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Rapid one-pot four component synthesis of bioactive pyranopyrazoles using citric acid as a mild organocatalyst

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ABSTRACT

An efficient one-pot multicomponent synthesis of pyranopyrazoles from aryl aldehydes, ethyl acetoacetate, malononitrile and hydrazine hydrate in the presence of citric acid as a highly effective organocatalyst is reported. This method offers good yield, clean reaction, short reaction time, and easy purification of product.

Keywords: Citric acid, multicomponent reaction, pyranopyrazole.

INTRODUCTION

Pyranopyrazoles are fused heterocyclic compounds that possess many biological properties such as fungicidal [1], bactericidal [2], vasodilatory activities [3] and act as anticancer agents [4]. They also find application as pharmaceutical ingredients and biodegradable agrochemicals [5-8]. Apart from this, pyrano[2,3-c]pyrazoles have been shown to act as potential insecticidal [9a] and molluscidal agents [9b]. As a result, considerable attention has been focused on the development of new methodologies for the synthesis of these heterocycles.

Substituted 6-aminopyrano[2,3-c]pyrazoles were first synthesized by a reaction between 3-methyl-5-pyrazolone with tetracyanoethylene [10]. After that, numerous methods were developed for the synthesis of these compounds from arylidenemalononitriles and 3-methyl-5-pyrazolone [11], 4-arylidene-3-methyl-5-pyrazolones and malononitrile, and the condensation of aromatic aldehydes, malononitrile, and 3-methyl-5-pyrazolone [12]. Shestopalov et al. reported a chemical [13] as well as electrochemical method [14] for their synthesis. Peng et al. developed a two-component reaction involving pyran derivatives and hydrazine hydrate under combined microwave and ultrasound irradiation [15], and recently Vasuki and coworkers reported a four-component synthesis of pyranopyrazoles from ethylacetoacetate, hydrazine hydrate, aldehyde, and malononitrile [16]. Recently, some methods involving the use of glycine [17], L-proline [18], imidazole [19], per-6-amino-β-cyclodextrin [20], nanosized magnesium oxide [21] and Mg/Al hydrotalcite [22] are developed.

Multicomponent reactions play an important role in modern organic chemistry, because they generally exhibit higher atom economy and selectivity as well as produce fewer by-products compared to classical multistep syntheses [23]. Furthermore, MCRs are easy to perform, inexpensive, quick, consuming less energy and involves simple experimental procedures [24]. The first multicomponent reaction was described in 1850 by Strecker [25], and thereafter many such reactions have been reported in the literature.

Literature survey reveals that several methods have been developed for organic transformation reactions utilising various organocatalysts such as imidazole [27-29], acetic acid [32] and oxalic acid [33]. Citric acid acts as a mild, non-toxic and inexpensive acid catalyst which makes the process convenient, more economic and environmentally benign and hence more versatile.

All these facts have strengthened ourselves to find newer eco-friendly method and prompted us to employ citric acid as catalyst for efficient and high-yielding synthesis of pyranopyrazole derivatives at 80^{o}C **(Scheme 1)**. The reported method is rapid and facile, also devoid of unnecessary derivatization and generation of hazardous substance.

MATERIALS AND METHODS

All reactants were obtained from commercial source and used without purification. The ^{1}H and ^{13}C NMR spectra were measured with Avance-300 NMR spectrophotometer. Chemical shifts are reported in ppm in $CDCl_3$ with TMS as an internal standard. IR spectra were obtained using potassium bromide pellets on Bruker ALPHA FT-IR Spectrometer. Melting points were measured by open capillary method on DBK-programmable melting point apparatus. The purity determination of the substrates and reactions monitoring were accomplished by TLC on Merck silicagel 60 F_{254} plates.

General Procedure for the Synthesis of Pyranopyrazoles

In a 25mL round-bottom flask, hydrazine hydrate (1mmol), ethyl acetoacetate (1mmol), aldehyde (1mmol), malononitrile (1mmol) in water (1mL), 20 mol% citric acid was added. Then the reaction mixture was heated at 80^{o}C with constant stirring for appropriate time. The progress of reaction was monitored by TLC. The crude product was separated by filtration, washed with water to remove the catalyst and air-dried. The pure product was obtained by recrystallization from ethyl alcohol.

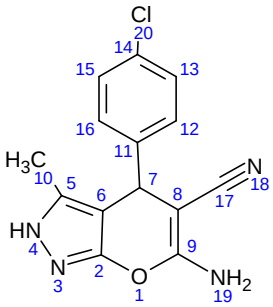


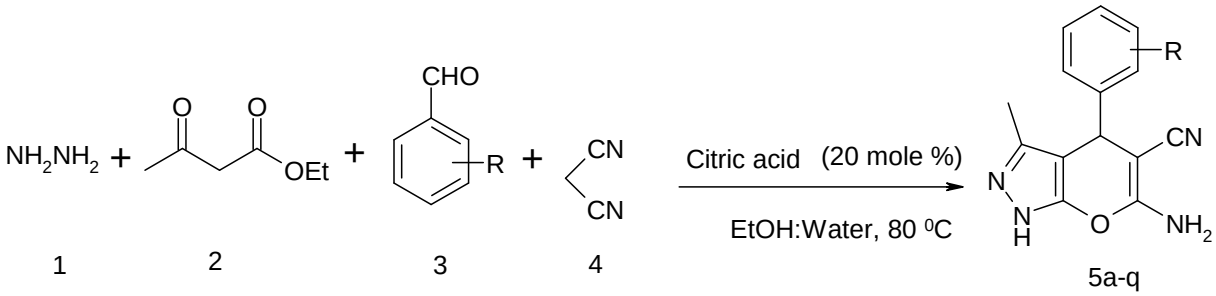
Figure 1: ***6-Amino-3-methyl-4-(4-chlorophenyl)- 2,4-dihydropyrano-[2,3-c]pyrazole-carbonitrile (5a)***

Table 1: Selected spectral data of synthesized compounds

Product	IR (cm^{-1})			^{1}H NMR δ (ppm)			^{13}C NMR δ (ppm)		MS (m/z)
	-CN	-NH_2	-NH	C_7H	-NH_2	-NH	C_7	-CN	$M^{+\cdot}$
5a	2193	3373,3311	3171	4.58	6.91	12.03	35.67	118.39	286.13
5b	2185	3470,3385	3170	4.58	6.87	12.11	31.92	116.91	282.42
5c	2184	3440,3370	3168	4.78	6.91	12.05	41.09	116.84	252.89
5d	2193	3391,3320	3160	4.62	6.87	12.01	34.21	117.68	286.38
5e	2211	3411,3342	3125	4.42	6.91	12.10	35.28	115.54	268.73
5f	2191	3430,3350	3148	4.82	6.81	12.04	41.56	118.91	268.39
5g	2172	3392,3311	3165	4.34	6.88	12.03	37.87	120.53	267.44
5h	2193	3482,3410	3159	4.71	6.92	11.97	34.91	118.93	268.92
5i	2189	3470,3401	3120	4.69	6.97	12.19	40.12	120.23	242.83
5j	2192	3370,3302	3126	4.52	6.87	11.87	39.18	119.82	270.69
5k	2210	3481,3421	3150	4.57	6.86	11.91	34.98	117.47	297.85
5l	2187	3446,3378	3166	4.29	6.84	12.01	39.14	116.63	312.90
5m	2202	3389,3317	3170	4.81	6.87	12.07	40.09	118.27	282.69
5n	2218	3375,3312	3155	4.66	6.95	11.94	38.63	117.28	352.82
5o	2192	3491,3431	3180	4.76	6.80	12.11	33.91	116.53	313.78
5p	2198	3380,3321	3145	4.72	6.91	12.11	32.98	117.57	298.65
5q	2206	3420,3351	3167	4.56	6.87	12.11	40.08	118.81	297.73

RESULTS AND DISCUSSION

In continuation of our efforts to develop new methods for the synthesis of biologically active nitrogen containing heterocyclic compounds using readily available, inexpensive, and environment friendly catalysts [34], herein, we wish to report method for the synthesis of some pyranopyrazole derivatives, utilizes a one-pot four-component reaction of, hydrazine hydrate (1), ethyl acetoacetate (2), aromatic aldehydes (3) and malononitrile (4) in the presence of readily available, inexpensive, mild, and common laboratory chemical citric acid as an organocatalyst (**Scheme 1**).



Scheme 1 : Synthesis of pyranopyrazoles by using citric acid as an organocatalyst

An initial study was performed by treating a mixture of ethyl acetoacetate (1mmol), hydrazine hydrate (1mmol), 4-methoxy benzaldehyde (1mmol) and malononitrile (1mmol) in water (1ml) without any catalyst and found that, the reaction was not possible in water at room temperature as well as at 80^{o}C temperature (**Table 2,** entry 1,2). As the reaction requires a catalyst, we performed the reaction using 5 mol% citric acid and result reveals that the reaction was possible at higher temperature with moderate yield (**Table 2,** entry 3). To improve the yield of product we continued our efforts by changing the mol% of catalyst from 5 to 30 and good result (**Table 2,** entry 6) was given by model reaction within 50 min, when 20 mol% citric acid was employed.

Table 2. Optimization of the catalytic amount of citric acid for model reaction

Entry	Catalyst load (mol%)	Temperature (^{o}C)	Time (min)	Yield (%)
1	--	RT	240	00
2	--	80	240	00
3	5	80	240	38
4	10	80	60	67
5	15	80	60	78
6	20	80	50	83
7	25	80	50	80
8	30	80	50	80

It was noticed that, the reaction is also possible by citric acid in refluxing EtOH, CH_3CN, THF, DCM, and chloroform. The results reported in **(Table 3)** indicate that solvents affect the efficiency of the reaction. Initially, the model reaction was carried out under solvent free condition, the product was not observed on TLC plate even after 240 min. Interestingly, the use of polar protic and aprotic organic solvents such as ethanol, acetonitrile and tetrahydrofuran **(Table 3, entries 3-5)** afforded good results for pyranopyrazole derivatives within 40-60 minutes. After this we have carried out the model reaction using equi-volume of organic solvents and water **(Table 3, entries 8–12).** We were pleased to see that, the reaction proceeds smoothly at 80^{o}C in EtOH:Water (1:1) solvent system **(Table 3, entry 8)** with 91% yield of product in 30 minutes.

This can be explained in terms of homogeneous solution of reaction mixture with the catalyst in polar organic solvent. In case of less polar organic solvents, the reactants were in different phase than the catalyst, resulting poor yield of the product. Carrying out the same reaction in a 1:1 mixture of organic solvent:water (**Table 3**, entries 8-12) can indirectly prove this explanation. It was observed that the reaction completed with lower yield after 120 min in a heterogeneous 1:1 mixture of less polar organic solvent:water system (**Table 3**, entries 11,12). On the other hand, a

homogeneous 1:1 mixture of polar organic solvent:water systems was showed improved results (**Table 3**, entries 8-10).

Table 3. Optimization of reaction conditions using various solvents[a]

Entry	Solvent	Time (min)	Yield(%)[b]
1	Neat	240	00
2	Water	50	83
3	EtOH	40	82
4	CH_3CN	55	71
5	THF	60	70
6	CH_2Cl_2	60	43
7	Chloroform	120	55
8	EtOH:Water(1:1)	30	91
9	CH_3CN:Water(1:1)	40	76
10	THF:Water(1:1)	35	75
11	CH_2Cl_2:Water(1:1)	120	62
12	Chloroform:Water(1:1)	120	66
[a]Reactions were carried out at 80°C by using 20 mol% of citric acid			

On the basis of these observations, 1:1 EtOH:Water was optimized solvent system for the reported method.

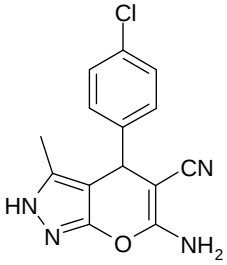
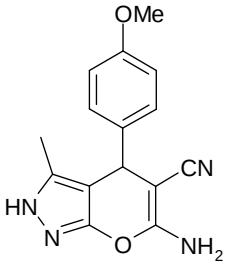
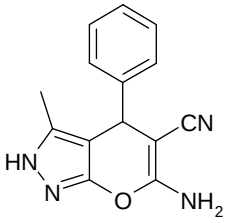
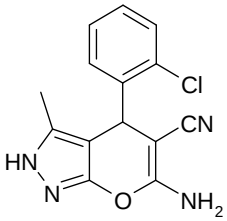
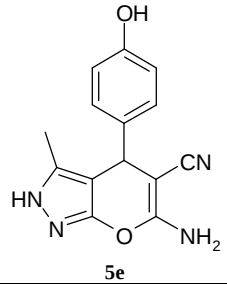
As the reaction requires catalyst, for comparison purpose we performed the reaction using 20 mol% of oxalic acid, picric acid, succinic acid, p-Toluene sulfonic acid, sulfamic acid and citric acid. We found that, citric acid is the best in terms of yield and duration of the reaction **(Table 4,** entry 6**)**.

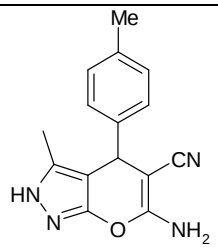
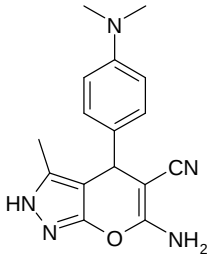
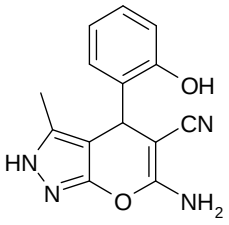
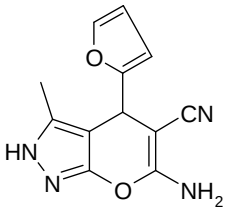
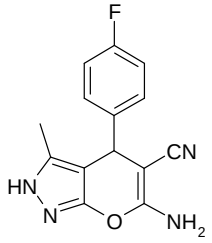
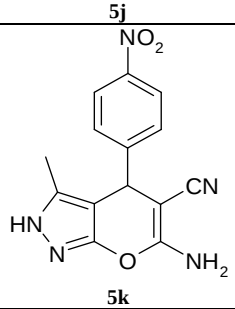
Table 4. Comparison of various organocatalysts for the synthesis of 5a

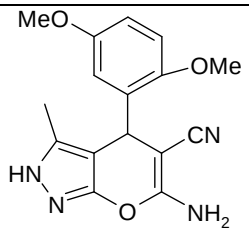
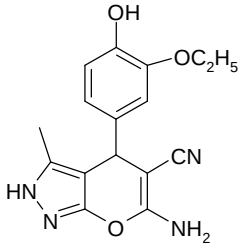
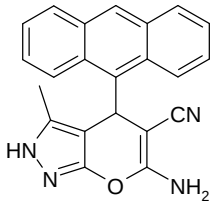
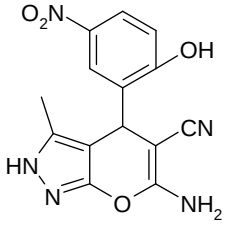
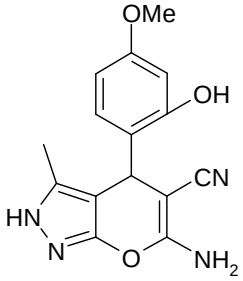
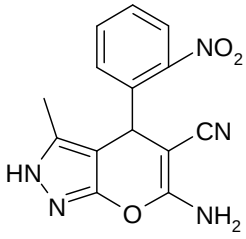
Entry	Catalyst	Catalytic amount (mol%)	Time (min)	Yield (%)
1	Oxalic acid	20	45	64
2	Succinic acid	20	45	67
3	Picric acid	20	50	65
4	p-Toluene sulfonic acid	20	30	85
5	Sulfamic acid	20	40	62
6	Citric acid	20	30	91

With the optimized reaction conditions in hand, we next examined the feasibility of the citric acid for synthesis of pyranopyrazole derivatives by condensing variously substituted aromatic aldehydes, ethyl acetoacetate, hydrazine hydrate, and malononitrile **(Scheme 1)** with 20 mol% citric acid in ethanol:water (1:1, v/v) system at 80°C and results were incorporated in **(Table 5)**. The reactions proceeded efficiently to furnish the corresponding pyranopyrazoles **5a-q** in good to excellent yields. All the products were confirmed by their physical constants and spectral characterization by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data **(Table 1)**.

Table 5. Synthesis of pyranopyrazoles by using citric acid

Entry	Product	Time (min)	Yield (%)	m.p. (°C)
1	 **5a**	30	90	230-232
2	 **5b**	30	91	210-212
3	 **5c**	35	87	240-242
4	 **5d**	40	89	243-245
5	 **5e**	30	87	220-222

6	 **5f**	30	91	200-204
7	 **5g**	35	89	232-234
8	 **5h**	35	88	213-215
9	 **5i**	35	90	240-244
10	 **5j**	35	88	244-246
11	 **5k**	30	90	240-244

12	 **5l**	40	88	215-217
13	 **5m**	40	89	232-234
14	 **5n**	45	87	250-252
15	 **5o**	35	88	245-247
16	 **5p**	40	87	212-214
17	 **5q**	35	89	236-238

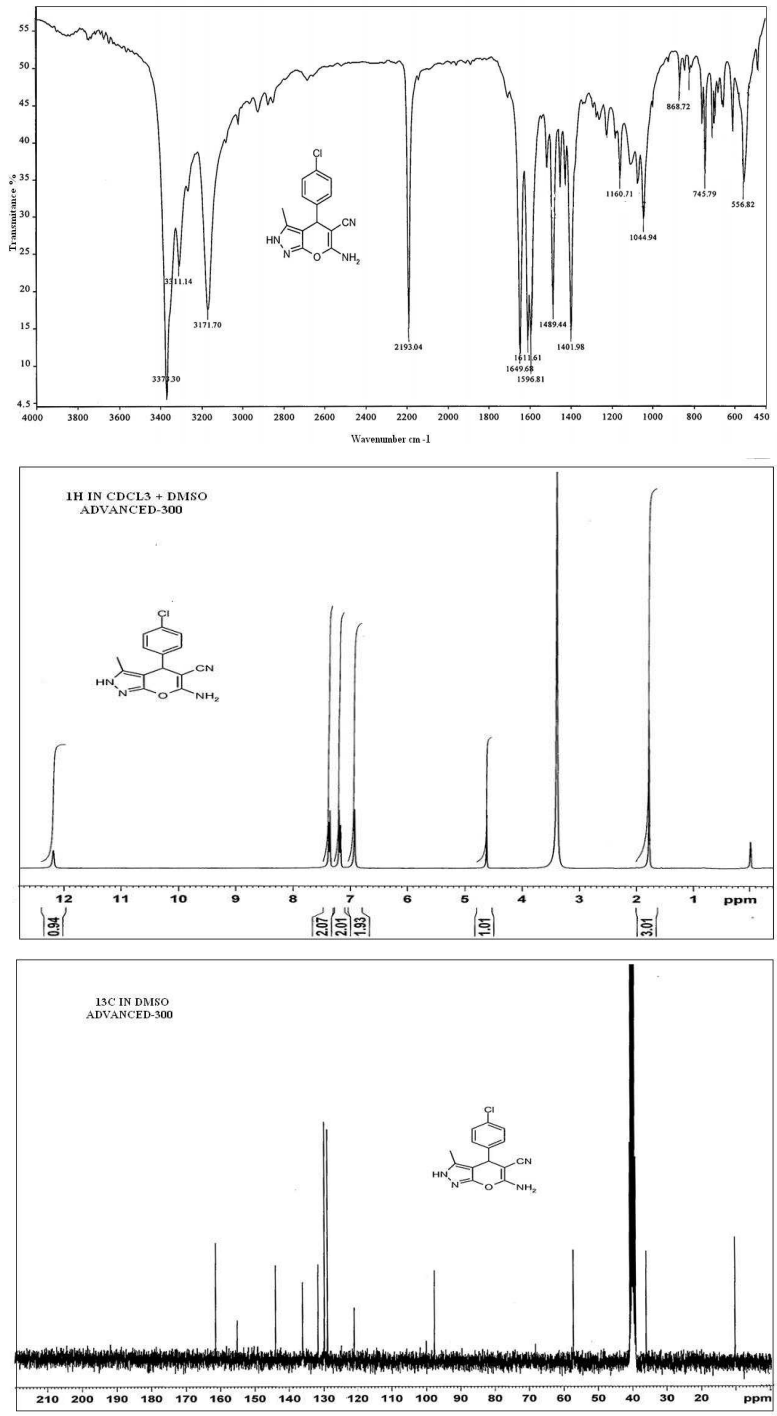


Figure 2: IR, ^{1}H and ^{13}C NMR spectra of compound 5a

CONCLUSION

In conclusion, we have developed an efficient protocol for the synthesis of pyranopyrazoles by a one-pot multicomponent reaction of hydrazine hydrate, ethylacetoacetate, aldehydes, malononitrile using catalytic amount of citric acid in 1:1ethanol:water at 80^{o}C. The catalyst is simple, inexpensive and nontoxic. The reaction procedure is very mild and involves simple workup procedure to obtain the desired products in good to excellent yields.

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