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Lemon juice as an Efficient Biocatalyst for One Pot Three Component Green Synthesis of Substituted 5-amino-1-(2,4-dinitrophenyl)-1H-pyrazole-4-carbonitriles

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Abstract

An eco-friendly one pot three component green synthesis of substituted 5-amino-1-(2,4-dinitrophenyl)-1H-pyrazole-4-carbonitriles have been carried out in presence of lemon juice as a recyclable catalyst. The use of biocatalysts is focusing on eco-friendly organic synthesis. Here, we have shown that Lemon juice is an inexpensive, safe and eco-friendly catalyst in the one pot three components reaction of aryl aldehydes, malononitrile and hydrazinehydrate for the synthesis of pyrazole derivatives under mild conditions. After optimization of reaction conditions for synthesis of pyrazoles it was found that 4.0 mL of lemon juice gave 82% yield in 1.4 hrs at room temperature in solvent free conditions. This novel and eco-friendly pathway has the merits of high yield, simple handling and benign synthesis.

Keywords: pyrazoles; organic synthesis; biocatalyst; lemon juice

Introduction

Multicomponent reactions are efficient tools for organic synthesis that have high atom economy, easy bonding and selectivity. Pyrazole is an important class of heterocyclic compounds, widely present as the core structure in large variety of compounds that possess important agrochemical and pharmaceutical activities [1-2]. In recent times, various modern homogenous and heterogenous catalysts have also been introduced for the synthesis of pyrazoles, such as guanidine [3], sodium benzoate [4], zeolites [5], Al_2O_3 [6] and ionic liquid [7]. However in spite of their merits, most of these pathways suffer from one or more demerits, such as laborious work-up, high waste generation, long reaction time and unsatisfactory product yields.Lemon juice is economical and non toxic and environmentally benign catalyst for synthesis of pyrazoles. Lemon juice is acidic in nature (pH, about 2-3) due to presence of citric acid which is a 2-hydroxypropane-2,3-tricarboxylicacid (Figure.1) The main ingredients of the extract of Citrus limonium species of lemon are moisture (85%), carbohydrates (11.2%), citric acid (5-7%), protein (1%), ascorbic acid or vitamin-C (0.5%), fat (0.9%), minerals (0.3%), fibres (1.6%) and some other organic acids [8]. Therefore the focus lies on clean synthesis of pyrazole derivatives.

Figure 1: Chemical structure of citric acid

Experimental

Most of the chemicals used during the research work were of laboratory grade. All commercial reagents and solvents were obtained from SRL (Sisco Research Laboratory) & CDH (Central Drug House) and used without purification. Melting points were determined in open capillaries on a Ganson electric melting point apparatus and are uncorrected. Infrared spectra (4000-350 cm^{-1}) of the synthesized compounds and intermediates were recorded in KBr pellets on Perkin Elmer FT-IR-R2X spectrophotometer and frequency is expressed in cm^{-1}. The ^{1}HNMR spectra were recorded in $CDCl_3$ or DMSO-D_6 using tetra methyl silane (TMS) as internal reference on “Brucker Ac 400 F” (400 MHz) nuclear magnetic resonance spectrometer. The chemical shifts values are expressed in delta (ppm), while J value in Hz and are compatible with the assigned structures.

Preparation of catalyst

Fresh lemon was taken and washed it thoroughly with water and cut by using a knife and then pieces were pressed manually. Then the juice was filtered through muslin cloth to remove solid material and to get clear juice which was used as a catalyst.

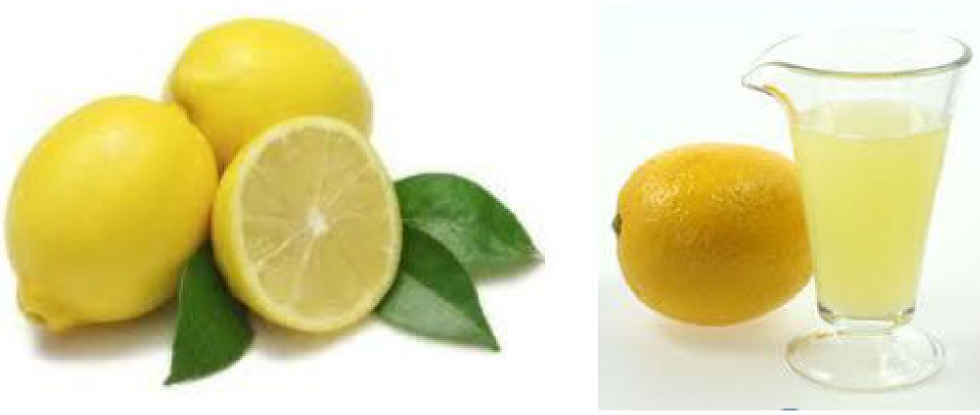

Figure 2: Prepation of catalyst.

General procedure for synthesis of pyrazole compounds

A mixture of the selected aldehyde (10 mmol), Malanonitrile (10 mmol), 2,4-dinitrophenyl hydrazine (10 mmol)and catalyst juice (lemon juice) (4 ml) were added and stirred at room temperature. The progress of the reaction was monitored by TLC. The product was dried and recrystallized from ethylacetate to obtain the pure product. The reaction was found to complete within 1.4 hours to give 5-amino-1-(2,4-dinitrophenyl)-3-(4-methoxyphenyl)-1H-pyrazole-4-carbonitrile 4(i) as product in quantitative yield (**Table 2, entry 1**). Various derivatives of pyrazoles and their yield formed are shown in **Table 2** under (**Scheme-1**), also the speciality of the catalyst in comparison of others are shown in **Table 3**.

Scheme-1: Synthesis of pyrazoles.

Result and Discussion

The model reaction between 4-methoxy benzaldehyde 1(i) (10 mmol), malanonitrile (2) (10 mmol) and 2,4-dinitrophenyl hydrazine (3) (10 mmol) in presence of Lemon juice was taken in flask and stirred for 1.4 hours on magnetic stirrer. Progress of the reaction was monitored with the help of TLC. After completion of the reaction, the solid that separated out and worked up with cold water and recrystallized from ethyl acetate to furnish 4(i) as product in quantitative yield (**Table 2, Entry 1**). Inspired by this result concentration of catalyst was optimized through the above reaction by using different concentrations 1.0, 2.0, 3.0, 4.0, 5.0 and 6.0 ml (Table 1, Entry 1-6) of Lemon juice at room temperature for 1.4 hours to give the desired products 4(i). The reaction procedure was performed in absence of catalyst at the same condition a low yield is obtained which shows the value of the prescribed catalyst. Lemon juice is a reusable biocatalyst which shows catalytic behaviour without any loss of activity (**Table 3**). The use of citric acid in the synthesis of pyrano-pyrazoles [16] which have shown that use of citric acid requires ethanol as a solvent and 80°C temperature to synthesize desired product. Hence lemon juice was found, very economic and safe biocatalyst.

Table 1: Optimization of Lemon juice for the synthesis of 4(i).

Entry	Amount of Catalyst (ml)	Time (hours)	Yield (%)
1	1	3.3	63
2	2	2.5	71
3	3	2	78
4	4	1.4	82
5	5	1.4	80
6	6	1.3	80

Table 2: Synthesis of pyrazoles in presence of Lemon juice.

Reactant	R_1	R_2	R_3	Compound No	Yield	M.pt
No					(%)	(o C) [Ref]
1(i)	H	H	OCH_3	4(i)	82	229-231[9]
1(ii)	H	H	Cl	4(ii)	74	178-179[9]
1(iii)	Cl	H	CH_3	4(iii)	81	183-184 [10]
1(iv)	H	H	H	4(iv)	80	168-170 [10]
1(v)	H	NO_2	H	4(v)	81	179-180[9]
1(vi)	OH	H	H	4(vi)	82	232-234 [10]
1(vii)	H	H	OH	4(vii)	84	188-190[9]
1(viii)	H	OH	OH	4(viii)	79	214-215 [10]

1(ix)	H	OH	H	4(ix)	76	244-246 [10]

Table 3: Reusability of catalyst (Lemon juice).

Reuse Cycle	Fresh	First	Second	Third
Time (hrs)	1.4	1.4	1.45	1.45
Yield (%)	82	82	80	81

Plausible Mechanism for Synthesis of Pyrazoles in presence of Lemon juice

We proposed a possible mechanism for synthesis of pyrazoles (**Scheme 1**). Nitrile ion is activated by removal of acidic hydrogen from malanonitrilecatalyzed by acidic catalyst. Finally, the arylidene nitrile intermediate formed through the Knoevenagel condensation reaction of the intermediate nitrile anion with aldehyde. On the other hand, the reaction of 2,4-dinitrophenylhydrazine with arylidene nitrile afforded an intramolecular cyclized product.

Spectral data of some selected compounds

4(i) 5-amino-1-(2,4-dinitrophenyl)-3-(4-methoxyphenyl)-1H-pyrazole-4-carbonitrile: yellow solid. mp: 228–230ºC; ^{1}H NMR (400 Hz, CDCl3): δ 2.53 (s, 3H, OCH3); 6.09-7.11 (m, 3H, Ar-H); 7.15-7.61 (m, 4H, Ar-H); 9.67 (s, 2H, NH2), IR (KBr) cm^{-1} 3165 (N-H), 3031(C=CH), 2229 (CN), 1618 (C=C, aromatic), 1335 (NO_2)

4(iii) 5-amino-1-(2,4-dinitrophenyl)-3-(4-methylphenyl)-1H-pyrazole-4-carbonitrile: pale yellow solid. mp: 183-184ºC; ^{1}H NMR (400 Hz, CDCl3):δ 2.42 (s, 3H, CH3); 7.32-7.44 (m, 3H, Ar-H); 7.66-7.83 (m, 4H, Ar-H); 8.13 (s, 2H, NH2);IR(KBr)cm−1: 3262 (NH), 3110 (C=CH), 2221(C=N), 1614 (C=C, aromatic), 1331(NO2)

4(iii) **5-amino-1-(2,4-dinitrophenyl)-3-(3-nitrophenyl)-1H-pyrazole-4-carbonitrile:** pale yellow solid. mp: 177-178ºC; ^{1}H NMR (400 Hz, CDCl3): δ 7.41-7.55 (m, 3H, Ar-H); 7.69-7.80 (m, 4H, Ar-H); 8.12 (s, 2H, NH2); IR (KBr) cm^{-1}: 3261 (NH), 3108 (C=CH), 2229 (C=N), 1616 (C=C, aromatic), 1335 (NO2)

4(vi) 5-amino-1-(2,4-dinitrophenyl)-3-(3-nitrophenyl)-1H-pyrazole-4-carbonitrile: pale yellow solid. mp: 177-178ºC; ^{1}H NMR (400 Hz, CDCl3): δ 7.41-7.55 (m, 3H, Ar-H); 7.69-7.80 (m, 4H, Ar-H); 8.12 (s, 2H, NH2); IR (KBr) cm^{-1}: 3261 (NH), 3108 (C=CH), 2229 (C=N), 1616 (C=C, aromatic), 1335 (NO_2).

Comparison of the results of the present method for the synthesis of pyrazoles with the reported methods

Table 4 indicates the comparison of the activity of different catalysts by considering the yield of the reaction. We observed that the lemon juicegive catalytic activity in terms of product yield, solvent and reaction time compared to other catalysts in the literature such as I_2/K_2CO_3, $ZnCl_2$, Al_2O_3, NaH, Glycine and citric acid. Lemon juice easily available and inexpensive catalyst, which makes this method green and mild. In addition, above catalyst is a renewable catalyst which follows one of the green chemistry principles regarding the maximum yield of renewable resources.

Table 4 (VI): Comparison of the results of the present methods used for synthesis of pyrazoles with the reported methods.

S.No.	Catalyst	Solvent	Temperature (ºC)	Time (hours)	Yield (%)	Reference
1	I_2/K_2CO_3	THF	100	40	65	[11]
2	ZnCl2	THF	80	14	46-70	[12]
3	Al2O3	DMF	RT	10	72	[6]
4	NaH	THF	100	20-24	60-80	[13]
5	Chloranil	Toluene	RT	4	62-90	[14]
6	Glycine	DMSO	RT	9	80	[15]

8	Lemon juice	Solvent Free	RT	1.4	82	Present work

Conclusion

The present study focused on the importance of fruit juice in organic synthesis with natural and biocatalyst exclusivity. Therefore benefit of fruit juice in organic synthesis is based on acidic nature, benign, safe and cheap biocatalyst. Catalyst based activity is consisting of the appraisal of fruit juices in various organic transformations including the carbon-carbon and carbon-nitrogen bond formation in various biologically important organic compounds. Hence green chemistry willinvade an era of benign design regarding organic synthesis and their mechanisms in near future.

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Conflict of interest

Authors declare that there is no conflict of interest regarding the publication of this article.

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