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Lime juice as an efficient and green catalyst for the synthesis of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile derivatives

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Abstract: A new and green method for the one-pot four-component synthesis of highly functionalized 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles was developed using hydrazine monohydrate or phenylhydrazine , ethylacetoacetate, malononitrile and arylaldehydes under thermal solvent-free conditions in the presence of lime juice as catalyst. The reaction proceeds smoothly to generate corresponding product. The use of non-toxic and inexpensive materials, simple and clean work-up, short reaction times and good yields of the products are the advantages of this method.

Keywords: 6-Amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles, Solvent-free condition, lime juice.

Introduction

One of the most challenges for chemists is use of materials that don't have any fatal for eco-system and can biodegrable easily. Mineral acids have an important role as catalyst in chemical reactions but they are corrosive and hazardous [1]. Recently the use of fruit juice as catalyst has been investigated [2].The lime juice contains various vitamins, carbohydrates, fibers, organic and inorganic compounds and different acids such as tartaric acid, nitric acid and citric acid (Figure **1**) [3]. About 60 percent of lime juice is made from citric acid [3] which could act as an effective acid catalyst by activating the carbonyl group of the aldehyde in organic synthesis. Easy access, inexpensive, short reaction time and easy work-up are reasons that make it as green catalyst.

Pyrano[2,3-c]pyrazoles constitute one of the privileged heterocyclic scaffolds known to exhibit important biological activities, such as analgesic [4a] , anti-tumor, anti-cancer [4b], anti-inflammatory properties [4c] and also serve as potential inhibitors of human Chk1 kinase [5]. Since the pioneering studies by Otto [6] on the base-catalyzed cyclization of 4-aryliden-5-pyrazolone, there have been more and more profound research activities studying dihydropyrano[2,3-c]pyrazoles [7–11]. Recently, Laufer and colleagues [12] performed a library of diverse dihydropyrano[2,3-c]pyrazoles in ethanol. However, most of these synthetic methods suffer from drawbacks such as employing toxic reagent, strongly basic conditions, expensive and complex catalysts or reagents, many tedious steps, in most cases low yields of the products and long reaction times that restrict their usage in practical applications. In continue of our researches on application green catalysts in different reactions [13-15], in this research we report green and easy synthesis of 6-amino-4- aryl-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles under thermal solvent-free conditions in the presence of lime juice as catalyst (Scheme **1**).

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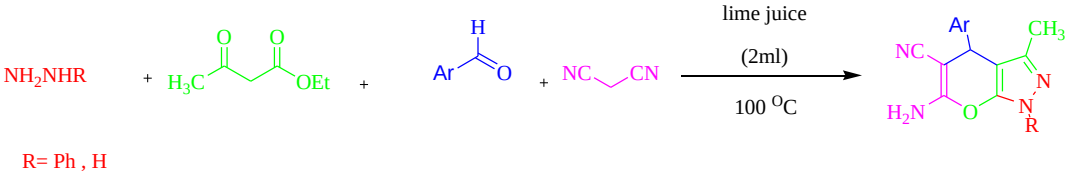
Results and discussion

In order to be able to carry out preparation of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano [2,3-c]

pyrazole-5-carbonitriles in a more efficient way, minimizing the time and amount of catalyst, the reaction of hydrazine monohydrate or phenylhydrazine, ethyl acetoacetate, benzaldehyde and malononitrile was selected as model system, catalyst reactivity at different reaction temperatures (80, 100, 110 and 120 ^{o}C) was performed. The best result was obtained by carrying out the reaction with (1.0:1.0:1.0:1.0) molar ratios of hydrazine monohydrate or phenylhydrazine, ethylacetoacetate, benzaldehyde and malononitrile, in the presence of lime juice (2 ml) at 100 $^{\circ}$C. The scope and efficiency of the reaction were explored for the synthesis of a wide variety of substituted 6-amino-4-aryl-3-methyl-1,4- dihydropyrano[2,3-c]pyrazole -5-carbonitriles using hydrazine mono hydrate or Phenylhydrazine , ethylacetoacetate, arylaldehydes and malononitrile. The results summarized in Table **1**.

Figure 1: Image of lime.



Scheme 1: Synthesis of 6-amino-4- aryl-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles under thermal solvent-free conditions in the presence of lime juice as green catalyst.

Table 1: Four component synthesis of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles derivatives under thermal solvent-free conditions.

Entry	R	Ar	Time (min)	Yield (%)[a]	Found M.P.(^{o}C)/ [Lit.M.P (^{o}C)][6,7]
1	H	C_6H_5	15	85	243-245 [244-246]
2	H	4-$N(CH_3)_2C_6H_4$	15	86	165-168 [167-169]
3	H	2-$NO_2C_6H_4$	15	86	218-220 [220-222]
4	H	4-$NO_2C_6H_4$	15	86	247-249

					[249-252]
5	H	3-$NO_2C_6H_4$	19	86	190-192 [193-195]
6	H	2-ClC_6H_4	17	85	143-145 [145-147]
7	H	4-ClC_6H_4	18	87	233-235 [234-236]
8	H	2,5-$(CH_3O)_2C_6H_3$	25	75	209-211 [210-212]
9	H	2,4-$Cl_2C_6H_3$	15	85	235-237-182 [235-237]
10	H	4-MeC_6H_4	20	74	204-206 [206-208]
11	Ph	C_6H_5	15	90	165-167 [166-168]
12	Ph	2-ClC_6H_5	15	85	144-146 [145-147]
13	Ph	4-ClC_6H_5	14	86	143-145 [144-146]
14	Ph	4-BrC_6H_5	17	86	182-184

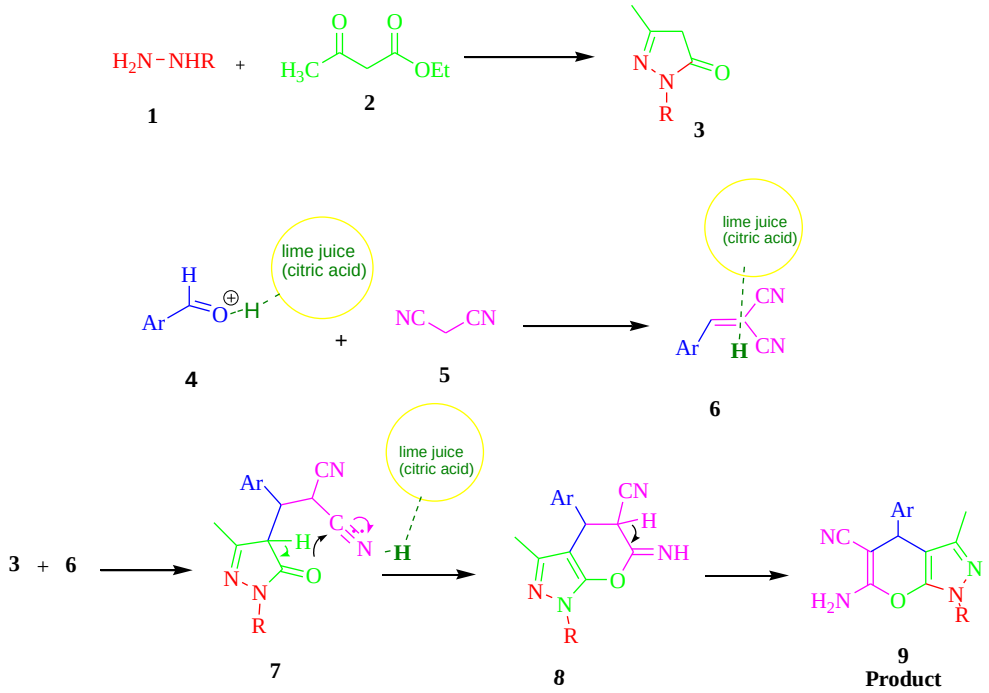
					[184-185]
15	Ph	2,4-$Cl_2C_6H_3$	18	85	180-182 [182-184]
16	Ph	4-$NO_2C_6H_4$	15	87	190-192 [191-193]
17	Ph	3-$NO_2C_6H_4$	15	88	188-190 [189-191]
18	Ph	4-OHC_6H_4	14	89	207-109 [209-210]
19	Ph	4-$OMeC_6H_4$	19	75	167-169 [169-170]
20	Ph	4-MeC_6H_4	19	75	173-175 [175-177]
21	Ph	2,4-$(CH3O)_2C_6H_3$	20	74	174-177 [176-178]
22	ph	n-heptanal	24 hr	Trace	-

[a] Yields refer to pure products.

We saw that a variety of arylaldehydes including electron withdrawing or releasing substituents (*ortho*-, *meta*-, and *para*-substituted) participated well in this reaction and gave the 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles in good to excellent yield.

According to literature [6,7] , we proposed mechanism for the synthesis of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles in the presence of lime juice as catalyst. Citric acid could act as an effective acid catalyst by activating the carbonyl group of the aldehyde. First, pyrazolone **3** was formed by the reaction between **1**

and **2**, Knoevenagel condensation between **4** and **5** produced 2-benzylidenemalononitrile **6**, Michael addition of **3** with **6**, followed by cyclization and tautomerization afforded the corresponding product (Scheme **2**).



Scheme 2: Proposed mechanism for the synthesis of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles under thermal solvent-free conditions in the presence of lime juice as catalyst.

Experimental

All reagents were purchased from Merck and Sigma-Aldrich and used without further purification. All yields refer to isolated products after purification. Products were characterized by comparison physical data with authentic samples and spectroscopic data (IR and NMR). The NMR spectra were recorded on a BrukerAvance DRX 400 MHz instrument. The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). IR spectra were recorded on a JASCO FT-IR 460 plus spectrophotometer. Melting points were determined on an Elecrothermal 9100 apparatus. TLC was performed on Silica–gel Polygram SILG/UV 254 plates.

General procedure for the synthesis of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile derivatives:

A mixture of hydrazine monohydrate or phenyl hydrazine (1 mmol) and ethyl acetoacetate (1 mmol) was stirred at 0 °C, until 3-methyl-2-pyrazolin-5-one was precipitated and its formation completed (5 min). Then it warmed to room temperature. To this reaction mixture, aryl aldehyde (1 mmol) and malononitrile (1mmol) in the presence of lime juice (2 mL) at 100 ^{o}C was added. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, and diluted with water. The mixture was filtered for separation of the product. The crude product was recrystallized from ethanol to afford the pure pyranopyrazole derivatives in good yields.

All of the products are known. Selected spectroscopic data of one known product are given below:

*Spectral data for 6-amino-1,4-dihydro-3-methyl-4-(2-chlorophenyl)pyrano[2,3- c]pyrazole-5-carbonitrile(Table **1**, Entry 6):*

IR (KBr, cm^{-1}): 3776, 3391, 3357, 3314, 3169, 2803, 2710, 2351, 2190, 1489, 1408, 1350, 1052, 763; ^{1}H NMR(400 MHz, (DMSO-d_6): δ (ppm) =1.78 (3H, S), 5.08 (1H, S), 6.96 (2H, S), 7.19-7.54 (4H, m), 12.14 (1H, S); ^{13}C NMR (100 MHz, DMSO-d_6): 10, 34, 56, 97, 120, 128, 129, 130, 131, 132, 136, 141, 155, 162.

Acknowledgments

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