



Catalyst-free and solvent-free visible light irradiation-assisted Knoevenagel–Michael cyclocondensation of aryl aldehydes, malononitrile, and resorcinol at room temperature

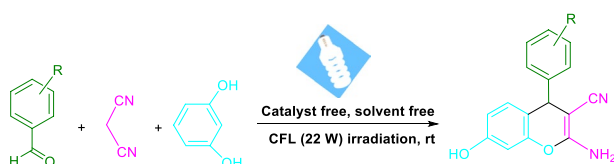
Farzaneh Mohamadpour¹

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Abstract

Catalyst-free and solvent-free three-component tandem approach can synthesize 2-amino-4*H*-chromene scaffolds by Knoevenagel–Michael cyclocondensation of aryl aldehydes, malononitrile, and resorcinol via visible light irradiation as a green promoter at room temperature. The significant advantages of the present protocol include energy-effectiveness, catalyst-free, excellent yields, solvent-free, operational simplicity, and high atom-economy, commercially accessible inexpensive preliminary substances, so it meets some features of sustainable and green chemistry.

Graphic abstract



Keywords Catalyst-free · Solvent-free · Visible light irradiation · 2-Amino-4*H*-chromene scaffolds

Introduction

Given the increased requests for influential, sustainable, and eco-friendly synthesis methods in catalyst and solvent free, green chemistry use has been very useful for preparing the organic mixtures over the last years due to low expense, easy workup, low pollution, and precluding the catalyst and solvent effect on substrates. In addition, visible light irradiation has been a reliable approach for green chemists because of its plentiful reserves of the energy, low cost and its renewable source of energy in the eco-friendly synthesis of organic compounds [1, 2]. In general, we employed light emitting diodes and compact fluorescent lights as the sources of visible light for various transformations.

We report 4*H*-chromenes with various pharmacological features as (Fig. 1) antiallergenic [3, 4], antimicrobial [5], antifungal [6], anti-inflammatory [7], antibacterial [8], antioxidant [9], antileishmanial [10], anti-HIV [11, 12], anticancer [13, 14], and hypotensive [15]. Some of these compounds could also be used as inhibitors [16, 17].

Many approaches are accessible such as glycine [18], mesolite [19], potassium phthalimide [20], MgFe₂O₄NPs [21], POM@Dy-PDA [22], P4VPy-CuI [23], nanozeolite clinoptilolite [24], water extract of lemon fruit shell ash (WELFSA) [25], tungstic acid functionalized SBA-15 [26], MIL-101(Cr)-SO₃H [27], [Et₂NH(CH₂)₂CO₂H][AcO] [28], and {[4,4'-BPyH][C(CN)₃]₂} [29].

The reported procedures may result in several cases. Some of synthetic policies include restrictions regarding metal catalyst, the expensive reagents, intense reaction conditions, uniform training process, environmental hazard, and long reaction time.

✉ Farzaneh Mohamadpour
mohamadpour.f.7@gmail.com

¹ School of Engineering, Apadana Institute of Higher Education, Shiraz, Iran

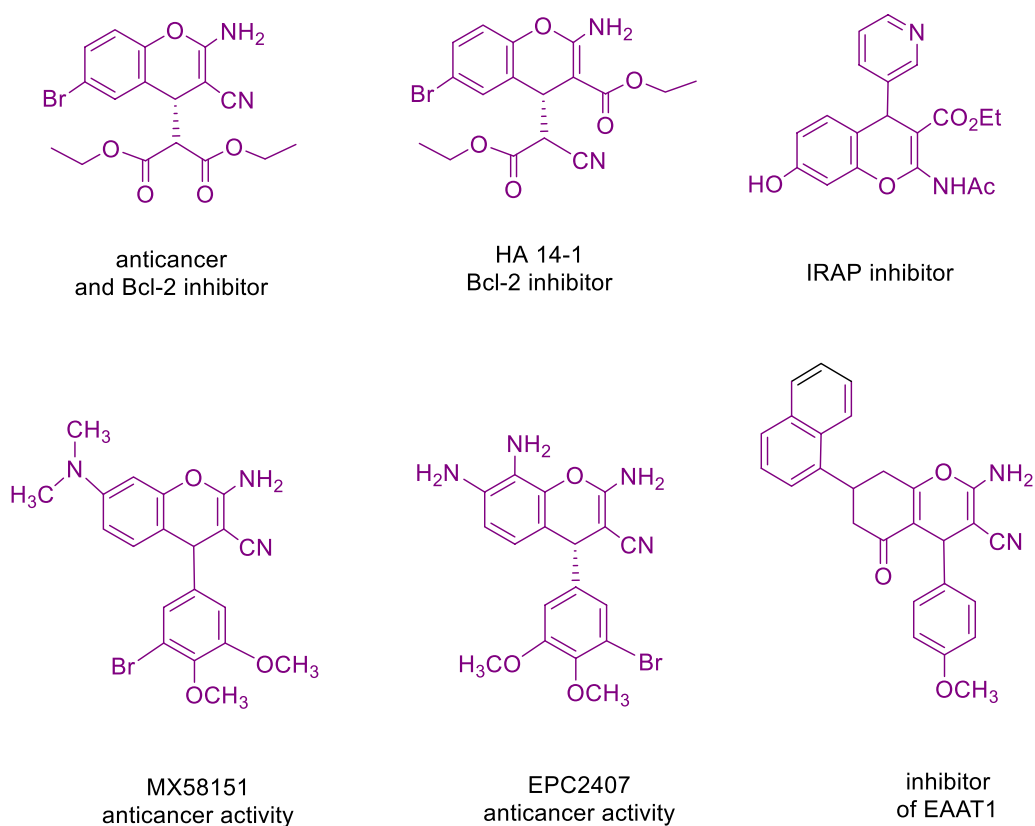


Fig. 1 Some medicinally important compounds containing chromene motifs

Table 1 Optimization of the solvent on the synthesis of **4a**

Entry	Solvent	Time/min	Isolated yield/%
1	EtOH	20	61
2	H ₂ O	20	73
3	MeOH	30	55
4	H ₂ O/EtOH (1:1)	20	68
5	Solvent free	20	92
6	EtOAc	40	34
7	DMF	55	28
8	THF	60	36
9	CHCl ₃	75	25
10	DCM	75	21
11	CH ₃ CN	60	64
12	DMSO	40	52

Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), and resorcinol (1 mmol) in 3 cm³ solvent in the presence of CFL (22 W) irradiation under catalyst-free circumstances at rt

Table 2 Optimization of the CFL on the synthesis of **4a**

Entry	Reaction conditions	Time/min	Isolated yield/%
1	CFL (18 W)	20	73
2	CFL (20 W)	20	84
3	CFL (22 W)	20	92
4	CFL (23 W)	20	92
5	CFL (32 W)	20	92

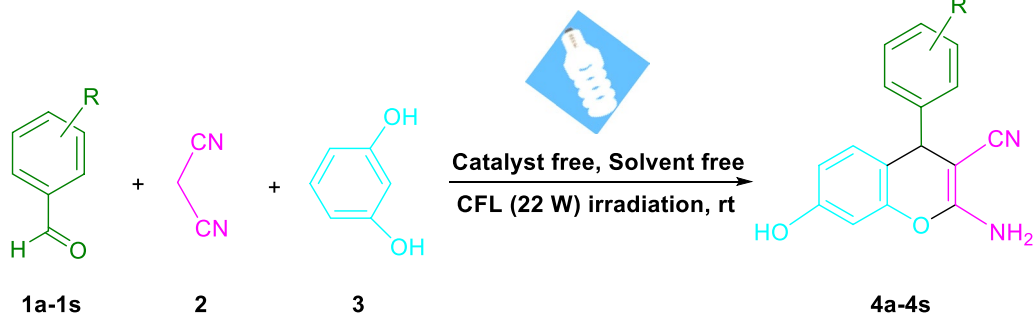
Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), and resorcinol (1 mmol) in the presence of CFL irradiation under catalyst and solvent free conditions at rt

Searching for simple, effective, and eco-safe strategies, which, under green circumstances, can increase organic reactions has fascinated many researchers due to the mentioned difficulties and our considerations for on environmentally benign protocols [30–32]. Therefore, we report the catalyst-free and solvent-free synthesis of 2-amino-4*H*-chromene scaffolds with the CFL irradiation as green endorsing media at room temperature via tandem Knoevenagel–Michael cyclocondensation of aryl aldehydes, malononitrile, and resorcinol which can provide short reaction times and the anticipated products in excellent yields to overcome some expense problems in industry.

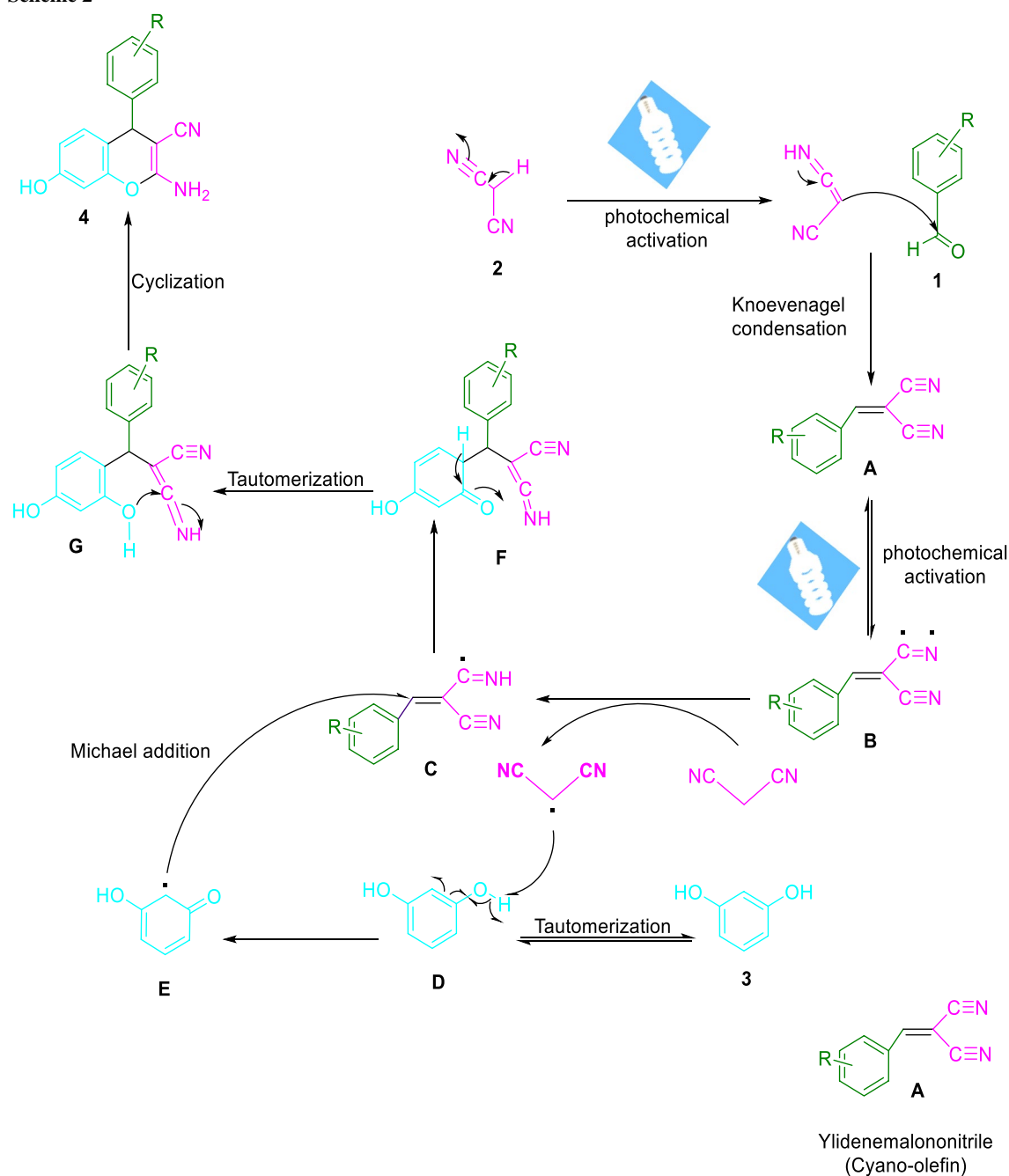
Table 3 Catalyst and solvent free synthesis of 2-amino-4*H*-chromene scaffolds

Entry	Ar	Product	Time/min	Yield/% ^a	M.p./°C	Lit. m.p./°C
1	C ₆ H ₅	4a	20	92	231–233	232–234 [23]
2	4-Me-C ₆ H ₄	4b	15	94	184–186	186–188 [24]
3	3-O ₂ N-C ₆ H ₄	4c	15	88	166–168	168–170 [28]
4	4-Br-C ₆ H ₄	4d	30	81	223–225	222–224 [20]
5	2-Cl-C ₆ H ₄	4e	20	84	187–189	189–191 [23]
6	3-OMe-C ₆ H ₄	4f	25	89	182–184	180–182 [29]
7	4-F-C ₆ H ₄	4g	10	94	187–189	188–190 [23]
8	4-OH-C ₆ H ₄	4h	30	82	251–253	250–252 [19]
9	4-Cl-C ₆ H ₄	4i	30	82	163–165	162–163 [23]
10	4-O ₂ N-C ₆ H ₄	4j	15	85	167–169	166–168 [19]
11	3-F-C ₆ H ₄	4k	10	92	150–152	148–150 [25]
12	4-OMe-C ₆ H ₄	4l	25	86	211–213	210–212 [25]
13	3-OH-C ₆ H ₄	4m	30	80	217–219	219–221 [29]
14	2-Me-C ₆ H ₄	4n	10	93	229–231	228–231 [21]
15	2-Furanyl	4o	15	94	192–194	190–192 [28]
16	3,4-(OMe) ₂ -C ₆ H ₃	4p	30	90	228–230	227–229 [29]
17	4-(Me ₂ N)-C ₆ H ₄	4q	15	90	194–196	194–196 [20]
18	2-Thienyl	4r	15	91	212–214	210–212 [20]
19	2,4-(Cl) ₂ -C ₆ H ₃	4s	30	87	255–257	257–259 [23]

^aIsolated yield

Scheme 1

Scheme 2



Results and discussion

At first, Table 1 shows the results of the reaction between benzaldehyde (1 mmol), malononitrile (1 mmol), and resorcinol (1 mmol) in different solvents under catalyst-free conditions opposite compact floating lamp radiation (CFL (22 W)) at room temperature. Accordingly, a small

amount of EtOH, H₂O, MeOH, H₂O/EtOH (1:1), EtOAc, DMF, THF, CHCl₃, DCM, CH₃CN, and DMSO products was found. Extraordinary improvements were clear under solvent-free conditions (Table 1, entry 5). In addition, by changing the intensity of CFL (18 W, 20 W, 22 W, 23 W, and 32 W) irradiation, the optimized conditions were defined. According to Table 2, the best results were opposite the

Table 4 Comparison of the catalytic ability of some of the catalysts in the manuscript for producing of 2-amino-4*H*-chromene scaffolds

Entry	Catalyst	Conditions	Time/yield/%	References
1	Glycine	H ₂ O, Sonication	9 min/94	[18]
2	Mesolite	EtOH, reflux	30 min/93	[19]
3	Potassium phthalimide	Ball milling, rt	15 min/94	[20]
4	MgFe ₂ O ₄ NPs	EtOH, 65 °C	12 min/74	[21]
5	POM@Dy-PDA	H ₂ O/EtOH, reflux	15 min/95	[22]
6	P4VPy-CuI	H ₂ O, reflux	15 min/94	[23]
7	Tungstic acid functionalized SBA-15	H ₂ O, 100 °C	12 h/86	[26]
8	MIL-101(Cr)-SO ₃ H	H ₂ O, 100 °C	3 h/82	[27]
9	[Et ₂ NH(CH ₂) ₂ CO ₂ H][AcO]	Solvent-free, 60 °C	12 min/92	[28]
10	[4,4'-BPYH][C(CN) ₃] ₂	Solvent-free, 80 °C	15 min/90	[29]
11	Catalyst-free	Solvent-free, CFL (22 W) irradiation, rt	20 min/92	This work

Based on the three-component reaction of benzaldehyde, malononitrile, and resorcinol

compact fluorescent lamp (CFL (22 W)) irradiation (Table 2, entry 3). Using CFL (22 W) irradiation without further catalyst, an 92% yield was established under solvent-free conditions. Table 3 and Scheme 1, shows that its functionality with different substrates.

Scheme 2 shows the suggested mechanism for synthesizing 2-amino-4*H*-chromene scaffolds. The reaction was encouraged by creating an inclusion the radical intermediate ylidene-malononitrile (cyano-olefin) **B** was readily created in situ from Knoevenagel condensation between aryl aldehyde **1** and active methylene compound **2** in the presence of visible light irradiation. This can be demonstrated by the aryl aldehydes' steric influences on the reaction effectiveness (Table 3). Intermediate **B** absorbs one hydrogen from methylene malononitrile, thereby converting malononitrile to a radical malononitrile, consequently, it consists of intermediate **C**. Then, malononitrile radical absorbs one hydrogen from form **3** and converts it to form intermediate **E**. Intermediate **E** attacks to intermediate **C** as Michael acceptor to give **F** that after tautomerizing and cyclizing affords the target products **4**. Comparison of the catalytic capacity of a number of catalysts referred to in the present paper for the production of 2-amino-4*H*-chromene scaffolds has been shown in Table 4. It may find a wide range of applications, such as the use of the short reaction time without any by-products under catalyst and solvent free conditions. The marvelous atom-economic protocol is effective on a multi-gram scale and has important industrial applications. These products achieve both excellent performance and excellent purity. Moreover, avoiding the hazardous reaction circumstances, simple experimental and easy work-up procedures with no necessity of chromatographic purification steps are the notable advantages of this green and convenient protocol. In addition, one key characteristic of the existing work is to use CFL irradiation as green endorsing media sufficiently remarking the rising potential of CFL irradiation in organic synthesis.

Conclusion

The study indicated a catalyst and solvent free preparation of 2-amino-4*H*-chromene scaffolds—a biologically significant scaffold—via visible light irradiation as a low cost and green promoter at room temperature according to the principles of green chemistry. The important points in the current study include the use of non-hazardous reaction circumstances, catalyst-free, application of cheap initiating substances, operational simplicity, solvent-free, separation of the pure product by easy filtration thus avoids the need for column chromatography, efficient features of the reaction, excellent yields, metal-free, one key characteristic of the existing work is to use CFL irradiation as green endorsing media sufficiently remarking the rising potential of CFL irradiation in organic synthesis.

Experimental

Using a 9100 electro-thermal device, the melting points of all compounds were found. In addition, the nuclear magnetic resonance recording, the spectrum (¹H NMR) was performed on a Bruker (DRX-300) instruments using DMSO-*d*₆ as solvent. All reagents were purchased from the chemical companies called Fluka, Merck, and Acros and used without additional treatment.

Overall process of preparing 4a–4s

A mixture of aryl aldehyde derivatives (**1**, 1.0 mmol), malononitrile (**2**, 1.0 mmol), and resorcinol (**3**, 1.0 mmol) was reacted in the presence of CFL (22 W) irradiation as a green promoter under catalyst and solvent free conditions at room temperature (Scheme 1). The reaction progress was

monitored by TLC utilizing ethylacetate/*n*-hexane (7:3) as an eluent. After completing the reaction, the achieved solid was filtered, rinsed with water and the crude solid was recrystallized from ethanol to provide the pure material without requiring more purification. The products were classified after the comparison of spectroscopic information (^1H NMR). Support for this manuscript can be found in the online version.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00706-021-02763-1>.

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