactions. In particular, mechanochemical techniques such as ball milling and grinding have proven highly effective for solid-phase processes, delivering notable advantages over conventional laboratory methods involving heating and stirring. Nanocatalysts are an important part of green chemistry because they make chemical processes more effective and long-lasting by having a high surface area-to-volume ratio and other special properties.

Thus, this study reports the applicability of Ni multi-doped ZrO₂ nanocomposites as catalyst for the synthesis of substituted indole. The study highlights the potential of multi-doped nanocatalysts in advancing sustainable heterocyclic synthesis.

In this study, we report the use of Ni multi-doped ZrO₂ nanocomposites as an effective heterogeneous catalyst for the synthesis of substituted indole derivatives. The investigation highlights the potential of multi-doped nanocatalysts to promote sustainable and efficient heterocyclic synthesis under both conventional methods and a mechanochemical solvent-free grinding method.

Experimental section

All chemical reagents were purchased from Loba Chem Pvt. Ltd. and Thermo Fisher Scientific India Pvt. Ltd. Thin-layer chromatography (TLC) was carried out on silica gel 60 F254 aluminum plates (0.25 mm thickness, Merck, Darmstadt, Germany) was used to monitor reaction progress, verify compound purity, and confirm uniformity of the synthesized products. Melting points were determined using open capillaries. Comparison of melting point values and spectral data with reported literature confirmed that the synthesized compounds correspond to known structures.

Preparation of catalyst system

The Ni, C, N, S multi-doped ZrO₂ catalyst (NiZr) was synthesized by adding ZrO(NO₃)₂ (1.0 mM) to a 0.1 mol L⁻¹ 100 mL HNO₃ solution. Polyethylene glycol-200 (1.0 mL) was then slowly dripped into the mixture, which was stirred for an hour. Next, a calculated amount of Ni(NO₃)₂·6H₂O was added based on the desired Ni:Zr ratio of 0.3%, 0.6%, or 1.0%, and the mixture was stirred for another hour. Thiourea (3 grams) was added and the mixture was stirred for two hours. The resulting homogeneous solution was dried in an open-air oven at 100°C for 12 hours, yielding a black residue that was subsequently calcined at 500°C for 3 hours to obtain a white powder of Ni, C, N, S doped ZrO₂. The synthesized Ni, C, N, S multi-doped ZrO₂ catalyst was characterized by X-ray diffraction analysis (XRD), TEM analysis, Scanning Electron Microscopy (SEM), X-ray spectroscopy (EDS) analysis, Fourier transform infrared spectroscopy (FT-IR), Diffuse reflectance spectroscopy (UV-DRS) analysis[11].

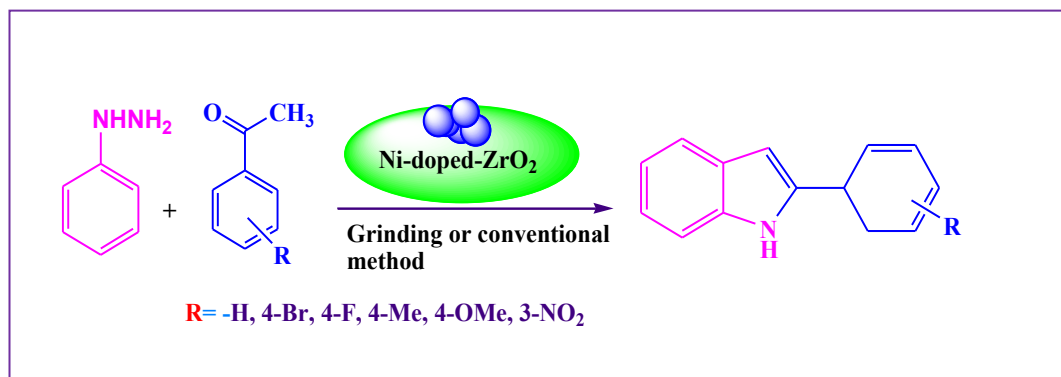
Conventional method for the synthesis of substitution indole.

A round-bottomed flask containing acetophenone (1 mmol), phenylhydrazine (1 mmol), a few drops of acetic acid, and 10 mL of ethanol was refluxed with stirring in the presence of a multi-doped Ni–ZrO₂ nanocatalyst in an oil bath maintained at 80–90 °C for 2–3 hours given in Table 1 (Scheme 1). Progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the catalyst was recovered by filtration and washed with ethanol. The

solvent was removed under reduced pressure to obtain desired product. The product was dried and recrystallized from suitable solvent.

Grinding method for the synthesis of substitution indole

A mixture of acetophenone (1 mmol), phenylhydrazine (1 mmol), 2–3 drops of acetic acid and 0.06 g of multi-doped Ni-ZrO₂ was crushed together in a mortar and pestle at room temperature for an appropriate duration, without using any solvents (Table 1, scheme 1). [11] The progress of the reaction was monitored using TLC. After completion of the reaction, the catalyst was recovered by filtration and washed with ethanol. The solvent was removed under reduced pressure to obtain desired product. The product was dried and recrystallized from suitable solvent.



Scheme 1. Synthesis of indole derivatives by using Ni multi-doped ZrO₂ nanocatalyst under conventional and grinding method

Optimization of the amount of multi-doped Ni-ZrO₂ nanocatalyst

The synthetic route for the preparation of aryl-substituted indole derivatives was explored using two different strategies. In the first method, conventional reflux was employed in ethanol as the reaction medium, while in the second method, a mechanochemical grinding procedure was utilized. In both procedures, acetophenone (1 mmol) and phenylhydrazine (1 mmol) were taken as the starting substrates and two to three drops of acetic acid were added as a catalyst promoter under ambient conditions. The influence of catalyst loading on the efficiency of the reaction was carefully studied and is summarized in Table 1. It was observed that the use of 0.06 g of the multi-doped Ni-ZrO₂ nanocatalyst afforded the most favourable outcome, delivering excellent yields of the desired indole derivatives within a relatively short reaction time (Table 1).

Table 1: Effects of the amount of catalyst on grinding and conventional methods.

Entry	Catalyst (g)	Grinding method		Conventional method	
		Time	yield%	Time	yield%
1.	0.02	55	75	60	70
2.	0.04	43	83	55	78
3.	0.06	30	94	45	90
4.	0.08	28	92	42	90
5.	0.10	28	92	40	88

Results and Discussion:-

In this study, acetophenone and phenylhydrazine were reacted in the presence of Ni multi-doped ZrO₂ nanocomposite catalysts to synthesize substituted indole derivatives using two distinct approaches: conventional heating and ball-milling. In typical experiments, the nanocatalyst was employed under both solvent-assisted and solvent-free conditions to obtain the target products. Reaction times and yields under each set of conditions are summarized in Table 2, highlighting the differences in efficiency and product formation observed between the two methodologies.

When using the conventional reflux method with ethanol as a green solvent, the presence of the nanocatalyst resulted in relatively longer reaction times but afforded higher yields of the desired indole derivatives. This suggests that while the traditional method is slower, it effectively drives the reaction toward completion. In contrast, the solvent-free mechanochemical grinding (ball-milling) approach significantly reduced the reaction time due to enhanced contact between reactants and catalyst. However, this method generally resulted in slightly lower yields of the final products. Overall, the comparative study demonstrates the trade-off between reaction speed and product yield, emphasizing the versatility of the Ni multi-doped ZrO₂ nanocatalyst under both conventional and green, solvent-free conditions.

Table2:Synthesis of indole derivatives using Ni multi-doped ZrO₂ nanocatalyst under both grinding and conventional methods.

Entry	Acetopheones	Conventional		Grinding		Melting Point °C	
		Time (min)	Yield %	Time (min)	Yield%	Found	Reported

1.	C ₆ H ₄ COCH ₃	45	90	30	92	187-188	188-190
2.	3-NO ₂ -C ₆ H ₄ COCH ₃	50	92	30	94	167-168	166-167
3.	4-F-C ₆ H ₄ COCH ₃	60	90	35	92	218-219	218-220
4.	4-Me-C ₆ H ₄ COCH ₃	56	88	45	94	172-173	172-174
5.	4-OCH ₃ -C ₆ H ₄ COCH ₃	50	90	42	92	220-222	220-221
6.	4-Br-C ₆ H ₄ COCH ₃	59	87	40	92	221-222	221-222

Furthermore, the results obtained from the reaction between acetophenone and phenylhydrazine in the presence of the multi-doped Ni–ZrO₂ catalyst were compared with several previously reported methods, as summarized in Table 3, to demonstrate the efficiency and broader applicability of this strategy. The comparative analysis shows that our protocol exhibits superior catalytic performance in terms of both reaction time and product yield. As indicated in Table 3, the multi-doped Ni–ZrO₂ nanocatalyst offers significant advantages over conventional catalytic systems, including reduced reaction times, environmentally benign operating conditions, and the feasibility of a solvent-free ball-milling (grinding) method. Notably, under reflux conditions, the reaction reached completion within just 45 minutes, affording yields that were comparable to, or even higher than, those reported in earlier studies employing ethanol or other alcohol-based solvents. Additionally, the structural stability of the doped nanomaterial under both thermal and mechanical stress ensures excellent reproducibility and consistent performance across varied experimental setups.

Table 3: Comparison of the current methods in relation to previously published methods

Entry	Nanocatysts	Solvent Condition	Energy Medium	Temp.in °C (room temp.)	Time (min.)	Yield (%)	Ref
1.	SBA-15-Pr SO ₃ H (2019)	EtOH	heat	Reflux	80	90	[12]

2.	[dsim] ₂ [ZnCl ₄]@HZSM-5 (2019)	-	heat	80	45	92	[13]
3.	Nano-Ce-W (2022)	EtOH	heat	80	120	99.8	[14]
4.	Ni-doped-ZrO ₂	-	Grinding	rt	30	92	This work
		EtOH	Heating	90	45	9	

Conclusion

Indole derivatives were synthesized using multi-doped Ni–ZrO₂ nanomaterials through a green, solvent-free grinding method at room temperature. Comparative studies showed that while both the grinding and conventional reflux methods effectively produced the desired products, the grinding approach provided notable benefits, including operational simplicity, shorter reaction times, and improved environmental sustainability. In contrast, the conventional method required solvents and longer reaction periods, reducing its overall eco-efficiency.

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Characterization data:-

The spectral (¹H NMR, ¹³C NMR, and MS) data of some representative indole are given below.

1. 2-Phenyl-1H-indole

Yellow crystals; m.p. 188°C–189.3°C ¹³C-NMR (CDCl₃); δ: 100.0, 110.9, 120.3, 120.7, 112.4, 125.2, 127.7, 129.9, 129.3, 132.4, 136.8, 137.9; ¹H NMR (300 MHz, CDCl₃); δ: 6.90 (1H, s), 6.99 (1H, t, J = 7.5 Hz), 7.10 (1H, t, J = 7.5 Hz), 7.3 (1H, t, J = 7.8 Hz), 7.41 (1H, d, J = 7.5 Hz), 7.46 (2H, t, J = 7.8 Hz), 7.51 (1H, d, J = 7.8 Hz), 7.54 (2H, d, J = 7.8 Hz), 7.71 (1H, s); HRES-MS m/z calcd for [M]⁺ C₁₄H₁₁N: 194.0970, found: 194.0961.

2. 2-(3-Nitrophenyl)-1H-indole

Dark yellow crystals; m.p. 170°C–171°C; ¹³C-NMR (CDCl₃); δ: 87.1, 111.7, 117.1, 118.5, 120.8, 123.3, 125.1, 130.2, 132.8, 138.7, 141.7, 146.5, 148.5, 161.0; ¹H NMR (300 MHz, CDCl₃); δ: 7.06 (1H, t, J = 7.8 Hz), 7.13 (1H, s), 7.16 (1H, t, J = 7.8 Hz), 7.40 (1H, d, J = 8.1 Hz), 7.57 (1H, d, J = 7.8 Hz), 7.73 (1H, d, J = 7.8 Hz), 8.19 (1H, d, J = 8.1 Hz), 8.52 (1H, d, J = 8.1 Hz), 8.53 (1H, s), 8.54 (1H, s); HRES-MS m/z calcd for [M]⁺ C₁₄H₁₁N₂O₂: 239.0821, found: 239.08082-

3. (4-Fluorophenyl)-1H-indole

Dark green crystals; m.p. 173.2°C–174°C; ¹³C-NMR (CDCl₃); δ: 99.2, 111.8, 116.2, 116.5, 120.0, 120.6, 122.2, 127.4, 127.5, 129.1, 137.2, 137.69; ¹H NMR (300 MHz, CDCl₃); δ: 6.87 (1H, s), 6.99 (1H, t, J = 7.5 Hz), 7.09 (1H, t, J = 7.5 Hz), 7.31 (2H, dd, J = 9.0, 9.0 Hz), 7.38 (1H, d, J = 7.5 Hz), 7.53 (1H, d, J = 7.5 Hz), 7.73 (2H, dd, J = 9.0, 5.4 Hz), 8.29 (1H, s); HRES-MS m/z calcd for [M]⁺ C₁₄H₁₁FN: 212.0876, found: 212.0865.

4. 2-(4-Methylphenyl)-1H-indole

Yellow crystals; m.p. 220°C–221°C; ¹³C-NMR (CDCl₃); δ: 21.0, 98.2, 111.3, 119.5, 120.0, 121.5, 125.0, 128.8, 129.5, 129.6, 136.9, 137.1, 137.9; ¹H NMR (300 MHz, CDCl₃); δ: 2.45 (3H, s), 6.83 (1H, s), 6.98 (1H, t, J = 7.8 Hz), 7.08 (1H, t, J = 7.8 Hz), 7.28 (2H, d, J = 8.1 Hz), 7.39 (1H, d, J = 7.8 Hz), 7.56 (1H, d, J = 7.8 Hz), 7.66 (2H, d, J = 8.1 Hz), 8.34 (1H, s); HRES-MS m/z calcd for [M]⁺ C₁₅H₁₄N: 208.1126, found: 208.1120.

5. 2-(4-Methoxyphenyl)-1H-indole

Dark yellow crystals; m.p. 220°C–222°C; ¹³C-NMR (CDCl₃); δ: 56.0, 98.5, 110.2, 114.5, 119.4, 119.8, 121.2, 125.0, 126.5, 131.0, 141.1, 145.0, 160.0; ¹H NMR (300 MHz, CDCl₃); δ: 3.84 (3H, s), 6.90 (1H, s), 6.97 (1H, t, J = 6.9 Hz), 7.03 (2H, d, J = 6.9 Hz), 7.06 (1H, t, J = 9.0 Hz), 7.37 (1H, d, J = 6.9 Hz), 7.49 (1H, d, J = 6.9 Hz), 7.77 (2H, d, J = 9.0 Hz), 7.79 (1H, s); HRES-MS m/z calcd for [M]⁺ C₁₅H₁₄NO: 224.1075, found: 224.1068

6. 2-(4-Bromophenyl)-1H-indole

Yellow crystals. Yield (1.63, 60%); m.p.: 221°C–222°C. ¹³C-NMR (CDCl₃); δ: 100.02, 111.0, 121.0, 121.0, 123.0, 124.2, 126.2, 127.4, 127.5, 129.1, 137.2, 137.69; ¹H NMR (300 MHz, CDCl₃); δ: 6.86 (1H, s), 7.17 (1H, t, J = 7.5 Hz), 7.23 (1H, t, J = 7.5 Hz), 7.31 (2H, dd, J = 9.0, 9.0 Hz), 7.38 (1H, d, J = 7.5 Hz), 7.53 (1H, d, J = 7.5 Hz), 7.68 (2H, dd, J = 9.0, 5.4 Hz), 8.32 (1H, s); HRES-MS m/z calcd for [M]⁺ C₁₄H₁₁BrN: 272.1400, found: 272.0059.

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