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PANI-ZrO_2 is a green and efficient Catalyst for One-pot multicomponent synthesis of 5-aminopyrazole-4-carbonitrile and its derivatives.

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Abstract:

The development of environmentally benign and efficient catalytic systems is a crucial aspect of modern green chemistry. In this study, Polyaniline-Zirconium dioxide (PANI-ZrO_2)is introduced as agreen, reusable, and highly effective heterogeneous catalystfor theone-pot multicomponent synthesis of 5-aminopyrazole-4-carbonitrile derivatives**.** The reactions were carried out under mildconditions, showcasing excellent yields, high selectivity, and short reaction times. The PANI-ZrO_2 catalyst exhibited remarkable reusability for up to five consecutive cycles without significant loss of activity. The method aligns with green chemistry principles by avoiding hazardous reagents, minimizing waste, and maximizing atom economy. The synergistic properties of PANI as a conducting polymer and ZrO_2 as a thermally stable, non-toxic support contribute significantly to the catalyst's efficiency and eco-friendliness. The synthesized 5-aminopyrazole-4-carbonitrile derivativeswas thoroughly characterized using FT-IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopic techniques, confirming its structural integrity.

Keywords: Polyaniline-Zirconium dioxide, Grinding, Aminopyrazole, Knoevenagel condensation, one-pot multicomponent, Green Chemistry.

Introduction:

In recent years, the demand for sustainable and environmentally friendly synthetic methodologies has increased significantly due to growing concerns about the environmental and health impacts of traditional chemical processes. The principles of green chemistry, introduced by Anastas and Warner, emphasize the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances [1]. Within this framework, the development of green catalystsandsolvent-free reactions has gained immense importance, particularly in the field of heterocyclic chemistry where many bioactive molecules are synthesized.

Multicomponent reactions (MCRs**)** offer an ideal platform for green synthesis because they involve the simultaneous reaction of three or more reactants in a single step, leading to the formation of complex molecules with high atom economy and minimal waste generation [2]. Among the heterocyclic compounds synthesized via MCRs, 5-aminopyrazole-4-carbonitriles are of considerable interest due to their broad spectrum of biological and

pharmacological activities, including antimicrobial, anti-inflammatory, antitumor, antiviral, and analgesic properties [3–5]. These derivatives also serve as versatile intermediates for the synthesis of other nitrogen-containing heterocycles and agrochemicals [6]. Traditional methods for the synthesis of 5-aminopyrazole-4-carbonitrile derivatives often require multiple steps, toxic solvents, prolonged reaction times, andharsh conditions, which contradict the principles of green chemistry [7]. Therefore, the search for cleaner, efficient, and eco-friendly alternatives has led to the exploration of heterogeneous catalystsinsolvent-freesystems. One such promising approach is mechanochemistry, particularly the grinding method, which facilitates chemical transformations through mechanical energy, without the need for bulk solvents or external heating [8]. This technique is not only energy-efficient and operationally simple but also leads to faster reactions with improved yields and reduced environmental footprint [9].

Among various heterogeneous catalysts, Polyaniline-Zirconium dioxide (PANI-ZrO_2) composites have emerged as a highly efficient and green catalytic system. Polyaniline (PANI) is a conducting polymer well known for its redox properties, chemical stability, and environmental friendliness [10]. Zirconium dioxide (ZrO_2), a non-toxic, high surface area metal oxide, possesses excellent Lewis acid properties and thermal stability, making it suitable for catalytic applications [11]. The combination of PANI with ZrO_2 creates a synergistic nanocomposite with improved surface area, enhanced acidity, and high electron transfer capability, leading to superior catalytic activity [12,13]. Additionally, the composite nature of PANI-ZrO_2 allows for easy recovery and reuse, further supporting its green credentials.While PANI-ZrO_2 has shown promising results in various organic transformations, its application as a catalyst under solvent-free grinding conditionsfor theone-pot synthesis of 5-aminopyrazole-4-carbonitrile derivatives has not been extensively studied. The mechanochemical grinding approach using PANI-ZrO_2 not only avoids hazardous solvents but also enhances reaction rates through efficient mixing and molecular interaction at the solid-solid interface. Moreover, the use of readily available starting materials such as aromatic aldehydes, malononitrile, and hydrazine derivatives under mild, catalyst-assisted conditions presents an ideal green route for accessing these important heterocyclic compounds.

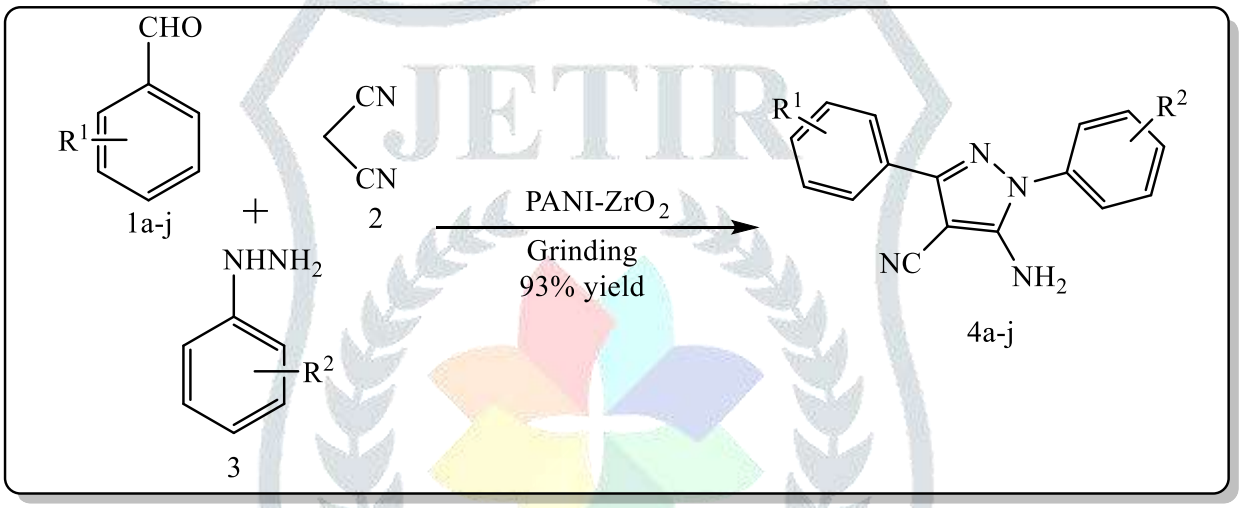
In this study, we report an efficient and environmentally benign protocol for the one-pot multicomponent synthesis of 5-aminopyrazole-4-carbonitrile and its derivatives using PANI-ZrO_2 as a green heterogeneous catalyst under grinding conditions. The protocol offers several advantages such asshort reaction times, excellent yields, operational simplicity, solvent-free conditions, andrecyclability of the catalyst, making it a valuable contribution to the field of green synthetic methodologies. The synthesized derivatives was characterized using techniques such asFT-IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopic technique. This approach aligns well with the sustainable development goals and demonstrates the practical applicability of green catalysis in heterocyclic chemistry.

Materials and methods

All the chemicals and synthetic grade reagent were procedure from Sigma Aldrich India and Merck Chemicals. Reactions were tracked and monitored through thin layer chromatography (TLC) performed on TLC silica gel plates with specification 60 F_{254} by Merck and visualized under UV illuminator chamber.Melting points were recorded in open capillaries using a Buchi melting point B-540 apparatus. The prepared derivative is characterized by FT-IR and was recorded in Nicolet impact 410. ^{1}H NMR spectra were obtained on Bruker instrument (400 MHz) and chemicals shift are reported in δ ppm. ^{13}C NMR was recorded on a Bruker on a DRX 100 MHz Spectrometer.Mass spectra were measured usinghigh-resolution ESI-MS. All the derivative was synthesized in mortal and pestle by grinding method.

General experimental procedure for 5-aminopyrazole-4-carbontrile derivatives. (4a-4j)

A mixture of substituted aryl aldehyde 1 (0.01 mol),malononitrile2 (0.01 mol),subatitutedphenylhydrazine 3 (0.01 mol) in PANI-ZrO2 (15% mol) were takes place in anmortal-pestleand grand until completion of the reaction. The reaction was monitored by TLC (ethyl acetate: n-hexane 8:2). The reaction mixture was poured in crushed ice and filtered it. Then crude product was collected and recrystallized in ethanol and dried. The entire product was characterized by physical constant and spectroscopic technique and compared with the standard method.



Result and Discussion

In the present work, we wish to report a new synthetic route for the preparation of 5-aminopyrazole-4-carbonitrile derivatives in the presence of PANI-ZrO2 as a new highly efficient and reusable catalyst. After the preparation of the catalyst, the condensation of Substituted aryl aldehyde 1 (o.1 mmol), malononitrile 2 (0.1 mmol), and substituted phenylhydrazine 3 (0.01 mmol) were designed as a model reaction for the optimization of parameters such as the amount of catalyst of the reaction. All reactions were carried out in mortal and pestle at a room temperature in order to optimize the amount of catalyst.

Table 1 provides a summary of the findings. At first, the blank reaction was conducted without a catalyst, and even 50 minutes later, no product was produced in a solvent-free environment. Therefore, the model reaction was carried out again with PANI-ZrO2 present at 5, 10, 15, 20, and 25 mol%. The optimum outcome in terms of reaction time (10 minutes) and yield (93%) was obtained using 15 mol% of the catalyst (Table 1, entry 4). However, the 25 mol% catalysts did not shorten the reaction time or boost the reaction yield. As a result, 15 mol% of the catalyst can be considered an optimized amount under solvent-free conditions. The use of green catalyst i.e. PANI-ZrO2 as a reaction medium can improve the efficiency of the reaction by improving the solubility of the reactants, and by reducing the formation of the by-products. The use of PANI-ZrO2 catalyst also allows for easy separation and purification of the product.

Table 1: Effect of different amount of catalyst on the model reaction

Entry	Catalyst	Catalyst Mol %	Time in min	Yield (%)
1	None	-	50	Trace
2	PANI-ZrO2	5	25	50
3	PANI-ZrO2	10	25	55
4	**PANI-ZrO2**	**15**	**10**	**93**
5	PANI-ZrO2	20	15	80
6	PANI-ZrO2	25	30	75

As seen from the results, **PANI-ZrO_2 (15% mol)** was found to be optimal, providing excellent yield (93%) in just 10 minutes under grinding at room temperature. Control reactions without catalyst or with individual components (PANI or ZrO_2) gave significantly lower yields and required longer reaction times. This confirms the synergistic effect of PANI and ZrO_2 in enhancing catalytic activity.

Table: 2 synthesized of 5-aminopyrazole-4-carbonitrile derivatives in PANI-ZrO2 under grinding method.

Entry	R1	R2	Product	Time (inmins.)	Product Yield (%)	m.p (^oC)
1	-H	H	4a	10	91	162–165
2	-Br	H	4b	10	92	140–144
3	-OCH_3	H	4c	15	90	114–118
4	-4-OH	H	4d	15	91	189–192
5	-4-Cl	H	4e	10	93	128–131
6	-3-OH	H	4f	15	91	198–201
7	-H	2,4-NO_2	4g	20	91	170–174
8	-Br	2,4-NO_2	4h	15	90	153–157
9	-OCH_3	2,4-NO_2	4i	25	85	125–129
10	-4-OH	2,4-NO_2	4j	20	87	201–205

Recycle Study

Recycling is the most significant component of the Green Chemistry principle as it can greatly increase the efficiency and cost-effectiveness of the reaction. The recyclability of PANI-$ZrO_2$was examined for the synthesis of 5-aminopyrazole-4-carbonitrile derivatives. A catalyst that was separated after the reaction was completed was employed in another reaction. It was found that the product's yield had not changed noticeably and that it could be utilized in three-cycle reactions without appreciably sacrificing any of its activity.

Table 3: Reusability of the catalytic material.

Number of cycle	1	2	3	4	5
Model reaction (% Yield)	93	92	91	88	86

Spectral analysis of synthesized compounds (4a-4j)

4a) 5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile : Pale yellow solid; Yield: 91%; M.P: 162–165 °C. **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ ppm.): δ 7.66 (d, J = 7.2 Hz, 2H); 7.40 (t, J = 3 Hz, 2H); 7.11 (t, 1H); 7.35 (d, J = 4.2 Hz, 2H); 7.26 (t, J = 6 Hz, 2H); 6.91 (t, 1H), 5.46 (s, 2H)·**^{13}C-NMR** ($CDCl_3$, 125 MHz, δ ppm.): 157.11; 145.89; 136.52; 135.55; 130.99; 129.55; 129.21; 129.90; 128.54; 126.42; 120.33; 118.85; 118.12; 93.55. **MS** (m/z): (M^+) found: 260.12.

4b) 5-Amino-3-(4-bromo-phenyl)-1-phenyl-1H-pyrazole-4-carbonitrile: Cream colored solid; Yield: 92%; M.P: 140–144 °C. **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ ppm.): 6.93 (t, 1H); 7.35 (t, J = 2.1 Hz, 2H); 7.79 (t, J = 2.4 Hz, 2H), 7.43 (d, J = 3.3 Hz, 2H); 7.50 (d, J = 3.6 Hz, 2H); 5.93 (s, 2H). **^{13}C-NMR** ($CDCl_3$, 125 MHz, δ ppm.): 160.24; 149.16; 139.75; 137.62; 135.54; 132.37; 129.98; 129.17; 128.87; 126.58; 123.14; 118.82; 118.19; 98.95. **MS** (m/z): (M^+) found: 338.1020.

4c)5-Amino-3-(4-methoxy-phenyl)-1-phenyl-1H-pyrazole-4-carbonitrile: Light yellow amorphous solid; Yield: 90%; M.P: 114–118 °C. **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ ppm.): 7.27 (t, 1H); 7.39 (t, J = 3.3 Hz, 2H); 7.55 (t, J = 3.1 Hz, 2H); 7.45 (d, J = 5.1 Hz, 2H); 6.89 (d, J = 2.1 Hz; 2H); 4.58 (s, 2H); 3.79 (s, 3H). **^{13}C-NMR** ($CDCl_3$, 125 MHz, δ ppm.): 160.10; 148.50; 139.75; 133.55; 129.19; 128.45; 125.54; 124.37; 121.90; 121.55; 121.14; 118.85; 119.01; 114.79; 115.40; 94.99; 57.34. **MS** (m/z): (M^+) Calcd. for $C_{17}H_{14}N_4O$: 290.0654; found: 290.06.

4d) 5-Amino-3-(4-hydroxy-phenyl)-1-phenyl-1H-pyrazole-4-carbonitrile: Pale yellow amorphous solid; Yield: 91%; M.P:189–192 °C. **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ ppm.): 7.62 (d, J = 4.2 Hz, 2H); 7.46 (t, J = 4.3 Hz, 2H); 7.27 (t, 1H); 7.34 (d, J = 6 Hz, 2H); 6.78 (d, J = 2.7 Hz, 2H); 5.57 (s, 2H); 5.14 (s, 1H). **^{13}C-NMR** ($CDCl_3$, 125 MHz, δ ppm.): 165.73; 156.88; 148.82; 139.43; 139.37; 135.65; 129.92; 29.85; 129.55; 129.30; 128.43; 128.15; 128.01; 118.89; 118.11; 116.25; 97.45. **MS** (m/z): (M^+) found: 276.10.

4e)5-Amino-3-(4-chloro-phenyl)-1-phenyl-1H-pyrazole-4-carbonitrile: Chrome yellow amorphous solid; Yield: 93%; M.P:128–131 °C. **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ ppm.): 7.58 (d, J = 5.7 Hz, 2H); 7.46 (t, J = 6.6 Hz, 2H); 7.24 (t, 1H); 7.48 (d, J = 4.8 Hz, 2H); 7.39 (d, J = 5.1 Hz, 2H); 5.39 (s, 2H). **^{13}C-NMR** ($CDCl_3$, 125 MHz, δ ppm.): 159.91; 149.97; 138.72; 135.61; 134.82; 131.12; 130.94; 129.85; 129.40; 129.16; 128.42; 126.76; 126.32; 118.93; 118.01; 96.05. **MS** (m/z): (M^+) Calcd. found: 294.06.

4f) 5-Amino-3-(3-hydroxy-phenyl)-1-phenyl-1H-pyrazole-4-carbonitrile: Pale yellow amorphous solid; Yield: 91%; M.P:198–201 °C. **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ ppm.): 7.66 (d, J = 3.3 Hz, 2H); 7.57 (t, J = 6.9 Hz, 2H); 7.39 (t, 1H); 7.43 (d, J = 6.6 Hz, 1H); 7.25 (t, 1H); 6.60 (d, 1H); 6.67 (s, 1H); 5.10 (s, 1H); 4.66 (s, 2H). **^{13}C-NMR** ($CDCl_3$, 125 MHz, δ ppm.): 162.10; 157.75; 149.24; 139.75; 137.94; 131.48; 131.12; 129.95; 129.65; 129.14; 128.95; 126.56; 119.67; 118.82; 115.67; 114.39; 95.28. **MS** (m/z): (M^+) Calcd. found: 276.10

4g) 5-Amino-1-(3,5-dinitro-phenyl)-3-phenyl-1H-pyrazole-4-carbonitrile: Orange-yellow amorphous solid; Yield: 91%; M.P:170–174 °C. **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ ppm.): 8.93 (s, 1H); 8.37 (s, 1H); 8.35 (s, 1H); 7.48 (d, J = 5.7 Hz, 2H); 7.39(t, J = 5.1 Hz, 2H); 7.29 (t, 1H); 5.44 (s, 2H). **^{13}C-NMR** ($CDCl_3$, 125 MHz, δ ppm.): 163.56; 149.95; 149.85; 148.89; 141.53; 136.52; 129.92; 129.67; 128.84; 127.59; 127.21; 121.18; 120.52; 118.48; 116.24; 105.08. **MS** (m/z): (M^+) Calcd. forfound: 350.07

4h) 5-Amino-3-(4-bromo-phenyl)-1-(3,5-dinitro-phenyl)-1H-pyrazole-4-carbonitrile : Ochre colored amorphous solid; Yield: 90%; M.P:153–157 °C. **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ ppm.): 9.28 (s, 1H); 8.66 (s, 1H); 8.65 (s, 1H); 7.45 (d, J = 4.8 Hz, 1H); 7.44 (d, J = 5.4 Hz, 1H); 7.38 (d, J = 5.4 Hz, 1H); 7.36 (d, J = 4.8 Hz, 1H); 5.38 (s, 2H). **^{13}C-NMR** ($CDCl_3$, 125 MHz, δ ppm.): 165.88; 149.98; 149.67; 148.87; 142.59; 135.58; 132.48; 132.24; 130.36; 129.13; 123.17; 120.45; 120.08; 118.62; 116.90; 106.24. **MS** (m/z): (M^+) found: 426.98

4i)5-Amino-1-(3,5-dinitro-phenyl)-3-(4-methoxy-phenyl)-1H-pyrazole-4-carbonitrile : Orange colored amorphous solid; Yield: 85%; M.P:125–129 °C. **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ ppm.): 9.37 (s, 1H); 8.74 (s, 1H); 8.60 (s, 1H); 7.36 (d, J = 7.5 Hz, 1H); 7.35 (d, J = 6.9 Hz, 1H); 6.78 (d, J = 11 Hz, 2H); 5.10 (s, 2H); 3.74 (s, 3H). **^{13}C-**

NMR ($CDCl_3$, 125 MHz, δ ppm.): 162.50; 149.92; 149.56; 148.83; 141.47; 128.94; 128.76; 128.57; 128.23; 120.72; 120.24; 118.60; 116.41; 114.83; 114.41; 97.45; 55.59. **MS** (m/z): (M^+) found: 380.07

4j)5-Amino-1-(3,5-dinitro-phenyl)-3-(4-hydroxy-phenyl)-1H-pyrazole-4-carbonitrile : Amber colored amorphous solid; Yield: 87%; M.P:201–205 °C. **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ ppm.): 9.22 (s, 1H); 8.70 (s, 1H); 8.63 (s, 1H); 7.30 (d, J = 7.2 Hz, 1H); 7.44 (d, J = 6.9 Hz, 1H); 6.98 (d, J = 6.9 Hz, 1H); 6.93 (d, J = 6.6 Hz, 1H); 5.93 (s, 2H); 5.36 (s, 1H). **^{13}C-NMR** ($CDCl_3$, 125 MHz, δ ppm.): 162.32; 158.54; 149.90; 149.91; 148.64; 140.21; 130.11; 129.67; 128.94; 128.76; 120.87; 120.54; 119.45; 118.25; 118.12; 116.25; 96.74. **MS** (m/z): (M^+) found: 366.07.

Conclusion

In conclusion, the present study successfully demonstrates that Polyaniline-Zirconium dioxide (PANI-ZrO_2) functions as an efficient, green, and reusable heterogeneous catalystfor theone-pot multicomponent synthesis of 5-aminopyrazole-4-carbonitrile derivativesusing thegrinding method under solvent-free conditions**.** The unique synergy between polyaniline and zirconia in the composite catalyst significantly enhances its catalytic activity by pro viding a high surface area, tunable acid-base sites, and excellent thermal stability. This study highlights PANI-ZrO_2 as a powerful green catalytic system for the eco-friendly synthesis of biologically significant heterocycles under ambient and solvent-free conditions. It provides a valuable contribution to the growing field of sustainable organic synthesis and opens new avenues for the application of polymer-supported metal oxide nanocomposites in mechanochemical catalysis.

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