

Cellulose-Supported Metal Nanocomposite as a Green and Reusable Catalyst for One-Pot Multicomponent Synthesis of 2-Amino-4*H*-Chromene Derivatives

Mohammad Farhadnia, Shahrzad Javanshir*

Department of Chemistry, Iran University of Science & Technology, Tehran 16846-13114, Iran

E-mail: shjavan@iust.ac.ir

Abstract: A simple and convenient approach for the synthesis of 2-amino-4*H*-chromene derivatives has been developed via a multicomponent reaction, which involves the condensation of 1,3-dicarbonyls compounds, aromatic aldehydes and malononitrile using cellulose-supported metal nanocomposite as a green, reusable and environmentally benign catalyst system. Environmental friendly, recyclability, cost-effectiveness, easy workup and excellent yields are the major attributes of this one-pot procedure.

Keywords: 2-amino-4*H*-chromenes, multicomponent reaction, nanocomposite.

Introduction

Multicomponent reactions (MCRs), an important subclass of tandem reactions, are one-pot processes in which three or more accessible components react to form a single product that incorporates essentially most or all atoms of the reactants used [1]. One-pot multicomponent strategies grant remarkable advantages over conventional bimolecular reactions owing to their convergence, atom-economy, operational simplicity, structural diversity and shortness of the synthetic pathway [2]. MCRs have recently gained a new

dimension in the field of designing methods to produce elaborate libraries of biologically active compounds. The fusion of biodynamic hetero systems has emerged as a useful tool for the design of new molecular frameworks for potential drugs with diverse pharmacological activities [3].

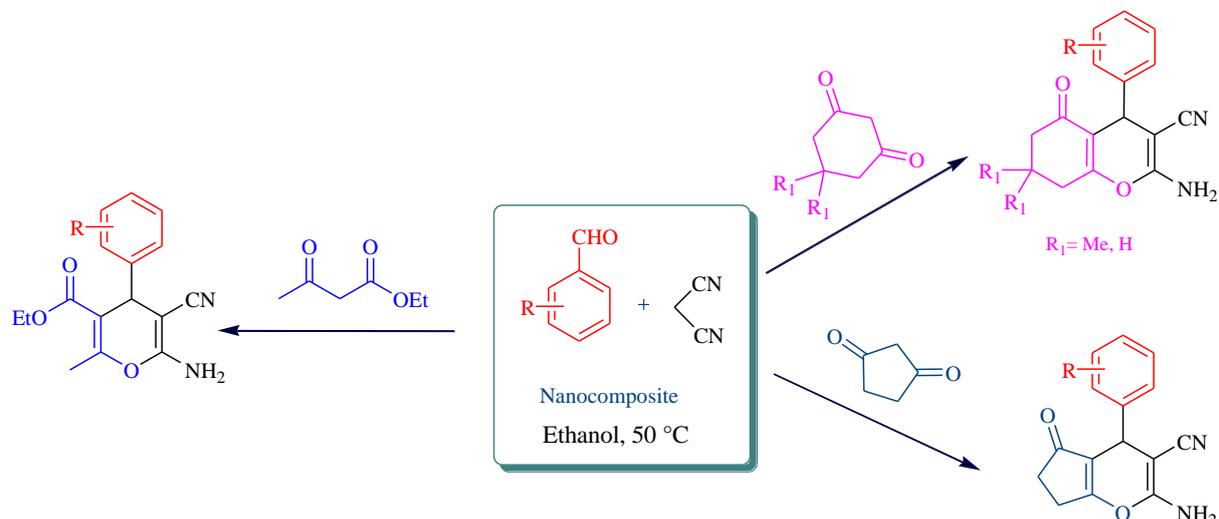
4*H*-Chromene and its derivatives are biologically interesting compounds known for their antimicrobial and antifungal, antioxidant, antitumor, hypotensive, anti-proliferation, local anesthetic, antiallergenic and anti HIV. Besides, 4*H*-chromenes can be employed as cosmetics or pigments, and useful as photoactive materials. Due to the important aforementioned properties of chromene derivatives, considerable attention has been focused on the development of environmentally friendly methodologies to synthesize 2-amino-4*H*-chromene scaffold [4].

Recent catalytic systems for MCR synthesis of 2-amino-4*H*-chromene derivatives consist of homogeneous or heterogeneous TiCl₄ [5a], Fe(HSO₄)₃ [5b], MeSO₃H [5c], nano-sized zeolite clinoptilolite [5d], tungstic acid functionalized mesoporous SBA-15 [5e], nano-sized CoFe₂O₄ [6a], CuO-CeO₂ [6b], Mg/Al hydrotalcite [6c-d], Alumina [6e], L-proline [7a], chitosan [7b], 4-dimethylaminopyridine [7c], morpholine [7d], different tetraalkylammonium halides [8] or an enzyme such as lipase [9]. Therefore, the search of improved catalysts for the synthesis of 2-amino-4*H*-chromene derivatives using an eco-friendly approach is of prime importance. Development of efficient and practical catalysts for organic synthesis is of considerable interest to both academia and industries.

In this regard, cellulose -supported metal nanocomposite possesses unique features such as environmental compatibility, non-toxicity, reusability, non-corrosively, chemical and physical stability and can be used over a prolonged duration of time.

As a part of our continuing efforts in laboratory towards the development of clean and environmentally benign methodologies for organic reactions [10], herein, we decided to use

cellulose-supported metal nanocomposite for the mild and highly efficient three-component synthesis of 2-amino-4*H*-chromene derivatives via a domino Knoevenagel-Michael condensation reaction of 1, 3-dicarbonyls compounds, aromatic aldehydes and malononitrile (Scheme 1).



Scheme 1. Three-component reaction of different enols with aromatic aldehydes and malononitrile.

Experimental

Materials and methods

All commercially available chemicals were obtained from Merck and Aldrich, and used without further purifications, except for benzaldehyde, which was used as a fresh distilled sample. All reactions and the purity of 2-amino-4*H*-chromene derivatives were monitored by thin-layer chromatography (TLC) using aluminum plates coated with silica gel F254 plates (Merck) using ethyl acetate and *n*-hexane as eluents. The spots were detected either under UV light or by placing in an iodine chamber. Melting points were determined in open capillaries using an Electrothermal 9100 instrument. IR spectra were recorded on a Shimadzu FT-IR400s. ¹H NMR spectra were recorded on an Avance Bruker DRX-300 MHz.

General procedure for the synthesis of 2-amino-4H-chromene derivatives

A 10 mL round-bottom flask was filled with aromatic aldehydes **1** (1 mmol), malononitrile **2** (1 mmol), 1,3-dicarbonyls compounds **3**, **6** (1 mmol), and cellulose-supported metal nanocomposite (20 mg). The reaction mixture was then stirred at 50 °C until the reaction was completed. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the catalyst was removed so simple then washed with acetone and after drying could be ready to use for the next reaction without loss in activity. The precipitated were separated by filtration and washed thoroughly with ethylacetat to afford the product. If necessary, simple recrystallization was carried out in EtOH/H₂O.

Results and discussions

First, the reaction of dimedone (**3a**), 4-chlorobenzaldehyde (**1a**), and malononitrile (**2**) (molar ratio: 1:1:1) was chosen as the model reaction. These were stirred at ambient temperature in ethanol. The reaction did not proceed to completion even after 2 h with only 20% of the product **4a** was being isolated. In order to improve the yield and optimize the reaction conditions, the same reaction was carried out in the presence of cellulose-supported metal nanocomposite as a catalyst under similar conditions. Surprisingly, a significant improvement was observed and the yield of the product **4a** was enhanced to 60% after stirring the reaction mixture for 1 h. Next, we optimized the catalyst loading for this reaction and we noted that although the product could be formed with low catalyst loading (10 mg/mmol of the reactant), the best outcome, in terms of yield and the reaction time, was obtained with 20 mg/mmol of cellulose-supported metal nanocomposite (Table 1).

Table 1. Optimization of the amount of the catalyst.^a

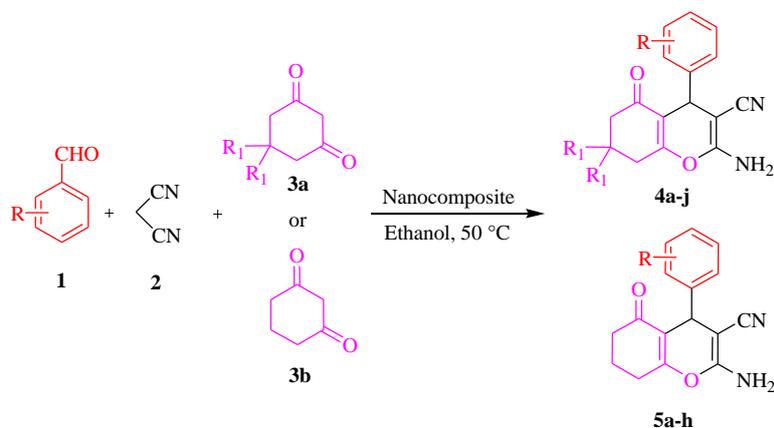
Entry	Catalyst (mg)	Time (min)	Yield ^b (%)
1	0	120	20
2	10	60	75
3	20	20	96
4	30	20	96

^a Reaction conditions: dimedone **3a** (1 mmol), 4-chlorobenzaldehyde **1a** (1 mmol), malononitrile **2** (1 mmol); catalyst: cellulose-supported nanocomposite; ethanol (2 mL). ^b Isolated yields.

We also examined the effect of temperature on this reaction. It was found that the optimum temperature was 50 °C from the point of view of yield and reaction time. At higher temperatures, no further improvement on yield and reaction time was observed. On the other hand, the reaction did not proceed at room temperature. At 50 °C, the reaction proceeded smoothly and almost complete conversion of the reagent was observed.

In order to generalize the optimum conditions, different derivatives of 2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyran (**4a-i**) were prepared from the one-pot reaction mixture of aromatic aldehyde (**1a-i**), malononitrile (**2**) and dimedone (**3a**). The results are summarized in Table 2. In addition to dimedone, 1,3-cyclohexadione (**3b**), was also examined for the synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyran (**5a-h**).

Table 2. Three-component synthesis of different 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyrans (**4a-5h**) via condensation of various aldehydes (**1**), malononitrile (**2**), dimedone (**3a**) and 1,3-cyclohexadione (**3b**).^a



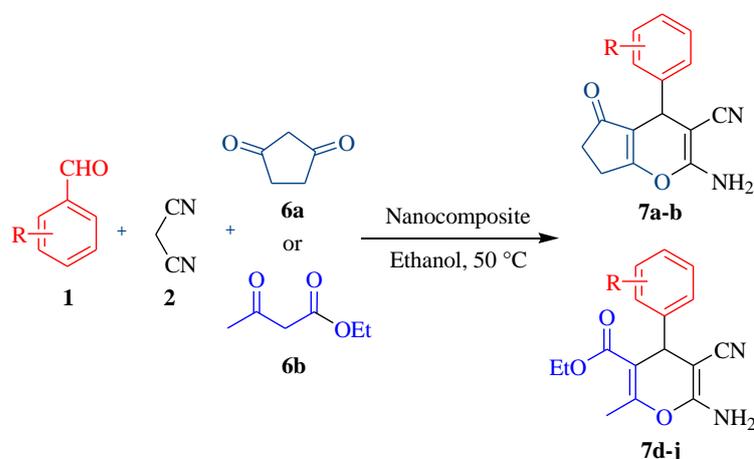
Entry	R	Product ^b	Time (min)	Yield ^c (%)	Mp (°C) Found	Mp (°C) Reported
1	4-Cl	4a	20	96	213-216	215-217 ^[7a]
2	4-Br	4b	25	94	215-218	214-216 ^[7a]
3	2,4-dichloro	4c	30	94	191-193	192-194 ^[10c]
4	4-NO ₂	4d	20	95	180-183	179-180 ^[7a]
5	3-NO ₂	4e	25	95	212-215	214-216 ^[24]
6	4-H	4f	35	92	230-232	234-235 ^[10c]
7	4-Me	4g	40	93	218-220	220-222 ^[11]
8	4-Ome	4h	40	90	198-200	201-202 ^[12]
9	2-Furyl	4i	45	91	219-221	220-223 ^[11]
10	4-Cl	5a	25	95	240-242	241-243 ^[13]
11	2,4-dichloro	5b	30	93	224-225	224-225 ^[14]
12	4-NO ₂	5c	25	95	237-238	235-236 ^[12]
13	3-NO ₂	5d	25	94	200-202	201-202 ^[12]
14	4-H	5e	35	90	214-217	213-215 ^[15]
15	4-Me	5f	40	92	213-216	214-216 ^[15]
16	4-OH	5g	40	90	235-238	234-236 ^[12]
17	2-Furyl	5h	45	90	198-200	199-200 ^[15]

^a Reaction conditions: aldehyde (1 mmol), malononitrile (1 mmol), dimedone or 1,3-cyclohexadione (1 mmol); catalyst: nanocatalyst (20 mg); temp: 50 °C; ethanol (2 mL).

^b All compounds are known and their structures were established from their spectral data and melting points as compared with authentic samples or literature values. ^c The yields refer to isolated products.

In order to demonstrate the scope of this new efficient methodology, the optimized reaction conditions were developed to another activated C-H acidic 1,3-diketone, 1,3-cyclopentadione (**6a**) and ethyl acetoacetate (**6b**), at the next stage. The results are summarized in Table 3. Again, almost quantitative yields were obtained for the desired products (**7a-j**) under the optimized conditions.

Table 3. Three-component synthesis of different 2-amino-5-oxo-4*H*-benzo[*b*]pyrans (**7a-j**) via condensation of various aldehydes (**1**), malononitrile (**2**), 1,3-cyclopentadione (**6a**) and ethyl acetoacetate (**6b**).^a



Entry	R	Product ^b	Time (min)	Yield ^c (%)	Mp (°C) Found	Mp (°C) Reported
1	4-Cl	7a	5	96	232-235	234-237 ^[16]
2	4-Br	7b	5	94	212-214	213-215 ^[16]
3	4-Cl	7c	15	97	174-175	172-174 ^[17]
4	4-Br	7d	15	97	262-265	262-263 ^[17]
5	4-NO ₂	7e	15	96	175-177	176-178 ^[18]
6	3-NO ₂	7f	15	96	224-226	225 ^[9]
7	4-H	7g	20	92	187-189	191-192 ^[17]
8	4-Me	7h	20	94	280-282	280-282 ^[17]
9	4-OH	7i	25	94	274-277	274-275 ^[17]
10	2-Furyl	7j	25	90	273-274	274-275 ^[17]

^a Reaction conditions: aldehyde (1 mmol), malononitrile (1 mmol), 1,3-cyclopentadione or ethyl acetoacetate (1 mmol); catalyst: nanocatalyst (20 mg); temp: 50 °C; ethanol (2 mL). ^b All compounds are known and their structures were established from their spectral data and melting points as compared with authentic samples or literature values. ^c The yields refer to isolated products.

Conclusion

In summary, cellulose-supported nanocomposite has been demonstrated as an efficient and environmentally benign catalyst for the multicomponent synthesis of 2-amino-4*H*-chromene derivatives. This protocol further demonstrates in avoiding hazardous organic solvents and toxic catalysts, reusability of the catalyst, increasing yields, reducing reaction time, and streamlining high-throughput chemistry. The mildness, experimental convenience and compatibility are also the key advantages which make this method a superior alternative to the existing protocols.

Acknowledgements

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