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One pot three component synthesis of 2-amino-4*H*-chromenes under green and high efficient conditions

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ABSTRACT

A simple, mild and high efficient procedure for one pot three component synthesis of 2-amino 4-H chromene derivatives was studied. The reaction was performed in water using aryl aldehydes, malononitrile and resorcinol, phloroglucinol or naphtholes in the presence of N-methyl D-glucamine (Meglumine) as a green high efficient catalyst. The reaction was studied in thermal, microwave (MW) and ultrasonic (US) conditions. Obtained results show that meglumine, as a green catalyst, has high efficiency in all reaction conditions and the yield of products (in all cases) is high to excellent. Environment friendly solvent and catalyst, short reaction times and high yield products are the advantageous of presented research.

Keywords: *Chromenes, Meglumine, One-pot, Green conditions, Ultrasonic, Microwave.*

1. Introduction

One pot multi component reactions (MCRs) are much favourable by chemists because avoid a long separation process and purification of the intermediate chemical compounds. The one-pot reactions have some advantages such as increasing the reaction yield and saving time. Also multi-component reactions are very powerful tools for the construction of complex organic molecules by using readily available starting materials [1-9]. MCRs have been frequently used by synthetic chemists as a facile route to generate molecular diversity from substrates that react sequentially in an intra molecular fashion. An example of a one pot synthesis is the synthesis of benzopyran derivatives. Benzopyran is a polycyclic organic compound that results from the fusion of a benzene ring to a heterocyclic pyran ring. According to IUPAC nomenclature, it is called chromene.

In recent years, cheromenes have been prepared in the presence of different catalysts like $InCl_3$ [10], Al_2O_3 [11], $GaCl_3$ [12], $Fe(HSO_4)_3$ [13], $pd(OCOCF_3)_2$ [14], $AuCl_3$ [15], $H_6P_2W_{18}O_{62}.18H_2O$ [16], K_2CO_3 [17] and MgO [18] that they are not environment friendly however, most of the reported methods require prolonged reaction time, stoichiometric reagents, and toxic solvents but generate only moderate yields of the product. Meglumine is an amino sugar derived with molecular formula $C_7H_{11}NO_5$, which can be considered as an environmental friendly catalyst [19,20]. The green meglumine (as catalyst) show several advantages including its easy work-up, short reaction time and no side reaction. In recent years, microwave and ultrasonic irradiation has been known for accelerating the organic reactions [21-23]. Here we report a green method for synthesis of 4-H chromene derivatives using meglumine as environment friendly catalyst (Scheme 1,2) in thermal, microwave and ultrasonic conditions. The reaction performed in water, and high to excellent yield products were obtained after short reaction times. Chromene derivatives were characterized, using FTIR, ^{1}HNMR and ^{13}CNMR methods.

2. Experimental

2.1. Chemicals and apparatus

Chemical reagents were purchased from the Merck Company. Melting points were determined in open capillaries using an Electro thermal MK3 apparatus. Infrared (IR) spectra were recorded using a Perkin-Elmer FT-IR 550 spectrometer. ^{1}H NMR and ^{13}CNMR spectra were recorded with a Bruker Avance DPX-400 spectrometer at 400 and 100 MHz, respectively. Probic ultrasound instrument SONOPULS-HD-3200 from

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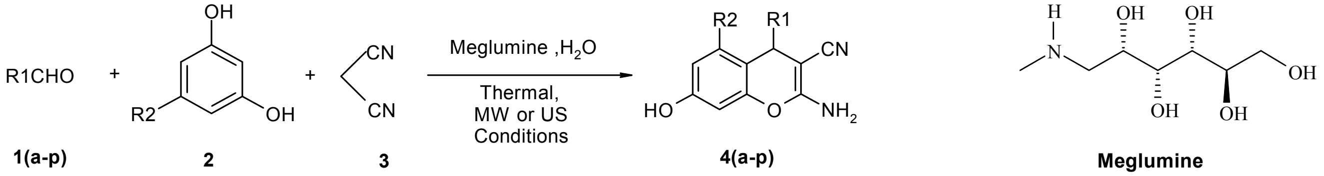


Scheme 1. Synthesis of 4-*H* chromenes in aqueous media and meglumine as catalyst. The reaction was performed in thermal, microwave, and ultrasonic conditions.

Bandlin Electronic Company was used for preparing the green conditions for chromens synthesis.

2.2. General procedure for the synthesis of 2-amino-4H-chromenes

Aldehyde derivatives (1mmol), resorcinol, phloroglucinol or naphthol (1mmol), malononitrile (1mmol) and meglumine as catalyst (10 mol %) were dissolved in 4 ml of water in a pyrex tube at 80°C for specific time. The progress of the reaction is monitored by TLC. Upon completion of the reaction, the reaction mixture was filtered and then the products were recrystallized from ethanol.

In microwave conditions, the mixture of reactants and 10 mol% of catalyst were dissolved in 2 ml of water in a pyrex tube at power of 450 w for specific time. Also in ultrasonic conditions, the mixture of reactants and 10 mol% of catalyst were dissolved in 2 ml of water in 19°C and power of 60 w for specific time. After completion of the reaction, the separation of products (in Microwave and ultrasonic conditions) performed according to thermal conditions.

3. Results and discussion

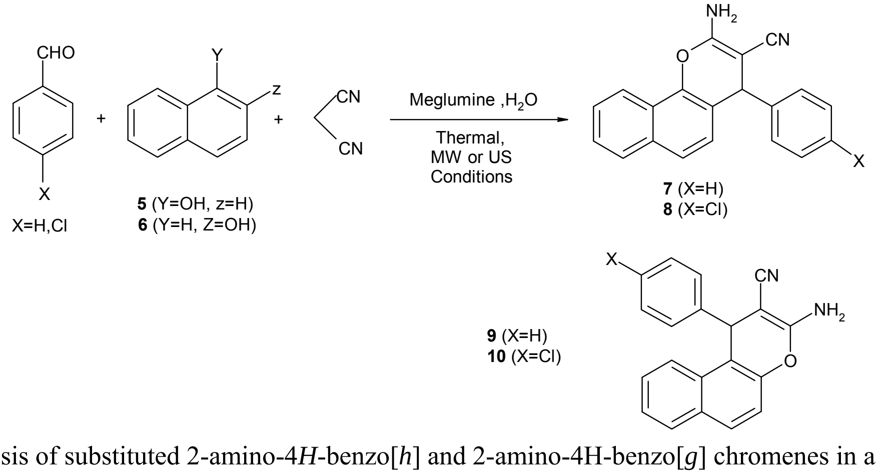
In first step of our purposed method, we investigated the optimization of the reaction conditions include catalyst amount, solvent and reaction temperature, using resorcinol, malononitrile and *p*-Nitro benzaldehyde as model reaction.

For comparison of meglumine efficiency with other catalysts, various catalysts (10 mol%) were examined in model reaction. The results were summarized in Table 1. As shown in this Table, in the absence of catalyst, only 10% yield of product was observed after 24h also other catalysts such as Iodine, Cupper oxide and sodium acetate have no special efficiency in the reaction. Some of results reported in previous articles were collected in Table 1. It is clearly observed that meglumine was the best catalyst in the reaction and the product was obtained in 98% yield in 10 min and this shows the high efficiency of this catalyst.

In second step of optimization of the reaction conditions, we screened the effect of the solvents in yield and time of the reaction in the presence of meglumine as catalyst. Results in Table 2 claimed that water is the best solvent in term of reaction time, yield and green chemistry agreeable.

After choose of suitable solvent for the reaction, the amount of the catalyst must be evaluate in model reaction. The results in Table 3 show that 10 mol% (0.019 g) of catalyst was the best amount for completion of reaction in water.

After the optimization of the reaction conditions, to investigate the scope and limitation of our catalytic presented method, we try to study on the synthesis of 2-amino-4H-chromenes in various reaction conditions include thermal, microwave and ultrasound irradiation conditions. In this way, we use a variety of benzaldehyde derivatives, malononitrile and resorcinol, phloroglucinol or naphtholes for three component reaction in the presence of meglumine as efficient catalyst. In thermal conditions, the optimized temperature of the reaction was 80°C.



Scheme 2. Synthesis of substituted 2-amino-4*H*-benzo[*h*] and 2-amino-4H-benzo[*g*] chromenes in aqueous media and meglumine as catalyst.

Table 1. Comparison of meglumine efficiency with several catalysts.

Entry	catalyst	Time (min)	Yield (%)[a]	Ref.
1	Free	24 h	10[b]	This work
2	I_2	50	58[b]	This work
3	$Bi(NO_3)_3$	50	8[b]	This work
4	K_2CO_3	50	75[b]	This work
5	CuO	50	60[b]	This work
6	CH_3CO_2Na	50	55[b]	This work
7	DBU	40[c]	72	[24]
8	2,2,2-trifluoroethanol	5 h	93	[25]
9	K_2CO_3	2.8[c]	91	[26]
10	SiO_2-polyamine	3 h	90	[27]
11	Rochelle salt	2-4 h	84	[28]
12	MCM-41-NH_2	30	89	[29]
13	$K_3PO_4,3H_2O$	4[d]	83	[30]
14	Poly(4-vinylpyridine)	10	90	[31]
15	Nano MgO	60	89	[32]
16	Meglumine	10	98	This work

[a] Isolated yield.

[b] 4-Nitro benzaldehyde (1mmol), resorcinol (1mmol), malononitrile (1mmol) in water and 10 mol% of catalyst in thermal conditions.

[c] MW condition.

[d] Ultrasonic condition.

Table 4 shows the structure, time and yield of the reaction products in thermal conditions. All reactions performed efficiently, and the products were obtained in high to excellent yield in short reaction times and also no by-product was formed during the reaction.

The results indicated that in aryl aldehydes with electron donating groups (entry 6, 8-12), a decrease of the reaction rate was observed. Also the reaction was sensitive to the steric effect in two substituted aryl aldehydes and in the other position substituted ones (entry 11), that the time of the reaction is longer than others. On the other hand, electron withdrawing substituted aldehydes have high yield in short reaction times. To show the fairly advantages of meglumine, we use our protocol in microwave and ultrasound conditions.

The model reaction performed in optimized conditions under microwave and ultrasound irradiation.

Table 2. Effect of the solvent on the reaction time and yield of the model reaction.[a]

Entry	Solvent	Time (min)	Yield (%)[b]
1	Free	40	80
2	Ethanol	35	85
3	Methanol	25	80
4	Water	10	98
5	Ethanol/Water (1:1)	40	87
6	Ethanol/Water (1:2)	20	86

[a] 4-Nitro benzaldehyde (1mmol), resorcinol (1mmol), malono nitril (1mmol) and 10 mol% of catalyst and thermal conditions (80°C).

[b] Isolated yield.

Table 3. Effect of the amount of the catalyst on yield and time of the model reaction.[a]

Entry	Catalyst (mol%)	Time (min)	Yield (%)[b]
1	Free	24(h)	10
2	2	240	85
3	5	120	80
4	7	30	85
5	10	10	98

[a]4-Nitro benzaldehyde (1mmol), resorcinol (1mmol), malononitrile (1mmol) and various amount of catalysts in water under thermal conditions (80°C).

[b]Isolated yield.

As shown in Table 5, it clearly observed that in these two conditions, the reaction products were obtained in excellent yields in very short reaction times and similar to thermal conditions, aryl aldehydes caring electronwithdrawing groups, reacted faster than those with electron donating groups. Similar results were obtained when naphtholes were used for the synthesis of 2-amino 4H-chromenes. As shown in Table 6, the yield of products in three reaction conditions are high to excellent and the reactions performed in short time with a simple procedure (Table 6).

The reusability of the meglumine was also studied. After the completion of every reaction, the product was filtered and purified by recyclization from ethanol then the filtrate was evaporated and dried. Finally, recovered catalyst was washed with diethyl ether, dried and reused. The recovered catalyst show high activity after three consecutive cycles (Table 7).

According to previous studies on the mechanism of the 4-*H* Chromene synthesis from aryl aldehydes, malononitrile and resorcinol (phloroglucinol or naphtholes), we presented here a mechanism using meglumine role as a basic catalyst due to NHMe group existed on the meglumine structure (Scheme 3).

Table 4. Synthesis of 2-amino-4H-chromenes in thermal conditions.[a]

Entry	R^1	R^2	Time (min.)	Product	Yield (%)[b]	m.p. (°C) Found	m.p. (°C) Reported	Ref.
1	$4\text{-}NO_2C_6H_4$	H	10	4a	98	215-217	216-218	[23]
2	$4\text{-}ClC_6H_4$	H	10	4b	95	166-164	163-164	[23]
3	$3\text{-}NO_2C_6H_4$	H	15	4c	98	187-190	188-190	[33]
4	$2,4\text{-}(Cl)_2C_6H_3$	H	30	4d	96	256-258	256-258	[34]
5	$2\text{-}ClC_6H_4$	H	40	4e	90	94-95	96-98	[33]
6	$3\text{-}OHC_6H_4$	H	65	4f	80	217-219	216-218	[34]
7	Ph	H	40	4g	95	234-237	232-234	[33]
8	$3\text{-}CH_3C_6H_4$	H	45	4h	90	199-201	-	-
9	$4\text{-}CH_3C_6H_4$	H	75	4i	90	183-186	182-184	[33]
10	$4\text{-}OHC_6H_4$	H	80	4j	85	267-269	248-250	[33]
11	$2,3(OCH_3)_2C_6H_4$	H	95	4k	85	221-224	-	-
12	$4\text{-}OCH_3C_6H_4$	H	90	4l	85	110-113	110-111	[33]
13	$4\text{-}NO_2C_6H_4$	OH	5	4m	98	212-213	-	-
14	$2\text{-}ClC_6H_4$	OH	45	4n	95	215-217	-	-
15	Ph	OH	35	4o	95	228-230	-	-
16	2-Furyl	H	60	4p	90	208-210	208-210	[34]

[a]Aldehyde derivatives (1mmol), malononitrile (1mmol), resorcinol or phloroglucinol (1mmol) and catalyst 10 mol% in water and 80°C.

[b]Isolated yield

Table 5. Synthesis of 4H-chromenes under microwave and ultrasound irradiation.

Entry	R^1	Product	Microwave conditions[a]		Ultrasonic conditions[b]	
			Time (min)	Yield (%)[c]	Time (min)	Yield (%)[c]
1	$4\text{-}NO_2C_6H_4$	4a	3.30	98	2.30	98
2	$4\text{-}ClC_6H_4$	4b	3.35	98	3	98
3	$3\text{-}NO_2C_6H_4$	4c	3.5	98	3.30	98
4	$2,4\text{-}(Cl)_2C_6H_3$	4d	7	93	4.30	95
5	$2\text{-}ClC_6H_4$	4e	13	95	13	95
6	$3\text{-}OHC_6H_4$	4f	14	90	16	92
7	Ph	4g	9.30	96	5	97
8	$3\text{-}CH_3C_6H_4$	4h	10.5	92	6	94
9	$4\text{-}CH_3C_6H_4$	4i	16	90	9.30	90
10	$4\text{-}OHC_6H_4$	4j	18	95	10	95
11	$3,4(CH_3)_2C_6H_4$	4k	17	90	11	92
12	$4\text{-}OCH_3C_6H_4$	4l	18	90	11.30	92

[a] Aldehyde derivatives (1mmol), malononitrile (1mmol), resorcinol (1mmol) and catalyst 10 mol% in water and power of 450 w.

[b] Aldehyde derivatives (1mmol), malononitrile (1mmol), resorcinol (1mmol) and catalyst 10 mol% in water and power of 60 w in 19°C.

[c] Isolated yield.

In first step of reaction, meglumine plays a major role in condensation of malononitrile and aryl aldehyde through absorption the acidic hydrogen of malononitrile and also activation the aryl aldehyde with hydrogen bonding between N atom of meglumine and carbonyl oxygen. In second step of reaction mechanism, catalyst converted the resorcinol to active moiety for attachment to ylidenemalononitrile (**I**) through Michael addition type reaction. In continue, after the aromatization of **II** to **III**, intramolecular cyclization of (**IV**) by nucleophilic addition of phenolate anion to nitrile group, generated of intermediate **V** (in the presence of meglumine). In final step, the tautomerization of V gave 4-H chromene (**4**).

4. Conclusions

Meglumine, a bio-based chemical, was demonstrated to be a highly efficient and reusable catalyst for the synthesis of a series of benzopyran derivatives via a one-pot, three component reaction of carbonyl compounds, malononitrile and aromatic aldehyde derivatives in water. Unlike the existing method using potentially dangerous catalysts, we have developed efficient and green approach for the one pot three component synthesis of chromenes using meglumine as biodegradable, inexpensive and reused catalyst in three reaction conditions (thermal, microwave and ultrasonic conditions). The salient features of our methodology are simplification of workup, high-yield products, easy isolation and purification, mild reaction conditions, reusability of catalyst and the absence of hazardous solvents and also agreement with the green chemistry.

Acknowledgment

We are grateful to the University of Kashan Research Council for the support of this work.

Table 6. Synthesis of 4H-benzo chromenes under thermal, microwave and ultrasound irradiation[a].

Entry	Naphthol	X	Time (min)			Yield (%)[b]			m.p (°C)		Ref.
			Thermal	MW	US	Thermal	MW	US	Found	Reported	
1	5	H	60	14	7	90	94	92	208-210	210-211	[35]
2	5	Cl	55	12	7	92	90	90	229-231	231-232	[35]
3	6	H	80	16	10	90	92	90	275-278	278-279	[36]
4	6	Cl	85	16	12	89	90	90	211-212	210-211	[36]

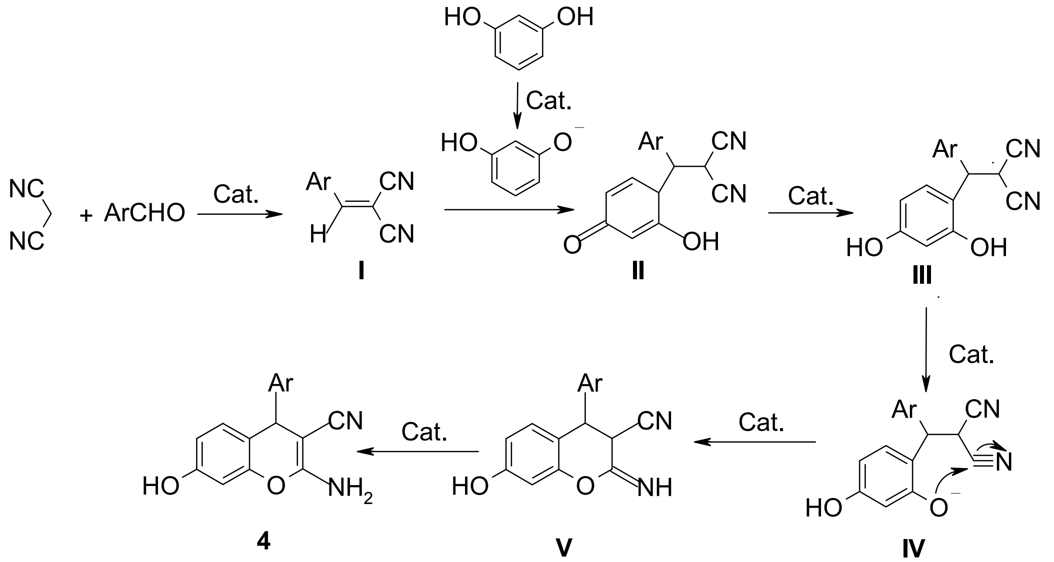
[a] The reaction procedure is according to synthesis method of 4H-Chromenes.

[b] Isolated yields.

Table 7. Reusability of meglumine.

Entry	Recycling	Yield (%)[a]
1	0	98
2	1	95
3	2	90
4	3	90

[a] Isolated yield



Scheme 3. The mechanism of 4-*H* chromenes synthesis in the presence of meglumine as catalyst.

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