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Lactic acid: Novel, ecofriendly and efficient catalyst for the one-pot synthesis of 1, 4-dihydropyrano [2, 3-c] pyrazole derivatives in aqueous media

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ABSTRACT

An efficient one-pot synthesis of dihydropyrano [2, 3-c] pyrazole derivatives was developed by using novel ecofriendly "Lactic acid" as a green catalyst in presence of water as a green solvent. The attractive features of this protocol is environmentally benign mild reaction conditions, cost effective easily available catalyst, non-toxic to the environment, shorter reaction time, easy isolation of product without use of chromatographic separation, reusability of the reaction media, and excellent yields.

Keywords: Lactic acid; 1, 4-dihydropyrano [2, 3-c] pyrazole derivatives; Ethyl acetoacetate; Hydrazine hydrate; Malononitrile; Solvent –water; Multi-component reaction.

1. INTRODUCTION

Multicomponent reaction (MCR) is a one-pot reaction in which three or more reactants are combined together to form a new desired compound without isolation of any intermediate. Multi-component reactions (MCRs) are attractive strategies for organic synthesis due to their atom efficiency, operational simplicity, and usually excellent productivity. [1] Advances in multicomponent reactions (MCRs) have resulted in the rapid access to large libraries of biological active compounds, the development of molecular designs, and improvements in combinatorial chemistry. In recent years every organic chemists are focusing on the development of greener approach for the synthesis of biologically active compounds using environmentally benign, reagent, solvent and catalysts. The quest for alternative reaction media to replace volatile, flammable, and often toxic reaction media commonly used in organic synthesis is an important objective in the development of green chemical processes. [2] Designing MCRs in water is another attractive thrust area in chemistry [3] because water is a cheap, safe, and environmentally benign solvent. There is need for MCRs in water with suitable catalysts and without any harmful organic solvents.

1,4-Dihydropyrano [2, 3-c] pyrazole-5-carbonitriles and its derivatives are important class of heterocyclic scaffold which are exhibiting biological activities such as anticancer [4], antimicrobial [5], anti-inflammatory [6], insecticidal[7], and molluscicidal [8] activity. These molecules are also used as potential inhibitors of human chk1 kinase. [9] Junek and Aigner [10] first established the synthesis of pyrano [2, 3-c] pyrazole derivatives from 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene in the presence of triethylamine.

Recently, four-component reactions of aldehydes, 1,3-dicarbonyl compounds, malononitrile, and hydrazine have been developed for the synthesis of pyranopyrazoles [11] using L-proline, [12] piperidine, morpholine,[13] triethylamine,[14] imidazole, [15] c-alumina, [16] cetyltrimethylammonium chloride (CTACl), [17] I_2, [18] and glycine. [19] N-methylmorpholine [20] heteropolyacids, [21] alumina, [22] sodium benzoate, [23] amberlyst A21,[24] per-6-amino-b-cyclodextrin, [25] imidazole [26]. However these methods are having their demerits like long reaction time, excess heating, and tedious work-up procedure. To overcome these demerits we have devised an efficient and environmentally benign green synthetic protocol for preparation of 6-amino-4-aryl-3-methyl-1, 4-dihydropyrano [2, 3-c] pyrazole-5-carbonitriles by four-component reaction of hydrazine hydrate, ethyl acetoacetate, aryl aldehydes, and malononitrile, in the presence of water as greener solvent using environmental

benign, non-hazardous biodegradable "Lactic acid" as an expedient and recyclable catalyst.

This protocol has several advantageous over reported methods like mild reaction conditions, cleaner reaction medium, in-expensive, easily available and reusable catalytic system, simple isolation of the product and scalable approach.

Lactic acid is an alpha-hydroxy acid containing a hydroxyl group adjacent to a carboxylic acid functional group is a green and biodegradable material. Generally it is manufactured via chemical synthesis or through fermentation of some carbohydrates like glucose, maltose, sucrose or lactose [27].

There are a few reports regarding the application of Lactic acid in the preparation of organic compounds. As a part of our current studies on the development of efficient methods for the synthesis of dihydropyrano [2, 3-c] pyrazole heterocyclic derivatives, we herein report an environmental friendly and straightforward protocol for the synthesis of dihydropyrano [2, 3-c] pyrazole derivatives by using a Lactic acid in water at room temperature.

2. EXPERIMENTAL

2.1. General

All of the chemicals used were purchased from Sigma Aldrich and used as such. All the synthesized compounds are reportedly herein are known, and were identified by the comparison of spectral and physical data with the literature. Thin layer chromatography was used to monitor the reaction progress. Compounds were purified by crystallization from water: ethanol (1:1) solvent mixture. Melting points were determined using a melting point apparatus. IR (KBr) spectra were recorded on JASCO FTIR 4600 spectrophotometer and the values are expressed as ν max cm^{-1}. Mass spectral data were recorded on a Waters micromass LCT Mass Spectrometer and on JEOL-AccuTOF JMS-T100 mass spectrometer having a DART source. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Spectrospin spectrometer and Jeol JNM ECX-400P at 300 MHz and 100 MHz, respectively using TMS as an internal standard. The chemical shift values are recorded on δ scale and the coupling constants (J) in hertz.

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

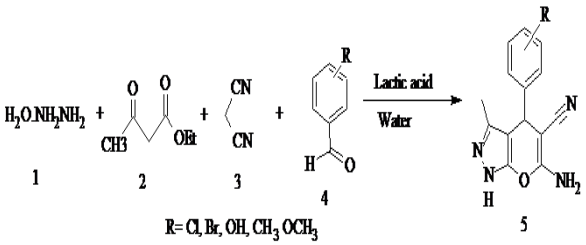
A mixture of hydrazine hydrate (1 mmol) and ethyl acetoacetate (1 mmol) was stirred at room temperature until 3-methyl-2-pyrazolin-5-one were precipitated as white solid and its formation was complete (within 5 min). Then to the reaction mixture aryl aldehyde (1 mmol), malononitrile (1 mmol), Lactic acid (0.25 mmol) and water (5.0 ml) were added at room temperature and stirred for the completion of the reaction. The progress of the reaction was monitored by TLC. After completion of the reaction, the precipitated solid was collected by filtration. The aqueous filtrate containing Lactic acid was used as such for investigating the recyclability of the catalyst. The crude product was recrystallized from ethanol: water to afford the pure pyrano pyrazole derivatives in 85–97 % yields.

All the products were obtained in an excellent yield as summarized in table 3.

3. RESULTS AND DISCUSSION

Initially, attempts were made to carry out the model reaction of 4-chlorobenzaldehyde (1, Scheme 1), malononitrile (2), ethyl acetoacetate (3), and hydrazine hydrate (4) at room temperature without any catalyst in water, but very little formation of solid product (7a, 20%) was observed after 3 hr. Thin-layer chromatography (TLC) of the reaction mixture indicated the presence of starting materials, and when the reaction was performed using Lactic acid as the catalyst, yield was drastically increased with very short reaction time. Then condensation of hydrazine hydrate, ethyl acetoacetate, benzaldehyde, and malononitrile (molar ratio 1:1:1:1) was performed in the presence of different amounts of the catalyst at room temperature. The results (Table 1) clearly indicate that 10 mmol Lactic acid is an effective amount of catalyst for this transformation.

After the optimization of the reaction conditions, the reaction of diversely substituted aromatic aldehydes were attempted with hydrazine hydrate, ethyl acetoacetate and malononitrile in water at room temperature in the presence of 10 mole % of Lactic acid. All the reactions yielded corresponding dihydropyrano [2, 3-c] pyrazole derivatives (Table 3, entries) in excellent yields.



Scheme-1

Table -1: Effect of catalyst in reaction of hydrazine hydrate, ethyl acetoacetate, 4-chlorobenzaldehyde, and malononitrile

Entry	Catalyst (mole %)	Time min/hr.	% Yield
1	Catalyst(10)	15 min	94
2	Catalyst(5)	23 min	86
3	Catalyst(3)	30 min	81
4	Catalyst(20)	15 min	92
5	No catalyst	4 hr	<20
6	Morpholine	8 hr	70[13]
7	L-proline	24 hr	10[12]
8	CATCL	4 hr	50[17]
9	Piperidine	10 hr	68[13]

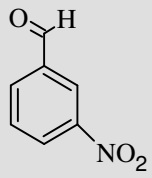
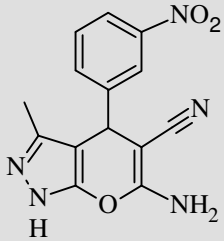
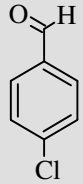
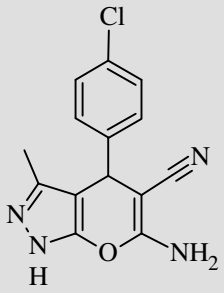
The yields are referring to isolated products.

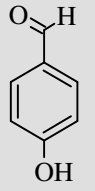
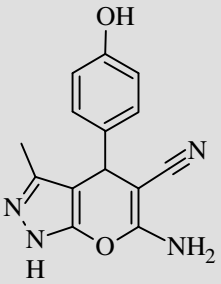
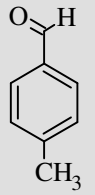
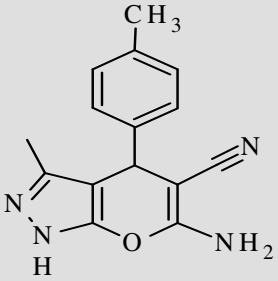
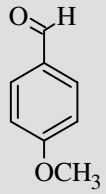
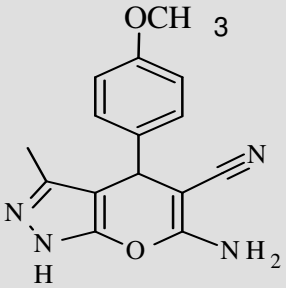
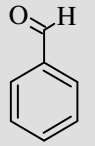
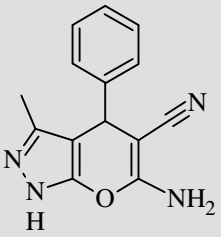
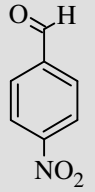
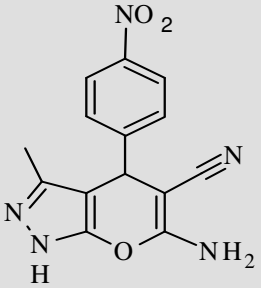
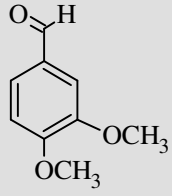
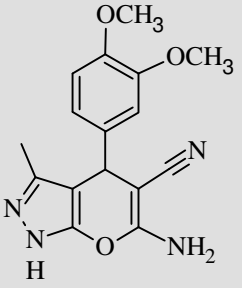
Table – 2: Effect of solvent in reaction of hydrazine hydrate, ethyl acetoacetate, 4-chlorobenzaldehyde, and malononitrile.

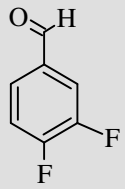
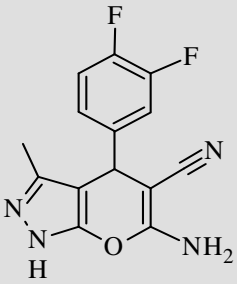
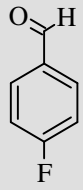
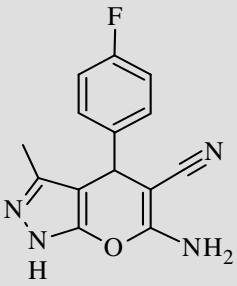
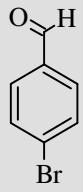
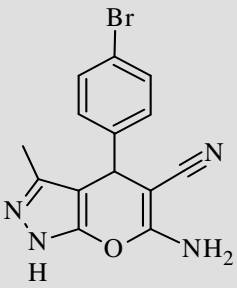
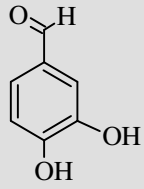
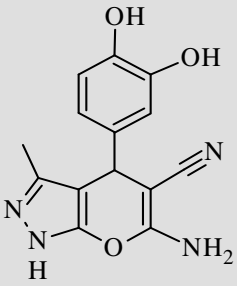
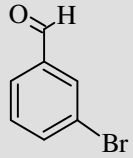
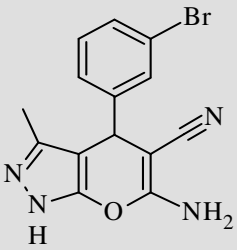
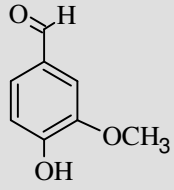
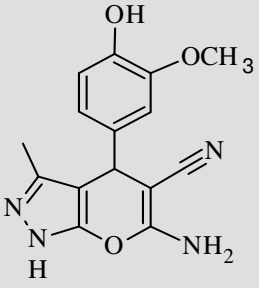
Entry	Solvent	Temp/°C	Time/hr	%Yield
1	Ethanol	Room temperature	3 hr.	60
3	Acetonitrile	Room temperature	7 hr.	55
4	Water	Room temperature	25 min	90
5	Tetrahydrofuran	Room temperature	8 hr.	<40
6	1,4-dioxane	Room temperature	6 hr.	<50

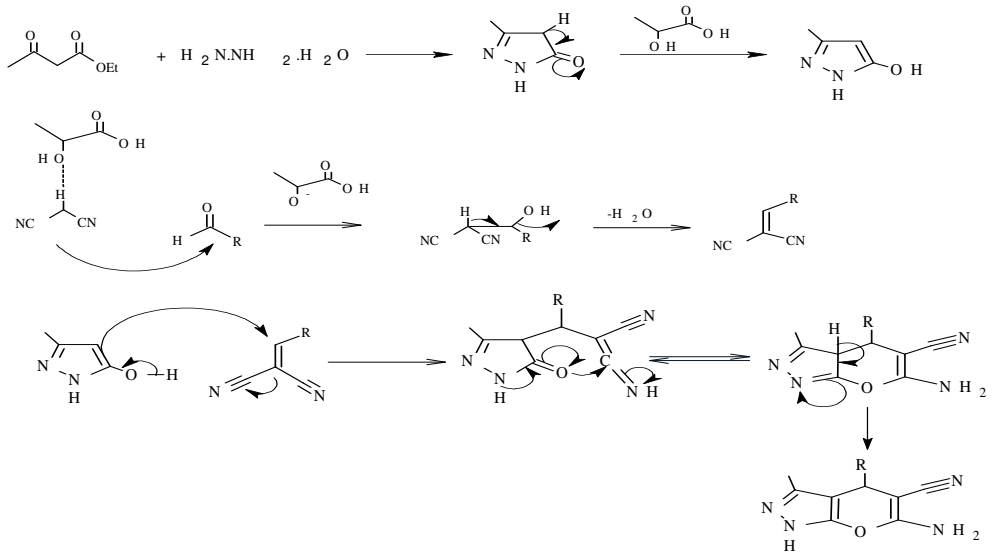
The yields are referring to isolated products

Table - 3: Lactic acid catalyzed four component synthesis of substituted 1, 4 dihydropyrano [2, 3-c] Pyrazole-5-carbonitrile Derivatives

Entry	Aldehyde	Product	Time/ min	Yield	M.P/°C	
					Found	Lit
1			15	91	190-193	190-192[29]
2			20	93	233-235	234-235[16]

3			25	90	223-226	223-224[28]
4			20	95	204-206	206-208[16]
5			25	95	210-212	210-212[16]
6			20	93	245-247	244-245[16]
7			15	95	248-250	244-245[16]
8			22	90	190-192	190-191[30]

9			25	94	170-172	--
10			18	94	172-173	171-172[31]
11			20	94	179-181	179-180[32]
12			25	84	210-212	--
13			18	84	223-225	223-224[16]
14			27	84	233-235	233-235[33]



Scheme - 3: Plausible synthetic mechanism.

3.1. Spectral Data of Some Representative Products

3.2.1. 6-Amino 1, 4-dihydro-3-methyl-4-(3-nitrophenyl)-pyrano [2, 3-c] pyrazole-5-carbonitrile (1)

Yellow color powder; yield 91 %; mp 190-193° C, IR (ν max): 3382, 3284, 3083, 2194, 1714, 1674,1644, 1591 1512, 1490, 1379, 1349 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ, 1.81(s, 3H, CH_3), 4.88(s, 1H, CH), 7.05 (s, 2H, NH2), 7.63-7.69(t, 2H, Ar-H), 8.02 (s, 1H, Ar–H), 8.11-8.14(t, 1H, Ar–H), 12.21 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ, 9.70, 29.0, 56.5, 112.6, 120.2, 123.2, 128.4, 128.6, 135.7, 141.3,146.3, 151.3, 154.6, 160.9. ppm; Mass (*m/z*): 297.27(M^+); anal. calcd. for $C_{14}H_{11}N_5O_3$: C, 56.52; H, 3.7; Found: C, 56.60; H, 3.7%.

3.2.2. 6-Amino 1, 4-dihydro-3-methyl-4-(4-chlorophenyl)-pyrano [2, 3-c] pyrazole-5-carbonitrile (2)

Off-white color powder; yield 93 %; mp 233-235° C, IR (ν max): 3371, 3182, 3083, 2192, 1710, 1677,1643, 1593 1512, 1489, 1442, 1400 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ, 1.78(s, 3H, CH_3), 4.58(s, 1H, CH), 6.8 (s, 2H, NH2), 7.15(t, 2H, Ar-H), 7.32 (d, 2H, Ar-H), 12.20 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ, 9.80, 30.0, 57.5, 111.6, 118.2, 124.2, 128.2, 128.6, 134.2, 141.5, 147.3, 151.8, 155.2, 161.6. ppm; Mass (*m/z*): 286.71(M^+); anal. calcd. for $C_{14}H_{11}N_4OCl$: C, 58.59; H, 3.84; Found: C, 58.65; H, 3.80%.

3.2.3. 6-Amino 1, 4-dihydro-3-methyl-4-(4-hydroxyphenyl)-pyrano [2, 3-c] pyrazole-5-carbonitrile (3)

Off-White color powder; yield 90 %; mp 223-226° C, IR (ν max): 3372, 3182, 3083, 2187, 1710, 1659,1610, 1580, 1536, 1512, 1487, 1453, 1402 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ, 1.96(s, 3H, CH_3), 4.62(s, 1H, CH), 6.68 (s, 2H, NH2), 6.93(t, 1H, Ar-H), 7.01-7.05 (m, 2H, Ar-H), 7.16 (t, H, Ar-H), 10.87(s, 1H, -OH), 12.20 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ, 9.9, 30.6, 58.5, 112.8, 118.6, 124.9, 126.2, 125.6, 133.2, 142.3, 146.3, 152.4, 153.9, 164.8. ppm; Mass (*m/z*): 268.27(M^+); anal. calcd. for $C_{14}H_{12}N_4O_2$: C, 62.62; H, 4.47; Found: C, 62.68; H, 4.40%.

3.2.4. 6-Amino 1, 4-dihydro-3-methyl-4-(4-methylphenyl)-pyrano [2, 3-c] pyrazole-5-carbonitrile (4)

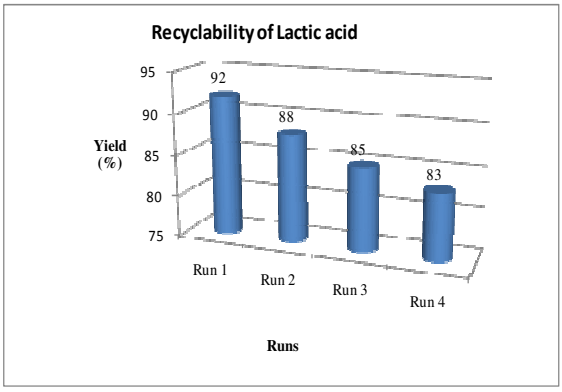
Off-White color powder; yield 95 %; mp 204-206° C, IR (ν max): 3371, 3182, 3083, 2192, 1710, 1677,1643, 1593 1512, 1489, 1442, 1400 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ, 1.77(s, 3H, CH_3), 2.27(s, 3H, CH_3) 4.54(s, 1H, CH), 6.83 (s, 2H, NH2), 7.03(t, 2H, Ar-H), 7.01-7.12 (t, 2H, Ar-H), 12.07 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ, 9.9, 30.6, 58.5, 112.8, 118.6, 124.9, 126.2, 125.6, 133.2, 142.3, 146.3, 152.4, 153.9, 164.8. ppm; Mass (*m/z*): 266.29 (M^+); anal. calcd. for $C_{15}H_{14}N_4O$: C, 67.59; H, 5.26; Found: C, 68.05; H, 5.30%.

3.2.5. 6-Amino 1, 4-dihydro-3-methyl-4-(4-methoxyphenyl)-pyrano [2, 3-c] pyrazole-5-carbonitrile (5)

Off-White color powder; yield 95 %; mp 210-212° C, IR (ν max): 3410, 3187, 3083, 2192, 1710, 1677,1642, 1596, 1513, 1491, 1442, 1400 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ, 1.77(s, 3H, CH_3), 3.71(s, 3H, OCH_3) 4.54(s, 1H, CH), 6.83 (s, 2H, NH2), 7.03(t, 2H, Ar-H), 7.01-7.12 (t, 2H, Ar-H), 12.07 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ, 11.1, 24.6, 56.2, 62.0, 114.4,114.9, 127.5, 128.7, 140.0, 143.4, 152.9, 158.8, 166.3 ppm; Mass (*m/z*): 282.29 (M^+); anal. calcd. for $C_{15}H_{14}N_4O_2$: C, 63.76; H, 4.96; Found: C, 64.05; H, 4.89%.

4. CONCLUSION

In summary, we have developed a novel synthetic methodology for the synthesis of Pyrano [2, 3-c] pyrazole annulated heterocyclic systems using 10 mole % lactic acid as a green nontoxic, inexpensive efficient catalyst. This methodology not only offers great advantages like substantial reaction conversions, high yields, recyclability of reaction media and easy isolation which avoids use of column chromatography, but also avoids use of hazardous solvent media and the catalysts helping in to protect environment and safeguards mankind.



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