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Et_3N as a catalyst for the synthesis of indeno[1,2-*b*]chromene derivatives *via* three-component condensation reaction

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ABSTRACT

Functionalized indeno[1,2-*b*]chromene derivatives have been synthesized *via* condensation reaction of 1*H*-indene-1,3(2*H*)-dione with benzaldehyde and cyclization with 2-hydroxynaphthalene-1,4-dione in the presence of a catalytic amount of triethylamine (Et_3N) in EtOH at room temperature. It was observed that benzaldehyde bearing electron donating group gave high yield of product, whereas, benzaldehyde having electronic withdrawing substituent does not participate in this reaction. The structures were confirmed spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and Mass). A plausible mechanism for this reaction is proposed (Scheme 2). Good yields and easy purification are the main advantages of the present method. Products of these reactions have structural similarity to naturally occurring pyranokunthone B, lambertellin**,** β-lapachone, and α-xiloidone.

***Keywords**: Indeno[1,2-b]chromene, Condensation reaction, 1H-Indene-1,3(2H)-dione, 2-Hydroxynaphthalene-1,4-dione.*

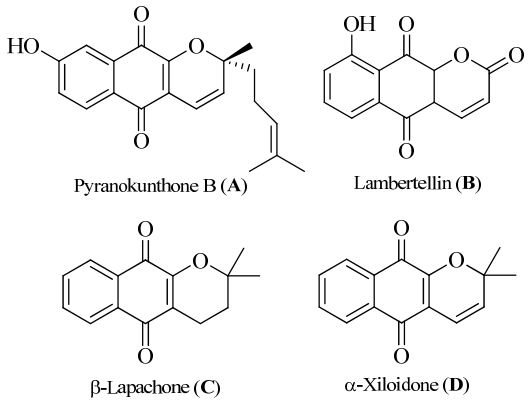
1. Introduction

Naturally occurring chromenes show biological activities including anti-cancer [1-2], anti inflammatory [3], antimalarial [4-5] and pesticides activities [6]. This moiety is core fragment of different natural products including pyranokunthone B (A), lambertellin (B), β-lapachone (C), α-xiloidone (D) (Scheme 1) [7-10]. Because of broad pharmacological activities of chromenes, different synthetic methods have been introduced by different research groups [11-16].

Several syntheses have been reported for chromene core structure, which includes catalytic Petasis reaction of salicylaldehydes [11], $RuBr_2(PPh_3)_4$ catalyzed ring closure [12], base [13], L-proline [14], PEG-SO_3H [15], and periodic mesoporous silica chloride (PMSCl) [16] catalyzed reaction, electrocyclic ring closure of vinylquinone derivatives [17], and isocyanide-based multicomponent reactions [18]. Usually, these synthetic approaches include a multi-step procedure. A semi-synthetic method has been introduced, too [19].

Multi-component reactions (MCRs), due to their productivity, simple procedures, convergence, and facile execution, are one of the best tools in combinatorial chemistry. The design of novel MCRs have attracted great attention from research groups working in areas such as drug discovery, organic synthesis and materials science [20-21].

Considering the above reports, and as part of our program aimed at developing new methodology for the preparation of heterocyclic compounds [18, 22-24], we undertook the synthesis of chromene derivatives through a multi-component reaction.



Scheme 1. Some biologically active chromenes.

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2. Experimental

2.1. General

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a Shimadzu spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}CNMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz. NMR spectra were obtained in DMSO-d_6. The chemicals used, were purchased from Merck and Fluka Chemical Companies.

*2.2. Typical procedure for the synthesis of 12-o-tolylbenzo [g] indeno [1,2-b] chromene - 6, 11, 13 (12H) - trione (**4c**)*

1*H*-indene-1,3(2*H*)-dione (**1**, 1 mmol, 0.17 g) has been reacted with 2-metylbenzaldehyde (**2c**, 1 mmol, 0.12 g) in EtOH (5 mL) in the presence of a triethylamine (0.02 g, 20 mol%). Reaction mixture was stirred for 2 h at room temperature. Then, 2-hydroxynaphthalene-1,4-dione (**3**, 1 mmol, 0.17 g) has been added to reaction media. The reaction mixture was stirred for 24 h. After completion of reaction (monitored by TLC method), precipitated product has been separated by filtration.

Selected spectral data

*12- (4- Methoxyphenyl) benzo [g] indeno [1,2-b] chromene- 6,11,13(12H)-trione (**4a**)*

Orange powder (0.31 g, yield 74%). m.p.= 234 °C (dec). IR (KBr): $\bar{\nu}$ = 1669, 1601, 1565, 1350 cm^{-1}. MS (%):m/z= 420 (M$^+$, 2), 384 (25), 342 (20), 313 (10), 261 (17), 231 (23), 191 (20), 171 (50), 133 (25), 105 (100), 86 (90), 50 (50). ^{1}HNMR (300 MHz, DMSO-d_6): δ= 3.88 (3H, s, OCH_3), 6.17 (1H, s, CH), 6.72-8.60 (12H, m, aromatic) ppm.

*12-m-tolylbenzo [g] indeno [1,2-b] chromene-6, 11, 13 (12H)- trione (**4b**)*

Orange powder (0.29 g, yield 71%). m.p.= 238 °C (dec). IR (KBr): $\bar{\nu}$ =1714, 1685, 1613, 1558 cm^{-1}. MS (%):m/z = 404 (M$^+$, 8), 387 (75), 376 (15), 313 (15), 300 (45), 207 (30), 171 (15), 149 (45), 128 (10), 105 (20), 91 (60), 70 (10), 44 (100). ^{1}HNMR (300 MHz, DMSO-d_6): δ= 2.15 (3H, s, CH_3), 5.60 (1H, s, CH), 6.73-8.87 (12H, m, aromatic) ppm.

*12-o-tolylbenzo [g] indeno [1,2-b] chromene- 6, 11, 13 (12H) -trione (**4c**)*

Orange powder (0.27 g, yield 68%). m.p.= 246 °C (dec). IR (KBr): $\bar{\nu}$ = 1722, 1672, 1606, 1562 cm^{-1}. MS (%): m/z= 404 (M$^+$, 4), 384 (75), 313 (15), 356 (20), 287 (20), 207 (25), 171 (10), 149 (15), 128 (22), 105 (17), 70 (10), 44 (100). ^{1}HNMR (300 MHz, DMSO-d_6): δ= 2.07 (3H, s, CH_3), 5.75 (1H, s, CH), 6.51-8.94 (12H, m, aromatic) ppm. ^{13}CNMR (75 MHz, DMSO-d_6): δ= 20.1 (CH_3), 33.0 (CH), 109.7, 113.5, 117.3, 122.6, 125.3, 125.5, 125.6, 126.2, 127.4, 128.9, 130.0, 130.5, 130.9, 131.4, 132.4, 133.5, 134.3, 135.8, 135.9, 140.5, 151.3, 151.5 (C-alkene and aromatic), 172.9, 182.6, 183.9 (C=O) ppm.

*12- (2-Hydroxyphenyl) benzo [g] indeno [1,2-b] chromene-6,11,13(12H)-trione (**4d**)*

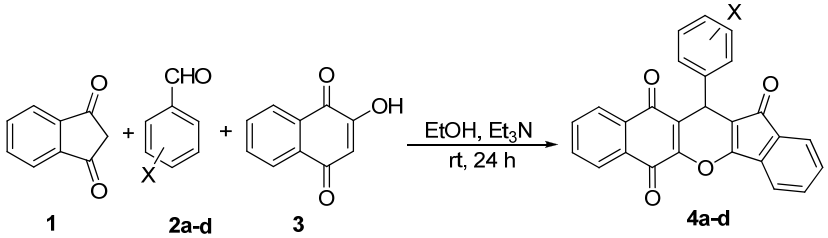
Reddish orange powder (0.30 g, yield 75%). m.p.= 215°C (dec). IR (KBr): $\bar{\nu}$ =3450, 1760, 1711, 1607, 1573 cm^{-1}. MS (%):m/z = 405 (M$^+$-1, 5), 372 (25), 344 (5), 314 (8), 287 (20), 171 (20), 143 (10), 104 (100), 76 (50), 50 (20). ^{1}HNMR (300 MHz, DMSO-d_6): δ= 5.60 (1H, s, CH), 7.15-8.99 (12H, m, aromatic), 11.40 (1H, bs, OH) ppm.

3. Results and Discussion

In the present study we report our results on the three-component reaction (3-MC) of 1*H*-indene-1,3(2*H*)-dione (**1**), aldehyde **2** and 2-hydroxynaphthalene-1,4-dione (**3**) into the substituted indeno[1,2-*b*]chromene derivatives **4a-c** (Scheme 2).

First, to evaluate the synthetic potential of the procedure proposed and to optimize the general conditions, the base initiated 3-MC of 1*H*-indene-1,3(2*H*)-dione (**1**), 4-methoxy benzaldehyde (**2a**) and 2-hydroxynaphthalene-1,4-dione into 2-amino-4H-chromene **4a** in EtOH as a solvent was studied (Table 1). A variety of catalysts were first examined, and the results are collected in Table 1. There was no reaction in the absence of the catalysts (Table 1, entry 1). In the presence of ^{i}Pr$_2$NEt, piperidine, pyridine, K_2CO_3 or NaOAc in EtOH, the reactions became sluggish (Table 1, entries 5-9).

Different solvents were also tested in the presence of Et_3N as a catalyst, for example, EtOH, CH_3OH, CH_3N, CH_2Cl_2, and H_2O but unfortunately they resulted in low yields (Table 2, entries 3-6).



Scheme 2. Synthesis of indeno[1,2-*b*]chromenes *via* 3-CR.

Table 1. Investigation of catalyst in reaction yields.[a]

Entry	Base (0.2 mmol)	Time (h)	Yield (%)
1	-	24	-
2	Et_3N (0.1 mmol)	24	40
3	**Et_3N**	**24**	**74**
4	Et_3N (0.3 mmol)	24	73
5	$^{i}Pr_2NEt$	24	45
6	Piperidine	24	52
7	Pyridine	24	48
8	K_2CO_3	24	trace
9	NaOAc	24	trace

[a]4-Methoxybenzaldehyde (1 mmol), 1*H*-indene-1,3(2*H*)-dione (1 mmol), and 2-hydroxynaphthalene-1,4-dione (1 mmol) in EtOH as a solvent.

Table 2. Investigation of solvent effect in reaction yield.[a]

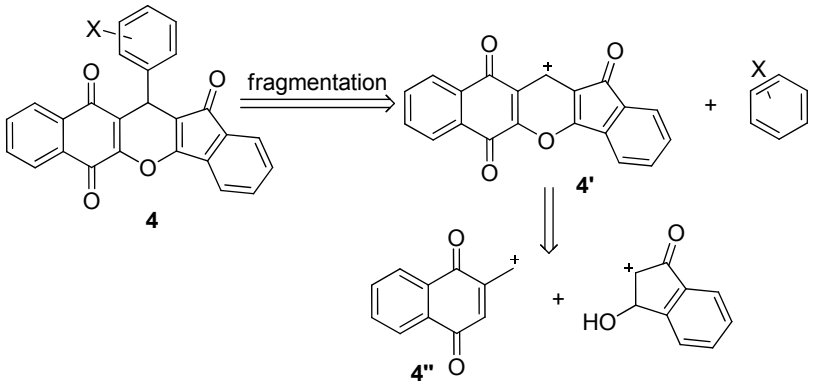
Entry	Solvent	Temp (°C)	Time (h)	Yield (%)
1	**EtOH**	**rt**	**24**	**74**
2	EtOH	78	24	75
3	CH_3OH	rt	24	63
4	CH_3CN	rt	24	40
5	CH_2Cl_2	rt	24	23
6	H_2O	rt	24	trace

[a]4-Methoxybenzaldehyde (1 mmol), 1*H*-indene-1,3(2*H*)-dione (1 mmol), and 2-hydroxynaphthalene-1,4-dione (1 mmol) in the presence of Et_3N (0.2 mmol) as a catalyst.

This results show that, protic organic solvents can participate in hydrogen bonding, which is active aldehyde for nucleophilic attack by anion **1′** (Scheme 3).

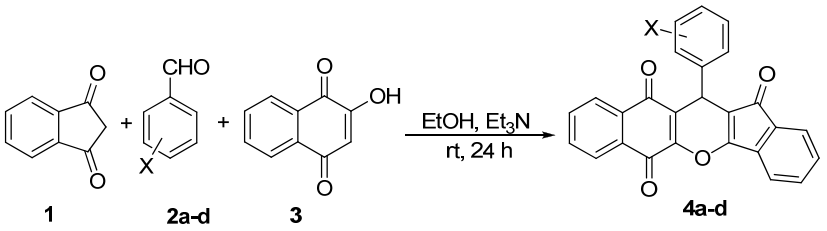
The yields of **4a** were not further improved with increased temperature of reaction (Table 2, entries 2). Thus, it is clear from the experiments that the best condition for the synthesis of **4a** could be entry 1, employing Et_3N (20 mol%) as a base and EtOH as a solvent at room temperature.

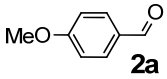
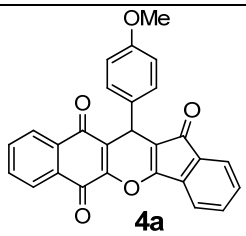
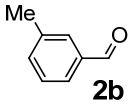
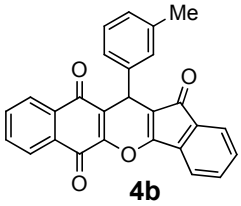
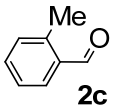
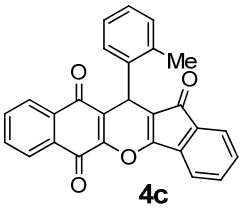
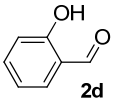
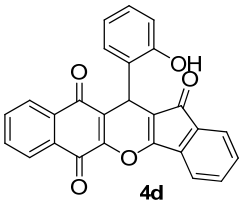
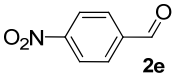
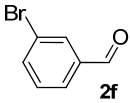
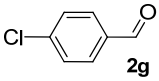
We have studied the electronic effect of the substituent on the reaction. It was observed that benzaldehyde bearing electron donating group (Table 3, entries 1-4) gave high yield of product, whereas, benzaldehyde having electronic withdrawing substituent does not participate in this 3-RC (Table 3, entries 5-7).



Scheme 3. The similar fragments of compounds **4a-d.**

Table 3. Synthesis of indeno[1,2-*b*]chromene derivatives.



Entry	Aldehyde	Product	Yield (%)
1	 **2a**	 **4a**	74
2	 **2b**	 **4b**	71
3	 **2c**	 **4c**	68
4	 **2d**	 **4d**	75
5	 **2e**	N.R.	-
6	 **2f**	N.R.	-
7	 **2g**	N.R.	-

The structures of compounds **4a-d** were deduced from their IR, mass, ^{1}H NMR, and ^{13}C NMR spectral data.

For example, the ^{1}H NMR spectrum of **4c** exhibited a singlet for methyl protons at 2.07, a singlet for CH at 5.75 and a multiplet for the aromatic protons (12 H) at 6.51-8.94 ppm. The mass spectra of these compounds displayed similar fragments of the suggested structures at appropriated m/z values (Scheme 3), for example, in the fragmentations of all compounds were observed similar peaks at 313 and 171 m/z.

Although the mechanism of this reaction hasn't been investigated experimentally, it could be assumed that

in the first step, a condensation reaction could occur between an aldehyde (**2**) and 1*H*-indene-1,3(2*H*)-dione (**1**). Such an intermediate **5** could be attacked by 2-hydroxynaphthalene-1,4-dione (**3**). After intramolecular cyclyzation and subsequently dehydration of intermediate **6**, desired products **4a-d** could be produced (Scheme 4).

In comparison with other catalysts in use for the synthesis of chromene core structre (**4a-d**) under different conditions, showed more catalytic reactivity than the others in terms of reaction time and simplified conditions (Table 4).

4. Conclusions

In conclusion, we have developed an efficient synthetic approach for the synthesis of the functionalized indeno[1,2-*b*]chromene derivatives from readily available substrates in good yields. The advantages of the presented procedures are as following: i) the reactions are performed by simple mixing of the starting materials at room temperature; ii) workup procedure is very easy and products could be separated from reaction media with simple filtration; iii) variety of products could be produced by a simple procedure; iv) the products contain biologically active moieties which increases the value of the products and the proposed procedure. We hope this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry.

Acknowledgment

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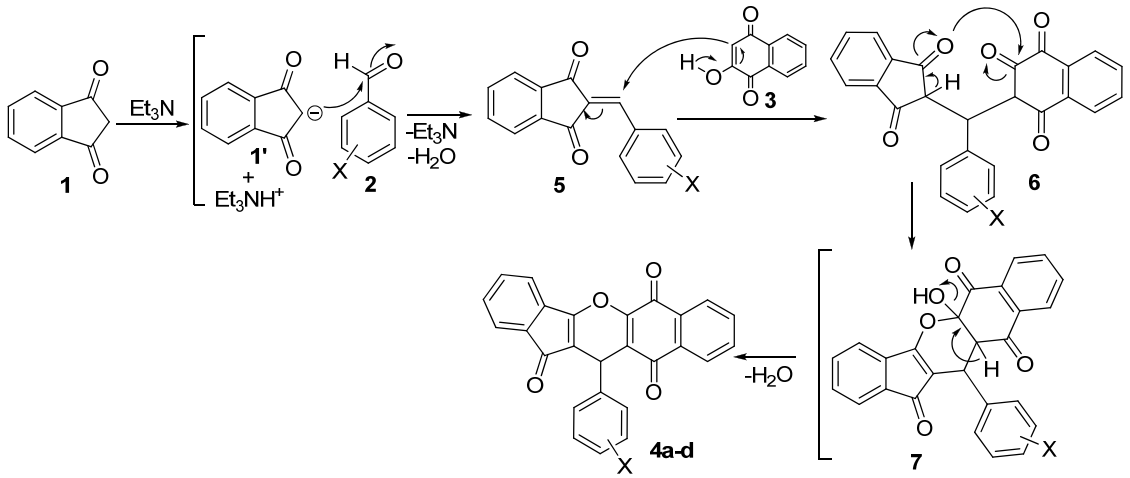

Scheme 4. Proposed mechanism pathway.

Table 4. The synthesis of chromene core structre under different conditions.

Entry	Catalyst (mol %)	Solvent	Temp (°C)	Time (h)	Yield (%)	Ref.
1	PEG-SO3H (10)	-	80	10	74-91	[15]
2	PMSCl (7)	-	130	1	82-94	[16]
3	$RuBr_2(PPh_3)_4$ (5)	MeOH	Reflux	1	75-87	[12]
4	Piperidine (5)	CH_2Cl_2	-15	48	61-85	[13]
5	**Et_3N (2)**	**EtOH**	**rt**	**24**	**68-75**	**This work**

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