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Farzaneh Mohamadpour

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OPPI BRIEF

Caffeine as a Naturally Green and Biodegradable Catalyst for Preparation of Dihydropyrano[2,3-*c*]pyrazoles

Farzaneh Mohamadpour

School of Engineering, Apadana Institute of Higher Education, Shiraz, Iran

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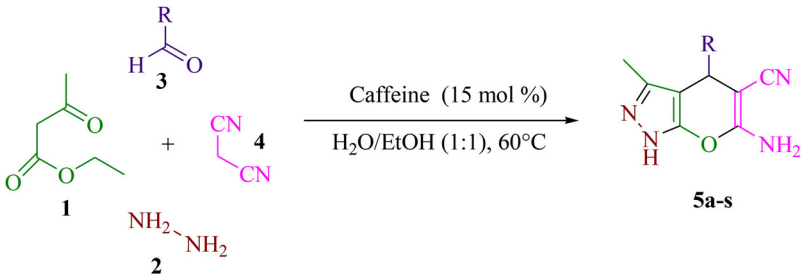
The dihydropyrano[2,3-*c*]pyrazole structure is a common motif in a variety of useful natural and non-natural products. For example these heterocyclic compounds have been used as therapeutic agents.[1] They are potential inhibitors of human Chk1 kinase,[2] and they have anticancer,[3] molluscicidal[4] and antimicrobial[5] properties. The known procedures for the synthesis of dihydropyrano[2,3-*c*]pyrazoles include the reaction of hydrazine hydrate and phenylhydrazine with malononitrile, three-component reactions of aldehydes, malononitrile, and pyrazolones, and the cyclocondensation reactions of ethyl acetoacetate, hydrazine hydrate, aldehydes and malononitrile.[6, 7]

Typically, the syntheses of these important compounds are catalyzed by ZrO_2 nanoparticles,[8] choline chloride/urea deep eutectic mixtures,[9] isonicotinic acid,[10] molecular sieves,[11] meglumine,[12] CAPB,[13] L-proline/KF-alumina,[14] CTACl,[15] lipase,[16] bovine serum albumin,[17] β-cyclodextrin,[18] morpholine triflate,[19] TPSPPTNM,[20] [Dabco-H][AcO][21] and DABCO.[22] All of these methodologies are attractive and have merits; but common problems encountered are low yields, the toxicity of both solvents and catalysts, harsh reaction conditions and expensive materials. Based on these considerations and our interest in efficient and environmentally benign methodologies,[23–30] we now report a green, simple and efficient procedure for the multi-component synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives *via* the domino Knoevenagel-Michael cyclocondensation reaction of ethyl acetoacetate, hydrazine hydrate, aryl aldehydes and malononitrile; we used caffeine as a catalyst in aqueous ethanol and found good yields and short reaction times.

To begin our study, the optimal conditions for this reaction (Scheme 1) were investigated. Conducting the reaction for compound **5c,** we examined catalyst loading, solvents, and reaction times. The best result was obtained with 15 mol % of the caffeine as catalyst at 60 °C in H_2O/EtOH (1:1) and gave **5c** in 25 min in 83% yield (Table 1, entry 5).

After optimizing the conditions, the scope of this process was studied by varying the aldehyde component. The results of this study are presented in Table 2. The reaction does not appear to be particularly sensitive to substrate structure, with good yields generally observed for the reactions involving aryl aldehydes. In our hands, the process was not satisfactory for aliphatic aldehydes. After completion of the reaction (as

CONTACT Farzaneh Mohamadpour mohamadpour.f.7@gmail.com School of Engineering, Apadana Institute of Higher Education, Shiraz, Iran.



Scheme 1. Synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives.

determined by thin layer chromatography), the solid product was collected by simple filtration and the analytical sample was recrystallized from ethanol.

We made a comparison of caffeine's catalytic ability in this process to those of previously reported catalysts for this purpose, and the comparison can be seen in Table 3. Yields for all of these processes tend to be good, with comparatively short reaction times. The principal advantage to using caffeine as a catalyst for this process is its ready availability, biodegradability and eco-friendliness. Another important advantage of our procedure is its simplicity. We hope that the convenience of our method will lead to an increase in the preparation of these useful compounds and further exploration of their applications.

Experimental section

Melting points of all compounds were determined using an Electrothermal 9100 apparatus and are corrected. ^{1}HNMR spectra were recorded on a Bruker DRX-400 Avance instrument with DMSO-d_6 as solvent. All reagents and solvents were purchased from Merck, Fluka and Acros chemical companies and were used without further purification. Completion of the reaction was determined by thin layer chromatography (silica gel, *n*-hexane/ethyl acetate 9/3).

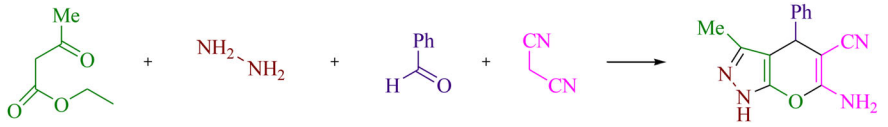
General procedure for preparation of dihydropyrano[2,3-c]pyrazole derivatives (5a-s)

Caffeine (15 mol%) was added to a mixture of ethyl acetoacetate (**1**, 1 mmol), hydrazine hydrate (**2**, 1 mmol), aryl aldehyde (**3**, 1 mmol) and malononitrile (**4**, 1 mmol) in H_2O/EtOH (3 mL, 1:1) at 60 °C. After completion of the reaction (as determined by TLC) the mixture was cooled to rt, the precipitated product was filtered and washed with aqueous ethanol. The crude material was purified by recrystallization from ethanol to afford the desired product (**5a-s**). All of the compounds were known and were identified by comparing their corrected melting points with those in the literature cited. For the sake of completeness, spectral data of selected products are given below.

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

Yield: 83%; mp 246-248 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.79 (3H, s, CH_3), 4.61 (1H, s, CHAr), 6.89 (2H, s, NH_2), 7.18 (2H, d, $J = 9.2$ Hz, ArH), 7.21-7.26 (1H, m, ArH), 7.31-7.36 (2H, m, ArH), 12.11 (1H, s, NH).

Table 1. Optimization of the reaction condition on the synthesis of **5c**.



Entry	Caffeine (mol %)	Solvent/Conditions	Time (min)	Isolated Yields (%)
1	Catalyst free	H_2O/EtOH, rt	180	trace
2	Catalyst free	H_2O/EtOH, 60 °C	180	trace
3	5	H_2O/EtOH, 60 °C	60	27
4	10	H_2O/EtOH, 60 °C	40	59
5	**15**	**H_2O/EtOH, 60 °C**	**25**	**83**
6	15	Solvent free, 60 °C	60	34
7	15	H_2O , 60 °C	40	52
8	15	EtOH, 60 °C	35	57
9	15	MeOH,60 °C	55	34
10	15	H_2O/EtOH, rt	40	48
11	15	H_2O/EtOH, 40 °C	30	62
12	15	H_2O/EtOH, 50 °C	25	74
13	15	H_2O, rt	65	38
14	15	EtOH, rt	55	42
15	15	MeOH, rt	80	27
16	15	THF, rt	75	35
17	15	$CHCl_3$, rt	85	28
18	15	CH_3CN, rt	55	49
19	15	CH_2Cl_2, rt	85	26
20	20	H_2O/EtOH, 60 °C	25	83

Table 2. Caffeine catalyzed synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives.

Entry	R	Product	Time (min)	Isolated Yields (%)	mp °C	Lit mp°C
1	2-OHC_6H_4	**5a**[a]	25	80	209-211	210-212[22]
2	3-FC_6H_4	**5b**	20	89	241-243	242-243[12]
3	C_6H_5	**5c**	25	83	246-248	244-246[13]
4	4-ClC_6H_4	**5d**	35	79	235-237	234-235[12]
5	4-$OMeC_6H_4$	**5e**	25	84	208-210	210-212[12]
6	2-$O_2NC_6H_4$	**5f**	20	86	244-245	243-244[12]
7	4-OHC_6H_4	**5g**	35	72	221-223	220-223[11]
8	3-ClC_6H_4	**5h**	30	81	228-230	230-231[12]
9	3,4-$(OMe)_2C_6H_3$	**5i**	30	82	188-190	188-191[11]
10	3-BrC_6H_4	**5j**	35	77	221-223	223-224[13]
11	3-OHC_6H_4	**5k**	35	76	224-226	225-228[13]
12	3-$O_2NC_6H_4$	**5l**	20	83	192-194	190-193[13]
13	3,4,5-$(OMe)_3C_6H_2$	**5m**	30	85	211-213	210-212[22]
14	2-$OMeC_6H_4$	**5n**	20	86	248-250	249-250[12]
15	2,4-$Cl_2C_6H_3$	**5o**	35	78	227-229	229-230[12]
16	4-BrC_6H_4	**5p**	35	81	180-182	180-181[8]
17	2-ClC_6H_4	**5q**	30	78	246-248	245-246[12]
18	4-$O_2NC_6H_4$	**5r**	25	87	248-250	248-249[12]
19	4-MeC_6H_4	**5s**	25	85	206-208	205-208[13]

[a]Displayed the characteristic infrared nitrile function band near 2250 cm^{-1}.

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

Yield: 81%; mp 228-230 °C; ^{1}H NMR (400 MHz, DMSO-d_6): 1.77 (3H, s, CH_3), 5.08 (1H, s, CHAr), 7.19–7.45 (6H, m, ArH and NH_2), 12.15 (1H, s, NH).

Table 3. Comparison of catalytic ability some of catalysts reported in the literature for synthesis of dihydropyrano[2,3-*c*]pyrazole derivatives.[a]

Entry	Catalyst	Conditions	Time/Yield (%)	References
1	ZrO_2 NPs	EtOH/H_2O,rt	5 min/95	[8]
2	Choline chloride	Urea Deep, 80 °C	10 min/95	[9]
3	Isonicotinic acid	Solvent-free, 85 °C	30 min/90	[10]
4	Molecular sieves	EtOH, Reflux	1 h/84	[11]
5	Meglumine	EtOH/H_2O, rt	15 min/95	[12]
6	CAPB	H_2O,50-60 °C	4 min/96	[13]
7	L-proline	H_2O, Reflux	10 min/87	[14]
8	KF-alumina	EtOH, Reflux	12 min/80	[14]
9	CTACl	H_2O,90 °C	240 min/89	[15]
10	Lipase	EtOH, 30 °C	1h/90	[16]
11	**Caffeine**	**H_2O/EtOH, 60 °C**	**25 min/83**	**This work**

[a]Based on the four-component reaction of benzaldehyde, hydrazine hydrate, malononitrile and ethyl acetoacetate.

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