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Zn(L-proline)$_2$: An efficient and reusable organocatalyst for the synthesis of polyfunctionally substituted pyrans and 2-amino-4-aryl-8-oxo-4,8-dihydropyrano[3,2-b]pyran derivatives

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ABSTRACT

Efficient synthesis of non-annulated 2-amino-4*H*-pyrans and 2-amino-8-oxo-4,8-dihydropyrano[3,2-b]pyran derivatives, which are biologically relevant heterocycles is achieved, utilizing a domino three-component reaction of ethyl acetoacetate or kojic acid with aromatic aldehydes and malononitrile catalyzed by Zn(L-proline)$_2$ as reusable organometallic catalyst. The process exhibits high atom economy, short reaction time, simple work up, high yields and environmentally friendly nature. Excellent yields of the targeted molecules have been obtained.

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1. Introduction

Polyfunctionally substituted pyrans and pyrano[3,2-b]pyran derivatives are interesting privileged scaffolds of heterocyclic compounds in fields related to biological, medicinal and industrial importance. They possess a wide range of activities including anticancer, antihypertensive and anti-HIV [1-6]. In addition, they were efficiently utilized as pigments and biodegradable agrochemicals [7,8].

Although, the general approaches of non-annulated 2-amino-4*H*-pyrans involve cyclization of the Michael adducts formed by the reaction of α,β-unsaturated nitriles with active methylene carbonyl compounds [9,10], α,β-unsaturated carbonyl compounds with active methylene nitriles or a three-component reaction of active methylene carbonyl compounds with aromatic aldehydes and active methylene nitriles mainly in ethanol with basic catalysts (triethylamine, morpholine, piperidine and sodium ethoxide. Few reports utilizing the use of acidic catalysts were reported [11]. In addition, 2-amino-6-(hydroxymethyl)-8-oxo-4,8-dihydropyrano[3,2-b]pyran derivatives have limited synthetic approaches [12-14].

L-proline is very efficiently coordinate with zinc through the carboxylate function and the secondary amino group which renders Zn(L-proline)$_2$ complex a moderately soft Lewis acid that catalyzed several organic reactions [15,16]. Moreover, Zn(L-proline)$_2$ has specific merits such as efficient, stable, green, recyclable nature, stability under reaction conditions, high solubility in water and simple dealing with in performing the reaction or working up product which make it an attractive catalyst.

Multi-component reactions (MCRs) have major advantages that relied in the synthesis of complex molecules from simple molecules [17,18].

Extensive efforts have been developed for the adaption of environmentally techniques in heterocyclic synthesis. Hence the development of a green synthetic protocol remains a challenge [19,20]. One such protocol involves the use of cheap, recyclable and easy handle catalyst.

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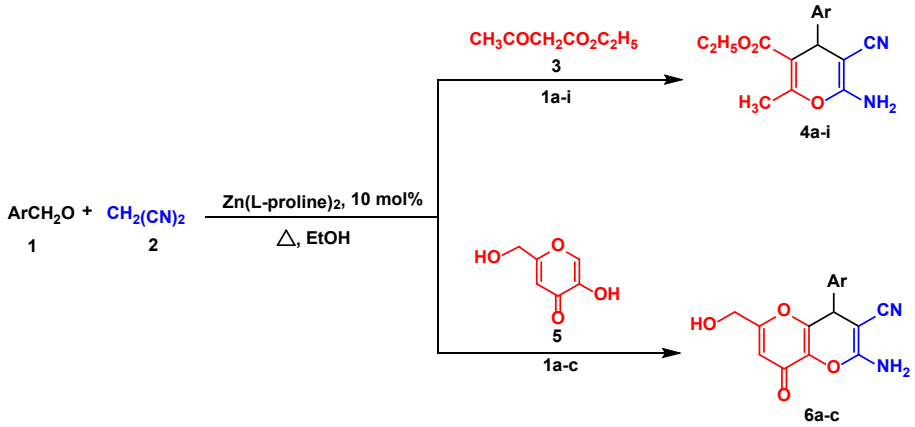


Scheme 1. Synthesis of polyfunctionallly substituted pyrans **4** and 2-amino-4-aryl-8-oxo-4,8-dihydropyrano[3,2-b]pyran derivatives **6**.

In continuation of our efforts [21-26] aimed at performing reactions under green conditions we reported herein efficient three-component domino reaction for the synthesis of non-annulated 2-amino-4*H*-pyrans and 2-amino-8-oxo-4,8-dihydro pyrano[3,2-b]pyran derivatives via reaction of aromatic aldehydes, malononitrile and ethyl acetoacetate or kojic acid catalyzed by Zn(L-proline)$_2$ as soft Lewis acid.

2. Experimental

2.1. Chemical and instrumentation

Zn(L-proline)$_2$ was prepared following the literature procedure [27,28]. Other chemicals were purchased from Sigma Aldrich and were used as such. All reactions were monitored by thin layer chromatography and products were purified by crystallization from ethanol. ^{1}H NMR and ^{13}C NMR spectra were carried out using a Broker DPX instrument at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR using DMSO-d_6 and CD_2Cl_2 as solvent and TMS as internal standard, chemical shifts are expressed in δ ppm. Mass spectra (EI, *m/z*) were made with the EI (70 eV) mode, the melting points of the products were determined by a Gallene Kamp instrument and are uncorrected.

2.2. General procedure for the domino three component reactions

A solution of aromatic aldehyde 1 (0.1 mmol), malononitrile 2 (0.1 mmol), ethyl acetoacetate 3 (0.12 mmol) or kojic acid 5 (0.1 mmol) in ethanol (20 mL) in presence of 10 mol% of Zn(L-proline)$_2$ was heated under reflux for 30 minutes to 6 hours (TLC control), after cooling to room temperature, 20 mL of water was added .The solid product formed on standing-was collected by filtration, dried and crystallized from ethanol to afford analytically pure samples. The filtrate was evaporated under vacuo till dryness and then (1 mL) of ethanol was added, Zn(L-proline)$_2$ was collected, dried in an oven at 60 °C and reused (Scheme 1 and 2).

This general procedure was examined utilizing 10 mol% of SiO_2, Al_2O_3 and *p*-toluenesulfonic acid (PTSA) instead of Zn(L-proline)$_2$ under the same experimental conditions and lower yields of products were obtained (50-60%).

Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-car boxylate (**4a**): Color: White. Yield: 92%. M.p.: 192-193 °C. ^{1}H NMR (400 MHz, CD_2Cl_2, δ, ppm): 7.12-7.17 (m, 5H, ArH), 5.40 (s, 2H, NH_2), 4.35 (s, 1H, CH), 3.98 (m, 2H, CH_2), 3.27(s, 3H, CH_3), 1.01 (t, 3H, CH_3). MS (EI, *m/z*): 284 [M$^+$]. Anal. calcd. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.51; H, 5.62; N, 9.80%.

Ethyl 6-amino-5-cyano-2-methyl-4-(4-chlorophenyl)-4H-pyran-3-carboxylate (**4b**): Color: White. Yield: 90%. M.p.: 170-172 °C. ^{1}H NMR (400 MHz, CD_2Cl_2, δ, ppm): 7.94-7.28 (m, 4H, ArH), 5.48 (s, 2H, NH_2), 4.35 (s, 1H, CH), 3.98 (m, 2H, CH_2), 2.27 (s, 3H, CH_3), 1.02 (t, 3H, CH_3). MS (EI, *m/z*): 318 [M$^+$]. Anal. calcd. for $C_{16}H_{15}ClN_2O_3$: C, 60.29; H, 4.74; N, 8.79. Found: C, 60.24; H, 4.70; N, 8.75%.

Ethyl 6-amino-5-cyano-2-methyl-4-(3-nitrophenyl)-4H-pyran-3-carboxylate (**4c**): Color: Yellow. Yield: 93%. M.p.: 187-188 °C. ^{1}H NMR (400 MHz, CD_2Cl_2, δ, ppm): 7.44 (s, 1H, ArH), 7.21- 7.18 (m, 3H, ArH), 4.57 (s, 2H, NH_2), 4.51 (s, 1H, CH), 3.97 (q, 2H, CH_2), 2.31 (s, 3H, CH_3), 1.02 (t, 3H, CH_3). MS (EI, *m/z*): 329: [M$^+$]. Anal. calcd. for $C_{16}H_{15}N_3O_5$: C, 58.36; H, 4.59; N, 12.76. Found: C, 58.31; H, 4.55; N, 12.70%.

Ethyl 6-amino-5-cyano-4-(2-methoxyphenyl)-2-methyl-4H-pyran-3-carboxylate (**4e**): Color: White. Yield: 89%. M.p.: 198-200 °C. ^{1}H NMR (400 MHz, CD_2Cl_2, δ, ppm): 7.30-8.00 (m, 4H, Ar-H), 4.50 (s, 2H, NH_2), 4.40 (s, 1H, CH), 4.00 (q, 2H, CH_2), 3.80 (s, 3H, OCH_3), 2.40 (s, 3H, CH_3), 1.10 (t, 3H, CH_3). MS (EI, *m/z*): 314 [M$^+$]. Anal. calcd. for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C,64.95; H, 5.79; N, 8.92%.

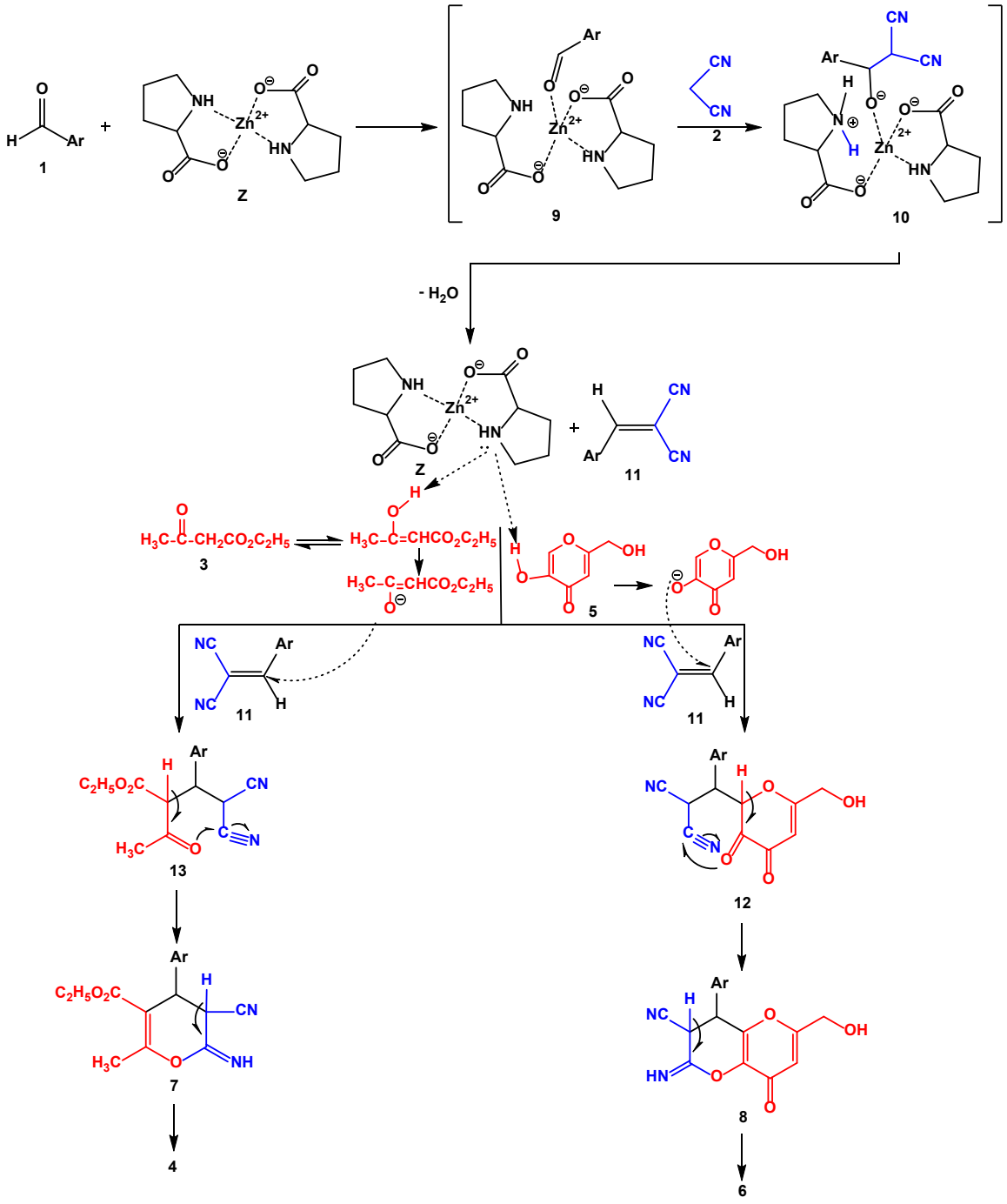
Ethyl 6-amino-5-cyano-2-methyl-4-(2-furyl)-4H-pyran-3-carboxylate (**4i**): Color: Brown. Yield: 92%. M.p.: 203-204 °C. ^{1}H NMR (400 MHz, CD_2Cl_2, δ, ppm): 7.25-7.24 (d, 1H, CH), 6.23-6.22 (t, 1H, CH), 6.03 (d, 1H, CH), 4.53 (s, 2H, NH_2), 4.64 (s, 1H, CH), 4.09-4.07 (m, 2H, CH_2), 2.25 (s, 3H, CH_3), 1.11 (t, 3H, CH_3). MS (EI, *m/z*): 274 [M$^+$]. Anal. calcd. for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.50; H, 5.12; N, 10.57%.

2-Amino-4-(4-chlorophenyl)-6-(hydroxymethyl)-8-oxo-4,8-dihydropyrano[3,2-b]pyran-3-carbonitrile (**6b**): Color: Colourless. Yield: 89%. M.p.: 200-202 °C. ^{1}H NMR (400 MHz, CD_2Cl_2, δ, ppm): 8.52-7.28 (d, 4H, ArH), 7.29 (s, 2H, NH_2), 6.31 (s, 1H, =CH), 5.69 (t, 1H, OH), 4.83 (s, 1H, CH), 4.86-4.12 (m, 2H, CH_2). ^{13}C NMR (100 MHz, CD_2Cl_2, δ, ppm): 25.89, 55.80, 59.59, 82.71, 114.50, 119.61, 129.40, 130.50, 131.59, 132.58, 133.08, 136.91, 140.18, 148.92, 159.77, 160.52, 168.74, 170.09. MS (EI, *m/z*): 330 [M$^+$]. Anal. calcd. for $C_{16}H_{11}ClN_2O_4$: C, 58.11; H, 3.35; N, 8.47. Found: C, 58.07; H, 3.31; N, 8.44%.

2-Amino-6-(hydroxymethyl)-4-(3-nitrophenyl)-8-oxo-4, 8-dihydropyrano[3,2-b]pyran-3-carbonitrile (**6c**): Color: Reddish brown. Yield: 92%. M.p.: 230-232 °C. ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 8.14-8.18 (m, 4H, ArH), 7.34 (s, 2H, NH_2), 6.36 (s, 1H, =CH), 5.64 (t, 1H, OH), 5.10 (s, 1H, CH), 4.19-4.07 (m, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 54.68, 59.03, 111.44, 118.94, 122.46, 122.98, 130.61, 134.63, 136.57, 142.80, 147.70, 148.03, 159.41, 168.24, 169.48). MS (EI, *m/z*): 341 [M$^+$]. Anal. calcd. for $C_{16}H_{11}N_3O_6$: C, 56.31; H, 3.25; N, 12.31. Found: C, 56.28; H, 3.21; N, 12.27%.

Table 1. Zn(L-proline)$_2$ catalyzed synthesis of compounds **4** and **6**.

Entry	ArCHO	Time (h)	Product	Yield (%)	M.p. (°C)	
					Reported	Literature
1	C_6H_5	0.5	**4a**	92	192-193	193-195 [11]
2	C_6H_4-Cl-*p*	0.5	**4b**	90	170-172	171-172 [11]
3	C_6H_4-NO_2-*m*	0.5	**4c**	93	187-188	-
4	C_6H_4-OMe-*p*	1.0	**4d**	90	155-157	157-158 [11]
5	C_6H_4-OMe-*o*	1.0	**4e**	89	198-200	-
6	C_6H_4-Me-*p*	1.0	**4f**	91	177-178	177-178 [11]
7	C_6H_3-$(OMe)_2$-*o,p*	1.0	**4g**	88	165-168	-
8	C_6H_4-NO_2-*p*	0.5	**4h**	88	175-176	175-176 [11]
9	2-Furyl	1.0	**4i**	92	203-204	-
10	C_6H_5	6.0	**6a**	88	225-227	224-226 [12]
11	C_6H_4-Cl-*p*	6.0	**6b**	89	200-202	200-202 [12]
12	C_6H_4-NO_2-*o*	6.0	**6c**	91	230-232	-



Scheme 2. A proposed mechanism for the formation of polyfunctionallly substituted pyrans and 2-amino-4-aryl-8-oxo-4,8-dihydropyrano[3,2-b]pyran derivatives.

3. Results and discussion

With the aim of optimizing the reaction conditions, we examined the reaction of benzaldehyde **1a**, malononitrile **2** and ethyl acetoacetate **3** in EtOH under different catalyst molar ratios, reaction temperature and aldehyde aryl-substituent. We began the reaction under catalyst free conditions. No reaction product was detected even after reflux for 1 hour. Consequently, we tried different molar ratios of Zn(L-proline)$_2$ (2, 5, 10, 20 and 30%) and the best yield was obtained with 10% mole of the catalyst. These result demonstrated that the catalyst plays a crucial role in the reaction course. We examined different catalysts (SiO_2, Al_2O_3, and PTSA) whereby moderate to low yields were obtained under similar reaction conditions. We then performed the reaction in different solvents (H_2O, MeCN, $CHCl_3$, and C_6H_5-CH_3), the results showed that the highest yield was obtained in EtOH as solvent. The effect of temperature on reaction rate and overall yield was also investigated. Our results revealed that the yield and rate was improved upon increasing temperature from ambient temperature to the boiling point of ethanol.

The effect of aldehyde aryl-substituent was also studied with both electron-donating and electron-withdrawing substituents, the reaction proceeds smoothly with little increase in case of electron-withdrawing substituent. Then, we examined aliphatic aldehydes such as ethanal (CH_3CHO) and butanal ($CH_3(CH_2)_2CHO$), and no product was obtained even after long reaction time. Finally, the recyclability of the catalyst was examined. It was found that it can be used efficiently up to four times without any pronounced loss in its activity.

The scope of the reaction was investigated with a variety of aromatic aldehydes **b-i**, malononitrile **2** and ethyl acetoacetate **3** to afford the corresponding non annulated pyrans **4b-i**. Although it has been reported that a multi-component asymmetric synthesis of compound **4a** was achieved via reacting of compounds **1a**, **2** and **3** utilizing L-proline as catalyst through initial formation of active-imine ion intermediate which resulted from condensation of active methylene carbonyl compound with proline NH. The enantiomeric excess (ee) for the reaction product was of (70% ee) [29]. In our protocol, almost a racemic mixture was obtained via a chiral column separation process. It can be rationalized for by the unavailability of proline NH through coordination with Zn metal. The enantiomeric excess (ee) for the reaction product was determined via chiral column. In all cases a mixture ranging from 49-51% was obtained.

The synthesis of 2-amino-4-aryl-6-(hydroxymethyl)-8-oxo-4,8-dihydropyrano[3,2-b]pyrans have not been extensively utilized. To the best of our knowledge, their synthesis in acidic medium has not been reported. In order to generalize the scope of such protocol, we investigated the reaction of aromatic aldehyde **1a-c**, malononitrile **2** and kojic acid **5** under the same reaction condition (Scheme 1). In all cases the corresponding 2-amino-4-aryl-6-(hydroxymethyl)-8-oxo-4,8-dihydropyrano[3,2-b]pyrans **6a-c** were obtained in excellent yields (Table 1).

To evaluate the efficiency of such protocol, we calculated its atom economy. The three component reaction of benzaldehyde **1a**, malononitrile **2** and ethyl acetoacetate **3** as well as benzaldehyde **1a**, malononitrile **2** and kojic acid **5** were chosen. Our protocol has atom economy values of 94.03 and 99.20%, respectively, which is of high impact.

A plausible mechanism in rationalization of products formation is summarized in Scheme 2. The reaction proceeds via formation of arylidene malononitrile from facile condensation of aromatic aldehydes and malononitrile catalyzed by Zn(L-proline)$_2$. We do believe that the catalyst has a dual catalytic effect, the favorable formation of ethyl acetoacetate enol form and the generation of ethyl acetoacetate or kojic acid nucleophiles followed by Oxo-Michael addition to nitrile function and cyclization that afford the imines **7** and **8**. A tautomeric proton shift affords the final isolable products **4** and **6** (Scheme 2).

4. Conclusion

We have developed an efficient synthesis of non-annulated 2-amino-4*H*-pyrans and 2-amino-4-aryl-6-(hydroxymethyl)-8-oxo-4,8-dihydropyrano[3,2-b]pyrans utilizing recyclable Zn(L-proline)$_2$ as a Lewis acid catalyst. This process proved to be simple, environmentally friendly, economic and promising strategy. To the best of our knowledge, their synthesis in Lewis acids has not been previously described. Moreover, utility of some Lewis acids as (SiO_2, Al_2O_3) or Bronsted acid as (PTSA) affords lower yields than those observed with Zn(L-proline)$_2$. The recyclability of Zn(L-proline)$_2$ is up to excessive four uses with no pronounced decrease in its reactivity.

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Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
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