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Research Note

Mn(III) complex catalyzed a green synthesis of 2-amino-4*H*-chromen-5(6*H*)-ones in basic aqueous solution at ambient temperature

E. Mosaddegh* **and A. Hassankhani**

Department of New Materials, Institute of Science and High Technology and Environmental Sciences, Graduate University of Advanced Technology, Kerman, P.O. Box 76315-117, Iran.

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Heterogeneous catalyst;
Environmentally friendly;
Green chemistry.

Abstract. An efficient and environmentally friendly method for the synthesis of 2-amino-chromen-5(6*H*)-ones as important pharmaceutical compounds has been developed using [N,N′-bis(benzoylacetone)-1,2-ethylenediimine]Mn(III) chloride (2.5 mol%) as a heterogeneous and inorganic catalyst. A mixture of an appropriate aldehyde, malononitrile and dimedone in the presence of a catalytic amount of Mn(III) complex resulted in excellent yields (95-100%) of the corresponding products at ambient temperature. This new methodology is of interest due to use of water as a green solvent, its short reaction time, high yields and no further purification.

1. Introduction

2-Amino-4*H*-chromens and their derivatives are of considerable interest due to their pharmacological activities [1], such as spasmolytic, diuretic, anti-coagulant, anti-cancer and anti-ancaphylactia activity [2-6]. In addition, they have been shown to act as cognitive enhancers for the treatment of neurodegenerative disease, including Huntington disease, Alzheimer's disease, amyotrophic lateral Sclerosis, AIDS associated dementia and Down's syndrome as well as for the treatment of schizophrenia and myoclonus [7]. In this regards, their synthesis has received more attention, recently. The titled compounds were synthesized by reaction of malononitrile with dimedone in the presence of an appropriate aldehyde. A variety of reagents and conditions were employed to catalyze these reactions [8-23]. In spite of the potential utility of the aforementioned routes for the synthesis of 2-amino-4*H*-chromen-5(6*H*)-one derivatives, many of these methods involve expensive reagents, acidic conditions, long reaction times, low yields, the use of an excess of reagents/catalyst and use of toxic organic solvents as well as complicated work-up methods. The lack of a facile and general synthetic methodology under essentially natural, practical and mild reaction conditions has encouraged us to develop an efficient and convenient procedure for the one-pot green synthesis of 2-amino-4*H*-chromen-5(6*H*)-ones in aqueous media. To the best of our knowledge a complex catalyst has not been previously used in the synthesis of this class of compounds.

Green chemistry emphasizes the development of environmentally benign chemical processes and technologies [24]. According to the principle of safe chemistry, a synthetic method should be designed to use substances that exhibit little or no toxicity to human health and the environment [24]. In this regard, the synthesis of 2-amino-7,8-dihydro-4*H*-

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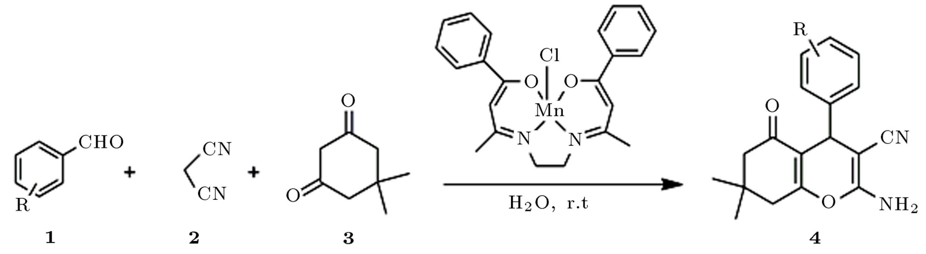
*. *Corresponding author. Tel.: +98 3426226617;*
Fax: +98 3426226611-12
E-mail addresses: emosaddegh@gmail.com (E. Mosaddegh); hassankhani_a@yahoo.com (A. Hassankhani)



Scheme 1. Synthesis of 2-amino-4*H*-chromene-5(6*H*)-one s in the presence of Mn(III) complex.

chromen-5(6*H*)-ones via a one-pot three-component tandem Knoevenagel-cyclo condensation reaction using (bzacen)MnCl (bzacen= N,N′-bis(benzoylacetone)-1,2-ethylenediimine) (2.5 mol%) as a heterogeneous complex catalyst is reported herein. The reaction was completed with high catalytic activity and reusability in a very short reaction time in basic aqueous media (Scheme 1).

2. Experimental

2.1. Materials and instruments

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. NMR spectra were recorded at 500 (^{1}H) and 125.77 (^{13}C) MHz on Bruker DRX-500 Avance spectrometer at 500 and 125.77 MHz, respectively. All compounds were known in the literature. The NMR and IR spectra of the products were in agreement with earlier data.

2.2. Catalyst preparation

N,N′-bis (benzoylacetone) ethylenediamine H_2(benzen) ligand was prepared according to the literature [25]. Anhydrous ethylendiamine was refluxed with benzoylacetone (2:1 mol stoichiometric ratio of amine to ketone) in ethanol for 10 h. A brown solid crude product was separated by filtration, washed several times with ethanol and finally with diethyl ether. The product was recrystallized from hot ethanol and dried. Then N,N′-bis (benzoylacetone) ethylenediamine manganese (III) chloride was synthesized according to the reported procedures [26,27]. The structure of Mn(III) complex is reported in the literature [25-27].

2.3. General procedure for the preparation of 2-amino-3-cyano-7,7-dimethyl-4-(4-chloro)-5-oxo-5,6,7,8-tetra-4H-chromene (4c)

In a typical general procedure, a mixture of aromatic aldehyde (1 mmol), malononitrile (1 mmol) and dimedone (1 mmol) in H_2O (3 mL) at ambient temperature, were stirred thoroughly in the presence of a catalytic amount of (bzacen)MnCl (10 mg, 2.5 mol%) to afford the 2-amino-4*H*-chromen-5(6*H*)-ones in excellent yields. After completion of the reaction (TLC), the solid product was filtered and washed with EtOH/H_2O (2:1) to separate it from the soluble catalyst. Pure 2-amino-4*H*-chromen-5(6*H*)-one 4 was obtained in 100% yield without further purification. The structures of the products were confirmed from physical and spectroscopic data (IR and ^{1}H NMR) in comparison with the literature data. The selected spectral data of three representative compounds are given below.

2-Amino-3-cyano-7,7-dimethyl-4-(2-chloro)-5-oxo-5,6,7,8-tetra-4*H*-chromene (4h). IR (KBr, cm^{-1}): 3478, 3329, 3180, 2957, 2187, 1666, 1592, 1368, 1219, 797. ^{1}H NMR (500 MHz, $CDCl_3$, δ/ppm): 1.07 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.18 (d, 1H, J = 16.3 Hz, CH-8) 2.24 (d, 1H, J = 16.3 Hz, CH-8), 2.45 (m, 2H, CH-6), 4.85 (s, 1H, CH-4), 4.63 (s, 2H, NH_2), 7.12-7.33 (m, 4H, ArH).

2-Amino-3-cyano-7,7-dimethyl-4-(3-methoxyphenyl)-5-oxo-5,6,7,8-tetra-4*H*-chromene (4i). IR (KBr, cm^{-1}): 3404, 3329, 3205, 2907, 2187, 1641, 1617, 1567, 1517, 1393, 1368, 1195, 822. ^{1}H NMR (500 MHz, $CDCl_3$, δ/ppm): 1.05 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 3.78 (S, 3H, CH_3), 2.23 (d, 1H, J=16.2 Hz, CH-8) 2.26 (d, 1H, J=16.7 Hz, CH-8), 2.44 (d, 1H, J= 17.1 Hz, CH-6), 2.49 (d, 1H, J= 17.6 Hz, CH-6), 4.37 (s, 1H, CH-4), 4.57 (s, 2H, NH_2), 6.73-7.22 (m, 4H, ArH).

2-Amino-3-cyano-7,7-dimethyl-4-(4-methylphenyl)-5-oxo-5,6,7,8-tetra-4 H-chromene (4k). IR (KBr, cm^{-1}): 3445, 3180, 2957, 2882, 2187, 1667, 1617, 1592, 1368, 1219, 1145, 1046. ^{1}H NMR (500 MHz, $CDCl_3$, δ/ppm): 1.04 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.29 (S, 3H, CH_3), 2.21 (d, 1H, J=16.3 Hz, CH-8) 2.26 (d, 1H, J=16.3 Hz, CH-8), 2.44-2.45 (m, 2H, CH-6), 4.37 (s, 1H, CH-4), 4.52 (s, 2H, NH_2), 7.08-7.12 (m, 4H, ArH).

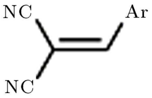
3. Results and discussion

In continuation of our interest in the application of heterogeneous catalysts in organic reactions [28], we wish to report a simple, mild and efficient method for the synthesis of 2-amino-7,8-dihydro-4*H*-chromen-5(6*H*)-one derivatives at ambient temperature (Scheme 1).

To show that Mn(III) complex is an efficient catalyst, we accomplished the reaction at room temper-

Table 1. Effect of solvents in the synthesis of 2-amino-3-cyano-7,7-dimethyl-4-(4-chloro)-5-oxo-5,6,7,8-tetra-4*H*-chromene using 2.5 mol% of Mn(III) complex at room temperature.

Entry	Catalyst (g)	Solvent	Time	Yield (%)
1	0.01 g, 2.5 mol%	EtOH	20 min	90
2	0.01 g, 2.5 mol%	EtOH/H_2O (2:1)	10 min	94
3	0.01 g, 2.5 mol%	H_2O	5 min	100
4	0.01 g, 2 mol%	H_2O	10 min	95
5	0.005 g, 1 mol%	H_2O	50 min	87
6	0.001 g, 0.2 mol%	H_2O	2 h	87



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Scheme 2. Benzylidene malononitrile.

ature in absence of any catalyst. The reaction produced only alkene **5** and no 2-amino-4*H*-chromen-5(6*H*)-one 4 was formed (Scheme 2) even after 4 h.

This proves the essential effect of Mn(III) complex as a mild and efficient catalyst in the reaction. In order to improve the yield, we performed the reaction using different quantities of reagents (Table 1). The best results were obtained with a 0.01:1:1:1.5 ratio of Mn(III) complex, aldehyde, dimedone and malononitrile. Further increase in the catalyst amount up to 0.1 g has not shown any significant effect on the reaction time or yield of the products.

Further, we carried out control reactions in different solvents (Table 1). The results show that the reaction proceeds in the inorganic and portic solvent (H_2O) more rapid and H_2O at room temperature provides the best reaction conditions. To investigate the versatility of the catalyst, the reaction of dimedone, malononitrile and various aromatic aldehydes was carried out in H_2O at room temperature using 2.5 mol% of Mn(III) complex. 2-amino-4*H*-chromen-5(6*H*)-one derivatives containing electron-withdrawing groups such as nitro and halide groups or electron-donating groups such as hydroxyl and alkoxy groups (Table 2) were formed in very short reaction time (5-13 min) with excellent yields (95%-100%).

Recently, there have been some reports on the synthesis of 2-amino-4*H*-chromen-5(6*H*)-ones by using different catalysts which are presented in Table 3. As shown in Table 3, in all cases, the reaction time is longer and the products yield is lower than the present procedure. In the present work, the condensation using the Mn(III) complex proceeds rapidly in just 5 min with higher product yield of 100% and is superior to the reported procedures.

Table 2. Synthesis of 4 catalyzed by Mn(III) complex at ambient temperature in water as solvent.

Product	Ar	Time (min)	Yield[a] (%)	m.p. (°C)
4a	C_6H_5	12	97	222-224
4b	4-Br-C_6H_4	13	100	207-209
4c	4-Cl-C_6H_4	5	100	208-209
4d	2,4-Cl_2-C_6H_3	7	99	178-179
4e	4-OH-C_6H_4	10	96	207-209
4f	3-OH-C_6H_4	12	97	231-233
4g	4-$(H_3C)_2N$-C_6H_4	15	95	212-214
4h	2-Cl-C_6H_4	5	100	209-210
4i	3-H_3CO-C_6H_4	10	98	188-190
4j	4-H_3CO-C_6H_4	10	95	122-124
4k	4-H_3C-C_6H_4	7	90	214-216

[a] Yields refer to the isolated products.

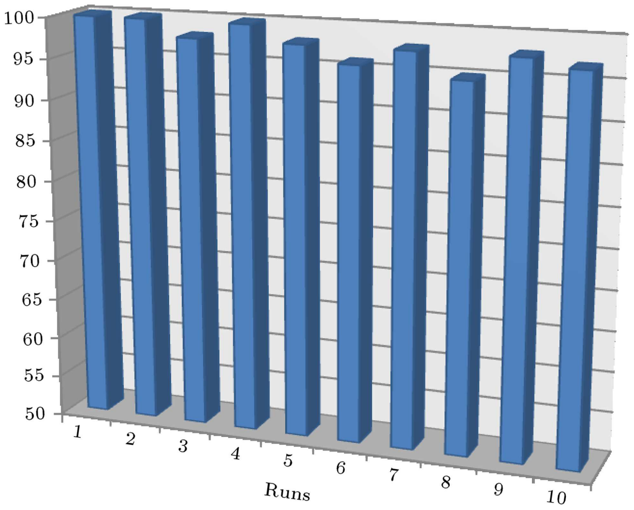

Figure 1. Recycling experiment of the catalyst.

3.1. Reusability of Mn(III) complex

The reusability of catalysts is one of the most important benefits and makes them useful for commercial applications. Thus, the recovery and reusability of Mn(III) complex were investigated. The reaction mixture was filtered and washed with cold EtOH/H_2O (2:1). The soluble catalyst was easily reused after distillation of solvent, being washed with $CHCl_3$ and dried at room temperature. The recycled catalyst could be re-used in the next run in the reaction between 4-chlorobenzaldehyde, malononitrile and dimedone. It was very beneficial that the (bzacen)MnCl could be re-used in ten cycles (Figure 1). Thus, the new procedure

Table 3. Synthesis of 2-amino-3-cyano-7,7-dimethyl-4-(4-chloro)-5-oxo-5,6,7,8-tetra-4*H*-chromene using different reagents and reaction conditions.

Entry	Reagent	Conditions	Time	Yield^a (%)^{ref}
1	$Ni(NO_3)_2.6H_2O$ (10 mol%)	H_2O, reflux	20 min	88 [13]
2	[TETA]TFA (0.1 mmol)	EtOH/H_2O (1:1), reflux	10 min	94 [14]
3	$[H_3N^+\text{-}CH_2\text{-}CH_2\text{-}OH][HCOO^-]$	r.t	4 min	83 [15]
4	SB-DABCO (6 mol%)	EtOH, r.t	25 min	95 [18]
5	Fe_3O_4@SiO_2/DABCO (5 g)	H_2O, 80°C	25 min	90 [19]
6	Silicagel polyamine (10 wt%)	EtOH/H_2O (8:2), reflux	2.30 h	94 [20]
7	Urea:ChCl (2:1), 1 mL	EtOH/H_2O, 80°C	1-4 h	92 [21]
8	$PhB(OH)_2$ (5 mol%)	EtOH/H_2O (1:1), reflux	30 min	84 [22]
9	Mn(III) complex (2.5 mol%)	H_2O, r.t	5 min	100 (Present work)

[a] Yields refer to the isolated products.

is very simple and clean, environmentally friendly, cost effective, more efficient and provides easier work-up than reported methods.

4. Conclusions

In conclusion, the present method is an operationally simple and environmentally friendly procedure for the synthesis of compound **4** using a catalytic amount of N,N′-bis(benzoylacetone)-1,2-ethylenediimine) Mn(III) chloride at ambient temperature. Other benefits include recyclability and moderate Lewis acidity of the catalyst, safe conditions, very short reaction time and excellent yields of the products. Extensive purification make this methodology a valid contribution to the existing processes in the field of 2-amino-7,8-dihydro-4*H*-chromen-5(6*H*)-ones synthesis.

Acknowledgments

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Biographies

Elaheh Mosaddegh was born in Kerman, Iran, in 1981. She obtained her PhD degree in Organic Chemistry from Shahid Bahonar University of Kerman, Iran, in 2009. She is currently assistant professor of Organic Chemistry at the Graduate University of Advanced Technology. Her main research interests include: multi-component reactions, synthetic methodology, green chemistry, nano-catalysts and nano-composites.

Asadollah Hassankhani was born in Hashtrood, Iran, in 1977. He obtained his PhD degree in Organic Chemistry from University of Sistan and Baluchestan, Iran, in 2008. He is currently assistant professor of Organic Chemistry at the Graduate University of Advanced Technology. His main research interests include: catalysis, multi-component reactions, heterocycle synthesis and methodology.