Short communication

A Novel Method for the One-pot Five-component Synthesis of Highly Functionalized Pyranopyrazoles Catalyzed by CuI Nanoparticles

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Abstract

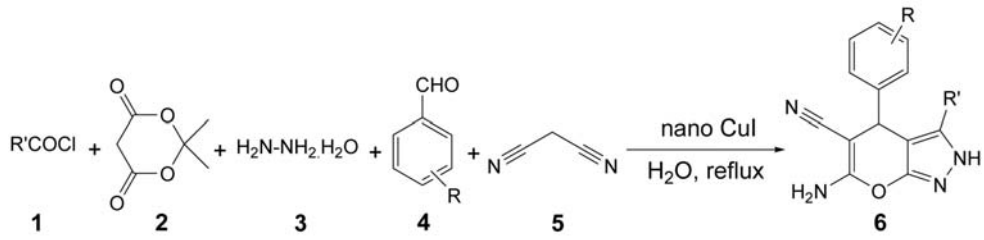
A novel one-pot, five-component reaction for the synthesis of highly functionalized pyranopyrazoles from acid chlorides, Meldrum's acid, hydrazine hydrate, aromatic aldehydes and malononitrile in the presence of catalytic amount of CuI nanoparticles in aqueous media is reported. This method provides several benefits such as *in situ* preparation of β-ketoester, mild reaction conditions, and environmentally friendly, waste-free and simple work-up procedure with excellent yields. The catalyst could be recovered and reused for several times with almost consistent catalytic activity.

Keywords: Pyranopyrazoles, one pot, five-component reaction, *in situ* preparation, CuI nanoparticles.

1. Introduction

One of the principal challenges in medicinal chemistry is the design and synthesis of pharmacologically active molecules. Pyranopyrazoles are fused heterocyclic compounds that possess an important role in the field of pharmacological chemistry due to the various potential medicinal and biological activities. Many of these compounds posses anti-tumor,[1] anti-cancer,[1] anti-bacterial,[2] and vasodilatory activitity;[3] analgesic,[4] and anti-inflammatory properties,[5] and also serve as potential inhibitors of human Chk1 kinase.[6] Therefore, considerable attention has been focused on the development of new methodologies for the synthesis of pyranopyrazoles. The first catalytic synthesis of pyranopyrazoles was reported by Otto,[7,8] in which he initiated the reaction sequence by the base-catalyzed cyclization of 4-aryliden-5-pyrazolone. By extending the work of Otto, Klokol and co-workers carried out the direct conversion of 3-methyl-3-pyrazolin-5-one by using malononitrile and weak base.[9] Recent approaches for the preparation of pyranopyrazole derivatives include synthesis in aqueous media,[10–13] using microwave irradiation[14] under solvent-free conditions.[15–17]

Multicomponent reactions (MCRs) are highly important transformations due to their capacity to combine three or more substrates into a single target in one step.[18–20] MCRs typically obtain a substantial increase in molecular complexity and offer chance for diversity-oriented synthesis. Therefore, these reactions are important in drug synthesis,[21–24] as well as in the total synthesis of natural compounds.[25] In recent years interests for *in situ* preparation of chemical reagents have been developed. This approach is an efficient and facile alternative pathway which reduces the use of expensive and toxic rea-



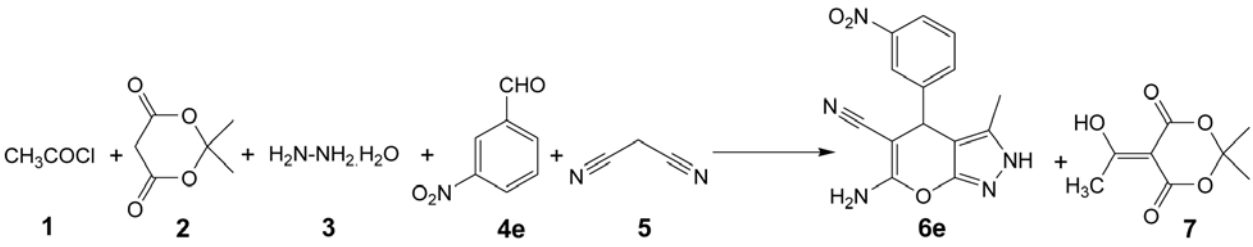
Scheme 1. Synthesis of pyranopyrazole derivatives catalyzed by CuI nanoparticles under reflux conditions.

gents.[26–28] Furthermore; many catalytic systems recently found application in organic synthesis such as *in situ* preparation of reagents.[29–34] The chemical synthesis productivity can be increased by nano-sized catalysts because of low size and high surface to volume ratios. Moreover, this productivity was improved by using heterogeneous catalysts because of their simplicity of separation.[35–38] It was also reported that CuI nanoparticles as heterogeneous catalysts offer huge opportunities for a wide range of applications in chemical synthesis and chemical manufacturing procedures.[39–41]

The demand of environmentally benign procedure with *in situ* preparation of reagents by using heterogeneous and reusable catalyst, promoted us to develop alternate and safe method for the synthesis of pyranopyrazoles using acid chlorides, Meldrum's acid, hydrazine hydrate, aromatic aldehydes and malononitrile in the presence of nano CuI (Scheme 1).

2. Results and Discussion

In the beginning of our study, the standard reaction was chosen on the treatment of acetyl chloride **1**, Meldrum's acid **2**, hydrazine hydrate **3**, 3-nitrobenzaldehyde **4e** and malononitrile **5** (Scheme 2). This reaction was carried out with various catalysts, solvents and at different reaction conditions (Table 1). Experiments with various aprotic (Table 1, entries 1–3) and protic (Table 1, entries 4,5) solvents revealed the best results in water as solvent (Table 1, entry 5). Subsequently, we studied the model reaction in water at different temperatures (Table 1, entries 5, 6). When the reaction was carried out at room temperature, intermediate **7** was produced via nucleophilic substitution of Meldrum's acid to acetyl chloride (Table 1, entry 5). Intermediate **7** was further converted to ethyl acetoacetate which reacts with other reagents giving the product **6e** at reflux conditions. To assess the catalytic efficiency, the same model reaction was studied by using four types of catalysts (Table 1, entries 6–9). Results obtained and collected in Table 1 indicated that in the absence of catalyst no product was generated, however, in the presence of CuI nanoparticles the reaction proceeds in high yield. We believe that nano CuI surface chemistry plays an important role in this reaction. The best results were obtained by using 1.2 mol% of nano CuI (Table 1, entry 10). The modification of the main reaction is *in situ* preparation of β-ketoester by Meldrum's acid and acid chlorides.[26] Although, β-ketoester is commercially accessible commercially accessible reagent, because of the restriction of products and its toxicity, it is more favorable to prepare it via *in situ* procedure. Namely, *in situ* preparation of reagent introduces clean production of a wide range of synthetically useful products in a eco-friendly path with fewer amounts of waste products.



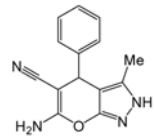
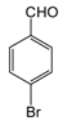
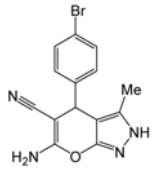
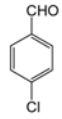
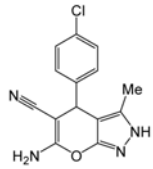
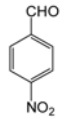
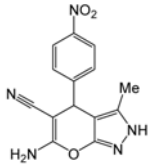
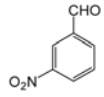
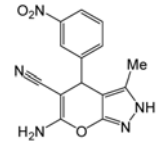
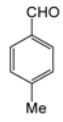
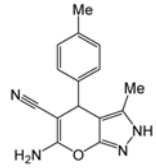
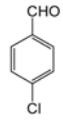
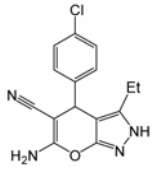
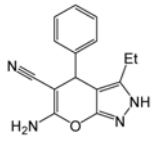
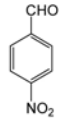
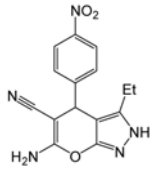
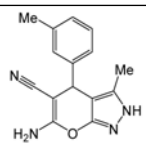
Scheme 2. The model reaction for the preparation of pyranopyrazoles using CuI nanoparticles as catalyst.

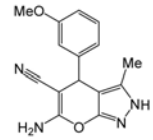
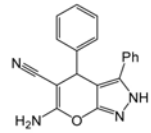
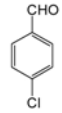
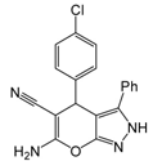
Table 1. Optimization of model reaction at different reaction conditions.

Entry	Solvent	Condition	Catalyst (mol %)	Product	Yield (%)[a]
1	Toluene	reflux	CuI (10)	**6e**	60
2	MeCN	reflux	CuI (10)	**6e**	58
3	CH_2Cl_2	reflux	CuI (10)	**6e**	71
4	EtOH	reflux	CuI (10)	**6e**	74
5	H_2O	r.t.	CuI (10)	**7**	75
6	H_2O	reflux	CuI (10)	**6e**	87
7	H_2O	reflux	Nano AgI (4)	**6e**	82
8	H_2O	reflux	Nano ZnO (4)	**6e**	76
9	H_2O	reflux	Nano CuI (1)	**6e**	92
10	H_2O	reflux	Nano CuI (1.2)	**6e**	95
11	H_2O	reflux	Nano CuI (1.5)	**6e**	95
12	H_2O	reflux	none	–	–

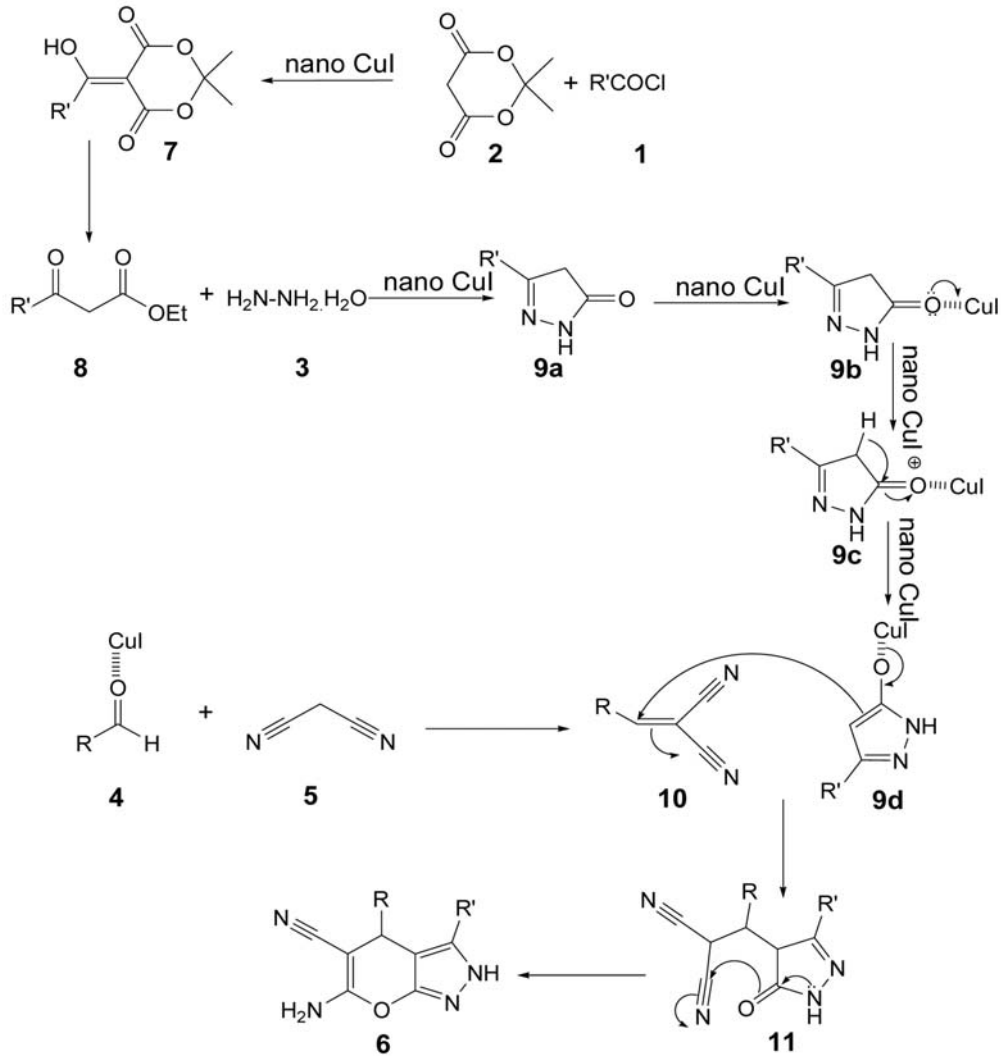
[a] Isolated yields.

Table 2. One-pot synthesis of pyranopyrazoles catalyzed by CuI nanoparticles.

Entry	Acid chloride (**1**) (R', Scheme 1)	Aldehyde (**4**) (R, Scheme 1)	Product (**6**)	Time (min)	Yield (%)[a]	Mp (°C)[b]
a	CH_3			40	90	244–246 [43]
b	CH_3			35	91	178–180[17]
c	CH_3			35	93	234–236[43]
d	CH_3			35	92	251–253[43]
e	CH_3			30	95	193–195[43]
f	CH_3CH_2			40	87	206–208[44]
g	CH_3CH_2			40	87	216–218
h	CH_3CH_2			40	85	181–183
i	CH_3CH_2			45	88	207–209
j	CH_3			50	86	170–172[17]

Entry	Acid chloride (1) (R', Scheme 1)	Aldehyde (4) (R, Scheme 1)	Product (6)	Time (min)	Yield (%)[a]	Mp (°C)[b]
k	CH_3			40	88	174–176[17]
l	Ph			45	84	196–198
m	Ph			35	90	208–210

[a] Isolated yield. [b] Literature references.



Scheme 3. Proposed mechanism for the formation of pyranopyrazoles.

The study was extended to the application of nano CuI in the synthesis of substituted pyranopyrazoles by using various aldehydes and acid chlorides, Meldrum's acid, hydrazine hydrate and malononitrile. The results obtained by using reaction conditions of model reaction (Table 1, entry 10) are listed in Table 2. All products were characterized by using of IR, ^{1}H and ^{13}C NMR spectroscopy, and elemental analysis.

The proposed mechanism for this five-component reaction is outlined in Scheme 3.[12,26,42] In the frst step of reaction nano CuI catalyses *in situ* formation of β-ketoester **7**.[45–47] Similarly, the aldehyde is activated by nano CuI and then Knoevenagel condensation with malononitrile takes place to afford intermediate **10**. Afterwards, β-ketoester is activated by nano CuI, followed by attack of hydrazine, which leads to formation of pyrazolone **9a**. On the other hand, high surface activity of nano CuI allowed that compound **9a** is adsorbed on its surface to transform into compound **9d**. This interaction facilitates Michael addition between **9d** and compound **10** to give intermediate **11**. Subsequently, the Thorpe-Ziegler like intramolecular cyclization, followed by tautomerization, affords product **6** (Scheme 3).

3. Experimental

3. 1. General

Chemicals were purchased from the Sigma-Aldrich and Merck in high purity. All materials were of commercial reagent grade and were used without further purification. Melting points were measured on an Electrothermal 9200 apparatus. ^{1}H and ^{13}C NMR spectra were obtained on Bruker 400 MHz spectrometer with DMSO-d_6 as solvent. The chemical shift values are in δ and referenced to tetramethylsilane (TMS) as an internal standard. FT-IR spectrum was recorded on Nicolet Magna 550 spectrometer in KBr pellets in the range of 400–4000 cm^{-1}. The elemental C,H,N analyses were obtained on Carlo ERBA Model EA 1108 analyzer. Powder X-ray diffraction (PXRD) was carried out on a Philips diffractometer of X'pert Company with mono chromatized Cu Ká radiation (λ = 1.5418 Å). The compositional analysis was performed by energy dispersive X-ray (EDAX, Kevex, Delta Class I) analysis. Electronic spectrum of the sample was taken on a JASCO UV-vis scanning spectrometer (Model V-670). Microscopic morphology of products was visualized by SEM (LEO 1455VP).

3. 2. Preparation of CuI Nanoparticles

The catalyst was prepared by ultrasonic irradiation approach. $CuSO_4$ was used as the Cu source. Firstly the copper substrate (1 mmol) was ultrasonically cleaned for 20 sec in acetone and then in a 2M HCl solution, followed by repeated rinsing with distilled water. After drying, the substrate was dipped slowly into a solution of KI (2 mmol) in 40 mL of distilled water and sonicated to react for 30 min. When the reaction was completed, gray precipitate was obtained. The solid was filtered and washed with distilled water and dried. The prepared CuI nanoparticles have been structurally characterized by SEM, XRD and EDAX analysis.

3. 3. Catalyst Recovery

The recovered catalyst from the experiment was washed by acetone (3 × 5 mL). Then, it was dried and reused in the synthesis of pyranopyrazoles for several times with a slight decrease in activity (Figure 1).

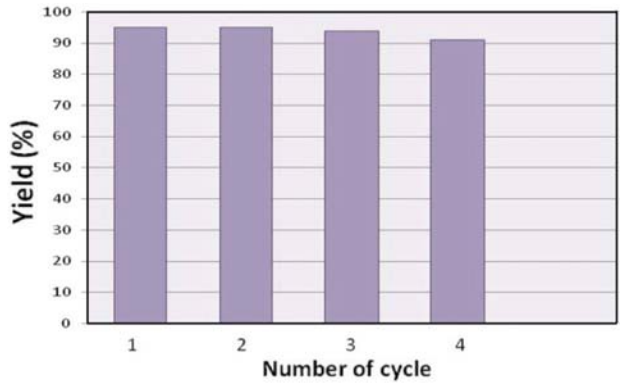


Figure 1. Recoverability of CuI nanoparticles.

The XRD pattern of the CuI nanoparticles is shown in Figure 2. The diffraction peaks match with the standard values and they can be indexed to pure cubic phase of CuI (F-43m) with lattice parameter a = 6.0590Å (JCPDS: 75-0832). The crystalline size of the synthesized copper iodide, D_c, was calculated from several main diffraction peaks using the Debye-Scherrer equation ($D_c = K\lambda/\beta\cos\theta$),[41,48] where K is a constant (ca. 0.9); λ is the X-ray wavelength used in XRD (1.5418 Å), θ is the Bragg angle, and β is the pure diffraction broadening of a peak at half-height

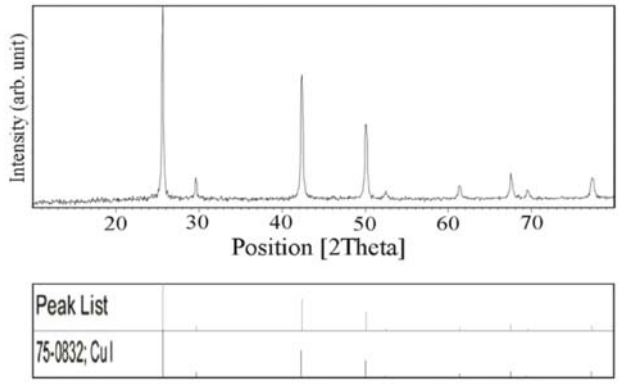


Figure 2. The XRD pattern of CuI nanoparticles.

(0.4723). The average diameter of the nanoparticles calculated by the Debye-Scherrer formula is 20 nm.

In order to investigate the morphology and particle size of CuI nanoparticles, SEM analysis was performed and is shown in Figure 3. These results show that spherical CuI nanoparticles were obtained with an average diameter of 10–30 nm as confirmed by XRD analysis. The increased surface area due to small particle size is beneficial for its reactivity and is responsible for the upward accessibility of the substrate molecules on the catalyst surface.

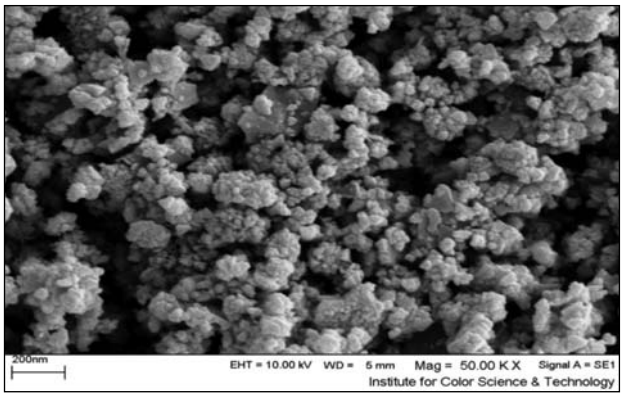


Figure 3. SEM images of CuI nanoparticles.

The chemical purity of the samples as well as their stoichiometry was tested by EDAX studies. The EDAX spectrum given in Figure 4 shows the presence of copper and iodide as the only elementary components.

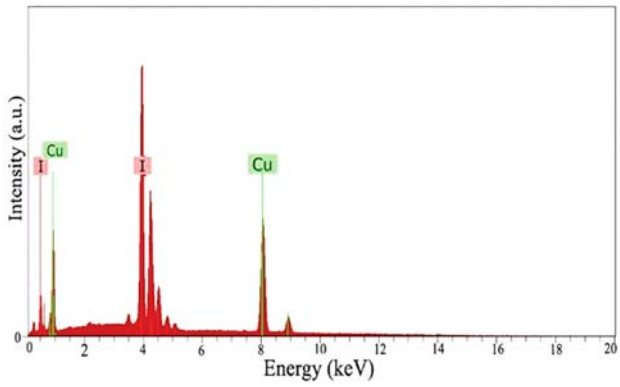


Figure 4. EDAX spectrum of CuI nanoparticles.

The UV-vis spectrum of the synthesized CuI nanoparticles was also recorded as shown in Figure 5. Compared with previous literature data which reported band gap at 405–406 nm,[49,50] the transmission of the obtained CuI nanoparticles exhibit a blue-shift, which is attributed to the quantum confinement of charge carriers in the nanoparticles.

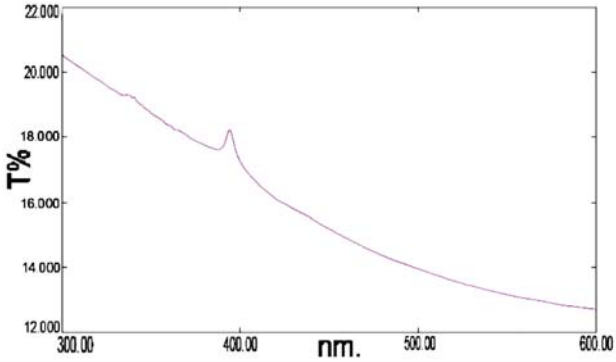


Figure 5. UV-vis spectrum of CuI nanoparticles.

3. 4. Typical Procedure for the Synthesis of Pyranopyrazoles (6a–m):

An mixture of acid chlorides **1** (1 mmol), Meldrum's acid **2** (1mmol) and nano CuI (1.2 mmol) was stirred under reflux for 10 min. Then hydrazine hydrate **3** (1 mmol), aldehyde **4** (1 mmol) and malononitrile **5** (1 mmol) in water (5 mL) were added, and vigorously stirred for the appropriate time (Table 2). Reaction was monitored by TLC. After completion of reaction the solid was filtered off and washed with cold chloroform. The residue was dissolved in hot acetone and then filtered until heterogeneous catalyst was recovered. The filtrate solution was evaporated to afford pure pyranopyrazoles **6** in 84–95% yields. Spectroscopic data of some products are given below.

6-amino-4-(4-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6c). White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76 (s, 3H, CH_3), 4.67 (s, 1H, H-4), 6.68 (s, 2H, NH_2), 7.23 (d, 2H, J = 8.6 Hz, ArH), 7.42 (d, 2H, J = 8.68 Hz, ArH.), 11.89 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.7, 18.5, 56.7, 114.6, 120.6, 128.4, 129.3, 131.2, 135.6, 143.4, 154.7, 160.9 ppm; FT-IR (KBr): υ 1077, 1414, 1498, 1607, 1649, 2196, 2926, 3190, 3388, 3472 cm^{-1}; Anal. Calcd for. $C_{14}H_{11}ClN_4O$: C, 58.65; H, 3.87; N, 19.54%; Found: C, 58.51; H, 3.79; N, 19.81%.

6-amino-4-(4-chlorophenyl)-3-ethyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (6g).

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76 (t, 3H, CH_2CH_3), 1.91 (q, 2H, CH_2CH_3), 4.43 (s, 1H, H-4), 6.04 (s, 2H, NH_2), 6.92 (d, 2H, J = 8.5 Hz, ArH), 7.11 (t, 2H,J = 8.4 Hz, Ar-H); 11.51 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.6, 14.3, 68.7, 104.6, 119.9, 127.8, 135.2, 138.6, 140.1, 142.2, 160.7, 163.2, 164.6 ppm; FT-IR (KBr): υ 1071, 1412, 1501, 1613, 1663, 2213, 2921, 3166, 3389 cm^{-1}; Anal. Calcd for $C_{15}H_{13}ClN_4O$: C, 59.91; H, 4.36; N, 18.63%; Found: C, 59.82; H, 4.31; N, 19.84%.

6-amino-4-phenyl-3-ethyl-2,4-dihydropyrano[2,3-*c*] pyrazole-5-carbonitrile (6h).

Yellowish solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.73 (t, 3H, CH_2CH_3), 1.89 (q, 2H, CH_2CH_3), 4.44 (s, 1H, H-4), 6.01 (s, 2H, NH_2), 6.59 (d, 2H, J = 8.4 Hz, ArH), 6.87 (t, 2H, J = 8.2 Hz, Ar-H); 6.90 (d, 1H, J = 8.2 Hz, Ar-H), 11.44 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.5, 14.1, 68.3, 104.1, 119.0, 126.5, 133.9, 134.0, 134.2, 141.3, 160.4,163.1, 164.3 ppm; FT-IR (KBr): υ 1068, 1416, 1503, 1611, 1655, 2201, 2928, 3163, 3391 cm^{-1}; Anal. Calcd for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04%; Found: C, 67.61; H, 5.48; N, 21.13%.

6-amino-3-ethyl-2,4-dihydro-4-(4-nitrophenyl)pyrano [2,3-*c*]pyrazole-5-carbonitrile (6i).

Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.74 (t, 3H, CH_2CH_3), 1.95 (q, 2H, CH_2CH_3), 4.44 (s, 1H, H-4), 6.15 (s, 2H, NH_2), 6.99 (d, 2H, J = 8.4 Hz, ArH), 7.14 (t, 2H, J = 8.6 Hz, Ar-H); 11.48 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.4, 14.1, 68.9, 104.4, 119.3, 127.5, 135.1, 138.3, 139.2, 142.4, 160.8, 163.7, 164.2 ppm; FT-IR (KBr): υ 1064, 1346, 1415, 1493, 1511, 1618, 1661, 2210, 2911, 3151, 3392 cm^{-1}; Anal. Calcd for $C_{15}H_{13}N_5O_3$: C, 57.87; H, 4.21; N, 22.50%; Found: C, 57.82; H, 4.14; N, 22.81%.

6-amino-4-phenyl-3-phenyl-2,4-dihydropyrano[2,3-*c*] pyrazole-5-carbonitrile (6l).

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.77 (s, 1H, H-4), 6.17(s,2H, NH_2), 7.51 (d, 2H,J = 7.9 Hz, ArH), 7.57 (m, 5H, ArH), 7.76 (t, 2H,J = 7.7 Hz, ArH), 11.41 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.9, 56.1, 113.3, 120.0, 122.7, 128.3, 128.9, 136.1, 138.9, 141.2, 145.6, 147.4, 150.1, 154.5, 161.6 ppm; FT-IR (KBr): υ 1076, 1407, 1527, 1600, 1653, 2196, 2932, 3118, 3217, 3469 cm^{-1}; Anal. Calcd for $C_{19}H_{14}N_4O$: C, 72.60; H, 4.49; N, 17.82%; found: C, 72.14; H, 4.58; N, 17.58%.

6-amino-4-(4-chlorophenyl)-2,4-dihydro-3-phenylpyrano[2,3-*c*]pyrazole-5-carbonitrile (6m).

White solid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.81 (s, 1H, H-4), 6.19 (s,2H, NH_2), 7.53 (d, 2H, J = 8.1 Hz, ArH), 7.61 (m, 5H, ArH), 7.78 (t, 2H, J = 7.8 Hz, ArH), 11.48 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 28.1, 56.4, 113.4, 120.4, 122.9, 128.2, 129.2, 136.3, 138.7, 142.2, 148.6, 147.9, 152.6, 161.8 ppm; FT-IR (KBr): υ 1079, 1411, 1532, 1604, 1651, 2199, 2931, 3127, 3214, 3477 cm^{-1}; Anal. Calcd for $C_{19}H_{13}ClN_4O$: C, 65.43; H, 3.76; N, 16.06%; found: C, 65.39; H, 3.69; N, 16.18%.

4. Conclusions

In conclusion, we have developed a one-pot, clean, efficient, and economic procedure for the synthesis of pyranopyrazoles via five-component coupling of acid chlorides, Meldrum's acid, hydrazine hydrate, aromatic aldehydes and malononitrile over the high surface area of CuI nanoparticles in water media. *In situ* synthesis, mild reaction conditions, wide range of non-polluted product, excellent yields, and using recyclable catalyst make this methodology highly attractive.

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Povzetek

V prispevku je predstavljena nova enostopenjska petkomponentna reakcija v vodnem mediju za pripravo visokofunkcionaliziranih piranopirazolov iz kislinskih kloridov, Meldrumove kisline, hidrazinhidrata, aromatskih aldehidov in malononitrila v prisotnosti katalitskih množin CuI nanodelcev. Metoda prinaša več prednosti, kot so *in-situ* priprava β-ketoestra, mili reakcijski pogoji, okolju prijazna, brez odpada in enostavna izolacija produktov z visokimi izkoristki. Pri reakciji uporabljen katalizator lahko regeneriramo in večkrat uporabimo ob skoraj nespremenjeni katalitski aktivnosti.