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Green approach for the synthesis of pyranopyrazoles and hexahydroquinoline-3-carboxamides using unripe grape juice (verjuice) as catalyst

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ABSTRACT

Unripe grape juice (verjuice) as a natural catalyst was successfully applied to perform the one-pot reaction of aryl aldehydes, malononitrile, hydrazine hydrate and ethyl acetoacetate to synthesize pyranopyrazole derivatives in aqueous ethanol at room temperature in excellent yields. Furthermore, unripe grape juice catalyzed one-pot synthesis of hexahydroquinoline-3-carboxamide derivatives by the four-component reaction of arylaldehydes, dimedone, acetoacetanilide and ammonium acetate in high to excellent yield in ethanol at 70 °C. The synthesized compounds were identified by FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopic techniques and elemental analysis. An environmentally benign procedure, short reaction time, high yields and biocompatible natural catalyst are some advantages of this research.

Keywords: *Unripe grape juice, Multi-component reactions, Pyranopyrazoles, Hexahydroquinoline-3-carboxamides.*

1. Introduction

Unripe grape juice (verjuice) is a highly acidic juice made by pressing unripe grapes. Unripe grape is rich in the antioxidant of polyphenolic compounds [1,2]. The protective role of grape seeds in the cardiovascular system is reported [3,4] and these effects are related to the presence of polyphenolic compounds in the grape. Unripe grape juice is characterized by high acidity, low sugar content and a sour/tart taste [5]. Verjuice has also been tested as a potential food preservative [6,7], due to its high organic acid content and elevated concentration of phenolic compounds [8]. Malic and tartaric acids accounting for 90% of the total acids are the predominant organic acids in grapes, [9]. The unripe grape juice has been evaluated for lipid lowering activity and for the ability to control hypertension [10], and to decrease risk of atherosclerosis [11,12]. These reported health benefits could relate to its known antioxidant activity and high content of polyphenolic compounds, which is considered as an astringent character [13]. Pyranopyrazoles have attracted considerable attention since they exhibit significant biological properties such as anticancer [14], anti-inflammatory [15], Chk1 kinase inhibitor [16], and molluscicidal activities [17]. Several catalysts have been reported for the synthesis of pyranopyrazole derivatives such as disulfonic acid imidazolium chloroaluminate [18], sodium benzoate [19], urea [20], morpholinetriflate [21], Fe_3O_4@SiO_2 nanoparticles [22], γ-alumina [23], *L*-proline [24], β-cyclodextrin[25], cetyltrimethylammonium chloride (CTACl) [26], silica-supported tetramethylguanidine [27], TUD [28], [bmim]OH [29], nano-ZnO [30], and lemon juice [31]. Some of the reported methods suffer from one or more difficulties, including long reaction times, unsatisfactory yields, and the use of hazardous and expensive catalysts. Also, quinolines including 1,4-dihydropyridines (1,4-DHPs) nucleus have shown a variety of pharmacological properties such as, anti-inflammatory [32], antitumor [33], antitubercular [34], analgesic [35] and antithrombotic activity [36]. Furthermore, 1,4-DHPs exhibits several medicinal applications which include neuroprotectant [37] and cerebral antischemic activity in the treatment of Alzheimer's disease [38]. Also, the synthesis of hexahydroquinoline-3-carboxamides was reported via the four component reaction of acetoacetanilide, aromatic aldehyde, dimedone and ammonium acetate in the presence of *p*-toluenesulfonic acid [39] and in a high temperature between 150-160 °C [40].

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2. Experimental

2.1. General

High-purity chemical reagents were purchased from the Merck Chemical Company. Melting points were determined using an Electrothermal Mk3 apparatus and were uncorrected. NMR spectra were recorded in DMSO-d_6 on a BrukerAvance DRX-400 MHz instrument spectrometer using TMS as an internal standard. Fourier transform infrared (FT-IR) spectra were performed in the transmission mode (Shimadzu, SP-1100, P-UV-Com instrument) on powder samples that were ground with KBr and compressed into a pellet.

2.2. Preparation of the catalyst

Unripe green grapes (verjuice) were pressed in a fruit juicer to obtain the juice extract. Then the juice was filtered through cotton cloth and finally through filter paper to remove solid material to get the clear juice. The juice was transferred into the bottle and was kept in the refrigerator and then was used as a catalyst. The pH of the verjuice was 2.9.

2.3. General method for the synthesis of 6-amino-4-aryl-1,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitriles

In a typical experiment, ethyl acetoacetate (1 mmol), hydrazine hydrate (1.5 mmol), aromatic aldehydes (1 mmol), malononitrile (1 mmol), and verjuice (5 drop) in water: ethanol (1:1, 5 mL) were placed in a 25 mL round-bottom flask at room temperature. The progress of the reaction mixture was monitored by TLC analysis. After completion of the reaction, the solid precipitate was filtered off and washed with water and purified by recrystallization from ethanol. The reaction products were identified by comparing their physical and spectral data with those reported in the literature.

2.4. General procedure for the synthesis of hexahydroquinoline-3-carboxamides

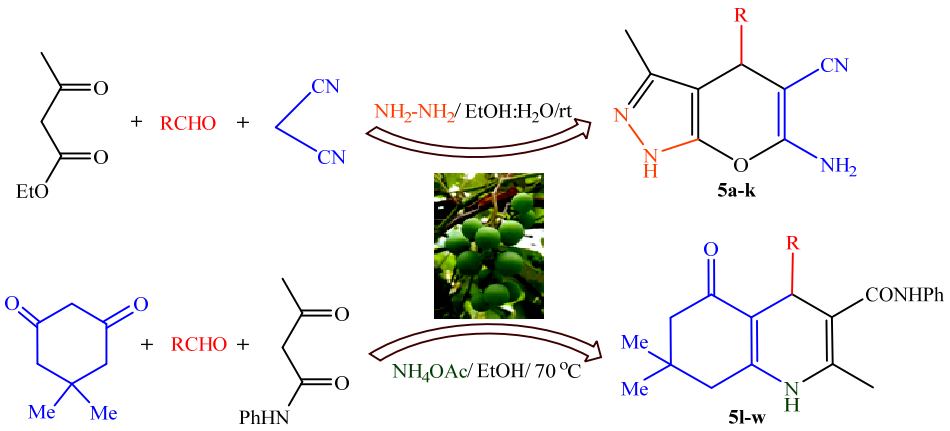
A mixture of aromatic aldehyde (1mmol), dimedone (1mmol, 0.14 g), acetoacetanilide (1 mmol, 0.126 ml) and ammonium acetate (1.2 mmol, 0.092 g) in the presence of verjuice (10 drop) were stirred in ethanol (5 mL) at 70 °C during the appropriate time, as shown in Table 1. Completion of the reaction was indicated by TLC monitoring. Then, the reaction mixture was cooled to ambient temperature, and the crude solid residue was recrystallized from ethanol to afford pure crystals of the proper hexahydroquinoline-3-carboxamide in 87-96% yields. The products were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and also by comparison of them with authentic samples reported in the literature (See supplementary data).

3. Results and Discussion

In this work, verjuice was applied as a cheap and easy available natural catalyst to provide a series of pyranopyrazole derivatives and hexahydroquinoline-3-carboxamides in good to excellent yields (Scheme 1).

To optimize the reaction conditions, the reaction of ethyacetoacetate, benzaldehyde, hydrazine hydrate and malononitrile were examined as a model reaction in the several solvents such as CH_2Cl_2, ethanol, acetonitrile, H_2O, EtOH: H_2O and solvent free conditions. In this study, it was observed that verjuice in EtOH: H_2O (1:1) at room temperature is more efficient with respect to the reaction time and the yield of the desired product (Table 1).

Furthermore, to study the effect of the catalyst amounts, the model reaction was carried out in the presence of different amounts of verjuice. The best amount of verjuice obtained was 5 drops which afforded the desired product **5a** to 96% yields (Table 2).



Scheme 1. Synthesis of pyranopyrazoles and hexahydroquinoline-3-carboxamidescatalyzed by verjuice.

Table 1. Synthesis of **5a** by verjuice in different solvents.[a]

Entry	Solvent	Yield (%)[b]
1	Solvent-free	50
2	H_2O	86
3	CH_3CN	62
4	CH_2Cl_2	44
5	EtOH	80
6	EtOH:H_2O (1:1)	96

[a]Reaction conditions: Benzaldehyde (1 mmol), ethyl acetocetate (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1 mmol), and verjuice (5 drop) at room temperature after 30 minutes.
[b]Isolated yields.

Table 2. Synthesis of **5a** in different amounts of verjuice.[a]

Entry	Verjuice (drop)	Yield (%)[b]
1	2	50
2	3	62
3	4	85
4	5	96

[a]Reaction conditions: Benzaldehyde (1 mmol), ethyl acetocetate (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1 mmol), in EtOH:H_2O (1:1, 5 mL) at room temperature after 30 minutes.
[b]Isolated yields.

After optimizing the reaction conditions, a variety of pyranopyrazole was synthesized using verjuice in excellent yields (Table 3, entries 1-11). The reactions worked well with all benzaldehydes with electron-donating or electron-withdrawing substituents.

In the next experiment, verjuice was applied to perform the reaction of arylaldehydes, dimedone, acetoacetanilide and ammonium acetate in ethanol at 70 ℃ to provide a series of hexahydroquinoline-3-carboxamides in excellent yields. To optimize the reaction conditions and get the best catalytic activity, the four-component reaction of benzaldehyde, dimedone, acetoacetanilide and ammonium acetate was examined as a sample reaction in several solvents. In this investigation, it was perceived that verjuice in ethanol at 70 °C is more efficient with respect to the efficiency of the desired product (Table 4).

To investigate the effect of the catalyst, the model reaction was also carried out by different amounts of verjuice. It was considered that the variation of the catalyst had an effective influence on the reaction yields. The results showed the best amount of verjuice is 10 drops which afforded the required product in good to excellent yields (Table 5).

In these optimized reaction conditions, a diversity of hexahydroquinoline-3-carboxamide derivatives were prepared from benzaldehyde, dimedone, acetoacetanilide and ammonium acetate using verjuice as a green catalyst (Table 6).

Table 3. Synthesis 6-amino-4-aryl-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles.[a]

Entry	R	Product	Time (min)	Yield (%)[b]	m.p. (°C)		Ref.
					Found	Reported	
1	C_6H_5	**5a**	18	96	244-246	244-245	[29]
2	4-Cl-C_6H_4	**5b**	15	97	232-234	233-234	[29]
3	3-Cl-C_6H_4	**5c**	12	94	180-182	181-183	[31]
4	3-MeO-4-HO-C_6H_4	**5d**	30	95	233-235	234-236	[30]
5	4-NO_2-C_6H_4	**5e**	35	98	250-252	251-252	[29]
6	4-Br-C_6H_4	**5f**	30	97	248-250	248-251	[29]
7	3-Br-C_6H_4	**5g**	20	96	222-224	222-223	[29]
8	3-NO_2-C_6H_4	**5h**	15	95	233-235	232-234	[29]
9	4-HO-C_6H_4	**5i**	20	96	222-224	224-226	[29]
10	2-MeO-C_6H_4	**5j**	25	94	250-252	251-252	[29]
11	4-$(CH_3)_2CH$	**5k**	15	96	229-230	-	-

[a]Reaction conditions: Ethyl acetoacetate (1 mmol), hydrazine hydrate (1.5 mmol), aromatic aldehydes (1 mmol), malononitrile (1 mmol), and verjuice (5 drops) in water: ethanol (1:1, 5 mL) at room temperature.
[b]Isolated yields.

Table 4. Synthesis of **5l** by verjuice in different solvents.[a]

Entry	Solvent	Yield (%)[b]
1	Solvent-free	55
2	CH_3CN	62
3	CH_2Cl_2	44
4	EtOH	95

[a]Reaction conditions: Benzaldehyde (1 mmol), dimedone (1 mmol), acetoacetanilide (1 mmol), ammonium acetate (1.2mmol), and verjuice (10 drop) at 70 °C.
[b]Isolated yields.

Table 5. Synthesis of **5l** in different amounts of verjuice.[a]

Entry	Verjuice (drop)	Yield (%)[b]
1	3	45
2	5	60
3	7	86
4	10	95

[a]Reaction conditions: Benzaldehyde (1 mmol), dimedone (1 mmol), acetoacetanilide (1 mmol), ammonium acetate (1.2mmol), and verjuice (10 drop) at 70 °C.
[b]Isolated yields.

Table 6. Synthesis of hexahydroquinoline-3-carboxamides by verjuice.[a]

Entry	R	Product	Time (min)	Yield (%)[b]	m.p. (°C)		Ref.
					Found	Reported	
1	C_6H_5	**5l**	20	95	242-244	243-245	[40]
2	4-Cl-C_6H_4	**5m**	15	96	251-253	252-254	[40]
3	2-Cl-C_6H_4	**5n**	20	90	225-227	-	-
4	3-Cl-C_6H_4	**5o**	20	93	240-241	238-240	[39]
5	3-NO_2-C_6H_4	**5p**	20	92	244-246	245-247	[40]
6	4-NO_2-C_6H_4	**5q**	20	94	209-211	208-210	[40]
7	2-NO_2-C_6H_4	**5r**	15	91	254-256	255-257	[39]
8	3-Br-C_6H_4	**5s**	15	96	211-213	-	-
9	4-HO-C_6H_4	**5t**	30	86	>300	>300	[39]
10	4-MeO-C_6H_4	**5u**	30	88	247-249	248-250	[40]
11	4-$N(Me)_2$-C_6H_4	**5v**	30	90	249-251	-	-
12	$CH(CH_3)_2$	**5w**	45	89	234-236	-	-

[a]Reactions and conditions: Aldehyde (1 mmol), dimedone (1 mmol), acetoacetanilide (1 mmol), ammonium acetate (1.2 mmol) and verjuice (10 drop) in EtOH (5 mL) at 70 °C.
[b]Isolated yields.

In order to explore the efficiency of the present method for the synthesis of pyranopyrazoles and hexahydroquinoline-3-carboxamides, compounds **5a** and **5l** were compared with some of those reported in the literature (Table 7). As one can see, our results show a very good comparative work with previously reported data when all terms, including yields, reaction times, and reaction conditions are taken into account.

4. Conclusions

In summary, we have extended a one-pot protocol for the synthesis of 6-amino-4-aryl-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles and hexahydroquinoline-3-carboxamides in the presence of verjuice as a biocompatible natural catalyst in aqueous ethanol at room temperature and in ethanol at 70 ℃, respectively. The high efficiency and the simple procedure are some of the advantages of this method.

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Table 7. Comparison of verjuice with some other catalysts for synthesis of **5a** and **5l**.

Product	Catalyst	Reaction conditions	Time (min)	Yield (%)	Ref.
5a	[bmim]OH	50-60 ℃	10	88	[29]
5a	nano-ZnO	H_2O/70 ℃	60	94	[30]
5a	L-proline	H_2O/reflux	10	90	[24]
5a	β-CD	EtOH:H_2O (1:9)/r.t.	15	90	[25]
5a	CTACl	H_2O/90 ℃	240	89	[26]
5a	Sodium benzoate	H_2O/r.t.	60	85	[19]
5a	Urea	EtOH:H_2O (1:1)/ r.t.	480	86	[20]
5a	SiO_2-TMG	100 ℃	30	96	[27]
5a	MorT	EtOH:H_2O (9:1)/reflux	540	92	[21]
5a	Lemon juice	EtOH:H_2O (1:9)/90 ℃	45	96	[31]
5a	Verjuice	EtOH:H_2O (1:1)/ r.t.	18	96	This work
5l	*p*-Toluenesulfonic acid	Grinding/EtOH (1 mL)/ r.t.	15	78	[39]
5l	-	150-160 ℃	10-20	89	[40]
5l	Verjuice	EtOH/70 ℃	20	95	This work

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