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Synthesis of 2-Amino-3-cyano-7-hydroxy-4H-chromenes Using *L*-Proline as a Biocatalyst

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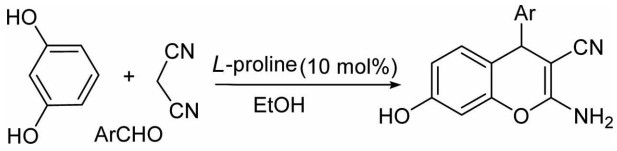
ABSTRACT. Three-component one-pot synthesis of 2-amino-3-cyano-7-hydroxy-4H-chromenes, which have been reported from condensation of malononitrile, aryl aldehydes and resorcinol in the presence of *L*-proline under reflux conditions in ethanol.

Key words: *L*-proline, Resorcinol, Chromene, Synthesis, Multicomponent reaction

INTRODUCTION

Chromene derivatives are an important class of compounds, widely present in plants, such as edible vegetables and fruits,[1] and natural products of the chromene-based structure has been associated with the capacity to prevent disease.[2] Various catalyst such as piperidine,[3] triethyl amine,[4] K_2CO_3,[5] CTABr[6] and basic ionic liquid[7] have been used for the synthesis of 2-amino-4H chromenes. Recently electrochemically induced multicomponent condensation of resorcinol, malononitrile and aldehyde in propanol in an undivided cell in the presence of NaBr as an electrolyte.[8] Many of the methods reported for the synthesis of these compounds[9–12] are associated with the use of hazardous organic solvents, long reaction time, use of toxic amine-based catalysts, and lack of general applicability. Along with other reaction parameters, the nature of the catalyst plays a significant role in determining yield, selectivity, and general applicability. Thus, development of an inexpensive, mild, general, and reusable catalyst for MCRs remains an issue of interest.

Also, recently, *L*-proline has gained importance as a versatile catalyst for effecting various organic transformations such as the synthesis of coumarone in ionic liquid,[13] density functional study of the *L*-proline-catalyzed α-aminoxylation of aldehydes,[14] unsymmetrical dihydro-1H-indeno[1, 2-b]pyridines[15] and 2-amino-4H-benzochromenes.[16] In recent years, *L*-proline and *L*-proline derivatives were successfully used as organocatalysts in asymmetric aldol and Michael addition reactions.[17] To the best of our knowledge, there was no attempt to use *L*-proline as a catalyst for the synthesis of 2-amino-4H-chromenes. In this study, malononitrile, resorcinol and aromatic aldehydes in the gained considerable attention in presence of *L*-proline under reflux condition in ethanol was subjected for the synthesis of 2-amino-3-cyano-7-hydroxy-4H-chromenes, in good-to-excellent yields, regarding to fully simple and efficient route, using less hazardous solvent and easy separation (*Scheme* 1).



***Scheme* 1.** Synthesis of 2-amino-3-cyano-7-hydroxy-4H-chromenes using *L*-proline.

EXPERIMENTAL

Mps were measured by using the capillary tube method with an electro thermal 9200 apparatus. IR spectra were recorded on Perkin Elmer FT-IR spectrometer did scanning between 4000–400 cm^{-1}. ^{1}HNMR spectra were obtained on Bruker DRX-300 MHZ NMR instrument. All products were characterized and compared with those of authentic sample in literature.

Synthesis of 2-amino-3-cyano-7-hydroxy-4-aryl-4H-chromenes. General procedure: A mixture of malononitrile (1 mmol), aromatic aldehyde (1 mmol), resorcinol (1 mmol), and *L*-proline (10 mol%) in ethanol was stirred under reflux condition for an appropriate time. After completion of the reaction which was monitored by TLC (ethyl acetate: n-hexane 1:1). Then ethanol was removed, water (10 ml) was added and the crude product was extracted by ethyl acetate (2×15 ml). The pure product was obtained by recrystallized from ethanol.

RESULTS AND DISCUSSION

The first efforts were focused on the evaluation of catalytic amount of the catalyst on rate and the yields of obtained 2-amino-3-cyano-7-hydroxy-4H-chromenes by reacting resorcinol, 4-chlorobenzaldehyde, malononitrile and *L*-proline in refluxing ethanol. The results on these reactions claimed that 10 mol% of *L*-proline is the best in terms of yield and reaction time (entry 4, *Table* 1).

Of solvents including ethanol, water, and ethanol/water, ethanol proved to be the best in terms of yield. Thus in present work has been used only ethanol, which is relatively benign organic solvent (entry 3; *Table* 2).

On the basis of the optimization of the reaction conditions, the scope of *L*-proline-catalyzed multicomponent reaction was explored. Not only electron-rich aryl aldehydes, but also electron-deficient aryl aldehydes in the reactions resulted 2-amino-3-cyano-7-hydroxy-4-aryl-4H-chromenes in 85–98% yields (*Table* 3). Comparatively, the rate of the reaction electron-deficient aryl aldehydes (4-Cl, 2-Cl, 2-Nitro, 3-Nitro, 3-OH) is faster than electron-rich (4-Me, 4-Me_2N-, 3,4-DiMeO) aryl aldehydes.

To show the fairly advantages of using *L*-proline as a biocatalyst in the synthesis of 2-amino-4-phenyl-7-hydroxy-4H-chromene-3-carbonitrile, our protocol was compared with previously reported methods (*Table* 4). From the results given in *Table* 3, the advantages of this work are evident regarding the yields of the reactions which are very important in chemical industry especially when it is combined by easy separation and reusability of the catalyst.

***Table* 1.** One-pot synthesis of 2-amino-4-(4-chlorophenyl)-7-hydroxy-4H-chromene-3-carbonitrile

Entry	*L*-proline (mol%)	τ (h)	Yield (%[a])
1	free	48	-
2	5	5.0	83
3	10	4.0	98
4	15	4.0	98

[a]Reaction condition: 4-Chloro benzaldehyde (1 mmol), resorcinol (1.0 mmol), malononitrile (1 mmol) and ethanol (5 ml) under reflux conditions.

***Table* 2.** One-pot synthesis of 2-amino-4-(4-chlorophenyl)-7-hydroxy-4H-chromene-3-carbonitrile

Entry	Solvent (5 ml)	Yield (%[a])
1	free	65
2	H_2O	48
3	EtOH	98

[a]Reaction condition: 4-Chloro benzaldehyde (1 mmol), resorcinol (1.0 mmol), malononitrile (1 mmol), *L*-proline (10 mol%) and under reflux conditions.

The following mechanism can be proposed for condensation of different aldehydes, resorcinol and malononitrile to afford 2-amino-4H-chromenes catalyzed by *L*-prolin in refluxing ethanol (*Scheme* 2). According to the results obtained, formation of the Knoevenagel product (intermediate **I**) is the first step of this condensation. Subsequent Michael like addition of resorcinol was facilitated by *L*-prolin to give intermediate **II**, which produced the desired products **IV** through intermediate **III**.

Finally, the reusability of the catalyst was investigated. At the end of the reaction, the aqueous layer was separated and washed with diethyl ether and reused in reaction. As indicated in *Table* 5, the recycled catalyst was used for three consecutive reactions without significant decrease of the yields, the yields regard from 88 to 98% (*Table* 5).

PHYSICAL AND SPECTRAL DATA

Compound **1**: C_6H_5CHO: Yield: 95%; m.p: 232–234 °C: IR (KBr, cm^{-1}): 3426 (-OH stretching), 3363(-NH stretching of amin), 2198(-CN stretching), 1622 (C=C Vinyl nitrile), 1593 (C=C aromatic); 1H-NMR (300 MHz, DMSO-d_6, δ / ppm): 4.61 (s,1H, H-4), 6.85(s, 2H, NH_2), 6.40-7.31 (m, 8H, Ar-H), 9.68 (s, 1H, OH).

Compound **2**: 4-Cl-C_6H_4CHO: Yield: 98%; m.p: 159–161 °C; IR (KBr, cm^{-1}): 3450 (-OH stretching), 3335 (-NH stretching of amine), 2191 (-CN stretching), 1642 (C=C Vinyl nitrile), 1589 (C=C aromatic): ^{1}H NMR (300 MHz, DMSO-d_6, δ / ppm): 4.62 (s, 1H, H-4), 6.85 (s, 2H, NH_2), 6.37–7.33 (m,7H, Ar-H), 9.68 (s, 1H, OH).

Compound **3**: 2-Cl-C_6H_3CHO: Yield: 96%; m.p: 94–96 °C; IR (KBr, cm^{-1}): 3419 (-OH stretching), 3335 (-NH stretching of amine), 2192 (-CN stretching), 1654 (C=C Vinyl nitrile), 1588 (C=C aromatic); ^{1}H NMR (300 MHz, DMSO-d_6, δ / ppm): 4.62 (s, 1H, H-4), 6.85 (s, 2H, NH_2), 6.37–7.33 (m,7H, Ar-H), 9.68 (s,1H,OH).

Compound **4**: 4-Me-C_6H_3CHO: Yield: 90%; m.p: 182–184 °C: IR (KBr, cm^{-1}): 3409 (-OH stretching), 3369 (-NH stretching of amine), 2191 (-CN stretching), 1615 (C=C Vinyl nitrile), 1510 (C=C aromatic); ^{1}H NMR (300 MHz, DMSO-d_6, δ / ppm): 4.56 (s, 1H, H-4), 2.24 (s, 3H, CH_3), 6.81 (s, 2H, NH_2), 6.38–7.10 (m,7H, Ar-H), 9.66 (s, 1H, OH).

Compound **5**: 2-Nitro-C_6H_3CHO: Yield: 89%; m.p: 160–162 °C: IR (KBr, cm^{-1}): 3409 (-OH stretching), 3343 (-NH stretching of amine), 2185 (-CN stretching), 1688 (C=C Vinyl nitrile), 1591/25 (C=C aromatic); ^{1}H NMR

***Table* 3.** 2-Amino-3-cyano-7-hydroxy-4-aryl-4H-chromenes using L-proline

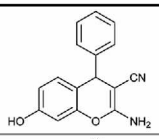
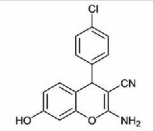
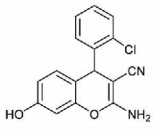
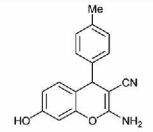
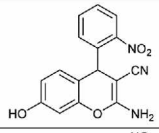
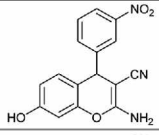
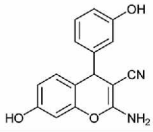
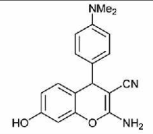
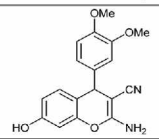
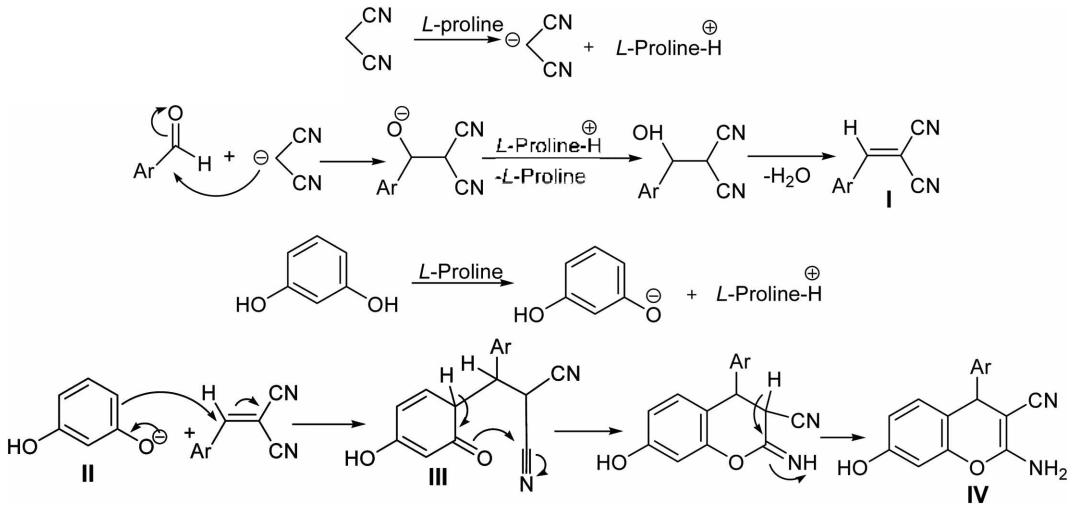
Entry	ArCHO	Product	τ (h)	Yield (%)	m.p (°C)	
					Found	Reported [lit.]
1	C_6H_5CHO		4	95	232–234	234–236[5]
2	4-Cl-C_6H_4CHO		5	98	159–161	160–162[8]
3	2-Cl-C_6H_3CHO		4.5	96	94–96	96–98[8]
4	4-Me-C_6H_3CHO		6	90	182–184	185–187[21]
5	2-Nitro-C_6H_3CHO		5	89	160–162	162–163[22]
6	3-Nitro-C_6H_4CHO		4	97	188–190	188–192[18]
7	3-OH-C_6H_4CHO		5.5	90	212–216	215–217 [19]
8	4-$(Me)_2$N-C_6H_4CHO		6	95	193–194	193–195[22]
9	3,4-DiMeO-C_6H_3CHO		6	88	213–216	215–217[18]

***Table* 4.** The synthesis of 2-amino-4-phenyl-7-hydroxy-4H-chromene-3-carbonitrile using variety of catalysts was compared

Entry	Catalyst (mol%)	Solvent	τ (h)	*t* (°C)	Yield (%)	Ref.
1	DBU (5 mol%)	EtOH	2- 4	50, MV	91	8
2	Mg Al/HT[a] (15 wt%)	H_2O	4	60	95	20
3	NaBr (50 mol%)	n-PrOH	4	r.t -50 mA	83	18
4	$NaHCO_3$ (5 mol%)	EtOH	2.0	r.t	25	22
5	TBAB (10 mol%)	EtOH	2.0	50	20	23
6	FHS (10 mol%)	CH_3CN	4.0	reflux	86	24
7	$FeHSO_3$	CH_3CN	4.5	"	83	25
4	*L*-proline (10 mol%)	EtOH	4.0	"	95	This work



***Scheme* 2.** Probable mechanism for the synthesis of 2-amino-3-cyano-7-hydroxy-4-aryl-4H-chromenes.

***Table* 5.** Reusability of the catalyst for synthesis of 2-amino-4-(4-chlorophenyl)-7-hydroxy-4H-chromene-3-carbonitrile

Run	1	2	3	4
Yield (%)[a]	98	95	91	88

[a]Reaction condition: 4-Chloro benzaldehyde (1 mmol), resorcinol (1.0 mmol), malononitrile (1 mmol), *L*-proline / 10 mol% in ethanol under reflux conditions.

(300 MHz, DMSO-d_6, δ / ppm): 5.14 (s,1H, H-4), 7.0 (s, 2H, NH_2), 6.43–7.86 (m,7H, Ar-H), 9.80 (s, 1H, OH).

Compound **6**: 3-Nitro-C_6H_4CHO: Yield: 97%; m.p: 188–190 °C; IR (KBr, cm^{-1}): 3438 (-OH stretching), 3329 (-NH stretching of amine), 2194 (-CN stretching), 1642 (C=C Vinyl nitrile), 1589 (C=C aromatic); ^{1}H NMR (300 MHz, DMSO-d_6, δ / ppm): 4.90 (s, 1H, H-4), 7.02 (s, 2H, NH_2), 6.44–8.10 (m, 7H, Ar-H), 9.77 (s, 1H, OH).

Compound **7**: 3-OH-C_6H_4CHO: Yield: 85%; m.p: 212–216 °C; IR (KBr, cm^{-1}): 3427 (-OH stretching). 3360 (-NH stretching of amine), 2192 (-CN stretching), 1600 (C=C Vinyl nitrile), 1506 (C=C aromatic); ^{1}H NMR (300 MHz, DMSO-d_6, δ / ppm): 4.49 (s, 1H, H-4), 6.87 (s, 2H, NH_2), 6.31–7.08 (m,7H, Ar-H), 9.68 (s,1H, OH).

Compound **8**: 4-$(Me)_2NC_6H_4CHO$: Yield: 95%; m.p: 193–194 °C; IR (KBr, cm^{-1}): 3437 (-OH stretching), 3340 (-NH stretching of amine), 2190 (-CN stretching), 1638 (C=C Vinyl nitrile), 1583 (C=C aromatic); ^{1}H NMR (300 MHz, DMSO-d_6, δ / ppm): 4.46 (s, 1H, H-4), 2.84 (s, 6H, $N(CH_3)_2$), 6.72 (s, 2H, NH_2), 6.37–6.97 (m,7H, Ar-H), 9.66 (s, 1H, OH).

Compound **9**: 3,4-DiMeOC_6H_3CHO: Yield: 88%; m.p: 213–216 °C; IR (KBr, cm^{-1}): 3447 (-OH stretching), 3350 (-NH stretching of amin), 2186 (-CN stretching), 1645 (C=C Vinyl nitrile), 1586 (C=C aromatic); ^{1}H NMR (300 MHz, DMSO-d_6, δ / ppm): 4.55 (s, 1H, H-4), 3.69 (s, 6H, OCH_3), 6.38 (s, 2H, NH_2), 6.45–7.12 (m, 6H, Ar-H), 9.66 (s, 1H, OH).

CONCLUSION

Disclosed work has demonstrated a protocol for the catalytic synthesis of 2-amino-3-cyano-7-hydroxy-4-aryl-4H-chromenes which proceeds efficiently in ethanol under reflux conditions. The reaction conditions are mild and the reaction gives excellent yields of products. This method does not involve the use of hazardous organic solvents and thus, is an environmentally friendly process.

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