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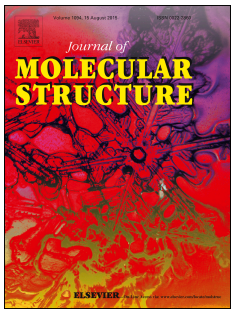

An eco-friendly approach for synthesis of novel substituted 4H-chromenes in aqueous ethanol under ultra-sonication with 94% atom economy

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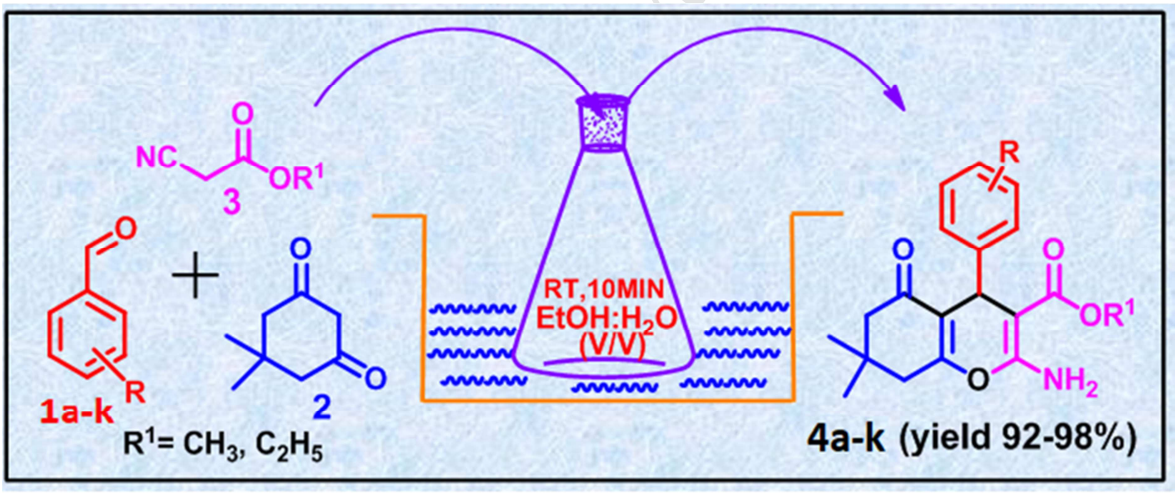
Graphical Abstract:



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Abstract

An operational approach for synthesis of eleven substituted 4*H*-chromene derivatives by one-pot, three-component reaction of aromatic aldehyde, methyl cyanoacetate and cyclic diketone through ultrasound irradiation, in the presence of aqueous ethanol under catalyst-free condition is reported. Different spectral methods, including ^{1}H, ^{13}C and ^{15}N NMR and HRMS were utilized to characterize the new molecules. Benefits of the eco-friendly method are fast reaction (10 min), excellent yields (92-98%), no column chromatography and no byproducts. Reaction offers 94% atom economy and 100 % carbon capture.

Keywords: Green synthesis; Heterocyclic compounds; Multicomponent reaction; Ultra sonication; atom efficiency

1. Introduction

Several investigations emphasized on novel synthetic organic approaches and prominence of one-pot multi-component reactions (MCRs) [1-3]. MCRs play a enormous role in the biological discovery, medicinal, pharmaceuticals and agrochemical industries [4,5]. MCRs afford higher chemical yields compared to multistep syntheses, by employing simple protocols, inexpensive reactants and green principles. These reactions, could generate different heterocyclic molecules with high yields, with no need to isolate the reaction intermediates [6,7]. Other advantages of MCRs are reduced reaction times, improved selectivity, simple work procedure, atom economy and scope for use of green solvents [6-8].

These days, green chemistry principles are highly encouraged to minimize environmental pollution, while accomplishing the set goals [8,9]. Advent of ultrasound irradiation has led to vital modifications in synthetic procedures for heterocyclic moieties and allowed the exploration of relatively less reactive substrates. Ultrasound (US) is an effect of acoustic wave cavitation, which accelerates appropriate chemical reactions [10,11]. These waves promulgate through alternating compressions and infrequent faction phases, induced in the assigning liquid, with the expansion cycles using destructive pressure on the liquid [12,13]. This applied destructive pressure is capable to breakdown the intermolecular van der Waals forces of the liquid, creating minor cavities or micro-bubbles [14]. These cavities continuously attract energy from ultrasonic waves and reach a stage, where they can no longer absorb energy and burst [12-14]. These fast and forceful breakdowns produce short-term regions with very high temperature and pressure. This cavitation-induced occurrence is known to activate the reactants inflowing into cavity and subsequently translate them into reaction intermediates.

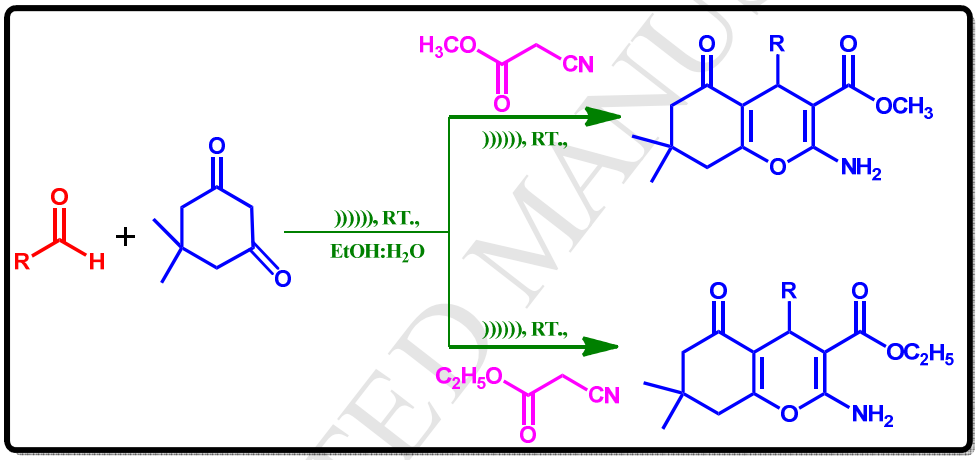
Many studies have been focused on the development of novel heterocyclic frameworks, because of their prominence in therapeutic, pharmacological, biological fields and pivotal role in computational, drug discovery and pharmaceutical industries [15-17]. Among the heterocyclic compounds, the oxygen containing heterocyclic compounds of 4*H*-chromenes or benzopyrans received ample attention, due their unique properties [18]. 4*H*-chromene derivatives form important class of structures, exhibiting notable biological properties, such as anticancer [19], antioxidant [20], antimicrobial [21], anti-mycobacterial [22], Alzheimer [23], anti-inflammatory [24] and antidiabetic [25] activities. Many molecules with chromene moiety display a broad range of pharmacological activities against urinary diseases, asthma, ischemia, blood pressure and central nervous system [26,27]. Literature survey reveals several synthetic approaches for substituted 4*H*-chromene derivatives using different catalysts, including $NbCl_5$ [28], Amberlite IRA-400 Cl [29], mesoporous silica [30], nano ZnO [31], CaO-ZrO_2 nanocomposite oxide [32], bovine serum albumin [33], silica gel supported polyamine [34] and fluoride ion [35], to mention a few. These methods have certain confines like lengthy reaction times, tedious handle approaches, harmful solvents, harsh reaction conditions or low yields. Therefore, the design of new greener and efficient methods for the synthesis of 4*H*-chromene derivatives is well sought after.

Invigorated by the success in preparation of different substituted heterocyclic frameworks [36-38], we have earlier reported green methods for synthesis of few medicinally valuable heterocyclic scaffolds [39,40]. In this communication, we describe the synthesis of functionalized 4H-chromenes, via a three-component/one-pot reaction at the room temperature through ultrasonication.

2. Experimental Section

2.1 Typical procedure for the preparation of 4H-chromenes (4a-j)

2-methoxybenzaldehyde (1 mmol), methyl cyanoacetate (1 mmol) and 5,5 dimethyl 1,3-cyclohexadione (1 mmol) were dissolved in aqueous ethanol in a conical flask (scheme1). The reaction mixture was ultra-sonicated in water bath at room temperature (RT). The reaction progress was monitored by TLC. After completion of the reaction, the residue was concentrated under vacuum. With no further purification needed, the target product was obtained. All the reaction products were characterised and confirmed by different spectral techniques. The experimental details and product characterization data (4a-k) are summarised in ESI



Scheme 1: Three-component ultra wave assisted synthesis of 4H-chromene derivatives

3. Results and Discussion

In initial experiments, 2-methoxybenzaldehyde (1.0 mmol), methyl cyanoacetate (1.0 mmol) and dimedone (1.0 mmol) taken in 1:1 EtOH/H_2O (v/v) were reacted at RT, under silent and ultrasound irradiation conditions and the efficacy of reaction was also investigated with different solvents, catalysts, and reaction times. The model reaction was performed with no catalyst or solvent at RT. No reaction occurred even after long time (Table 1, entries 1 and 2). Next, the model reaction was conducted at RT without any catalyst, but in presence of a different

of polar or non-polar solvents like n-hexane, toluene DMF, THF, CH_3CN, EtOH or MeOH. Table 1, entries 3-9 summarize the obtained results. Reaction gave impressive results in equal mixture of EtOH and H_2O with high yield of the anticipated product under US condition(Table 1, entry 10). To enhance the yield, the model reaction was investigated in the presence of EtOH and H_2O, with catalysts like $NaHCO_3$, K_2CO_3, TEA and pyridine at RT. All the reactions gave relatively low yields, both under silent and US conditions (Table 1 entries 11-14), proving ultra-sonification in aqueous ethanol is ideal.

Table 1: Optimization of different reaction methods for the formation of 4*H*-chromene derivatives under sonication and conventional conditions*

No	Reagent	Solvent	Without sonication		With sonication	
			Time (h)	Yield (%)	Time (h)	Yield (%)
1	No Catalyst	no solvent	12.0	--	6.0	--
2	No Catalyst	no solvent	10.0	--	6.0	--
3	No Catalyst	n-Hexane	10.0	--	4.0	--
4	No Catalyst	Toluene	10.0	--	4.0	--
5	No Catalyst	THF	5.0	5	2.5	13
6	No Catalyst	CH_3CN	5.5	6	3.0	10
7	No Catalyst	DMF	6.0	9	2.5	15
8	No Catalyst	MeOH	3.5	67	2.5	71
9	No Catalyst	EtOH	3.0	71	0.50	84
10	**No Catalyst**	**Aqueous ethanol**	**2.5**	**79**	**0.10**	**98**
11	$NaHCO_3$	Aqueous ethanol	2.5	58	0.50	78
12	K_2CO_3	Aqueous ethanol	2.0	62	0.45	81
13	TEA	Aqueous ethanol	2.0	65	0.50	79
14	Pyridine	Aqueous ethanol	2.0	55	0.45	85

Using the identified optimal reaction conditions, the versatility and substrate scope of the proposed protocol was examined for synthesis of diverse substituted 4*H*-chromenes via choice of varied substituted aromatic aldehydes to react with methyl cyanoacetate and cyclic diketone with aqueous ethanol as solvent (Table 2). An observation the results in Table 2 show that reactions involving all aromatic aldehydes, irrespective of electron withdrawing or donating substituents in ortho, meta and para positions, participated in the reaction smoothly, affording the target

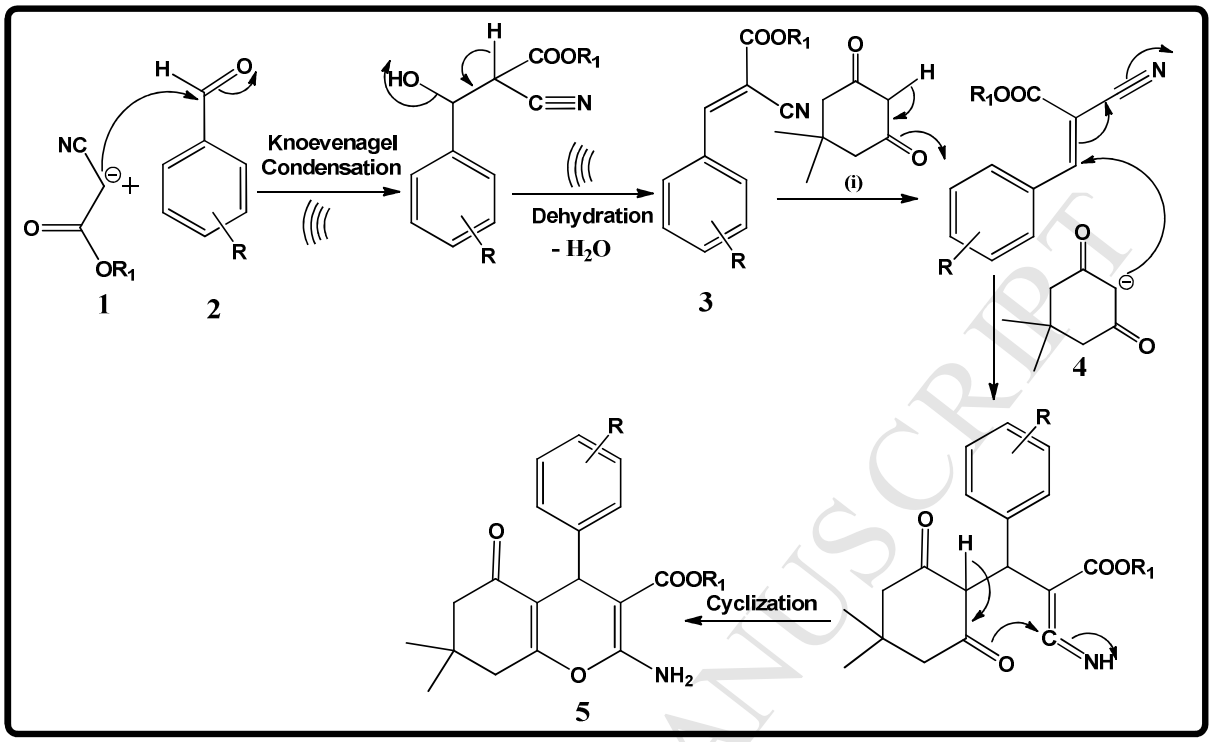
molecules with excellent yields. No byproducts were observed. The structures of all newly synthesized molecules (4a-k) were confirmed by appropriate spectral techniques. All the characterization related spectral data is incorporated in the supplementary material file.

The probable reaction mechanism for the formation of 4*H*-cromene derivatives under ultrasound irradiation is demonstrated in scheme 2. In the primary step, through the Knoevenagel condensation [2,3] between aromatic aldehyde and methyl cyanoacetate, formation of an intermediate, cyanophenylacrylate is predicted. In the next step, cyanophenylacrylate participate in Michel addition, and react with active methylene moiety to build the corresponding intermediate, which finally undergoes intramolecular cyclisation [9] to afford the anticipated functionalized 4*H*-chromene derivative.

Table 2: Preparation of new 4*H*-chromene derivatives in aqueous ethanol as solvent using US

Entry	R	Product	Yield (%)	Mp °C	Lit Mp °C
1	2-OMe-C_6H_4	**4a**	98	196-197	--
2	4-OMe-C_6H_4	**4b**	97	205-207	--
3	2,3-OMe-C_6H_3	**4c**	95	186-188	--
4	2,5-OMe-C_6H_3	**4d**	94	218-219	--
5	3-OMe-C_6H_4	**4e**	96	230-231	--
6	2-NO_2-C_6H_4	**4f**	92	211-213	--
7	2-F-C_6H_4	**4g**	96	237-239	--
8	2-OMe,4-OH-C_6H_3	**4h**	95	218-220	--
9	2,3-Cl--C_6H_3	**4i**	92	201-203	--
10	4-CF_3-C_6H_4	**4j**	96	222-224	--
11	3-C_5H_4N	**4k**	95	222-223	--

-- New compounds/no literature available.



Scheme 2: Possible reaction mechanism for formation of 4*H*-chromene derivative.

4. Conclusions:

In the current study, we described a clean and eco-friendly one-pot three-component catalyst free scheme, for ultrasound irradiation assisted synthesis of functionalized 4*H*-chromene derivatives in aqueous ethanol. The effectiveness of the environment-friendly ultrasound technique offering nine novel 4*H*-chromene derivatives in excellent yields (92-98%) is confirmed. The title reaction comprises 94% atom efficiency and 100% carbon capture. Other advantages of the protocol are mild conditions, short reaction times and inexpensive starting materials. This method proves an ideal alternate for synthesis of 4*H*-chromenes with high efficacy.

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HIGHLIGHTS

- Ultrasound synthesis of novel substituted 4*H*-chromene derivatives
- One-pot three component protocol with excellent yields (92-98%).
- 10 derivatives and 8 are new compounds
- Short reaction times (10 min)
- Reaction offers 94% atom economy and 100 % carbon capture.