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Leucine: green and efficient catalyst for the synthesis of 4*H*-chromenes

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ABSTRACT

Leucine, a naturally occurring α-amino acid, has been found as an effective catalyst to effect the one-pot three-component condensation reaction between aromatic aldehydes, malononitrile and 5,5-dimethyl-1,3-cyclohexanedione (dimedone). Various 2-amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile derivatives are conveniently prepared by these reactions in excellent yields. High yields, short reaction times, simple work-up, use of green and naturally occurring catalyst and solvent are the main merits of the present protocol.

Keywords

4*H*-chromene-3-carbonitrile; leucine; malononitrile; dimedone; one-pot condensation; catalyst

Academic Discipline And Sub-Disciplines

Organic chemistry

SUBJECT CLASSIFICATION

Synthetic organic chemistry

TYPE (METHOD/APPROACH)

Approach

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1. INTRODUCTION

Combined with the growing interest in the production of different industrial and synthetic organic and bioorganic products, there has also been great concern on the environmental issue in recent years. In this regard, the research workers in synthetic organic chemistry find themselves responsible to comply with the principles of green chemistry [1]. Accordingly, development of benign and environmentally friendly approaches employing non-polluting and naturally occurring reagents and catalysts such as amino acids and minerals has become an interesting challenge in synthetic organic chemistry [2].

Among the heterocyclic compounds, pyrans belong to an important class of heterocyclic compounds and constitute the largest portion of chemical scaffolds which are part of many natural products [3]. Some derivatives of pyrans including chromenes exhibit wide range of biological activities [4], and possess molluscicidal [5], anticancer [6], antitubercular, anticoagulant, antiallergic, antibiotic, hypolipidemic, and immunomodulating properties [7]. These compounds are also industrially important as cosmetics, pigments and potentially biodegradable agrochemicals [8]. As a result, in recent years, much research activities in synthetic organic chemistry have been dedicated to the synthesis of 4*H*-chromenes due to their biological and pharmacological activities. Until now, several methods have been reviewed in the literature for the synthesis of 4*H*-chromenes that employ various reagents and catalysts such as n-Bu4NF [9], magnetic nanocatalysts [10], lipase [11], mesoporous silica nanoparticles [12], lithium bromide [13], piperidine [14], magnesium oxide [15], and silica-bonded n-propyl-4-aza-1-azoniabicyclo [2.2.2] octane chloride [16]. However, many of these procedures suffer from certain drawbacks such as environmentally unpleasant use of huge organic solvents and hazardous reagents, long reaction time, low yield, costly preparation of catalysts, and stringent reaction conditions. Hence, development of more benign synthetic strategies in this field using non-toxic reagents and catalysts appears as interesting challenge. In compliance with this requisition, herein, we are encouraged to explore the hitherto unreported application of leucine amino acid as naturally occurring green catalyst to conveniently affect the synthesis of 4*H*-chromenes in excellent yields and short reaction times.

2. EXPRIMENTAL

2.1 General

All the chemicals used in this work were purchased from Merck chemical company and used without purification. Infrared (FT-IR) spectra were recorded on a Shimadzu 435-U-04 FT spectrophotometer from KBr pellets. ^{1}H NMR spectra were measured for samples in $CDCl_3$ or d_6-DMSO using a BRUKER AVANCE DRX-90 instrument at 90 MHz, using Me_4Si as internal standard. Melting points were measured on a BUCHI 510 apparatus in open capillary tubes.

2.2 Typical procedure for the synthesis of 4*H*-chromenes 4

To a mixture of aromatic aldehyde 1 (1 mmol), malononitrile 2 (0.066 g, 1 mmol), and dimedone (0.14 g, 1 mmol) in absolute ethanol (10 mL), was added leucine (0.02 g, 0.15 mmol). The mixture was refluxed for an appropriate time (Table 2). After completion of the reaction as monitored by TLC analysis, the resulting reaction mixture was cooled to room temperature, diluted with distilled water (30 mL) and stirred for few minutes. The precipitated product was collected by filtration, washed with water and dried in oven. Recrystallization of the crude products from EtOAc/n-hexane (1:3) provided pure products 4. All the products obtained are known compounds which were characterized based on their melting points and spectral (FT-IR, ^{1}H NMR) data as given below and compared with those reported in the literature (Table 2).

2.3 Characterization data of the synthesized 4*H*-chromenes 4a-k

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

White solid; m.p. 235–238 ˚C; IR (KBr) (ν_{max}, cm^{-1}): 3395, 3324, 3251, 3212, 2961, 2199, 1680, 1660, 1603, 1370, 1249, 1214, 1159, 1139, 1035, 696; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.049 (s, 3H, CH_3), 1.119 (s, 3H, CH_3), 2.23 (s, 2H, CH_2), 2.456 (s, 2H, CH_2), 4.411 (s, 1H, CH), 4.451 (s, 2H, NH_2), 7.249 (s, 5H, H-Ar) ppm.

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

White solid; m.p. 215–217 ˚C; IR (KBr) (ν_{max}, cm^{-1}): 3358, 3325, 3358, 3185, 3966, 2192, 1683, 1655, 1605, 1488, 1413, 1369, 1252, 1215, 1160, 1142, 1091, 1038, 1014, 847, 564, 514; ^{1}H NMR (90 MHz, d_6-DMSO): δ = 0.943 (s, 3H, CH_3), 1.031 (s, 3H, CH_3), 2.156 (s, 2H, CH_2), 2.505 (s, 2H, CH_2), 4.195 (s, 1H, CH), 7.058-7.305 (s, 6H, H-Ar and NH_2) ppm.

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

White solid; m.p. 212–215 ˚C; IR (KBr) (ν_{max}, cm^{-1}): 3361, 3328, 3256, 3199, 2962, 2198, 1681, 1665, 1602, 1368, 1251, 1214, 1159, 1142, 1038, 751, 561; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.078 (s, 6H, CH_3), 2.202 (s, 2H, CH_2), 2.439 (s, 2H, CH_2), 4.80 (s, 3H, CH and NH_2), 7.173 (s, 4H, H-Ar) ppm.

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

White solid; m.p. 220-223 ˚C; IR (KBr) (ν_{max}, cm^{-1}): 3473, 3394, 3329, 3198, 2960, 2199, 1682, 1654, 1604, 1370, 1214, 1037, 750, 562; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.073 (s, 6H, CH_3), 2.213 (s, 2H, CH_2), 2.447 (s, 2H, CH_2), 4.650 (s, 2H, NH_2), 4.845 (s, 1H, CH), 7.192 (s, 4H, H-Ar) ppm.

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

White solid; m.p. 190–192 ˚C; IR (KBr) (v_{max}, cm^{-1}): 3364, 3332, 3258, 3187, 2963, 2190, 1738, 1684, 1652, 1603, 1369, 1215, 1039, 850, 567; ^{1}H NMR (90 MHz, d_6-DMSO): δ = 0.952 (s, 3H, CH_3), 1.032 (s, 3H, CH_3), 2.163 (s, 2H, CH_2), 2.504 (s, 2H, CH_2), 4.194 (s, 1H, CH), 7.033-7.172 (m, 6H, H-Ar and NH_2) ppm.

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

White solid; m.p. 218-220 ˚C; IR (KBr) (v_{max}, cm^{-1}): 3430, 3335, 3251, 3203, 2957, 2204, 2186, 1680, 1661, 1638, 1599, 1530, 1417, 1374, 1349, 1251, 1210, 1158, 1138, 1038, 826, 733, 690; ^{1}HNMR (90 MHz, $CDCl_3$): δ = 1.057 (s, 3H, CH_3), 1.131 (s, 3H, CH_3), 2.240 (s, 2H, CH_2), 2.501 (s, 2H, CH_2), 4.534 (s, 1H, CH), 4.749 (s, 2H, NH_2), 7.565 (m, 3H, H-Ar), 8.043 (s, 1H, H-Ar) ppm.

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

White solid: m.p. 202-205 ˚C; IR (KBr) (v_{max}, cm^{-1}): 3564, 3471, 3328, 3184, 2959, 2934, 2880, 2835, 2199, 1686, 1662, 1600, 1493, 1463, 1368, 1254, 1214, 1162, 1143, 1034, 860, 755; 1H NMR (90 MHz, $CDCl_3$): δ = 1.053 (s, 3H, CH_3), 1.117 (s, 3H, CH_3), 2.215 (s, 2H, CH_2), 2.441 (s, 2H, CH_2), 3.832 (s, 3H, CH_3), 4.479 (s, 2H, NH_2), 4.710 (s, 1H, CH), 6.888 (m, 2H, H-Ar), 7.070 (m, 2H, H-Ar) ppm.

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

White solid; m.p. 212–215 ˚C; IR (KBr) (v_{max}, cm^{-1}): 3356, 3258, 3187, 3022, 2964, 2926, 2193, 1682, 1655, 1604, 1511, 1412, 1368, 1322, 1250, 1214, 1160, 1140, 1037, 843, 770, 567; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.098 (s, 6H, CH_3), 2.281 (s, 5H, CH_3 and CH_2), 2.455 (s, 2H, CH_2), 4.377 (s, 1H, CH), 4.495 (s, 2H, NH_2), 7.106 (s, 4H, H-Ar) ppm.

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

White solid; m.p. 183-186 ˚C; IR (KBr) (v_{max}, cm^{-1}): 3394, 3333, 3259, 3215, 2995, 2960, 2835, 2193, 1682, 1660, 1604, 1500, 1464, 1423, 1373, 1266, 1248, 1212, 1158, 1142, 1048, 797, 730, 561; ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.062 (s, 3H, CH_3), 1.105 (s, 3H, CH_3), 2.216 (s, 2H, CH_2), 2.430 (s, 2H, CH_2), 3.728 (s, 3H, CH_3), 3.796 (s, 3H, CH_3), 4.544 (s, 2H, NH_2), 4.682 (s, 1H, CH), 6.635-6.754 (m, 3H, H-Ar) ppm.

2-Amino-4-(p-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4j)

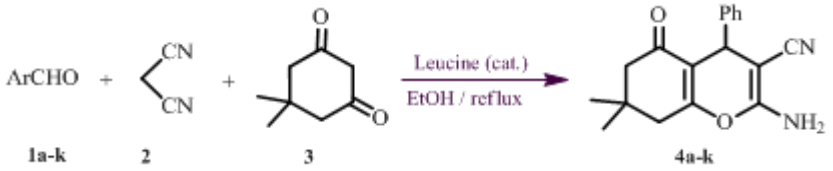
White solid; m.p. 207–209 ˚C; IR (KBr) (v_{max}, cm^{-1}): 3362, 3331, 3256, 3193, 2964, 2894, 2193, 1682, 1651, 1605, 1512, 1448, 1414, 1371, 1252, 1215, 1143, 1039, 846, 633, 561; ^{1}H NMR (90 MHz, d_6-DMSO): δ = 0.90 (s, 3H, CH_3), 0.974 (s, 3H, CH_3), 2.131 (s, 2H, CH_2), 2.445 (s, 2H, CH_2), 4.007 (s, 1H, CH), 6.630 (s, 2H, NH_2), 6.847 (s, 4H, H-Ar), 9.191 (s, 1H, OH) ppm.

2-Amino-4-(p-nitrophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4k)

Cream solid; m.p. 182–185 ˚C; IR (KBr) (v_{max}, cm^{-1}): 3482, 3451, 3374, 3333, 3257, 3216, 3074, 2960, 2876, 2196, 1688, 1671, 1594, 1511, 1471, 1362, 1345, 1218, 1159, 1141, 1039, 1010, 866, 828, 743, 700, 562; ^{1}H NMR (90 MHz, d_6-DMSO): δ = 0.967 (s, 3H, CH_3), 1.044 (s, 3H, CH_3), 2.173 (s, 2H, CH_2), 2.534 (s, 2H, CH_2), 4.371 (s, 1H, CH), 7.180-7.186 (m, 4H, H-Ar), 8.127 (s, 2H, NH_2) ppm.

3. RESULTS AND DISCUSSION

As part of our ongoing interest for developing more convenient and robust approaches for the synthesis of organic products including heterocyclic compounds of biological and synthetic importance such as 4*H*-chromenes [17-19], herein, we wish to report the useful application of leucine as highly efficient and green catalyst in one-pot three-component condensation of aromatic aldehydes 1a-k with malononitrile 2 and 5,5-dimethyl-1,3-cyclohexanedione (dimedone) 3 (Scheme 1). The reactions proceed within few minutes under reflux condition in EtOH to afford the respective 4*H*-chromenes 4a-k in excellent yields (Table 2).



Scheme 1. Leucine-catalyzed one-pot synthesis of 4*H*-chromenes 4a-k.

Initially, we chose the reaction between benzaldehyde, malononitrile and dimedone as the model reaction to establish the reaction conditions. The effects of solvent and other reaction conditions on this reaction were investigated using different solvents such as THF, EtOH, H_2O and CH_3CN under various temperatures and catalyst loadings (Table 1). As shown in Table 1, the best results in terms of yield (98%) and reaction time (10 min) were obtained when the reaction was conducted in absolute ethanol as the solvent of choice under reflux condition in the presence of leucine (15 mol%) as the

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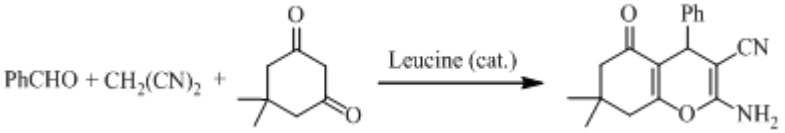
catalyst (entry 7). It was observed that further increasing the amount of the catalyst did not have any improving effect on the yield of the reaction. In addition, the important role of the catalyst in the reaction was substantiated when the reaction was performed in the absence of the catalyst that resulted in a very low yield (15%) of the expected product (entry 11).

Table 1. Screening the reaction parameters on the leucine-catalyzed model reaction between benzaldehyde, malononitrile and dimedone[a]



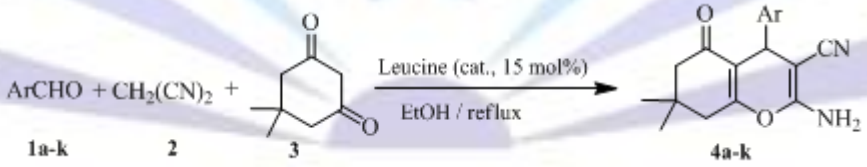
Entry	Solvent	Catalyst (mol %)	Temperature (°C)	Time (min)	Yield (%)[b]
1	EtOH	10	rt	60	40
2	EtOH	10	50	40	65
3	H_2O	10	50	60	58
4	CH_3CN	10	50	40	30
5	THF	10	50	40	46
6	EtOH	10	reflux	20	90
7	EtOH	15	reflux	10	98
8	EtOH	20	reflux	10	95
9	EtOH	30	reflux	20	92
10	EtOH	50	reflux	20	85
11	EtOH	0	reflux	60	15

[a] Conditions: benzaldehyde (1 mmol), dimedone (1 mmol), malononitrile (1 mmol), solvent (10 mL).

[b] Isolated yield.

To establish the generality of the reaction, we extended the scope of the reaction to a series of aldehydes bearing different substituents 1a-k under the aforementioned optimized conditions (leucine (15 mol%)/EtOH/reflux) (Scheme 1). According to the experimental results summarized in Table 2, all the reactions proceeded smoothly within short reaction times (10-50 min) to furnish the corresponding 4*H*-chromenes 4a-k with excellent yields (88-98%). All the products are known compounds which were characterized on the basis of their physical and spectral (FT-IR, ^{1}H NMR) data which were in accord with those reported in the literature (Table 2).

Table 2. Leucine-catalyzed synthesis of 4*H*-chromene-3-carbonitriles 4a-k in EtOH under reflux.[a]



Entry	Ar	Product	Time (min)	Yield (%)[b]	M.p. (°C)	
					Found	Reported
1	C_6H_5	4a	10	98	235-238	234-235 [8]
2	4-ClC_6H_4	4b	10	98	215-217	215-216 [8]
3	2-ClC_6H_4	4c	20	95	212-215	214-215 [20]
4	3-ClC_6H_4	4d	30	89	220-223	224-226 [21]
5	4-FC_6H_4	4e	20	90	190-192	191-193 [20]
6	3-$NO_2C_6H_4$	4f	20	98	218-220	213-217 [22]
7	4-$NO_2C_6H_4$	4g	10	95	182-185	181-184 [22]
8	2-$MeOC_6H_4$	4h	50	90	202-204	203-205 [11]

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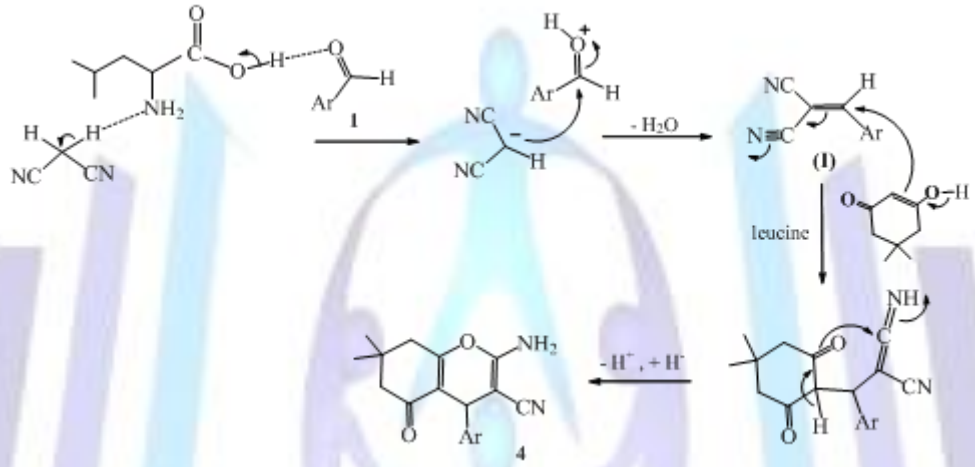
9	2,5-$(MeO)_2C_6H_3$	4i	30	94	180-183	178-180 [21]
10	4-MeC_6H_4	4j	20	94	212-215	210-213 [19]
11	4-HOC_6H_4	4k	40	88	207-209	206-208 [12]

[a] Conditions: aldehyde (1 mmol), dimedone (1 mmol), malononitrile (1 mmol), leucine (0.02 g, 15 mol%), EtOH (10 mL), reflux.

[b] Isolated yields.

A feasible mechanism suggested to explain the formation of 4*H*-chromenes **4** from the condensation of aldehydes **1** with malononitrile and dimedone under the catalytic effect of leucine is depicted in Scheme 2. As illustrated, leucine acts as an amino acid to make use of its ambivalent character to provide a 'proton' at acidic site to activate the aldehyde, while it accepts a 'proton' from malononitrile at amino site. The resulting malononitrile carbanion undergoes a Knoevenagel-type condensation with protonated aldehyde leading to the dehydrative formation of arylidenemalononitrile intermediate (**I**). Subsequently, the enolate formed from the proronated dimedone undergoes addition to intermediate (**I**) to form the intermediate adduct (**II**) followed by intramolecular cyclization to furnish the products **4**.



Scheme 2. A possible mechanism for the leucine-catalyzed formation of 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes 4.

CONCLUSION

In conclusion, we have explored the application of leucine as an efficient and naturally occurring green catalyst to effect the one-pot three-component condensation of aromatic aldehydes with acrylonitrile and dimedone. The reactions proceeded smoothly in EtOH under reflux condition to afford the 4*H*-chromenes in quantitative yields. Simple manipulation of the products, improved yields, shorter reaction times, application of leucine as an inexpensive and naturally occurring green catalyst, and also use of ethanol as a relatively environmentally benign solvent are the main advantages of the present procedure.

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