An Ultrasound and Microwave Assisted Benign Synthesis of 2-Amino-4-Aryl-7-Hydroxy-4h-Chromene-3-Carbonitriles Over Harsh Conventional Method

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Abstract. An Ultrasound and Microwave assisted fast, simple and environmentally benign method for the synthesis of substituted 2-Amino-4-Aryl-7-Hydroxy-4h-Chromene-3-Carbonitriles from resorcinol, malononitrile and aromatic aldehydes by using Rochelle salt as a catalyst in alcoholic media by maintaining temperature and frequency of ultrasonicator as well as by Microwave irradiation. This ultrasound and microwave assisted synthesis have several advantages over harsh conventional method and provides a green and improved pathway, simple work up procedure and excellent yields.

INTRODUCTION

The 4H-chromene and its derivatives constitute a major class of naturally occurring compounds[1,2]. Also the 4H-chromene derivatives demonstrate a wide range of biological activity and have received great interest as therapeutic agents, due to their low toxicity and use rates[3,4]. The fused and bridged chromenes are precursers of biologically active compounds, and shows antimicrobial[5], antiviral[6] activities. Therefore the synthesis of chromone derivatives is a research field of great interest and long history. Amongst recent catalytic systems, DBU[7], DABCO[8], piperidine[9], morpholine[10], triethyl amine[11], hexamethylenetetramine[12], ionic liquid[13] was developed for reaction. However, almost all these methods suffer from long reaction time, high temperature, reflux conditions, use of expensive and hazardous catalysts and solvent systems. Hence we introduced a milder, faster and more environmentally benign methods resulting in higher yields, low reaction time, cost effective, clean, rapid method.

Our aim is to synthesize Aminochromenes and their derivatives as a precursor. Here we use ethanol as a solvent in presence of inorganic double salt as a catalyst by using ultrasound waves as well as microwave synthesizer. This is advantage of our work to use such a system combination. 2-Amino-4-Aryl-7-Hydroxy-4h-Chromene-3-Carbonitriles have been prepared by ultrasound and microwave irradiation by mixing malononitrile, aromatic aldehyde, and resorcinol. Although different synthetic methods to prepare these heterocyclic systems have been reviewed[14-15], but ultrasound and microwave in combination of simple and novel catalyst and use of clean solvent has not been largely reported.

Using microwave and ultrasound irradiation synthesis of highly functionalized 2-Amino-4-Aryl-7-Hydroxy-4h-Chromene-3-Carbonitriles and their derivatives in excellent yields in the presence of catalyst at different temperature and frequency in few minutes over refluxing hours of conventional method. These approaches afford several advantages over conventional and contemporary reaction methodologies in terms of operational simplicity, simple work-up procedure, higher yield, and short reaction time and environment friendly protocols. The solvent alcohol and water play important role in organic synthesis and green chemistry[15,16]. The multicomponent reactions (MCR's) also have several advantages like reduced steps of reactions and economical:

PROCEDURE FOR SYNTHESIS

A mixture of equimolar amounts of aromatic aldehydes 1a–h, malonontirile (2), and resorcinol (3) (5mmol) in ethanol (10 mL), Rochelle salt (0.30 g) was added. Conventional Method- Then, the reaction mixture was heated at reflux temperature for 2–4 h. US Method- The mixture was ultrasonicated by using ultrasound bath sonicator at rt-60^{0}C for an appropriate time in ethanol as a solvent. MW Method- The mixture was placed in a sealed vial containing ethanol (7 mL) and irradiated by catalyst system microwave oven for appropriate time at 20 % power & 140 Watt for 2-5 minutes. The reaction was monitored by TLC, 2:8 EtOAc/n-hexane. The solid products (4a-h) were then washed and purified by recrystallization from EtOH.

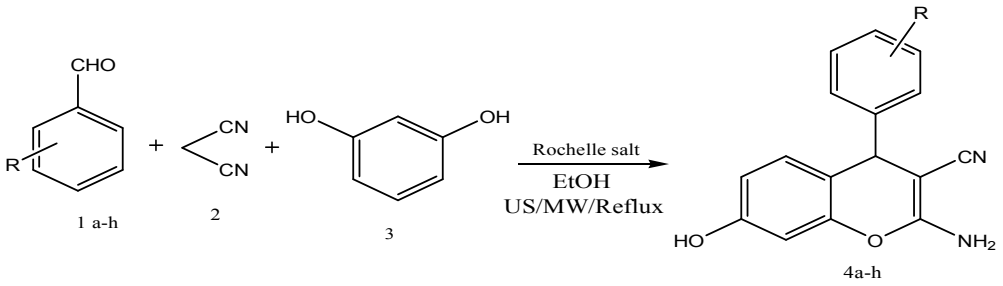

FIGURE 1. 2. Scheme-1- Synthesis of 2-Amino-4-Aryl-7-Hydroxy-4h-Chromene-3-Carbonitriles (4a–h)

TABLE 1. Comparative study between ultrasound, microwave and conventional method by condensation of aromatic aldehydes 1a-h, malononitrile 2 and resorcinol 3 under the optimized conditions. (4a-h)

		Ultrasound (40kHz, 40 ºC)		**MW (20% power, 140 Watt)**		**Conventional, reflux temp (ºC)**	
4	**R**	**Time (min)**	**Yield (%)**	**Time (min)**	**Yield (%)**	**Time (hrs)**	**Yield (%)**
a	H	20	90	05	92	03	75
b	2,4 Dichloro	22	85	05	85	03	74
c	O-hydroxy	20	81	05	81	03	76
d	p-hydroxy	20	82	05	82	03	77
e	p-Dimethyl amino	20	86	05	86	03	80
f	O-chloro	22	88	05	72	03	72
g	m-Nitro	25	85	05	75	03	76
h	p-chloro	22	79	05	79	03	70

TABLE 2. Melting points and yields of the synthesized compounds (4a-h)

Compound	**R**	**Observed m.p.(^{0}C)**			**Reported m.p. (^{0}C)**	**Yield %**		
		US	**MW**	**Conv**		**US**	**MW**	**Conv**
4a	H	230	226	228	231	90	92	75
4b	2,4 Dichloro	248	245	244	--	85	85	80
4c	O-hydroxy	120	115	116	--	81	81	78
4d	p-hydroxy	237	232	230		82	82	76
4e	p-Dimethyl amino	191	186	190	193-195	86	86	80
4f	O-chloro	80	80	182	--	88	72	72
4g	m-Nitro	120	120	120	--	85	75	84
4h	p-chloro	162	158	162	163-164	79	79	86

EXPERIMENTAL ANALYSIS OF SYNTHESIZED COMPOUNDS

IR Spectral Analysis- IR spectra were recorded with a JASCO FT-IR 6600 PC spectrophotometer in KBr disks having range of 4000-400 cm^{-1}.

^{1}H NMR spectra Analysis- Spectra were recorded with Bruker EXT40918 spectrometer at 400MHz with DMSO as solvents and TMS as an internal standards; chemical shifts (δ) are reported in ppm.

TABLE 3. Microbial Activity Shown By Synthesized Compounds

Name of the compound	Culture	Diameter (US)	Diameter (MW)	Diameter (Conv)	Result
H (4a)	*Staphillococcus*	13	10	17	positive
	E-coli	11	10	11	positive
	Pseudo	12	11	--	positive
	Bacillus subtilis	11	16	22	positive
p-hydroxy (4d)	*Staphillococcus*	10	10	13	positive
	E-coli	10	10	10	positive
	Pseudo	10	--	10	positive
	Bacillus subtilis	13	11	13	positive
p-dimethyl amino (4e)	*Staphillococcus*	--	--	--	negative
	E-coli	10	10	--	positive
	Pseudo	12	--	12	positive
	Bacillus subtilis	--	10	--	positive
o-chloro (4f)	*Staphillococcus*	--	10	24	positive
	E-coli	--	--	14	positive
	Pseudo	11	10	--	positive
	Bacillus subtilis	10	10	19	positive

TABLE 4. IR (cm^{-1}) Spectral data of the newly synthesized compounds

Compound	US	MW	Conv
4a	3430 & 3331 (OH and NH_2), 2188 (CN)	3429 & 3329 (OH and NH_2), 2189 (CN)	3430 & 3331 (OH and NH_2), 2188 (CN)
4b	3459–3306 (OH and NH_2), 2166 (CN)	3577 & 3329 (OH and NH_2), 2290 (CN)	3575 & 3332 (OH and NH_2), 2191 (CN)
4c	3576 & 3333 (OH and NH_2), 2189 (CN)	3576 & 3328 (OH and NH_2), 2188 (CN)	3576 & 3333 (OH and NH_2), 2189 (CN)
4d	3574 & 3343 (OH and NH_2), 2227 (CN)	3576 & 3337 (OH and NH_2), 2225 (CN)	3574 & 3343 (OH and NH_2), 2227 (CN)
4e	3573 & 3334 (OH and NH_2), 2206 (CN)	3576 & 3327 (OH and NH_2), 2115 (CN)	3573 & 3334 (OH and NH_2), 2206 (CN)
4f	3413 & 3331 (OH and NH_2), 2190 (CN)	3577 & 3327 (OH and NH_2), 2226 (CN)	3413 & 3331 (OH and NH_2), 2190 (CN)
4g	3431 & 3325 (OH and NH_2), 2190 (CN)	3432 & 3324 (OH and NH_2), 2190 (CN)	3431 & 3325 (OH and NH_2), 2190 (CN)
4h	3432 & 3329 (OH and NH_2), 2189 (CN)	3431 & 3328 (OH and NH_2), 2223 (CN)	3432 & 3329 (OH and NH_2), 2189 (CN)

TABLE 5. 1H NMR Spectral Analysis (DMSO-*d*6) (δ ppm)

4a-h	US	MW	Conv
4a	4.62 (s, 1H, H-4), 6.88 (s, 2H,NH2), 6.41–6.81 & 7.16-8.96 (each dd for 5H, ArH), 9.72 (br s, 1H, OH).	4.61 (s, 1H, H-4), 6.87 (s, 2H,NH2), 6.40–6.81 & 7.17-7.38 (each dd for 5H, ArH), 9.71 (br s, 1H, OH).	4.61 (s, 1H, H-4), 6.88 (s, 2H,NH2), 6.40–6.81 & 7.15-7.32 (each dd for 5H, ArH), 9.70 (br s, 1H, OH).
4d	3.35 (s, 1H, H-4), 6.98 (s, 2H,NH2), 6.41–6.73 & 7.20-8.05 (each dd for 4H, ArH), 5.13 (br s, p-OH of BA), 9.78 (br s, 1H, OH).	--	3.35 (s, 1H, H-4), 6.98 (s, 2H,NH2), 6.41–6.73 & 7.20-8.05 (each dd for 4H, ArH), 5.13 (br s, p-OH of BA), 9.78 (br s, 1H, OH).
4e	3.05 (6H), 3.35 (s, 1H, H-4), 6.84-6.86 (s,2H,NH2), 6.17–6.19 & 6.90-8.04 (each dd for 4H, ArH), 9.16 (br s, 1H, OH).	3.05 (6H), 3.34 (s, 1H, H-4), 6.85-6.87 (s,2H,NH2), 6.16–6.19 & 6.89-8.03 (each dd for 4H, ArH), 9.17 (br s, 1H, OH).	3.34 (s, 1H, H-4), 6.85 (s, 2H,NH2), 6.87–7.85 & 7.20-8.05, 8.06 (br s, 1H, OH).
4g	4.92 (s, 1H, H-4), 7.05 (s, 2H,NH2), 6.44- 8.11 (each dd for 4H, ArH), 9.80 (br s, 1H, OH).	5.13 (s, 1H, H-4), 6.98 (s, 2H,NH2), 6.41- 6.73 & 7.20-8.05 (each dd for 4H, ArH), 9.78 (br s, 1H, OH).	4.92 (s, 1H, H-4), 7.61-7.68 (s, 2H,NH2), 6.45- 7.05 & 7.61-8.11 (each dd for 4H, ArH), 9.81 (br s, 1H, OH).

RESULT AND DISCUSSION

Our synthesis Begans with the reaction of a mixture of aromatic aldehydes 1a–h, malononitrile (2), and resorcinol (3) in ethanol as a solvent containing a catalytic amount of Rochelle salt were irradiated by ultrasonic bath sonicator to give 2-amino-4-aryl-7-hydroxy-4H-chromene-3-carbonitriles and their derivatives (4a–h) (Scheme 1). The various synthetic routes are available for the synthesis of 2-amino-4H-chromenes using some hazardous bases also. So these methods have drawbacks like low product yield, harsh work up and long reaction time. It is difficult to develop a viable alternative, an already variety of catalysts were used for the typical multicomponent reaction of benzaldehyde 4a, malononitrile and resorcinol under conventional method. Here we use a Rochelle salt as a green and cheap catalyst under ultrasound bath sonicator and further extend the research work with microwave synthesizer. The outcome is given in Table 1& 2. The use of RS gives 75% yield (Table 1) under conventional conditions while US method gives 90% yield and MW method gives 92% yield. Different catalytic amount of catalyst were used but best result obtained with 0.30 gm of RS. It is interesting while we increase temp of sonicator there is increase in yield upto 40^{o}C only. A further increase in temperature could not improve the yield. We use the constant frequency of ultrasonicator, 40 kHz. The dramatic change shows in the reaction time, the best result being obtained using 40 kHz at 40ºC in just 20-25 minutes in the presence of RS catalyst. Under the optimized set of US reaction conditions (40 kHz and 40 ºC), a number compounds (4a-h) were synthesized. The further work was extend with the help of catalyst system microwave oven synthesizer. The series of same compound was synthesized by changing the watt power of microwave oven. But best result was met at 20% and 140 watt. So we synthesize our compound under 20% and 140 watt by varying the time. A number of compound (4a-h) were synthesize under similar condition. The structures of the isolated products 4a-h were confirmed on the basis of their IR spectrum of products which shows presence of both OH and NH_2 functions at 3580–3320 cm−1 and a cyano function at 2188-2227 cm−1. The ^{1}H NMR spectra shows the presence of one singlet at δ = 6.84–7.05 ppm attributed to amino (NH_2) function and 9.16–9.80 ppm attributed to the OH group. Also the strong evidence was observed for the formation of compounds 4a–h. The data shows the presence of the H-4 proton at δ = 4.57–5.13 ppm. The aromatic protons and other groups also show peaks in aromatic region (Table 5). Hence we go though proposed structures for synthesized compounds 4a-h. All known compounds were identical in all physical and spectroscopic aspects with the others which are reported in literatures.

CONCLUSIONS

We found a green and efficient synthetic route to synthesize some new chromenes, namely, 2-amino chromenes of expected biological interest, by using ultrasound bath sonicator and catalyst system microwave synthesizer. To the best of our knowledge, this is the first time for utilizing Rochelle salt as a catalyst with microwave synthesizer as an efficient, green, and fast method for one-pot three-component reactions. These methods have several advantages over former and conventional reaction methodologies in terms of operational simplicity, simple work-up procedure, higher yield, short reaction time, less hazardous solvents and environment friendly protocols.

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