



Mg(ClO₄)₂ as a Recyclable Catalyst for Synthesis of 4*H*-chromenes

MASOUD MOHAMMADI ZEYDI^{1*} and SOMAYEH AHMADI²

¹Department of Organic Chemistry, University of Guilan, University of campus 2, Rasht, Iran.

²Department of chemistry, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran.

*Corresponding author's E-mail Email: zedi.65@gmail.com

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ABSTRACT

The 4*H*-chromen derivatives were obtained in excellent yield by three component of an aromatic aldehyde, dimedon and malonitril in the presence catalyst Mg(ClO₄)₂ as a lewis acid catalyst, in the conditions reflux. The advantage of this method addition to the reusable catalyst, high yield and easy method.

Keyword: 4*H*-chromen, aromatic aldehyde, dimedon and malonitril.

INTRODUCTION

4*H*-chromenes are important heterocyclic structural with a number of biological and pharmacological properties including anti-cancer¹, anti-tumor², anti-proliferative³, antidiabetic⁴, anti-viral⁵, and anti-microbial⁶, antidepressant⁷, activities. They have also been widely employed as pigments, cosmetics⁸, and potent biodegradable agrochemicals⁹. Substituted 4*H*-chromene derivatives are potent apoptosis in ducting agents possessing vascular disrupting activity¹⁰.

In recent years new method have been developed for the synthesis of 4*H*-chromen derivatives using various reagents such ammonium salts¹¹⁻¹⁴, amino functionalized silica gel¹⁵, K₂CO₃¹⁶,

DBU¹⁷, SiO₂-Pr-SO₃H¹⁸, boric acid¹⁹, Piperidine²⁰, MgO²¹, CuO-CeO₂ nanocomposite²², CeCl₃.H₂O²³, Methane Sulphonic Acid²⁴ Potassium Phosphate²⁵, and different energy sources such as ultrasonic irradiation²⁶, microwave-irradiation^{27,28}, ionic liquid²⁹ and Grinding³⁰. Recently, a catalyst free method was reported for the synthesis of chromene derivatives in water³¹. In the study, we report Mg(ClO₄)₂ as a new lewis acid catalyst for the three component synthesis of 4*H*-chromene derivatives under conditions reflux.

RESULTS AND DISCUSSION

Mg(ClO₄)₂ were tested as the catalyst in the synthesis of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile

4a (Figure 1). At the start of this investigation, the one-pot three component reaction of benzaldehyde 1a, malononitrile 2 and dimedon 3 (1 mmol each) in ethanol was employed as a model reaction. The use of different amounts of catalyst (10, 20, 25, and 30W %) at different temperature was investigated. The best result was obtained with 25W% of starch solution at 100°C (Tables 1, Enter 11).

The model reaction was carried out in different solvent such as water, ethanol, methanol, chloroform acetonitrile in the conditions reflux and so solvent free condition at 100°C using 25 W% of $\text{Mg}(\text{ClO}_4)_2$ as catalyst (table 2). Further, we studied model reaction in water gave the highest yield (87%) of **4a** at reflux condition (tables 2, Enter 2).

To study the recyclability of the catalyst, the $\text{Mg}(\text{ClO}_4)_2$ were used for the same reaction repeatedly and the change in their catalytic activity was studied. The relation between the number of the reaction and the catalytic activity in terms of yield of product is presented in table 3. The $\text{Mg}(\text{ClO}_4)_2$ can be recycled and reused as a catalyst for at least four times without losing activity.

After optimization of the reaction conditions, the scope and generality of these conditions with other reactants were examined by using a variety of aromatic aldehydes, dimedon and malononitrile. The results are summarized in Table 4. All the reactions proceeded smoothly under the optimized conditions and all the reactions were satisfactorily completed within 2.5–3.5 hour.

In summary, a one-pot, three-component condensation reaction of various aldehydes aromatic, dimedon and malononitriles was successfully accomplished to give 4*H*-chromene derivatives. This methodology has advantages of mild reaction conditions, simple experimentation, and high yields.

Experimental materials and methods

Compounds were obtained from Merck and used without further purification. The melting points were obtained on an electro-thermal capillary melting point apparatus and are uncorrected. Thin-layer chromatography was performed using HF_{254} fluorescent silica gel plates (Merck), which were

examined under UV 254 and 365 nm light. Infrared spectra (μ/cm^{-1}) were recorded on a Shimadzu IR-470, using KBr disks. ^1H spectra were recorded on a DRX-400 MHz NMR Spectrometer at 293 K in CDCl_3 . Spectra were internally referenced to TMS. Peaks are reported in ppm downfield of TMS.

General procedure for the one-pot preparation of 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile(4a-I)

To a mixture of aldehydes aromatic (1 mmol) in ethanol (5 ml) was added a malononitril(1 mmol), dimedone (1 mmol) and $\text{Mg}(\text{ClO}_4)_2$ (25 mol%). The reaction mixture was stirred for appropriate time as given table 4. After completion of the reaction (monitored by TLC), $\text{Mg}(\text{ClO}_4)_2$ was filtered out using filter paper. Then, the solvent of the filtrate was evaporated and the crude product was purified by recrystallization from hot ethanol. The product were characterized by the comparison of their spectral (^1H NMR of IR) and physical data with those reported in the literature.

2-amino-7,7-dimethyl-4-phenyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chronene-3-carbonitril (4a)

Yellow Crystal. Yield (90%), m.p. 230-232°C. FT-IR ($\nu_{\text{max}}/\text{cm}^{-1}$) (KBr disc): 3415, 3339 (NH_2 Str.); 3050 (C-H_{arom} Str.); 2990 ($\text{C-H}_{\text{aliph}}$ Str.); 2243 ($\text{C}\equiv\text{N}$ Str.); 1686 ($\text{C}=\text{O}$ Str.); 1215 (C-O Str.). $^1\text{HNMR}$ (400.13 MHz, CDCl_3): δ 1.05 (3H, s, CH_3); 1.13 (3H, s, CH_3); 2.24 (2H, AB q, $^3J = 16.4, 9.4$ Hz, CH_2); 2.47 (2H, m, CH_2); 4.42 (H, s, CH); 4.57 (2H, s, NH_2); 7.19-7.32 (5H, m, CH_{arom}).

2-amino-7,7-dimethyl-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chronene-3-carbonitril (4b)

Yellow Crystall. Yield (95%), m.p. 216-218°C. FT-IR ($\nu_{\text{max}}/\text{cm}^{-1}$) (KBr disc): 3410, 3320 (NH_2 Str.); 3032 (C-H_{arom} Str.); 2900 ($\text{C-H}_{\text{aliph}}$ Str.); 2256 ($\text{C}\equiv\text{N}$ Str.); 1690 ($\text{C}=\text{O}$ Str.); 1550, 1347 (N_2O Str.). $^1\text{HNMR}$ (400.13 MHz, CDCl_3): δ 1.06 (3H, s, CH_3); 1.13 (3H, s, CH_3); 2.25 (2H, ABq, $^3J = 16.4, 10.4$ Hz, CH_2); 2.50 (2H, AB q, $^3J = 16.8, 4.0$ Hz, CH_2); 4.54 (H, s, CH); 4.79 (2H, s, NH_2); 7.50-8.10 (4H, m, 4CH_{arom}).

2-amino-7,7-dimethyl-4-(3-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chronene-3-carbonitril (4c)

White Crystal, Yield (93%), m.p. 220-222°C. FT-IR (V_{\max}/cm^{-1}) (KBr disc): 3355, 3298 (NH_2 Str.); 3120 (C-H_{arom} Str.); 2956 ($\text{C-H}_{\text{aliph}}$ Str.); 2186 (C°N Str.); 1651 (C°N Str.); 1215 (C-O Str.). ^1H NMR (400.13 MHz, CDCl_3): δ 1.06 (3H, s, CH_3); 1.13 (3H, s, CH_3); 2.24 (2H, AB q, $^3J=16.4, 3.2$ Hz, CH_2); 2.47 (2H, m, CH_2); 4.40 (H, s, CH); 4.65 (2H, s, NH_2); 7.17-7.28 (4H, m, 4CH_{arom}).

2-amino-7,7-dimethyl-4-(3-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chronene-3-carbonitril (4d)

White Crystal, Yield (87%), m.p. 190-193°C. FT-IR (V_{\max}/cm^{-1}) (KBr disc): 3379, 3301 (NH_2 Str.); 3085 (C-H_{arom} Str.); 2965 ($\text{C-H}_{\text{aliph}}$ Str.); 2288 (C°N Str.); 1670 (C=O Str.); 1219 (C-O Str.). ^1H NMR

(400.13 MHz, CDCl_3): δ 1.07 (3H, s, CH_3); 1.13 (3H, s, CH_3); 2.25 (2H, AB q, $^3J=16.4, 2.4$ Hz, CH_2); 2.46 (2H, m, CH_2); 3.80 (3H, s, CH_3); 4.39 (H, s, CH); 4.57 (2H, s, NH_2); 6.74-7.28 (4H, m, 4CH_{arom}).

2-amino-7,7-dimethyl-4-(4-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chronene-3-carbonitril (4e)

White Crystal, Yield (93%), m.p. 215-217°C. FT-IR (V_{\max}/cm^{-1}) (KBr disc): 3371, 3303 (NH_2 Str.); 3110 (C-H_{arom} Str.); 2980 ($\text{C-H}_{\text{aliph}}$ Str.); 2198 (C°N Str.); 1668 (C=O Str.); 1217 (C-O Str.). ^1H NMR (400.13 MHz, CDCl_3): δ 1.04 (3H, s, CH_3); 1.13 (3H, s, CH_3); 2.23 (2H, AB q, $^3J=16.4, 7.2$ Hz, CH_2); 2.47 (2H, s, CH_2); 4.40 (H, m, CH); 4.58 (2H, s, NH_2); 7.18-7.29 (4H, m, CH_{arom}).

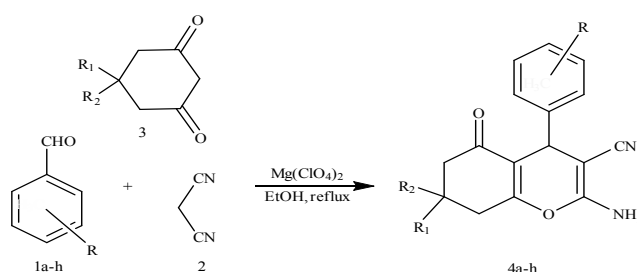


Fig. 1: Synthesis 4H-chromene under condition reflux

Table 1: Effect of quantity of $\text{Mg}(\text{ClO}_4)_2$ and temperature on the synthesis of 4a

Enter	Quantity (W%)	M.P. ($^{\circ}\text{C}$)	Time (h)	Yield (%)
1	6
2	100	6	33
3	10	80	5	35
4	10	90	5	38
5	10	100	5	42
6	20	80	4	39
7	20	90	4	43
8	20	100	4	42
9	25	80	3	63
10	25	90	3	82
11	25	100	3	87
12	30	80	3	78
13	30	90	3	80
14	30	100	3	80

Table 2: Synthesis of 4H-chromenes (4a) in different solvents

Enter	Solvent	Time (h)	(%)Yield
1	Solvent-free	3:30	45
2	Water	3	63
3	Aqueous Ethanol	3	87
4	Methanol	3	83
5	Chloroform	3:30	51
6	Acetonitrile	3:30	54

Table 3: recyclability of catalyst for the synthesis of 4H-chromene 4a

Number	Catalyst (g)	Yield (%)
1	0.057	87
2	0.055	85
3	0.051	82
4	0.045	72

Table 4: synthesis of different 4H-chromene derivatives 4a-h catalyzed by Mg(ClO₄)₂

Enter	product	Ar	Time (h)	Yield (%)	M.p. (obsd) (°C)	M.p. (lit.) (°C)
4a			3	90	230-232	235-237 ¹⁵
4b			2.3	95	216-218	209-211 ²⁷
4c			2.3	93	230-232	234-236 ³²
4d			3.3	87	190-193	—
4e			2:30	93	215-217	216-218 ³¹
4f			2.5	90	210-212	214-215 ³¹
4g			2.3	91	233-235	—
4h			3	89	213	208-210 ¹⁵

2-amino-7,7-dimethyl-4-(2-chlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitril (4f)

White Crystal, Yield (90%), m.p. 205-207 °C. FT-IR (V_{\max}/cm^{-1}) (KBr disc): 3320, 3272 (NH₂ Str.); 3117 (C-H_{arom} Str.); 2988 (C-H_{aliph} Str.); 2201 (C°N Str.); 1688 (C=O Str.); 1215 (C-O Str.). ¹H NMR (400.13 MHz, CDCl₃): δ 1.08 (3H, s, CH₃); 1.12 (3H, s, CH₃); 2.22 (2H, ABq, ³J=16.4, 8.4 Hz, CH₂); 2.47 (2H, s, CH₂); 2.47 (2H, s, CH₂); 4.67 (2H, s, NH₂); 4.86 (H, s, CH); 7.13-7.34 (4H, m, 4CH_{arom}).

2-amino-7,7-dimethyl-4-(2-fluorophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitril (4g)

White Crystal, Yield (91%), m.p. 233-235 °C. FT-IR (V_{\max}/cm^{-1}) (KBr disc): 3400, 3350 (NH₂ Str.); 3045 (C-H_{arom} Str.); 2950 (C-H_{aliph} Str.); 2210 (C°N Str.); 1620 (C=O Str.); 1225 (C-O Str.). ¹H NMR (400.13 MHz, CDCl₃): δ 1.06 (3H, s, CH₃); 1.13 (3H, s, CH₃); 2.24 (2H, ABq, ³J=16.4, 5.6 Hz, CH₂); 2.47 (2H, m, CH₂); 4.42 (H, s, CH); 4.55 (2H, s, NH₂); 7.21-7.32 (4H, m, 4CH_{arom}).

2-amino-7,7-dimethyl-4-(4-methylphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitril (4h)

White Crystal, Yield (89%), m.p. 225-227 °C. FT-IR (V_{\max}/cm^{-1}) (KBr disc): 3435, 3330 (NH₂ Str.); 3095 (C-H_{arom} Str.); 2964 (C-H_{aliph} Str.); 2201

(C°N Str.); 1630 (C=O Str.); 1205 (C-O Str.). ¹H NMR (400.13 MHz, CDCl₃): δ 1.06 (3H, s, CH₃); 1.12 (3H, s, CH₃); 2.23 (2H, ABq, ³J=16.4, 5.6 Hz, CH₂); 2.30 (3H, s, CH₃); 2.46 (2H, s, CH₂); 4.38 (H, s, CH); 4.55 (2H, s, NH₂); 7.09-7.28 (4H, m, CH_{arom}).

CONCLUSIONS

We report a novel one pot three component synthesis of functionalized 4H-chromene derivatives in the presence of Mg(ClO₄)₂ as catalyst. This reaction series was found to be highly effective under reflux conditions. Mg(ClO₄)₂ is an effective catalyst and provides a new and useful method for the synthesis of pyranulated heterocyclic systems by condensation of arylaldehydes, dimedon and malononitrile. The catalyst is environmentally friendly, inexpensive, clean, safe, nontoxic, and easily obtained. Moreover, the procedure offers several advantages including high yields, clean reaction conditions, and no pollution threat to the environment, which together make a useful and attractive process for synthesis of these compounds.

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