

An Efficient Synthesis of 4*H*-chromene Derivatives by a One-pot, Three-component Reaction

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ABSTRACT: A facile and efficient one-pot, multicomponent synthesis of 4*H*-chromenes is reported, through the reaction of arylglyoxal monohydrates with 1,3-diketones and malononitrile in ethanol in the presence of *L*-proline as a catalyst.

KEYWORDS: Arylglyoxal monohydrates; One-pot reaction; 4*H*-chromenes; *L*-proline.

INTRODUCTION

The synthesis of various heterocyclic compounds via Multicomponent Reactions (MCRs) is gaining importance in medicinal and organic chemistry. Heterocyclic compounds containing 4*H*-chromene rings are an important class of oxygen heterocyclic that display a broad spectrum of interesting biological activities such as anti-bacterial [1, 2], anti-cancer [3, 4], anti-coagulant [5], anti-anaphylactic [6], anti-proliferative [7], and anti-tumor [8] properties. In particular, 2-amino-4*H*-chromenes containing a nitrile or ester function at the 3-position are of interest because of their proapoptotic activity against various tumors [9-11].

The synthesis of 4*H*-chromene derivatives via a three-component Hantzsch reaction of cyclic 1,3-diketones, aryl aldehydes, and malononitrile has been performed under various reaction conditions. A variety of reagents, such as CBSA [12], TFE [13], DABCO [14], PhB(OH)₂ [15], nano-ZnO [16], and the use of microwave irradiation [17], infrared irradiation [18], amino-functionalized ionic liquids [19] were found to catalyze this reaction. The one-pot, three-component synthesis of pyrano[*c*]chromene

derivatives using sulfonic acid functionalized silica (SiO₂-Pr-SO₃H) as a catalyst and iron ore pellet as a natural catalyst has been reported [20, 21].

While these methods have achieved good results, they are limited by high cost, high reaction temperatures, low yields, use of toxic solvents and the requirement of special apparatus.

In continuation of our interest in the development of highly expedient procedures for the synthesis of heterocyclic compounds [22-33], we now wish to report a rapid and environmentally benign protocol for the synthesis of some new 2-amino-4-aryloxy-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile derivatives by the multicomponent condensation reaction of arylglyoxal monohydrates and 1,3-diketones such as dimedone or 1,3-cyclohexandione using *L*-proline as catalyst in ethanol under reflux conditions, in high yields.

EXPERIMENTAL SECTION

Melting points were measured on a Philip Harris C4954718 apparatus and are uncorrected. Infrared spectra

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were recorded on a Thermo Nicolet Nexus 670 FT-IR instrument using KBr discs. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance AQS 300 MHz spectrometer at 300 and 75.5 MHz, respectively. Chemical shifts were measured in DMSO- d_6 as solvent relative to TMS as the internal standard. Elemental analyses were performed by using a Leco Analyzer 932. The progress of the reaction was monitored by thin layer chromatography (TLC) on Merck's silica plates.

General procedure for synthesis of 2-amino-4-aryoyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitriles derivatives 4a-h:

A mixture of arylglyoxal (1 mmol), 1,3-diketone (1 mmol) and malononitrile (1.1 mmol) in the presence of *L*-proline (0.2 mmol) in EtOH (5 mL) was heated under reflux for the appropriate time (Table 2). After completion of the reaction, as indicated by TLC, the mixture was cooled to room temperature and the precipitate was separated by filtration. The pure product was obtained by recrystallized from EtOH, in 86-92% yields.

2-Amino-4-(4-chlorobenzoyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4a)

Grey crystals, mp 176-178 °C. FT-IR (ν_{max} , cm^{-1}): 3336, 3201, 2941, 2191, 1669, 1596, 1474, 1367, 845, 604. ^1H NMR (300 MHz, DMSO- d_6) δ (ppm): 1.95-2.00 (m, 2H, CH_2), 2.28-2.32 (m, 2H, CH_2), 2.49-2.60 (m, 2H, CH_2), 4.98 (s, 1H, CH), 7.27 (br. s, 2H, exchanged with D_2O , NH_2), 7.62 (d, $J = 8.4$ Hz, 2H, ArH), 8.07 (d, $J = 8.4$ Hz, 2H, ArH). ^{13}C NMR (75.5 MHz, DMSO- d_6) δ (ppm): 20.44, 26.67, 36.14, 36.46, 52.28, 112.11, 119.51, 129.34, 131.20, 135.01, 139.07, 196.61, 198.30. Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{ClN}_2\text{O}_3$: C, 62.11; H, 3.99; N, 8.52; Found: C, 62.29; H, 3.72; N, 8.63%.

2-Amino-4-(4-chlorobenzoyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4b)

Brown crystals, mp 181-183 °C. FT-IR (ν_{max} , cm^{-1}): 3388, 3330, 2951, 2192, 1665, 1590, 1372, 1216, 845, 552. ^1H NMR (300 MHz, DMSO- d_6) δ (ppm): 1.05 (s, 6H, $2 \times \text{CH}_3$), 2.11 (d, 1H, $J = 15.9$ Hz, CH), 2.34 (d, 1H, $J = 15.9$ Hz, CH), 2.40 (d, 1H, $J = 14.2$ Hz, CH), 2.53 (d, 1H, $J = 18.2$ Hz, CH), 4.99 (s, 1H, CH), 7.20 (br. s, 2H,

exchanged with D_2O , NH_2), 7.63 (d, 2H, $J = 7.8$ Hz, ArH), 8.08 (d, 2H, $J = 7.8$ Hz, ArH). ^{13}C NMR (75.5 MHz, DMSO- d_6) δ (ppm): 26.80, 29.07, 32.90, 36.29, 49.91, 52.27, 110.94, 119.51, 129.35, 131.27, 139.11, 160.45, 164.50, 196.56, 198.23. Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{ClN}_2\text{O}_3$: C, 63.96; H, 4.80; N, 7.85; Found: C, 63.77; H, 4.93; N, 7.78%.

2-Amino-4-(4-fluorobenzoyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4c)

Pink crystals, mp 169-171 °C. FT-IR (ν_{max} , cm^{-1}): 3438, 3320, 2941, 2191, 1669, 1595, 1218, 848, 600. ^1H NMR (300 MHz, DMSO- d_6) δ (ppm): 1.87-2.05 (m, 2H, CH_2), 2.22-2.39 (m, 2H, CH_2), 2.52-2.65 (m, 2H, CH_2), 4.98 (s, 1H, CH), 7.25 (br. s, 2H, exchanged with D_2O , NH_2), 7.41-7.35 (m, 2H, ArH), 8.11-8.13 (m, 2H, ArH). ^{13}C NMR (75.5 MHz, DMSO- d_6) δ (ppm): 20.44, 26.67, 36.16, 36.34, 52.37, 112.16, 116.09, 116.38, 119.53, 132.44, 132.99, 160.31, 166.10, 196.60, 197.79. Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{FN}_2\text{O}_3$: C, 65.38; H, 4.20; N, 8.97; Found: C, 65.49; H, 4.02; N, 9.04%.

2-Amino-4-(4-fluorobenzoyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4d)

White crystals, mp 184-186 °C. FT-IR (ν_{max} , cm^{-1}): 3396, 3318, 2956, 2194, 1665, 1596, 1373, 1221, 1154, 848, 608. ^1H NMR (300 MHz, DMSO- d_6) δ (ppm): 1.05 (s, 6H, $2 \times \text{CH}_3$), 2.11 (d, 1H, $J = 15.9$ Hz, CH), 2.33 (d, 1H, $J = 15.9$ Hz, CH), 2.46 (d, 1H, $J = 17.4$ Hz, CH), 2.61 (d, 1H, $J = 17.4$ Hz, CH), 4.99 (s, 1H, CH), 7.26 (br. s, 2H, exchanged with D_2O , NH_2), 7.46 (d, 2H, $J = 8.4$ Hz, ArH), 8.20 (d, 2H, $J = 8.4$ Hz, ArH). ^{13}C NMR (75.5 MHz, DMSO- d_6) δ (ppm): 26.77, 29.09, 32.90, 36.20, 49.93, 52.38, 111.00, 116.11, 119.55, 132.52, 132.89, 132.92, 160.46, 164.47, 196.55, 197.72. Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{FN}_2\text{O}_3$: C, 67.05; H, 5.03; N, 8.23; Found: C, 67.32; H, 4.88; N, 8.04%.

2-Amino-4-(4-methylbenzoyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4e)

Orange crystals, mp 216-218 °C. FT-IR (ν_{max} , cm^{-1}): 3365, 3317, 3190, 2942, 2190, 1669, 1604, 1367, 1205, 840, 541. ^1H NMR (300 MHz, DMSO- d_6) δ (ppm): 1.87-2.05 (m, 2H, CH_2), 2.22-2.34 (m, 2H, CH_2), 2.39 (s, 3H CH_3), 2.55-2.65 (m, 2H, CH_2), 4.95 (s, 1H, CH), 7.22 (br. s, 2H, exchanged with D_2O , NH_2), 7.35 (d, 2H,

$J = 7.2$ Hz, ArH), 7.94 (d, 2H, $J = 7.2$ Hz, ArH). ^{13}C NMR (75.5 MHz, DMSO- d_6) δ (ppm): 20.45, 21.66, 26.69, 36.14, 36.21, 52.66, 112.32, 119.58, 129.48, 129.72, 133.67, 144.50, 160.34, 166.04, 196.54, 198.46. Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3$: C, 71.41; H, 5.99; N, 8.33; Found: C, 71.23; H, 6.08; N, 8.21%.

2-Amino-7,7-dimethyl-4-(4-methylbenzoyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4f).

White crystals, mp 177-179 °C. FT-IR (ν_{max} , cm^{-1}): 3389, 3325, 3199, 2954, 2191, 1667, 1603, 1372, 1221, 1033, 846, 562. ^1H NMR (300 MHz, DMSO- d_6) δ (ppm): 1.05 (s, 6H, 2 \times CH $_3$), 2.09 (d, 1H, $J = 16.2$ Hz, CH), 2.33 (d, 1H, $J = 16.2$ Hz, CH), 2.39 (s, 3H, CH $_3$), 2.45 (d, 1H, $J = 17.4$ Hz, CH), 2.60 (d, 1H, $J = 17.4$ Hz, CH), 4.95 (s, 1H, CH), 7.23 (br. s, 2H, exchanged with D $_2$ O, NH $_2$), 7.35 (d, 2H, $J = 7.8$ Hz, ArH), 7.95 (d, 2H, $J = 7.8$ Hz, ArH). ^{13}C NMR (75.5 MHz, DMSO- d_6) δ (ppm): 21.66, 26.78, 29.13, 32.89, 35.98, 49.98, 52.66, 111.16, 119.60, 129.56, 129.73, 133.56, 144.54, 160.48, 164.41, 196.50, 198.38. Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3$: C, 70.12; H, 5.23; N, 9.09; Found: C, 70.22; H, 5.01; N, 9.11%.

2-Amino-4-(4-methoxybenzoyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4g)

Pink crystals, mp 210-212 °C. FT-IR (ν_{max} , cm^{-1}): 3428, 334, 3189, 2945, 2193, 1669, 1599, 1512, 1372, 1253, 1175, 1019, 842, 603. ^1H NMR (300 MHz, DMSO- d_6) δ (ppm): 1.94-1.97 (m, 2H, CH $_2$), 2.25-2.33 (m, 2H, CH $_2$), 2.55-2.64 (m, 2H, CH $_2$), 3.86 (s, 3H, OCH $_3$), 4.93 (s, 1H, CH), 7.06 (d, 2H, $J = 8.4$ Hz, ArH), 7.17 (br. s, 2H, exchanged with D $_2$ O, NH $_2$), 8.03 (d, 2H, $J = 8.4$ Hz, ArH). ^{13}C NMR (75.5 MHz, DMSO- d_6) δ (ppm): 20.45, 26.72, 35.99, 36.25, 52.94, 56.03, 112.39, 114.38, 119.60, 129.02, 131.75, 160.35, 163.93, 165.99, 196.50, 197.25. Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4$: C, 68.17; H, 5.72; N, 7.95; Found: C, 68.27; H, 5.69; N, 8.04%.

2-Amino-4-(4-methoxybenzoyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4h)

White crystals, mp 141-143 °C. FT-IR (ν_{max} , cm^{-1}): 3437, 3336, 3197, 2953, 2190, 1664, 1595, 1370, 1228, 1170, 1029, 820, 597. ^1H NMR (300 MHz, DMSO- d_6) δ (ppm): 1.06 (s, 6H, 2 \times CH $_3$), 2.10 (d, 1H, $J = 16.5$ Hz, CH), 2.32 (d, 1H, $J = 16.5$ Hz, CH), 2.46 (d, 1H, $J = 17.7$ Hz, CH), 2.60 (d, 1H, $J = 17.7$ Hz, CH), 3.83 (s, 3H, OCH $_3$),

4.95 (s, 1H, CH), 7.07 (d, 2H, $J = 8.7$ Hz, ArH), 7.21 (br. s, 2H, exchanged with D $_2$ O, NH $_2$), 8.05 (d, 2H, $J = 8.7$ Hz, ArH). ^{13}C NMR (75.5 MHz, DMSO- d_6) δ (ppm): 26.78, 29.13, 32.87, 35.73, 50.02, 52.85, 56.03, 111.2, 114.37, 119.65, 128.87, 131.85, 160.47, 163.87, 164.38, 196.49, 197.18. Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_4$: C, 66.66; H, 4.97; N, 8.64; Found: C, 66.75; H, 4.76; N, 8.70%.

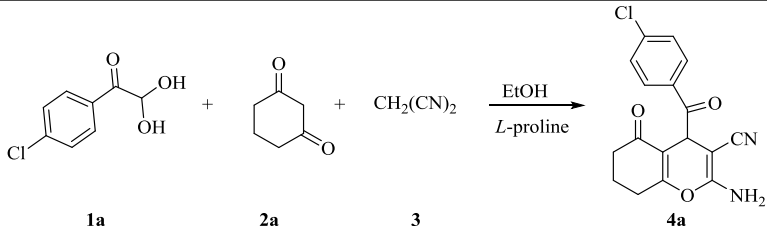
RESULT AND DISCUSSION

2-Amino-4-aryloxy-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitriles **4a-h** may be synthesized by the one-pot, three-component reaction of arylglyoxal monohydrates **1a-d**, 1,3-diketones such as 1,3-cyclohexanedione (**2a**) or dimedone (**2b**), and malononitrile (**3**) under a variety of different conditions (Scheme 1). We initially evaluated the yield and rate of reaction by using several catalysts such as Et $_3$ N, piperidine, CuFe $_2$ O $_4$, HCl, NH $_4$ Cl, (NH $_4$) $_2$ HPO $_4$, NH $_4$ H $_2$ PO $_4$, *p*-TSA, Na $_2$ CO $_3$, NaHCO $_3$, Glycine, and *L*-proline. Finally, the effects of solvent and temperature for this reaction have been evaluated, and are summarized in Table 1.

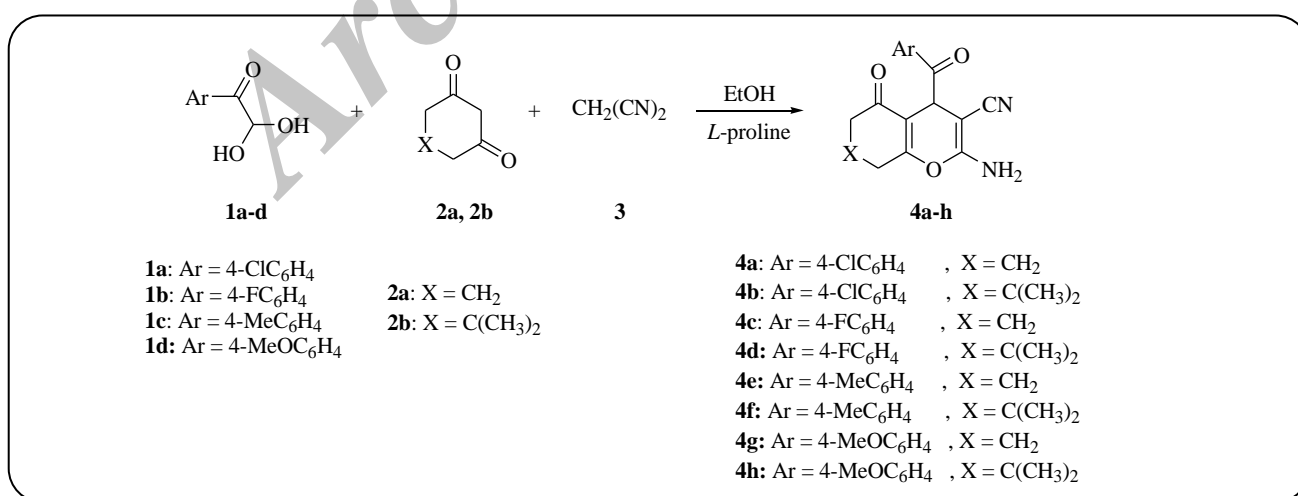
For the optimization of this reaction under several catalytic conditions, we used Lewis bases as catalyst under RT and reflux conditions to give the desired products in 32-45% yields (Table 1, Entry 1-5). Using Lewis acids as catalyst caused the yield increasing to 48% (Table 1, Entry 6, 7). When we used the catalytic amount of HCl, there was not significant in the reaction yields (Table 1, Entry 8). Repeating reaction in the presence of acidic salts such as NH $_4$ Cl, (NH $_4$) $_2$ HPO $_4$, NH $_4$ H $_2$ PO $_4$ as catalysts the highest yield was 52% (Table 1, Entry 9-12). Using *p*-TSA as an organocatalyst the yield of the reaction was 46% (Table 1, Entry 13). Using basic salts such as Na $_2$ CO $_3$, NaHCO $_3$ under reflux conditions did not increase the yield of reaction (Table 1, Entry 14, 15). Finally, using amino acid Glycine and *L*-proline in EtOH, H $_2$ O and aqueous EtOH gave the corresponding products in high yield (67-86%) as shown in Table 1. (Entry 16-18). According to the results mentioned in Table 1. The amino acids were found to be the best catalysts and EtOH was the best solvent system for this reaction. The list of products along with reaction times and yields are summarized in Table 2.

A possible mechanism for this reaction is proposed in Scheme 2. In this procedure, *L*-proline plays a crucial role in accelerating the reaction. Dehydration of arylglyoxal

Table 1: Optimizing the reaction condition for the synthesis of compound 4a.

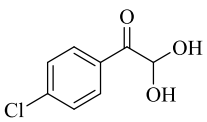
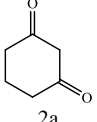
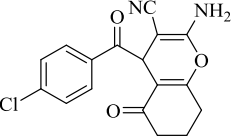
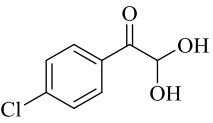
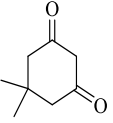
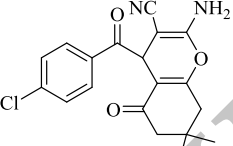
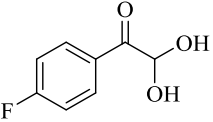
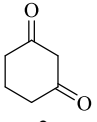
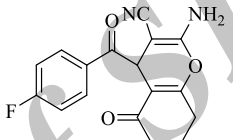
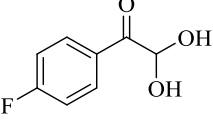
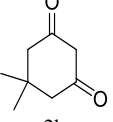
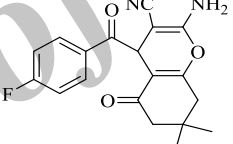
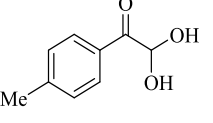
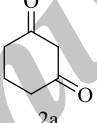
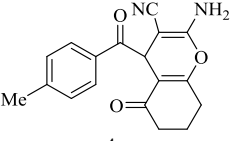
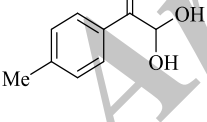
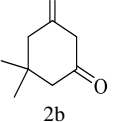
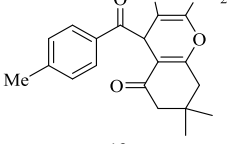
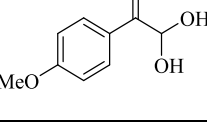
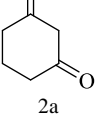
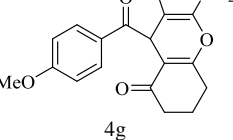
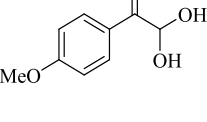
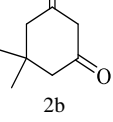
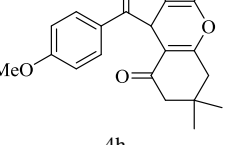


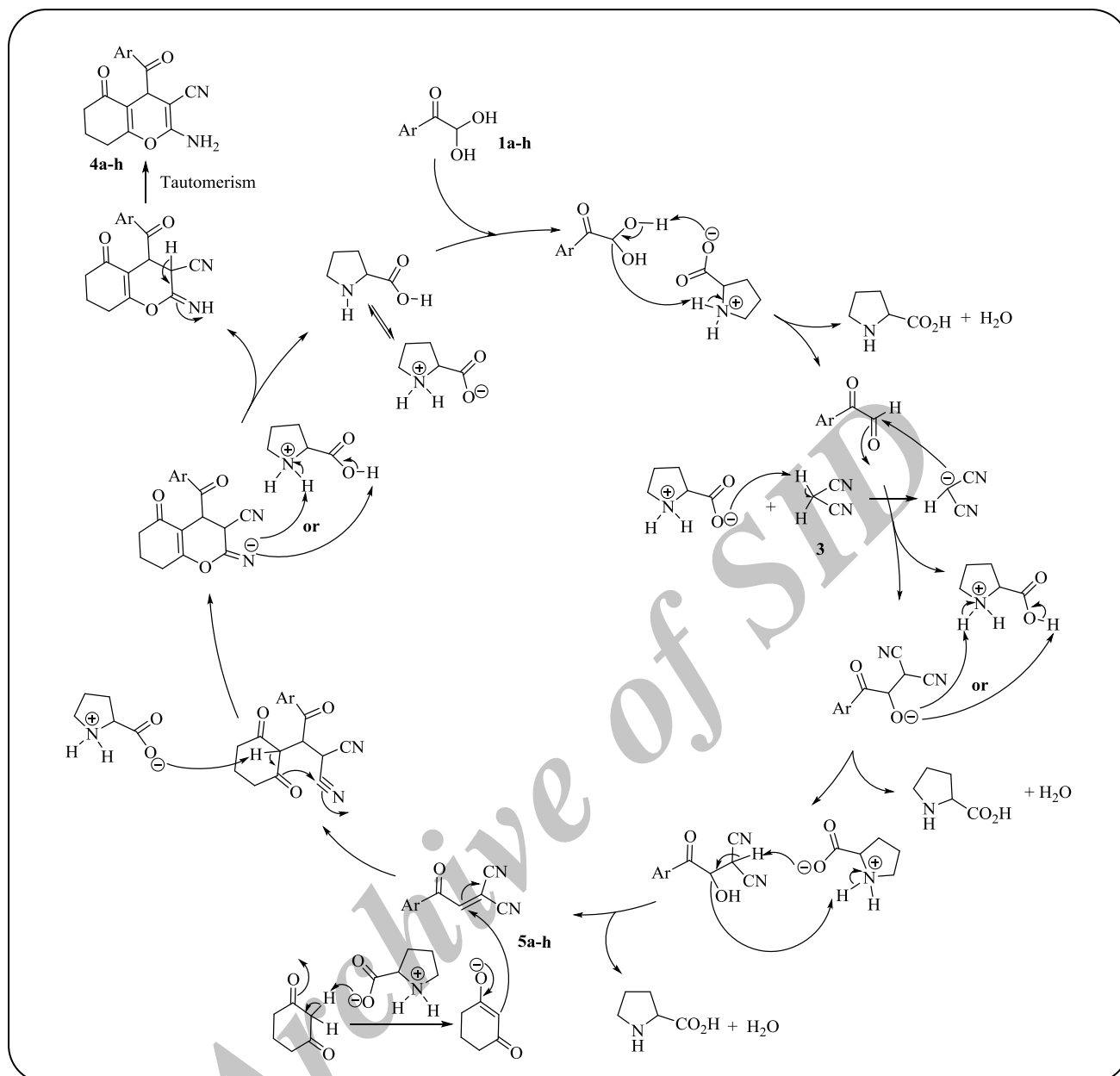
Entry	Solvent	Catalyst (20% mmol)	Condition	Time (h)	Yield (%)
1	EtOH	Et ₃ N	RT	12	32
2	EtOH	Et ₃ N	Reflux	12	32
3	EtOH	Et ₃ N	RT/Reflux	7/5	35
4	EtOH	Piperidine	RT	12	43
5	EtOH	Piperidine	RT/Reflux	8/4	45
6	EtOH	CuFe ₂ O ₄	Reflux	12	48
7	EtOH, H ₂ O	CuFe ₂ O ₄	Reflux	12	40
8	CH ₃ COOH	HCl	Reflux	12	40
9	EtOH, H ₂ O	NH ₄ Cl	RT/Reflux	9/3	48
10	EtOH, H ₂ O	(NH ₄) ₂ HPO ₄	RT/Reflux	8/4	52
11	CH ₃ CN	(NH ₄) ₂ HPO ₄	Reflux	12	47
12	CHCl ₃	NH ₄ H ₂ PO ₄	Reflux	12	47
13	EtOH, H ₂ O	<i>p</i> -TSA	Reflux	12	46
14	EtOH	Na ₂ CO ₃	Reflux	12	22
15	CH ₃ CN	NaHCO ₃	Reflux	12	34
16	EtOH	<i>L</i> -proline	Reflux	2	86
17	EtOH, H ₂ O	<i>L</i> -proline	Reflux	6	67
18	EtOH	Glycine	Reflux	8	77



Scheme 1: Synthesis of 4H-chromene derivatives 4a-h.

Table 2: Formation of compounds 4a-h using L-proline in ethanol.

Entry	Substrate		Product	Time (Min)	Yield (%)
1				120	86
2				75	89
3				95	92
4				76	91
5				120	87
6				115	90
7				150	89
8				130	91



Scheme 2: Proposed mechanism of the reaction.

hydrates **1a-h** in presence of *L*-proline gave the corresponding arylglyoxal, which was reacted with malononitrile (**3**) to give the corresponding cyanoolefines **5a-h** by subsequent dehydration of addition product. The reaction of 1,3-diketones **2a, 2b** with cyanoolefines **5a-h** in presence of *L*-proline gave the desired products **4a-h** after tautomerization.

All the products were characterized by FT-IR, $^1\text{H-NMR}$, and $^{13}\text{C-NMR}$ spectroscopy and CHN microanalysis. The structure of compound **4a** showed

FT-IR absorption for NH_2 at 3336 and 3201 cm^{-1} and 2191 cm^{-1} for the cyano group.

CONCLUSIONS

In conclusion, we have described an easy and efficient procedure for the synthesis of 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles with optical activity, using a one-pot, multicomponent reaction. Our method has several advantages including high yield, mild conditions, and simple workup.

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