AN EXPEDITIOUS AND GREEN APPROACH FOR THE SYNTHESIS OF 2-AMINO-4*H*-CHROMENES USING A CATALYST OF NATURAL ORIGIN

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A highly efficient three-component one step system for the synthesis of 2-amino-4H-chromens is developed. Excellent yields were obtained simply by mixing malononitrile, aromatic aldehyde and α-napthol in lemon juice as a catalyst of natural origin and solvent, avoiding using hazardous organic solvents. The main advantages of this method are its green method character, short reaction time and simple workup procedures and the lack of using any metal containing catalysts.

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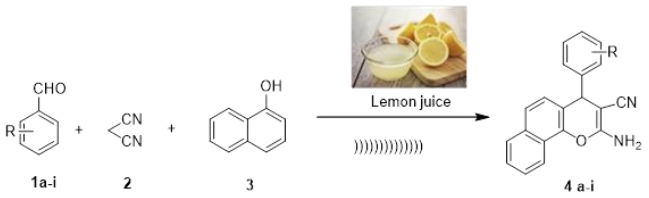
Introduction

Heterocyclic compounds containing chromene moieties are of considerable interest as they are a class of natural and synthetic compounds that possess a great variety of biological as well as pharmaceutical activities.[1–5] Chromene derivatives having a wide range of valuable pharmacological properties, such as diuretic, spasmolytic, analgesic, anticoagulant, anti-anaphylactic, anti-tumor activities.[6–8.] Some among them are extremely effective against such kind of diseases which influenced by nitrogen-activated protein kinase enzyme inhibitors. Some of them have antimicrobial activity ,[11] cytotoxic effect against human cancer cells,[12] antiallergic activity,[13] central nervous system influencing activity,[14] antiproliferation activty.[15] Several derivatives are also widely used as agrochemicals,[16] antioxidant[17] and anti-inflammatory agent.[18].

Literature survey revealed the several reports on one pot three components system for the synthesis of 2-amino-4H-chromenes. This reaction can be catalyzed by both basic as well as by acidic compounds. As acid catalyst can be used heteropoly acids like $H_{14}[NaP_5W_{30}O_{110}]$,[19] methanesulfonic acid (MSA),[20] p-toluenesulfonic acid (PTSA),[21] tungstic acid functionalized mesoporous SBA-15 silica,[22] Fe_3O_4@sulphochitosan nanoparticles (CS-SO_3H NPs),[23] sulfonic acid-functionalized metal-organic frameworks like MIL-101(Cr),[24] etc.

Recently, reactions carried out in green solvent like water have attracted much attention of researchers for environmentally benign. In the continuation of our previous work on the synthesis of 2 amino-4H-chromenes,[25-27] here we report three component one pot synthesis of biologically important substituted 2-amino-4H-chromenes using lemon juice as green catalyst and solvent under ultrasound waves irradiation.



Scheme 1. Synthesis of 2-amino-(substituted phenyl)-4H-benzo[h]chromene-3-carbonitriles

Experimental

All starting materials and chemical reagents were purchased from SD fine chemical company and used without further purification; melting points were determined in open capillaries using electrochemical MK3 apparatus. IR spectra were recorded using Perkin-Elmer FT-IR spectrometer by using KBr pellets, 1H & 13C NMR spectra were recorded on Bruker 250 MHz NMR spectrometer in $CDCl_3$ and chemical shift values were recorded in δ (ppm) by using tetramethylsilane (Me_4Si) as an internal standard.

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

In a single neck round bottom flask, p-methoxy benzaldehyde 1 (1 mmol), malononitrile 2 (1.2 mmol), α-napthol 3 (1 mmol) were taken and in it lemon juice (extract) 10 mL was added and this resulting reaction mixture was irradiated to ultrasound for 20-30 minutes. The progress of reaction was monitored by thin layer chromatography. After completion of reaction, the reaction mixture was poured on crushed ice and the solid obtained was filtered, washed with cold water and recrystallized from

methanol to afford pure product. The obtained product was characterized by using ^{1}H NMR and ^{13}C NMR spectroscopy. The NMR spectroscopic data of the known compounds (**4a-4i**) are agreed well with the literature data.[28-30]

2-Amino-4-(4-nitrophenyl)-4H-benzo[h]chromene-3-carbonitrile (4g)

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.25 (d, 1H, ArH), 7.79 (t, 1H, Ar-H), 7.51 (m, 3H, Ar-H), 7.43 (d, 2H, Ar-H), 7.15 (d, 2H, ArH), 7.01 (d, 1H, ArH), 6.92 (s, 2H, NH_2), 4.83(s, 1H, CH).

2-Amino-4-(2-bromophenyl)-4H-benzo[h]chromene-3-carbonitrile (4i)

^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 8.21 (d, 1H, ArH), 7.81 (d, 1H, Ar-H), 7.51 (m, 3H, Ar-H), 7.49 (m, 2H, Ar-H), 7.23 (m, 3H, ArH), 6.96 (s, 2H, NH2), 4.87 (s, 1H, CH).

Results and discussion

In this communication, we have reported the use of lemon juice as a catalyst and solvent for the synthesis of 2-amino-(substituted phenyl)-4H-benzo[h]chromene-3-carbonitrile derivatives (Scheme 1). We have performed the three-component condensation reaction using lemon juice under sonification conditions (45 ºC). We got better result regarding purity and product yield of synthesized compounds.

We have carried out the standard model reaction of p-methoxybenzaldehyde, malononitrile and α-naphthol in presence of lemon juice. In order to optimize reaction conditions we have carried out reaction at room temperature, 80 ºC and under ultrasonication conditions at (45 ºC) and found that reaction carried out under sonification condition have given good yield in short reaction time (Table 1).

Table 1. Model reaction of p-methoxybenzaldehyde, malononitrile and α-naphthol in presence of lemon juice

Reaction condition	*T*, C°	Time, h	Yield, %
Without catalyst	50 ºC	7	00
Room temperature	30 ºC	10	70
Heating	80 ºC	6	78
Sonification	45 ºC	1/3	84

The scope of catalyst on different substituted benzaldehydes has been examined such as electron donating or withdrawing groups, all the results obtained are presented in (Table 2).

Table 2. Synthesis of 2-amino-(substituted phenyl)-4H-benzo[h]chromene-3-carbonitrile (**4a-i**)

Arylaldehyde	Product	Time, min	Yield, %	Melting point, ºC	
				Observed	Reported
Benzaldehyde	**4a**	30	76	274-275	205-207[28]
o-Chlorobenzaldehyde	**4b**	28	77	231-232	253-254[28]
p-Chlorobenzaldehyde	**4c**	27	78	210-212	229-200[28]
m-Methoxybenzaldehyde	**4d**	29	74	247-248	248-250[29]
p-Methoxybenzaldehyde	**4e**	20	76	187-189	193-194[28]
m-Nitrobenzaldehyde	**4f**	25	82	233-237	212-214[30]
p-Nitrobenzaldehyde	**4g**	28	84	240-241	238-239[28]
p-Hydroxybenzaldehyde	**4h**	29	76	242-243	244-245[28]
p-Bromobenzaldehyde	**4i**	27	72	238-239	240-241[28]

Reaction works well for all substituted benzaldehydes which means reaction is compatible with this catalytic system. However, ortho substituted derivatives have shown less yield as compare to the meta and para substituted due to electronic effect.

Conclusion

In conclusion, we have successfully synthesized, 2-amino-4H-chromens by using ultrasound waves from malononitrile, benzaldehyde and α-napthol by using lemmon juice as an biocatalyst as well as it acts as solvent, it show high catalytic activity and clean reaction procedure, easy workup, with high yields of products and purity.

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