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Aluminum acetylacetonate-catalyzed, facile and efficient one pot synthesis of 2-amino-5-oxo-5, 6, 7, 8-tetrahydro-4*H*-chromenes Under mild conditions

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ABSTRACT

2-Amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes have been prepared in good to excellent yields in the presence of Aluminum acetylacetonate as a novel and recycling organometallic catalyst from a diversity of aromatic aldehydes, dimedone and malononitrile. The reaction was carried out in refluxing EtOH/H_2O and offers several advantages including high yields of the products and easy experimental workup procedure.

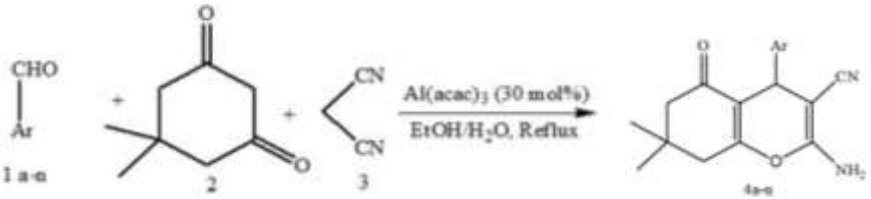
KEY WORDS: Multicomponent reaction, one-pot synthesis, tetrahydro-4*H*-chromenes, Aluminum acetylacetonate, organometallic catalyst.

1. INTRODUCTION

Tetrahydro-4*H*-chromene derivatives are an important class of compounds as besides of being the main components of many naturally occurring products (Hatakeyama, 1988), they possess several useful biological and pharmacological activities (Green, 1995) including antitumor (Wang, 2000), antibacterial (Kumar, 2007). In addition, these heterocycles are often used in cosmetics and pigments and as potentially biodegradable agrochemicals (Hafez, 1987).

The conventional synthesis of tetrahydro-4*H*-chromenes involves either the condensation of dimedone with aromatic aldehyde and malononitrile under reflux in acetic acid (Singh, 1996) or the cyclization of arylidene malononitriles with β-dicarbonyl compounds in the presence of base such as piperidine (Martin, 1987). Owing to the significant biological properties of tetrahydro-4*H*-chromene derivatives, several synthetic approaches have been reported using various catalysts and conditions such as piperidine (Ye, 2010), N-methylimidazole (Lian, 2008), (D,L)-proline (Guo, 2007), KF-alumina (Khan, 2011), microwave (Saini, 2006), ultrasonic irradiation (Tu, 2003), K_3PO_4 (Pore, 2009), tetrabutyl ammonium fluoride (Gao, 2008) and sucrose (Mousavi, 2015).

In continuation of our foregoing program in search of novel catalysts and multicomponent methodologies for the synthesis of biologically active heterocyclic compounds (Nemouchi, 2012) and given the importance of tetrahydro-4*H*-chromene derivatives, we set ourselves the objective to develop new, simple and efficient catalytic method for the preparation of such heterocycles using three components condensation of aromatic aldehydes, dimedone and malononitrile in the presence of aluminum acetylacetonate as catalyst under mild conditions (Scheme 1).



Scheme.1. Synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes catalyzed by Aluminum acetylacetonate

2. EXPERIMENTAL

Unless specified all solvents and reagents were of reagent grade and used without further purification. Melting points were determined in a capillary tube and are uncorrected. 1H and 13C NMR spectra were recorded as solutions in DMSO-d_6 and chemical shifts are reported in parts per million (ppm) on a BRUKER AVANCE DPX spectrometer at 250 and 62.5 MHz respectively using TMS as internal standard. Coupling constants *J* are reported in hertz (*Hz*). IR spectra were obtained as potassium bromide (KBr) pellets with a Shimadzu FT IR-8201 PC spectrometer

General method for the synthesis of 2-amino-4-aryl-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes: To a solution of the corresponding aldehyde (1.0 equiv.) in 50% aqueous ethanol (5ml, 1:1), malonodinitrile (1.0 equi.) and 5,5-dimethyl-1,3-cyclohexanedione (1.0 equi.), Aluminum acetylacetonate (30mol%) was added and the resulting mixture was stirred at reflux temperature for an appropriate time (The progress of the reaction was monitored by TLC). After the complete consumption of aldehyde; used as the blank reactant; the reaction mixture was poured onto crushed ice and stirred vigorously for 20 min. The precipitated solid was isolated by filtration, washed with cold ethanol, dried and recrystallized from hot ethanol to give the pure product 4.

Spectral data for select products:

2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4a): White solid; M.p.= 232-234°C; IR cm^{-1}: 3313, 3170 (NH_2), 2191 (CN), 1600, 1523 (Ar); ^{1}H NMR (250 MHz, DMSO-d_6) δ: 7.29-7.13 (m; 5H), 6.88 (s; 2H; NH_2), 4.18 (s; 1H), 2.50 (s; 2H; CH_2), 2.24 (d; J = 16.1 Hz; 1H), 2.10 (d; J = 16.1 Hz; 1H), 0.97 (s; 3H; CH3), 0.81 (s; 3H; CH_3); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 200.5, 166.8, 163.3, 149.0, 133.1, 132.2, 131.5, 124.5, 118.4, 65.0, 55.4, 45.4, 40.5, 36.8, 33.6, 32.3.

2-amino-7,7-dimethyl-5-oxo-4-*p*-tolyl-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4b): White solid; M.p.= 217-219°C; IR cm^{-1}: 3321, 3205 (NH2), 2191 (CN), 1662 (C=O),1604 (Ar); ^{1}H NMR (250 MHz, DMSO-d_6) δ: 7.07 (d; J = 8.1 Hz; 2H), 7.02 (d; J = 8.1 Hz; 2H), 6.88 (s; 2H; NH2), 4.17 (s; 1H), 2.49 (s; 2H; CH_2), 2.29 (s; 3H; CH_3), 2.12 (d; J = 16.9 Hz; 1H), 2.02 (d; J = 16.9 Hz; 1H), 1.05 (s; 3H; CH_3); 0.96 (s; 3H; CH_3); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 195.1, 161.3, 158.2, 141.9, 134.4, 128.7, 127.9, 119.1, 112.6, 58.4, 50.1, 40.2, 34.9, 31.6, 28.4, 27.0, 21.9.

2-amino-4-(3-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4d): White solid; M.p.= 210°C; IR cm^{-1}: 3380, 3190 (NH_2), 2187 (CN), 1680 (C=O), 1600 (Ar), 1099 (C-OMe); ^{1}H NMR (250 MHz, DMSO-d_6) δ: 7.13 (dd; J = 8.49, 7.97 Hz; 1H), 6.72 (s; 1H), 6.69-6.65 (m; 2H), 6.43 (s; 2H; NH_2), 4.17 (s; 1H), 3.70 (s; 3H; OCH_3), 2.44 (s; 2H; CH_2), 2.20 (d; J = 16.2 Hz; 1H), 2.09 (d; J = 16.2 Hz; 1H), 1.12-0.98 (s; 3H; CH_3), 0.98 (s; 3H; CH_3); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ: 195.4, 161.9,159.4, 158.3, 143.0, 128.7, 128.1, 112.9, 111.5, 119.3, 112.6, 58.4, 55.8, 50.1, 40.2, 34.9, 31.6, 28.4, 27.0.

2-amino-4-(2,5-dimethoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4e): White solid; M.p.= 179-181°C; IR cm^{-1}: 3380, 3190 (NH_2), 2187 (CN), 1680 (C=O), 1600 (Ar), 1099 (C-OMe); ^{1}H NMR (250 MHz, DMSO-d_6) δ: 6.76 (d; J = 8.8 Hz; 1H), 6.63 (d; J = 8.8 Hz; 1H), 6.53 (s; 1H), 6.31 (s; 2H; NH_2), 4.47 (s; 1H), 3.71 (s; 3H; OCH_3), 3.65 (s; 3H; OCH_3), 2.44 (s; 2H; CH_2), 2.19 (2d; J = 16.2 Hz; 1H), 2.07 (d; J = 16.2 Hz; 1H), 1.06 (s; 3H; CH_3), 0.99 (s; 3H; CH_3); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 195.4, 161.9, 158.3, 150.8, 148.2, 142.8, 131.5, 128.7, 127.9, 119.3, 112.6, 58.4, 55.8, 50.1, 40.2, 34.9, 31.6, 28.4, 27.0.

2-amino-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4f): Yellow solid; M.p.= 223-225°C; IR cm^{-1}: 3444 (OH), 3325, 3205 (NH_2), 2191 (CN), 1681 (C=O), 1589 (Ar); ^{1}H NMR (250 MHz, DMSO-d_6) δ: 8.93 (s; 1H; OH), 6.93 (d; 2H; J = 8.5 Hz; 2H), 6.64 (d; 2H; J = 8.5 Hz; 2H), 5.97 (s; 2H; NH_2), 4.06 (s; 1H), 2.51 (s; 2H; CH_2), 2.13 (m; 2H; CH_2), 1.10 (s; 3H; CH_3) 1. (s; 3H; CH_3); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 195.8, 161.5, 155.1, 155.7, 134.7, 128.1, 119.3, 115.0, 113.6, 60.3, 50.3, 34.5, 31.7, 28.5, 27.1, 26.4.

2-amino-4-(4-(dimethylamino)phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4h): Yellow solid; M.p.= 215-21°C; IR cm^{-1}: 3436, 3178 (NH_2), 2198 (CN), 1562 (Ar), 1245 (C-N); 1H NMR (250 MHz, DMSO-d_6) δ: 6.96 (d; J = 8.3 Hz; 2H), 6.62 (d; J = 8.3 Hz; 2H), 6.57 (s; 2H; NH_2), 4.07 (s; 1H), 2.85 (s; 6H; 2 CH_3), 2.45 (s; 2H; CH_2), 2.20 (d; J = 16.1 Hz; 1H), 2.07 (d; J = 16.1 Hz; 1H), 1.05 (s; 3H; CH_3), 0.97 (s; 3H; CH_3); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 196.0, 162.1, 158.1, 149.5, 132.9, 128.2, 120.3, 119.3, 112.6, 59.5, 50.6, 40.2, 39.5, 32.2, 29.0, 28.4, 27.0.

2-amino-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4j): Yellow solid; M.p.= 207-208°C; IR cm^{-1}: 3332, 3201 (NH_2), 2191 (CN), 1670 (C=O), 1600 (Ar), 1527 (C-NO_2); ^{1}H NMR (250 MHz, DMSO-d_6) δ: 8.00 (t; J = 7.24 Hz; 1H), 7.61 (d; J = 7.24 Hz;1H), 7.51 (d; J= 7.24 Hz; 1H), 7.56 (s; 1H; C2H), 6.92 (s; 2H; NH_2), 4.38 (s; 1H), 2.50 (s; 2H; CH_2), 2.23 (d; J = 16.2 Hz; 1H), 2.10 (d; J = 16.2 Hz; 1H), 1.06 (s; 3H; CH_3); 0.96 (s; 3H; CH_3); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ: 195.4, 161.6, 158.3, 142.8, 133.9, 129.4, 121.5, 119.3, 112.6, 58.4, 50.1, 40.2, 34.9, 31.7, 28.4, 27.0.

2-amino-7,7-dimethyl-5-oxo-4-(thien-2-yl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4n): White solid; M.p.= 222-223°C; IR cm^{-1}: 3379, 3178 (NH_2), 2630 (C-S), 2187 (CN), 1690 (C=O), 1602 (Ar); ^{1}H NMR (250 MHz, DMSO-d_6) δ: 7.17 (d; J = 3.80 Hz; 1H), 7.16 (d; J = 2.60 Hz; 1H), 6.87 (s; 2H; NH_2), 6.85 (dd; J = 3.80, 2.60 Hz; 1H), 4.54 (s; 1H), 2.48 (s; 2H; CH_2), 2.32 (d; J = 16.7 Hz; 1H), 2.20 (d; J = 16.7 Hz; 1H), 1.00 (s; 3H; CH_3), 0.92 (s; 3H; CH_3); ^{13}C NMR (62.9 MHz, DMSO-*d6*) δ: 195.4, 161.9, 158.3, 140.0, 129.5, 126.4, 124.9, 119.3, 112.6, 58.4, 50.1, 40.2, 34.9, 31.6, 28.4, 27.0.

3. RESULTS AND DISCUSSION

In our attempts to develop a facile and efficient one-pot protocol for the formation of tetrahydro-4*H*-chromenes, initially we carried out the model three-component reaction of 4-chlorobenzaldehyde 1l (1.0 mmol), dimedone 2 (1.0 mmol), and malononitrile 3 (1.0 mmol) under different conditions (Scheme.1). In aqueous ethanol and in the absence of the catalyst, the reaction provided the corresponding 2-amino-tetrahydro-4*H*-chromene 4l in a moderate yield after 6 hours stirring at room temperature (Table.1, entry 1). However, when 5 mol% of the catalyst was added, 50% and 85% yield were obtained after 6h stirring at room and reflux temperature respectively (Table.1, entries 2 & 3). On carrying out the same model reaction at 120°C under solvent-free conditions in the presence of 5 mol% of $Al(acac)_3$ no product was identified even after 12 hours (Table.1, entry 4). From these results, we conclude

that the reaction is solvent and catalyst dependent. With regard to the choice of the appropriate solvent, the above model reaction was screened in EtOH: H_2O (1:1), EtOH, H_2O, CH_3CN, and DCM (Table.1, entries 4-8). Among all these attempts, the reaction performed under refluxed aqueous ethanol with 5 mol% of Al $(acac)_3$ turned out to be completely successful and high yield of target product was obtained (Table.1, entry 3). Therefore, aqueous ethanol was selected as the solvent system for the subsequent reaction.

In order to optimize the catalyst loading, the model reaction was carried out in the presence of Al $(acac)_3$ with various catalyst loading, viz. 10, 20, 30 and 40 mol%. The results revealed that the reactions with 10 and 20 mol% of catalyst loadings were completed respectively in 4 and 3.5 h to obviate the desired product in comparable yields (Table.1, entries 9 and 10). The increase in catalyst loading to 30 mol% resulted in higher conversion leading to 92% yield within 1.5 hour (Table.1, entry 11).

Table.1. Optimization of reaction conditions[a]

Entry	Solvent	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield[b] (%)
1	EtOH/H_2O	none	Rt	6	48
2	EtOH/H_2O	5	Rt	6	50
3	EtOH/H_2O	5	Reflux	6	85
4	None	5	120	12	-
5	EtOH	5	Reflux	5.5	70
6	H_2O	5	Reflux	7	80
7	CH_3CN	5	Reflux	6.5	67
8	DCM	5	Reflux	8.5	71
9	EtOH/H_2O	10	Reflux	3.5	88
10	EtOH/H_2O	20	Reflux	2.5	80
11	EtOH/H_2O	30	Reflux	1.5	92
12	EtOH/H_2O	40	Reflux	1.5	90

[a]Reaction conditions: 4-chlorobenzaldehyde 1l (1.0 mmol), dimedone 2 (1.0 mmol), malononitrile 3 (1.0 mmol), and different loadings of the catalyst in different solvents (3 ml). [b]Isolated yields.

Having established the optimized reaction conditions, and in order to show the general applicability of this method, different aromatic aldehydes were examined under the optimized conditions (Scheme.2).

The results showed that the scope of the reaction is quite broad in regard to the aldehydes. Not only aryl aldehydes containing either electron donating groups (Table.2, entries 1–8) or electron-withdrawing groups (Table.2, entries 9–13) can be used, hetero aromatic aldehydes such as thienyl carbaldehyde also gave the corresponding 2-amino-tetrahydro-4*H*-chromene in good yield (Table.2, entry 14).

The activity of the recycled catalyst was also examined under the optimized conditions and the desired product was obtained in 92, 88, 85, 86% yields after 1-4 runs, respectively (Table.2, entry 12).

Table.2. Synthesis of compounds 4 from aldehydes, dimedone and malononitrile

Entry	Ar	Product	Time (h)	Yield[a]	M.p
1	C_6H_5	4a	1.25	92	232-234
2	4-Me-C_6H_4	4b	0.5	90	217-219
3	4-Et-C_6H_4	4c	1.25	89	224-226
4	3-OMe-C_6H_4	4d	0.5	83	210-212
5	2,5-$(OMe)_2$-C_6H_3	4e	2.5	87	179-181
6	4-OH- C_6H_4	4f	2.5	97	223-225
7	3-OH-C_6H_4	4g	1.25	97	234-236
8	4-N,N-$(Me)_2$-C_6H_4	4h	2.25	79	215-217
9	4-NO_2-C_6H_4	4i	2.25	97	151-153
10	3-NO_2-C_6H_4	4j	0.5	99	207-208
11	2-NO_2-C_6H_4	4k	1.5	93	232-234
12[c]	4-Cl-C_6H_4	4l	1.5	92, 88, 85, 86c	214-215
13	2,4-$(Cl)_2$-C_6H_4	4m	0.5	98	192-193
14	2-Thienyl	4n	1	81	222-223

[a]Reaction conditions: aldehyde 1 (1.0 mmol), dimedone 2 (1.0 mmol), malononitrile 3 (1.0 mmol), aluminum acetylacetonate (30 mol%) in aqueous ethanol (3 ml) at reflux temperature; [b]Isolated yields; [c]Catalyst was recycled for three times.

4. CONCLUSION

In conclusion, we have developed a potential and reusable catalyst for the one-pot, three-component synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes in good to excellent yields. The compatibility with various functional groups should make the present method useful and important. In addition, the operational simplicity, increased safety for small-scale high-speed synthesis, and the easy handling and workup are particularly the valuable features of this method. Furthermore, this series of derivatives may provide some biologically active compounds for biomedical screening, which is in progress in our laboratory.

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