

Eco-friendly Synthesis of 1, 4-Dihydropyrano-[2,3-c] Pyrazoles Using Copper Nanoparticles Grafted on Carbon Microsphere as a Heterogeneous Catalyst

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Abstract: A convenient and efficient one-pot three-component synthesis of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1, 4-dihydropyrano[2, 3-c] pyrazoles was achieved using copper nanoparticles grafted on carbon microsphere (Cu-NP/C) as a reusable heterogeneous catalyst. The synthesis of pyranopyrazoles was carried out under mild reaction conditions affording excellent yield of the corresponding products.

Keywords: Pyranopyrazole; Multi-component reaction; Cu-NP/C.

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1. Introduction

The shift of organic synthesis is prominently directed towards “Greenery”. Growing interest awakened among researchers that consequently resulted in the development of new environmentally benign procedures such as the use of the aqueous medium, multi-component reaction (MCR) strategy, and reusable catalysts to save resources and energy [1]. In recent years, the efficient synthesis of complex molecules from simple and readily available materials has become one of the important aspects of organic synthesis. Attempts have been made to develop several techniques for the efficient use of reusable catalysts and multi-component reactions [2-3]. Being powerful and bond-forming efficient tools in organic, combinatorial, and medicinal chemistry, MCRs have attracted researchers with increasing awareness to develop high atom economy, eco-friendly, one-pot, single step, energy minimized, and negligible waste production strategies. These features encourage MCRs as well-suited for the easy construction of diversified arrays of valuable bioactive heterocycles.

Constituting an important heterocyclic scaffold with a rich bioactive profile in medicinal chemistry, dihydropyrano [2, 3-c] pyrazoles exhibit anticancer [4], antimicrobial [5], antioxidant [6], anti-inflammatory [7]. Besides this, they also possess DNA-binding ability [8] and potential inhibitors of cholinesterases [9]. Hence, due to the existence of these precious scaffolds in biologically active molecules (Figure 1), considerable efforts have been documented for the synthesis of these heterocyclic motifs by using various methodologies [10]. From the literature survey, 1,4-dihydro-pyrano[2,3-c]pyrazoles can be synthesized in the

presence of catalysts like per- 6-amino- β -cyclodextrin [11], nano- $\text{Fe}_3\text{O}_4\text{-SiO}_2$, $(\text{CH}_2)_3$ -imidazole- $\text{SO}_3\text{H}]\text{Cl}$ [12], CsF [13], ionic liquid [bmim]OH [14], tungstate sulfuric acid [15], HTMAB [16], and SnS-NP [17]. Myrboh *et al.* reported the synthesis of pyranopyrazoles using L-proline and KF-alumina as a catalyst [18]. Synthesis of pyranopyrazoles using hydrazine hydrate, ethyl acetoacetate, malononitrile, and aromatic aldehydes is also been reported in the presence of catalysts such as β -cyclodextrin [19], triethylamine [20], cinchona alkaloid derivatives [21], and imidazole [22], meglumine [23], Amberlyst A21 [24], piperidine [25], potassium phthalimide [26], $\text{Ni}_{0.5}\text{Zn}_{0.5}\text{Fe}_2\text{O}_4$ [27], Ag/ TiO_2 [28], isonicotinic acid [29], [Bmim]BF₄ and L-Proline [30], CuI nanoparticles [31], 1-(carboxymethyl) pyridinium iodide [cmpyl]I [32]. These reported methodologies have shown good results in many instances. However, some of them also have limitations in terms of the metal catalyst, expensive reagents, long reaction time, environmentally hazardous, harsh reaction conditions, tedious work-up procedure, unsatisfactory yield, and homogeneous catalysts, which are difficult in separation from the reaction mixture.

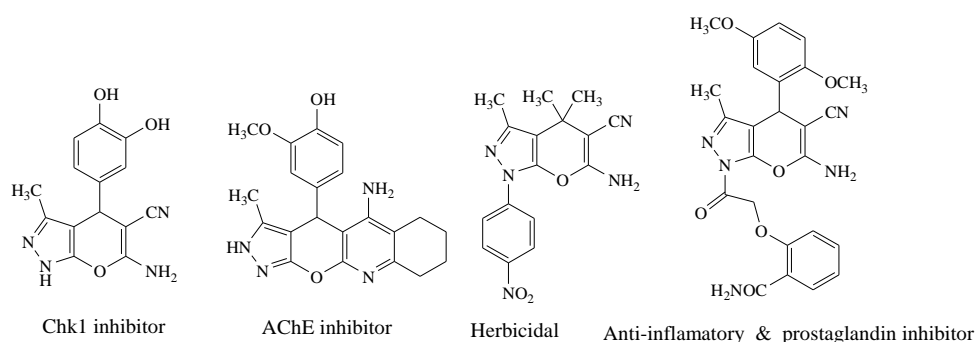
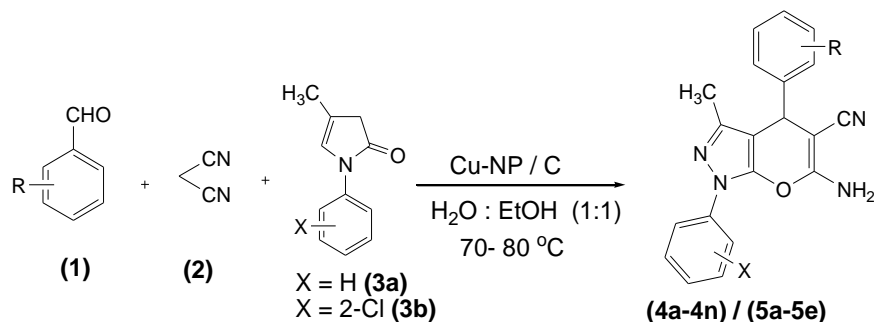


Figure 1. Some biologically active pyranopyrazole derivatives.

Heterogeneous catalysts have gained extensive applications as eco-friendly, economically viable, and easily separable catalysts in organic transformations [33]. Among the heterogeneous catalysts, various nanoparticles (NPs) have received considerable attention for their high catalytic activity and selectivity in various fields of synthetic organic and bioorganic chemistry [34].

Copper nanoparticles are an important group of nano-catalysts. Copper nanoparticle catalyzed reactions are advantageous over the conventional metal-catalyzed reactions in terms of low catalyst loading, high atom economy, better yields, inexpensive, shorter reaction times, and recyclability of the catalyst [35].



Scheme 1. One-pot synthesis of pyranopyrazole derivatives.

Nanoparticles may undergo self-aggregation; therefore, it is difficult to separate them from the reaction medium. To avoid the limitation of nanoparticles, they can be supported on some supports. These developed catalytic metallic nanoparticles are inexpensive, non or minimally poisonous, highly active, stable, and easily separable from reaction mixture are

highly useful. In our previous work, copper nanoparticles grafted on carbon microsphere (Cu-NP/C) were found to be useful for organic transformations [36-37]. In continuation of our previous work [38-40], herein, we report a new eco-friendly three-component protocol for the synthesis of 1,4-dihydropyrano[2,3-*c*] pyrazole derivatives using Cu NP/C as a heterogeneous catalyst in water and ethanol (1:1) solvent (Scheme 1).

2. Materials and Methods

2.1. General.

All chemicals were purchased from Sigma Aldrich, Alpha Aiser, Spectrochem, and used without further purification. TLC was carried out with Merck silica gel 60-F-254 aluminum plates. ¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker spectrometer using CDCl₃, DMSO-*d*₆ as solvent and tetramethylsilane as an internal standard. Mass spectrometric data were recorded by an electron spray ionization (ESI) technique on a Q-tof-micro quadrupole mass spectrometer (Micro mass). The catalyst synthesis and characterization have been well studied in our previous publications [35-36].

2.2. General procedure for the synthesis of 6-amino-4-aryl-5-cyano- 3-methyl-1-phenyl-1, 4-dihydropyrano [2, 3-*c*] pyrazoles.

A mixture of aromatic aldehyde (1 mmol), malononitrile (1.1 mmol), pyrazolin-5-one (1 mmol) in 1:1 water: ethanol (5 mL) in the presence of Cu-NP/C (10 mg) was refluxed for an appropriate period of time. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and washed with ethanol. The product and catalyst were separated by filtration. The product was used without further purification methods, and the catalyst was washed with ethyl acetate, dried, and reused.

2.3. Spectral data.

*6-Amino-3-methyl-4-(3-chlorophenyl)-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile, entry 3, (4c):* Melting point = 181–183°C; IR (cm⁻¹) 783, 831, 921, 955, 1062, 1182, 1242, 1294, 1394, 1435, 1537, 1627, 1820, 1896, 2017, 2185, 2569, 2777, 2895, 2964, 3070, 3315, 3421; ¹H NMR (300 MHz, DMSO-*d*₆): δ ppm H (ppm) 1.910 (s, 3H, CH₃), 4.649 (s, 1H chiral), 4.715 (s, 2H, NH₂), 7.165-7.208 (t, 2H, Ar-H), 7.273-7.283 (m, 1H, Ar-H), 7.302-7.347 (m, 2H, Ar-H), 7.451-7.491 (t, 2H, Ar-H), 7.641-7.659 (d, 2H, Ar-H) ; ¹³C NMR (500 MHz, DMSO *d*₆): δ ppm 78.05, 154.21, 161.52, 174.45; HRMS : 363.

*6-Amino-4-(4-methoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile, entry 10, (4j):* Melting point = 174-175°C; IR (cm⁻¹) 837, 962, 1026, 1068, 1107, 1128, 1174, 1253, 1301, 1336, 1390, 1456, 1514, 1587, 1656, 1894, 2189, 2843, 2920, 2968, 3201, 3267, 3317, 3387; ¹H NMR (300 MHz, DMSO *d*₆): δ ppm 1.898 (s, 3H, CH₃), 3.808 (s, 3H, OCH₃), 4.601 (s, 1H, chiral), 4.692 (s, 2H, NH₂), 6.869-6.890 (d, 2H, Ar-H), 7.159–7.181 (t, 2H, Ar-H), 7.298-7.333 (t, 1H, ArH), 7.444-7.484 (t, 2H, ArH), 7.643-7.665(d, 2H, ArH); HRMS : 359.

*6-Amino-1-(2-chlorophenyl)-1,4-dihydro-3-methyl-4-(3-nitrophenyl)pyrano[2,3-*c*]pyrazole-5-carbonitrile, entry 17, (5c):* Melting point = 199-201°C; IR (cm⁻¹) 889, 929, 1041, 1114, 1184, 1251, 1269, 1350, 1392, 1475, 1496, 1585, 1656, 2187, 2868, 2976, 3190, 3309, 4315; ¹H NMR (300 MHz, DMSO-*d*₆): δ ppm 1.796 (s, 3H, CH₃), 4.989 (s, 1H chiral), 7.222 (s, 2H, NH₂), 7.522-7.579 (m, 2H, Ar-H), 7.661-7.751 (m, 4H, Ar-H), 8.133-8.179 (t, 2H, Ar-H); ¹³C

NMR (500 MHz, DMSO d_6): δ (ppm) 12.44, 96.15, 119.61, 122.03, 122.15, 128.19, 129.88, 130.13, 130.25, 130.82, 131.14, 133.96, 134.40, 145.15, 145.38, 146.02, 147.88, 159.58; HRMS : 408.07.

3. Results and Discussion

Due to growing interest in solid catalysts for the synthesis of heterocycles [34], herein we describe an efficient and facile protocol for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives from aromatic aldehydes (1a-n), malononitrile (2) and 3-methyl-1-phenyl-2-pyrazolin-5-one (3a-b) using Cu NP/C as a reusable and safe catalyst in water-ethanol (1:1) at 70-80 °C (Scheme 1). The present work was performed by using this catalyst for the synthesis of pyranopyrazole derivatives. Cu NP/C was collected by a simple work-up procedure and could be reused several times without appreciable loss of catalytic activity. Another aspect of this work is the use of water:ethanol (1:1) system as a solvent.

Initially, *p*-anisaldehyde (1 mmol), malononitrile (1.1 mmol), and 3-methyl 1-phenyl 5-pyrazolone (1 mmol) were selected for the optimization of the reaction conditions at 70-80 °C in 5 mL water-ethanol (1:1). Firstly, in the absence of the catalyst, only a 25% yield of the desired product was obtained at 70-80°C. Then, to identify the suitable reaction condition, the effect of solvent and amount of catalyst was studied. The high yield was obtained using 10 mg of the catalyst in 1:1 H₂O-EtOH (Table 1).

Table 1. Optimization of reaction conditions.

Entry	Solvent	Catalyst (mg)	Temperature (°C)	Time (min.)	Yield (%)
1	EtOH	-	70-80	22 hr	25
2	CH ₃ CN	10	80-90	100	60
3	CH ₂ Cl ₂	10	40	140	65
4	H ₂ O	05	80-90	110	65
5	EtOH	05	70-80	90	70
6	H ₂ O : EtOH (1:1)	05	70-80	100	60
7	H ₂ O : EtOH (1:1)	10	70-80	15	93
8	H ₂ O : EtOH (1:1)	15	70-80	17	90

Afterward, a series of reactions were carried out by using diversely substituted aldehydes under the optimized reaction conditions. All the aldehydes underwent a three-component reaction with malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one to produce a library of 1, 4-dihydropyrano [2, 3-*c*]pyrazole derivatives in good to excellent yields (Table 2). The reactions of aromatic aldehydes with electron-withdrawing groups such as chloro, nitro, proceeded at faster rates and gave better yields than those with electron-donating groups such as methoxy and methyl.

Table 2. Synthesis of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1, 4-dihydropyrano [2, 3-*c*] pyrazoles catalyzed by Cu-NP / C.

Entry	Aldehyde	Enolizable Ketone	Time (min.)	Product	Yield ^b (%)	MP (°C)
1	Benzaldehyde	3a	20	4a	86	171-173 ¹⁵
2	2-Chloro benzaldehyde	3a	18	4b	88	145-146 ¹⁵
3	3-Chloro benzaldehyde	3a	20	4c	90	158-160 ¹⁶
4	3-Bromo benzaldehyde	3a	17	4d	90	159-160 ¹⁵
5	3-Nitro benzaldehyde	3a	15	4e	88	190-192 ¹⁵
6	4-Fluoro benzaldehyde	3a	17	4f	90	163-164 ¹³
7	4-Nitro benzaldehyde	3a	15	4g	93	195-197 ¹⁵
8	4-Bromo benzaldehyde	3a	18	4h	88	182-184 ¹⁵
9	4-Tolualdehyde	3a	24	4i	85	167-168 ¹⁵
10	4-Anisaldehyde	3a	30	4j	84	174-175 ¹⁵
11	4-Cyano benzaldehyde	3a	16	4k	91	218-220 ¹⁷

Entry	Aldehyde	Enolizable Ketone	Time (min.)	Product	Yield ^b (%)	MP (°C)
12	4-Hydroxy benzaldehyde	3a	24	4l	85	211-213 ¹⁶
13	Terphthaldehyde	3a	25	4m	90	238-240 ¹²
14	3,4-Dimethoxy benzaldehyde	3a	36	4n	86	192-194 ¹³
15	4-Fluoro benzaldehyde	3b	24	5a	88	173-175
16	4-Dimethylamino benzaldehyde	3b	28	5b	85	168-170
17	3-Nitro benzaldehyde	3b	20	5c	91	199-201
18	3-Chloro benzaldehyde	3b	22	5d	90	162-164
19	5-Bromo salicylaldehyde	3b	26	5e	88	212-214

^aAldehyde (1 mmol), malononitrile (1mmol), enolizable ketone (1 mmol) and Cu NP/C 10 mg, H₂O : EtOH (1:1) 5 mL, reflux; ^bIsolated yield.

The mechanism of the Cu-NP/C catalyzed synthesis of pyranopyrazoles has been depicted in Figure 2. Initially, the catalyst promotes the formation of arylidene malononitrile by the Knoevenagel condensation between aldehyde and malononitrile. Simultaneously there is the activation of the methylene group of pyrazolone, which combines with the arylidene malononitrile followed by cyclization, and tautomerization finally results in the formation of the desired product.

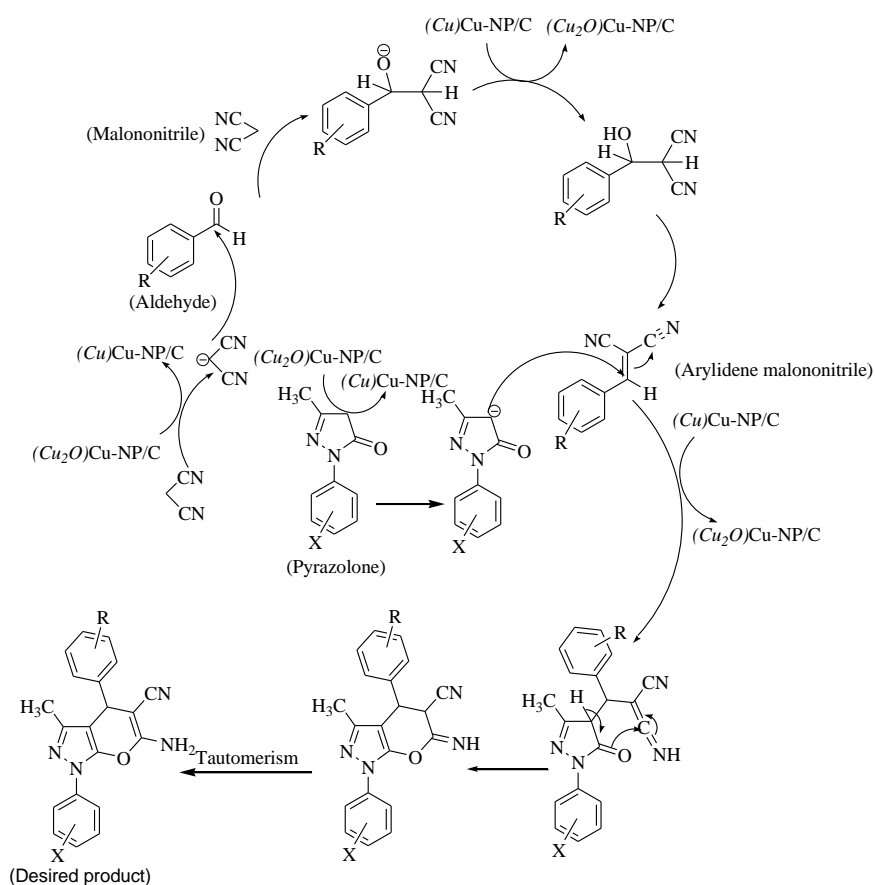


Figure 2. Mechanism of Cu-NP/C catalyzed synthesis of pyranopyrazoles.

4. Conclusions

In summary, we report an efficient one-pot three-component synthesis of 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1,4-dihydropyranopyrazoles by the reaction of various aldehydes, malononitrile and pyrazolin-5-one using copper nanoparticles grafted on carbon microsphere as a reusable heterogeneous catalyst. Use of easily separable Cu-NP/C as a heterogeneous catalyst, non-hazardous reaction conditions, clean reaction conditions, and the

use of aqueous ethanol as the reaction solvent makes the present protocol an environmentally benign and green approach for the synthesis of dihydropyranopyrazoles.

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Conflicts of Interest

The authors declare no conflict of interest.

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