Caffeine as A Catalyst for A Four-Component Synthesis of Dihydropyrano [2, 3-*C*]Pyrazoles in Water

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Abstract

We describe a one-pot four component synthesis of pyrano[2,3-*c*]pyrazoles from hydrazine hydrate or phenyl hydrazine, ethyl acetoacetate, an aldehyde, and malononitrile in the presence of catalytic amounts of a caffeine as a green catalyst in water at 50 ºC. The present protocol offers the advantages of a clean reaction, a short reaction time, a high product yield, and an environmentally-friendly, easily-purified, and economically-available catalyst.

Keywords: Four-Component Reaction, Caffeine, Green Catalyst, Aldehyde, Pyrano[2,3-*C*] Pyrazole.

Introduction

Multi-component reactions (MCRs) have emerged as a powerful tool for the construction of novel and complex molecular structures due to their advantages over the conventional multi-step synthetic reactions. The major advantages of MCRs include their lower cost, shorter reaction time, high atom-economy, and energy savings by avoiding the time-consuming and expensive purification processes [1]. This strategy is an important development in drug discovery in the context of rapid identification and optimization of biologically-active lead compounds [2]. Moreover, MCRs are environmentally friendly, and often proceed with excellent chemo-selectivities [3].

The “green chemistry” techniques continue to grow in importance, with the aim of conserving resources and reducing costs. The replacement of conventional solvents with water, which is harml

ess to the health and is available in large quantities, is an interesting basic approach along this line [4]. In recent years, the focus on “green chemistry” using environmentally benign reagents and conditions has been one of the most fascinating developments in the synthesis of widely used organic compounds. The use of water as a promising solvent for organic reactions has received considerable attention in the arena of organic synthesis owing to its green credentials [5]. Following the increasing demand for “green chemistry”, the search for more environmentally benign forms of catalysis has received overwhelming attention, and one of the leading contestants for environmentally acceptable alternatives is the biodegradable materials. Although some biodegradable materials such as chitosan [6], gluconic acid [7], cellulose sulfuric acid [8], xanthan sulfuric acid [9], starch sulfuric acid [10], sulfuric acid-modified PEG (PEG-OSO_3H) [11], and egg-shell [12] have been proposed as catalysts used in some organic transformations, the number of available bio-based catalysts is far from abundant at this stage.

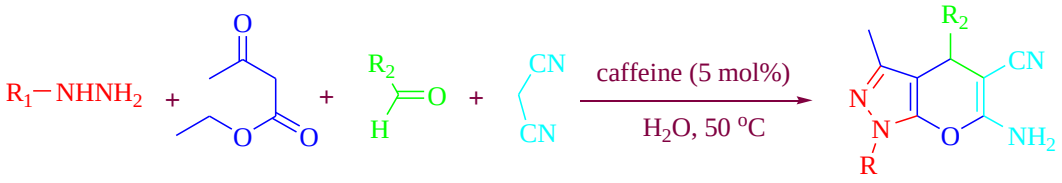
Caffeine (1,3,7-Trimethylpurine-2,6-dione) is a heterocyclic organic compound that is classified by the Food and Drug Administration as "generally recognized as safe". It consists of a pyrimidine ring fused to an imidazole ring with the chemical formula $C_8H_{10}N_4O_2$ [13]. Our approach was based upon caffeine, a cheap source of N-methyl imidazole resulting from the decaffeination of coffee. The use of caffeine has been recently reported for the synthesis and structural characterization of N-heterocyclic carbenes [14. Moreover, caffeine is inexpensive, non-corrosive, stabile to air and moisture, and readily available in the market.

Pyranopyrazoles are fused heterocyclic compounds that exhibit bactericidal [15], insecticidal [16], molluscicidal [17], analgestic [18], anti-inflammatory [19] and anti-cancer activities [20]. Due to their biological significance, there has been considerable interest in developing synthetic methods for the preparation of pyranopyrazole

derivatives [21]. As a result, several strategies have been developed for the synthesis of pyranopyrazoles through a two-component [22] or three-component reaction [23].

Recently, Zhang et al. have developed a four-component domino reaction using a hydrazine, α, β-keto ester, an aldehyde, and malononitrile in the presence of meglumine for the synthesis of pyranopyrazoles [24]. Pasha and coworkers have reported an efficient four-component reaction of meldrums acid, ethyl acetoacetate, hydrazine hydrate, and aromatic aldehydes for the synthesis of 3-methyl-4-aryl-4,5-dihydro-1H-pyrano[2,3-c]pyrazol-6-ones in refluxing water [25]. The one-pot, four-component synthesis of diverse pyranopyrazoles has also been accomplished, which consists of condensation of aldehydes, ethyl acetoacetate, malononitrile, and hydrazines. In this context, some catalysts have been used to promote these condensation reactions such as piperidine [26], trimethylamine [27], per-6-amino-β-cyclodextrin [28], imidazole [29], nano-sized magnesium oxide [30], and silica-bonded n-propyl-4-aza-1-azoniabicyclo [2.2.2]octane chloride (SB-DABCO) [31]. Although these methods are quite satisfactory, some of them suffer from the absence of "green chemistry", and have been associated with several shortcomings such as the use of volatile and hazardous organic solvents, low product yields, use of expensive and environmentally-hazardous reagents, extended reaction times, high temperature, and tedious procedures for the preparation of catalysts. Thus the development of general, economical, and environmentally benign synthetic methodologies for pyranopyrazoles is highly desirable.

The combination of an MCR, an environmentally benign form of catalyst, and a green solvent has become a promising frontier field of research in organic, medicinal, and combinatorial chemistry [32]. Considering the above subjects, and continuing our research program to develop selective, efficient, and green methods and catalysts in organic synthesis [33-35]. We herein report a simple, rapid, and high-yielding one-pot four-component reaction protocol for the synthesis of pyranopyrazole derivatives employing environmentally-friendly caffeine as a catalyst in water at 50 ºC (Scheme 1).



1 **2** **3** **4** **5**

Scheme 1

Experimental

General Remarks

The caffeine used was supplied from Aldrich. Melting points were recorded on an electrothermal type 9100 melting point apparatus. IR spectra were obtained on a 4300 Shimadzu spectrometer as KBr disk. ^{1}H-NMR spectra were recorded on a Bruker BRX 400 AVANCE spectrometer. Elemental analysis results were obtained using a Thermo Finnigan Flash EA microanalyser

Typical Procedure for Synthesis of Dihydropyrano[2,3-C] Pyrazoles 5

Caffeine (0.05 mmol, 0.1 g) was added to a mixture of aldehyde (1.0 mmol), hydrazine hydrate or phenylhydrazine (1.0 mmol), malononitrile (1.0 mmol, 0.054 g), and ethyl acetoacetate (1.0 mmol, 0.13 g) in water (3 mL). The resulting mixture was stirred at 50 ºC. After completion of the reaction (monitored by TLC), the precipitated product was filtered to separate the catalyst. The crude product was purified by recrystallization from ethanol to afford the desired product.

Selected Spectral Data

6-Amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 5a:

White solid; IR (KBr) ν: 3400, 3200, 2195, 1640, 1610, 1490, 1390, 1055 cm-1; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.82 (s, 3H, CH_3), 4.63 (s, 1H, CH), 6.90 (s, 2H, NH_2), 7.20-7.25 (m, 2H, HAr), 7.26-7.28 (m, 1H, HAr), 7.34-7.38 (m, 2H, HAr), 12.13 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 9.7, 36.1, 57.1, 97.6, 120.7, 126.7, 127.4, 128.4, 135.5, 144.4, 154.7, 160.8; Anal. Calcd for $C_{14}H_{12}N_4O$: C 66.65, H 4.79, N 22.21; found: C 66.85, H 4.90, N 22.03.

6-Amino-3-methyl-4-(4-N, N-dimethylamino-phenyl)-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile 5f.

White solid; IR (KBr) ν: 3410, 3200, 2190, 1640, 1600, 1492, 1390, 1050 cm-1; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.80 (s, 3H, CH_3), 2.87 (s, 6H, NMe_2), 4.46 (s, 1H, CH), 6.67 (d, J = 8.4 Hz, 2H, HAr), 6.77 (s, 2H, NH_2), 6.97 (d, J = 8.4 Hz, 2H, HAr), 12.05 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 10.2, 35.8, 58.4, 98.6, 112.7, 121.4, 128.4, 132.5, 132.7, 135.9, 149.7, 155.2, 160.9; Anal. Calcd for $C_{16}H_{17}N_5O$: C, 65.07; H, 5.80; N, 23.71. Found: C, 64.90; H, 5.71; N, 23.87.

6-Amino-3-methyl-4-(2-chlorophenyl)-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile 5h.

White solid; IR (KBr) ν: 3420, 3200, 2192, 1635, 1600, 1490, 1390, 1054 cm-1; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.85 (s, 3H, CH_3), 5.16 (s, 1H, CH), 7.03 (s, 2H, NH_2), 7.27 (d, J = 5.4 Hz, 1H, HAr), 7.33-7.43 (m, 2H, HAr), 7.50 (dd, J = 6.9, 0.9 Hz, 1H, HAr), 12.21 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 9.8, 34.19, 56.3, 96.8, 120.3, 127.7, 128.5, 129.4, 130.6, 131.9, 135.3, 140.8, 154.9, 162.2; Anal. Calcd for $C_{14}H_{11}ClN_4O$: C, 58.65; H, 3.87; N, 19.54. Found: C, 58.46; H, 3.79; N, 19.73.

6-Amino-3-methyl-4-(2,3,4-trimethoxy-phenyl)-1,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile 5o

White solid; IR (KBr) ν: 3400, 3206, 2200, 1635, 1600, 1490, 1101 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.85 (s, 3H, CH_3), 3.81 (s, 6H, OCH_3), 4.52 (s, 1H, CH), 6.42 (s, 2H, HAr), 6.84 (s, 2H, NH_2), 8.28 (s, 1H, OH), 12.08 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ ppm: 9.8, 36.2, 55.9, 57.3, 97.6, 104.8, 120.8, 134.3, 134.4, 135.6, 147.7, 147.8, 154.6, 160.7; Anal. Calcd for $C_{16}H_{16}N_4O_4$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.35; H, 4.80; N, 17.25.

6-Amino-3-methyl-4-(4-hydroxy-3,5-dimethoxy-phenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 5p.

White solid; IR (KBr) ν: 3392, 3210, 2192, 1641, 1600, 1491, 1100 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.80 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.74 (s, 1H, CH), 6.75-6.79 (m, 4H, HAr, NH_2), 12.01 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 9.9, 31.0, 56.1, 57.3, 60.6, 61.3, 98.4, 108.4, 121.5, 123.8, 130.1, 135.5, 141.9, 151.5, 152.5, 155.4, 161.4; Anal. Calcd for $C_{17}H_{18}N_4O_4$: C, 59.64; H, 5.30; N, 16.37. Found: C, 59.82; H, 5.21; N, 16.54.

6-Amino-3-methyl-4-(furan-2-yl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 5r.

White solid; IR (KBr) ν: 3390, 2200, 1640, 1600, 1100 cm^{-1}; ^{1}H NMR (DMSO-*d6*, 300 MHz) δ: 1.98 (s, 3H, CH_3), 4.78 (s, 1H, CH), 6.18 (d, J = 3.0 Hz, 1H, HAr), 6.37-6.39 (m, 1H, HAr), 6.96 (s, 2H, NH_2), 7.54 (t, J = 0.9 Hz 1H, HAr), 12.17 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 10.0, 30.2, 54.4, 95.5, 106.1, 110.7, 121.0, 136.1, 136.3, 142.7, 155.2, 156.1, 161.9; Anal. Calcd for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.70; H, 4.24; N, 23.32.

6-Amino-3-methyl-4-(2-chloroquinolin-3yl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 5s. White solid; IR (KBr) ν: 3400, 3290, 2202, 1645, 1610, 1490, 1100 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 1.79 (s, 3H, CH_3), 5.21 (s, 1H, CH), 7.11 (s, 2H, NH_2), 7.63-7.68 (m, 1H, HAr), 7.79-7.84 (m, 1H, HAr), 7.95 (d, J = 8.4 Hz, 1H, HAr), 8.08 (d, J = 8.4 Hz, 1H, HAr), 8.40 (s, 1H, HAr), 12.21 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 10.1, 34.1, 56.3,

96.5, 120.9,127.7, 127.9, 128.4, 131.3, 135.8, 136.0, 140.0, 146.6, 149.6, 155.5, 161.9; Anal. Calcd for $C_{17}H_{12}ClN_5O$: C, 60.45; H, 3.58; N, 20.73. Found: C, 60.66; H, 3.69; N, 20.90.

Results and Discussion

Initially, we selected hydrazine hydrate (1.0 mmol), ethyl acetoacetate (1.0 mmol), benzaldehyde (1.0 mmol), and malononitrile (1.0 mmol) as the model substrates in water to establish the optimum reaction conditions. When the reaction was attempted without a catalyst at 50 °C, it was found that only a trace amount of the product **5a** was obtained even after 6 h (Table 1, entry 1). This result suggests that a catalyst plays a critical role in this reaction. We also varied the amount of caffeine from 5 to 20 mol%, and the results obtained revealed that 5 mol% of caffeine gave an excellent

product yield in a short time, as shown in Table 1. Also the effect of temperature on the conversion and reaction time was checked, and the results obtained were tabulated in Table 1. It is obvious that at room temperature (25 °C), there was a low-yield product was formed. As the temperature increased from the room temperature to 80 °C, the product yield was found to increase. We obtained the best results at 50 °C (Table 1, entry 2).

Table 1. Investigation of catalyst effects and temperature in the synthesis of pyrano[2,3-*c*]pyrazole **5a**[a]

Entry	Caffeine (mol%)	Temp. (°C)	Time (min)	Yields (%)[b]
1	0	50	360	10
2	5	50	30	98
3	10	50	30	98
4	20	50	30	98
5	5	80	30	98
6	5	r.t	60	40

[a]Reaction conditions: hydrazine hydrate (1.0 mmol), ethyl acetoacetate (1.0 mmol), benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), H_2O (3 mL)

[b]Isolated yields.

To select the best catalyst, we carried out the above model reaction in the presence of 5 mol% of different base catalysts such as Et_3N, pyridine, piperidine, K_2CO_3, Na_2CO_3, and KOH (Table 2). We found that piperidine did not afford the product in good yield, and that the reaction time was very long. A similar result was obtained with K_2CO_3. When the same reaction was carried out in the presence of caffeine, the product was obtained in an excellent yield (98%) within 30 min (Table 2, entry 7).

Table 2. Effect of Catalysts on the synthesis of pyrano[2,3-*c*]pyrazole **5a**[a]

Entry	Catalyst (5 mol%)	Time (min)	Yields (%)[b]
1	Et_3N	120	75
2	Pyridine	45	50
3	Piperidine	120	40
4	K_2CO_3	180	50
5	Na_2CO_3	45	45
6	KOH	45	65
7	Caffeine	30	98

[a]Reaction conditions: hydrazine hydrate (1.0 mmol), ethyl acetoacetate (1.0 mmol), benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), H_2O (3 mL)

[b]Isolated yields.

The solvent used also played an important role in the studied transformation. We carried out the above reaction in various solvents in order to check the catalytic response of caffeine. As shown in Table 3, when the reaction was performed under solvent-free conditions, the target product was obtained with a low yield. To find the best solvent for this transformation, the present four-component reaction was screened in EtOH, THF, CH_3CN, 1,4-dioxan, toluene, and H_2O. Among all of these solvents, H_2O was found to be the best one, affording the highest product yield (Table 3, entry 7). Therefore, the subsequent reactions were performed in the presence of 5 mol% of the catalyst in water at 50 °C.

Table 3. Optimization of solvents study for the synthesis of pyrano[2,3-*c*]pyrazole **5a**[a]

Entry	Solvent	Temp. (°C)	Time (min)	Yields (%)[b]
1	Neat	50	30	60
2	EtOH	Reflux	60	65
3	THF	Reflux	120	70
4	CH_3CN	Reflux	180	50
5	1,4-Dioxan	Reflux	120	90
6	Toluene	Reflux	180	90
7	H_2O	50	30	98

Entry	R_1	R_2	Product	Time (min)	Yield[b] (%)	M. p. (ºC) (Lit.) [Ref.]
1	H	Ph	**5a**	30	98	240-242 (242-244) [24]
2	H	2-OH-C_6H_4	**5b**	120	80	205-207 (208-210) [36]
3	H	4-Me-C_6H_4	**5c**	60	98	196-198 (197-198) [37]
4	H	4-MeO-C_6H_4	**5d**	60	96	212-214 (210-212) [24]
5	H	2-MeO-C_6H_4	**5e**	60	85	249-251 (249-250) [24]
6	H	4-Me_2N-C_6H_4	**5f**	120	70	217-219 (219-220) [38]
7	H	4-Cl-C_6H_4	**5g**	120	70	232-234 (234-235) [24]
8	H	2-Cl-C_6H_4	**5h**	90	82	243-245 (245-246) [24]
9	H	2,4-Cl_2-C_6H_3	**5i**	60	70	194-196 (229-230) [24]
10	H	2,6-Cl_2-C_6H_3	**5j**	60	78	190-192 (188-190) [39]
11	H	4-Br-C_6H_4	**5k**	90	65	249-251 (247-248) [38]
12	H	2-NO_2-C_6H_4	**5l**	60	90	241-243 (243-244) [24]
13	H	3-NO_2-C_6H_4	**5m**	60	72	211-213 (232-233) [24]
14	H	4-NO_2-C_6H_4	**5n**	120	82	245-247 (248-249) [24]
15	H	2,3,4-$(OMe)_3$-C_6H_2	**5o**	30	85	222-224 (223-225) [24]
16	H	3,5-$(OMe)_2$-4-OH-C_6H_2	**5p**	90	80	212-214

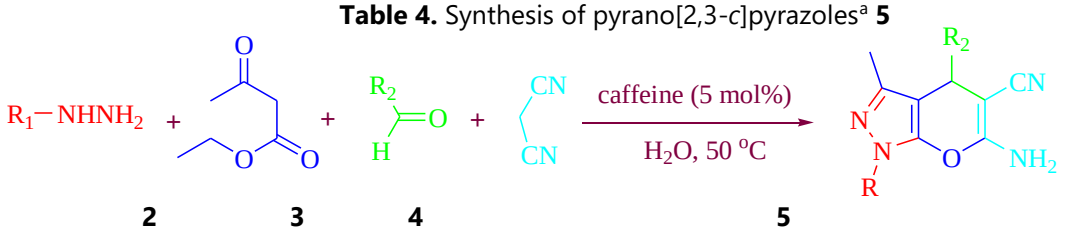
17	H	2'-thiophenyl	**5q**	45	96	222-224 (224-226) [24]
18	H	2'-Furanyl	**5r**	40	90	233-235 (230-231) [24]
19	H	2-chloroquinoline-3-yl	**5s**	60	83	235-237
20	H	CH_3-	**5t**	60	65	151-153 (155-157) [40]
21	H	$(CH_3)_2CH$-	**5u**	60	58	167-169 (166-168) [41]
22	H	$(CH_3)_2CHCH_2$-	**5v**	90	55	184-186 (186-188) [42]
23	H	$CH_3CH_2CH_2$-	**5w**	120	45	140-142 (143-145) [40]
24	Ph	Ph	**5x**	90	65	167-169 (168-170) [43]
25	Ph	4- Me-C_6H_4	**5y**	95	65	177-179 (176-178) [44]
26	Ph	4-MeO-C_6H_4	**5z**	95	70	165-167 (169-170) [44]
27	Ph	2-MeO-C_6H_4	**5aa**	180	55	85-87 (87-89) [45]
28	Ph	4-Cl-C_6H_4	**5ab**	60	70	170-172 (172-174) [46]
29	Ph	2-Cl-C_6H_4	**5ac**	90	75	140-142 (144-146) [46]
30	Ph	2,4-Cl_2-C_6H_3	**5ad**	120	60	183-185 (182-184) [46]
31	Ph	2-NO_2-C_6H_4	**5ae**	30	82	149-151 (152-155) [46]
32	Ph	4-NO_2-C_6H_4	**5af**	180	65	190-192 (187-188) [46]
33	Ph	4-Br-C_6H_4	**5ag**	120	70	185-187 (184-185) [44]

[a]Reaction conditions: hydrazine hydrate (1.0 mmol), ethyl acetoacetate (1.0 mmol), benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), caffeine (0.05 mmol), solvent (3 mL).

[b]Isolated yields.

After optimizing the experimental conditions, the generality of the method was examined by the reaction of different aldehydes with ethyl acetoacetate, malononitrile, and hydrazine hydrate in the presence of 5 mol% of caffeine in water at 50 ºC. As it is evident in Table 4, all reactions proceeded efficiently, and the desired products were obtained in high to excellent yields in relatively short times without the formation of any by-product. The nature of the functional group on the aromatic ring of the aldehyde exerted a slight influence on the reaction time. A decrease in the reaction rate was observed with aryl aldehyde carrying an electron-donating group, in comparison to the unsubstituted benzaldehyde. Heteroaromatic aldehydes such as furan-2-carbaldehyde, thiophene-2-carbaldehyde and 2-chloro-quinoline-3-carbaldehyde readily participated in the transformation,

Table 4. Synthesis of pyrano[2,3-*c*]pyrazoles[a] **5**



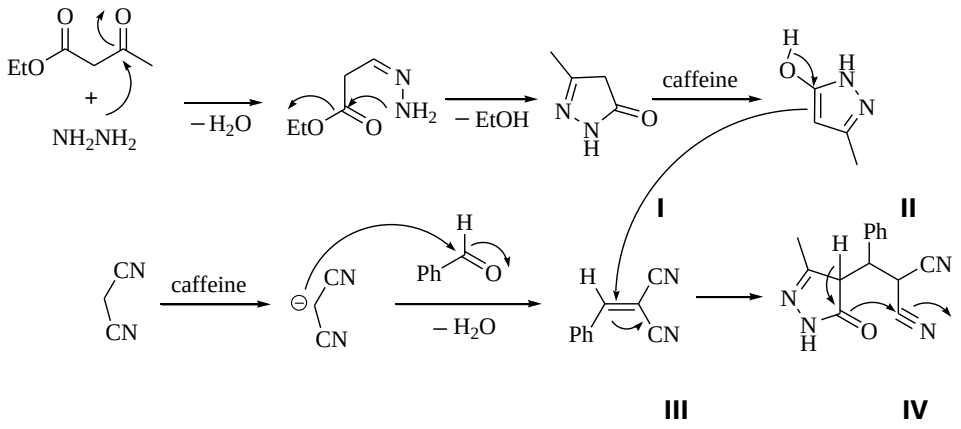
1 **2** **3** **4** **5**

[a]Reaction conditions: Hydrazin hydrate or phenyl hyrazine (1.0 mmol), ethyl acetoacetate (1.0 mmol), malononitrile (1.0 mmol), aldehyde (1.0 mmol), caffeine (0.05 mmol), H_2O (3.0 mL), at 50 ºC

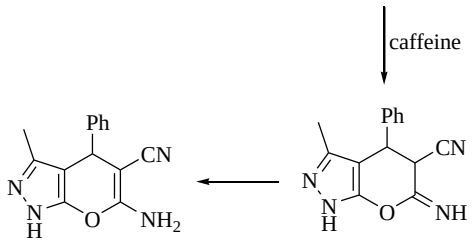
[b]Isolated yield.

affording the pyranopyrazoles in high yields (Table 4, entries 17-19). It is pertinent to note that aliphatic aldehydes have not been found to be appropriate starting materials in many reported procedures due to the formation of unwanted by-products *via* various side-reactions such as the aldol and Cannizzaro reactions. Fortunately, the caffeine-catalyzed transformations have not been found to be limited to the aliphatic aldehydes, and have given the pyranopyrazoles in good yields (Table 4, entries 20-23).

Mechanistically, the reactions occur *via* the initial formation of phenylidenemalononitrile (**III**) in a quantitative yield by the Knoevenagel addition of malononitrile to the bezaldehyde followed by the loss of water molecules (Scheme 2). Probably, the presence of caffeine plays a major role in its promoting activity for the formation of phenylidenemalononitrile (**III**) from the Knoevenagel condensation of the benzaldehyde and malononitrile. 3-Methyl-1*H*-pyrazol-5(4*H*)-one (**I**) was formed from the condensation of ethyl acetoacetate and hydrazine, which would be converted to its corresponding enolate form (**II**) in the presence of caffeine. Finally, the Michael addition of 3-Methyl-5-hydroxy pyrazole (**II**) to the intermediate (**III**) followed by cyclization and tautomerization yielded pyrano[2,3-*c*]pyrazole **5a**.



I **II** **III** **IV**



5a **V**

Scheme 2. Plausible mechanism for synthesis of pyrano[2, 3-*c*]pyrazole **5a**.

A comparative study of the reaction conditions for the synthesis of pyranopyrazole **5a** using the methods given in Table 5 and reported in the present letter demonstrates the advantages of the present methodology. As shown in Table 5, the use of caffeine leads to an improved protocol in terms of compatibility with environment, reaction time, and product yield when compared with other catalysts.

Table 5. Comparison of our results with previously reported methods for synthesis of pyrano [2,3-*c*]pyrazole **5a**

Entry	Catalyst (mol %)	Reaction conditions	Time (min)	Yield (%) [Ref.]
1	Et_3N (20)	EtOH, Reflux	15	65 [25]
2	Piperidine (5)	H_2O, rt	10	83 [24]
3	Meglumin (10)	EtOH: H_2O (9:1), rt	15	95 [23]
5	L-Proline (10)	H_2O, reflux	10	90 [47]
6	Imidazole (50)	H_2O, 80 °C	20	80 [27]
7	[bmim]OH (20)	50-60 °C	10	88 [48]
8	Nanosize MgO (6)	CH_3CN, rt	10	97 [28]
9	Caffeine (5)	H_2O, 50 °C	30	98 This work

Conclusions

We have described a simple, clean, efficient, green, and one-pot four-component protocol for the synthesis of some pyranopyrazoles from hydrazine hydrate or phenyl hydrazine, ethyl acetoacetate, an aldehyde, and malononitrile catalyzed by caffeine as a readily available, inexpensive, and efficient catalyst in water at 50 °C. Reaction conditions are very simple for substituted aldehydes through this tandem reaction The advantages offered by this method are simple reaction conditions, short reaction time, ease of product isolation, and high product yield. Only small amount of this catalyst is used, which is recovered by filtration of the aqueous solution of the product.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supplementary Information (SI)

Copies of ^{1}H NMR and ^{13}C NMR spectrum of some of products are given in the supporting information.

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