A GREEN CHEMICAL APPROACH: FOR AN ULTRASOUND ASSISTED SYNTHESIS OF SUBSTITUTED CHROMENES VIA THREE-COMPONENT REACTION BY USING INORGANIC DOUBLE SALT AS A CATALYST.

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Abstract
An Ultrasound assisted fast and environmentally benign method for the synthesis of substituted 2-amino-4H-chromenes using Inorganic Double Salt as a catalyst in alcoholic media at different temperature by using ultrasonication. These ultrasound syntheses have advantage over conventional method and provides a green and improved pathway, simple work up and excellent yields.
Keywords: Ultrasound Bath Sonicator with temperature control, Resorcinol, Malononitrile, Benzaldehyde and Substituted Benzaldehydes, Inorganic double salt (Rochelle salt).

1. Introduction

Chromones constitute one of the major classes of naturally occurring compounds, and hence interest in their chemistry is unabated because of their usefulness as biologically active agents. The fused and bridged chromenes are precursers of biologically active compounds, and shows antimicrobial[1,2], antiviral[3] activities. Therefore the synthesis of chromone derivatives is a research field of great interest and long history.

Our aim is to synthesize Aminochromenes. The solvent DMF or acetonitrile are used in the presence of hazardous organic bases as a catalyst such as piperidine and triethylamine[4,5]. Here we use alcohol as a solvent in presence of inorganic double salt as a catalyst. And this is advantage of our work to use heterogeneous catalyst. There are several methods to prepare this heterocyclic systems.[6-14]

The aim is to use the efficiency of Inorganic Double Salt as a green heterogeneous catalyst in the one pot reactions in organic synthesis. We report herein our results on the utility of Inorganic Double Salt as a green catalyst in different catalytic amount in the three-component condensations between aromatic aldehydes, active methylene reagents i.e. malononitrile, and resorcinol.

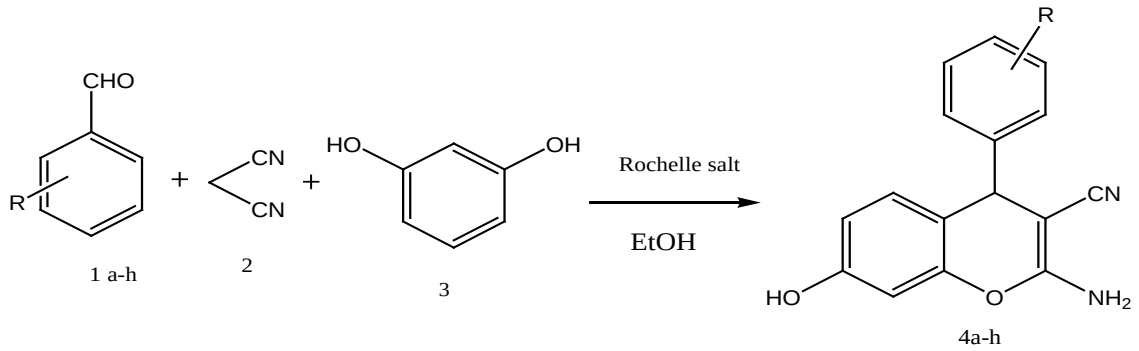
- Advantages of sonochemistry and MCR's

Using ultrasound irradiation, one-pot multi-component methods are described for syntheses of highly functionalized chromenes derivatives in excellent yields in the presence of catalyst at different temperature. These approaches afford several advantages over conventional and contemporary reaction methodologies in terms of operational simplicity, simple work-up procedure, higher yield, short reaction time and environment friendly protocols.

MCRs in alcohol and water play important role in organic synthesis and green chemistry[15, 16] Multi-component coupling reactions (MCR) is a powerful synthetic route for the synthesis of biologically active compounds. Because three-component reactions have reduced the steps of reactions by combination of three components to generate new products in a single step which is extremely economical.

2. Scheme-1: Synthesis of 2-Amino-4-Aryl-7-Hydroxy-4h-Chromene-3 Carbonitriles (4a–h) using Rochelle salt as a catalyst

2.1 Reaction



1 a-h 2 3 4a-h

2.2 Procedure for synthesis

A mixture of aromatic aldehydes (1a-h) (2 mmol), malononitrile (2) (2 mmol), resorcinol (3) (2 mmol), and Rochelle salt (0.3 gm) was ultrasonicated by using ultrasound bath sonicator at 30-60^{0}C for an appropriate time (table 2) in ethanol as a solvent. Reaction was monitored by TLC, 2:8 EtOAc/n-hexane. The solid products (4a-h) were then washed to remove catalyst and purified by recrystallization from EtOH.

2.3 Table 1-Optimization of the reaction conditions for synthesis of 2-amino-3-cyano-7-hydroxy-4-phenyl-4H-chromene (4a)1-5 by varying effect catalytic amount of catalyst

Entry	Base	Gm	Time (min)	Yield %
4a.1	Rochelle Salt	0.10 gm	15-20	--
4a.2	Rochelle Salt	0.15 gm	15-20	--
4a.3	Rochelle Salt	0.20 gm	15-20	74
4a.4	Rochelle Salt	0.25 gm	15-20	81
4a.5	Rochelle Salt	0.30 gm	15-20	90

a: Reaction conditions: benzaldehyde(4a) (2.0 mmol), malononitrile(2) (2.0 mmol), resorcinol(3) (2.0 mmol), and varying amount of catalyst, Rochelle Salt (different catalytic amount)

2.4 Table 2-Condensation of aromatic aldehydes 1a-h, malononitrile 2 and resorcinol 3 under the optimized conditions at constant frequency by varying temp and time

1	R	Temp ^{0}C	Solvent System (10 ml)	Time	Frequency KHz	% Yield
a	H	30	Ethanol	30	40	70
a	H	35	Ethanol	25	40	74
a	H	40	Ethanol	20	40	85
a	H	50	Ethanol	18	40	78

a: Reaction conditions: aromatic aldehyde (2.0 mmol), malononitrile (2.0 mmol), resorcinol (2.0 mmol), Rochelle salt (0.3 g), temp. and time controlled.

2.5 Table 3- Condensation of aromatic aldehydes 1a-h, malononitrile 2 and resorcinol 3 under the optimized conditions at 40 KHz, 40^{o}C temperature and appropriate time (table 2)

1	R	Catalyst	Catalytic amount	Time (min)
a	H	Rochelle Salt	0.30 gm	20
b	2,4 Dichloro	Rochelle Salt	0.30 gm	22
c	O-hydroxy	Rochelle Salt	0.30 gm	20
d	p-hydroxy	Rochelle Salt	0.30 gm	20
e	p-Dimethyl amino	Rochelle Salt	0.30 gm	20
f	O-chloro	Rochelle Salt	0.30 gm	22
g	m-Nitro	Rochelle Salt	0.30 gm	25
h	p-chloro	Rochelle Salt	0.30 gm	22

a:

Reaction conditions: aromatic aldehyde (2.0 mmol), malononitrile (2.0 mmol), resorcinol (2.0 mmol), Rochelle Salt (0.30 g)

2.6 Table 4- Here we report Yields, melting points and rf value of the synthesized compounds **4a-h**

Compound	R	Observed m.p.(^{0}C)	Reported m.p.	Yield %	Rf Value
4a	H	230	231	90	0.81
4b	2,4 Dichloro	248	--	81	0.67
4c	O-hydroxy	120	--	81	0.67
4d	p-hydroxy	237		82	0.78
4e	p-Dimethyl amino	191	193-195	86	0.69
4f	O-chloro	80	--	88	0.57
4g	m-Nitro	120	--	85	0.70
4h	p-chloro	162	164	79	0.83

M.P.:- 4a (Ref.17-20)

2.7 Table 5- Comparative study between ultrasound and conventional method for synthesis of 2-amino-4*H*-chromenes **4a-h**

Compound	R	Ultrasound (40kHz, 40 ºC)		Conventional, reflux temp (ºC)	
		Time(min.)	Yield (%)[a]	Time (hrs)	Yield (%)[a]
4a	H	15	90	3 hrs	75
4b	2,4 Dichloro	17	85	3 hrs	74
4c	O-hydroxy	15	81	3 hrs	76
4d	p-hydroxy	15	82	3 hrs	77
4e	p-Dimethyl amino	15	86	3 hrs	80
4f	O-chloro	16	88	3 hrs	72
4g	m-Nitro	17	85	3 hrs	76
4h	p-chloro	15	79	3 hrs	70

a: Reaction conditions: aromatic aldehyde (2.0 mmol), malononitrile (2.0 mmol), resorcinol (2.0 mmol), Rochelle Salt (0.30 g)

3. Experimental Analysis Section

3.1 General

- **Melting Points-** All melting points were measured accurately on a melting point apparatus and are uncorrected.
- **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}.
- **UV Spectra Analysis-** Visualization was accomplished by UV light on UV-Visible spectrophotometer having range of 200-1400 nm.
- **^{1}H NMRspectra 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.

3.2 Analytical

- **Thin-layer chromatography (TLC)**- Thin-layer chromatography (TLC) was performed on Merck silica gel 60 plates, 0.25mm thickness. Solvents for chromatography were pure and used as received.

3.3 Microbial Activity Against Given Compounds

Microbial activity of synthesized chemical compounds was studied by "microbial assay" process. The chromenes (4a-h) obtained were preliminarily evaluated for their in vitro antibacterial activity against a narrow spectrum of bacterial species procured from the Laboratory of Microbiology (Microbiology. Dept., Faculty of Science, Pratap College, Amalner).

Table 6- The Microbial activity results are shown by compounds

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

Table 7- Counter Results of Bacteria

Culture	Counter Result
Staphillococcus	--
E-coli	--
Pseudo	11
Bacillus subtilis	11

The compound 4(a,d,e,f) were show positive results to the all four microorganisms i.e. showing microbial activity or zone was observed & negative result to the some microorganism i.e. it did not show any zone of inhibition against microbial strains.

3.4 Table 8- Spectral data of the newly synthesized compounds

Compound	IR (cm^{-1})	^{1}H NMR (DMSO-*d*6) (δ ppm)
4a	3430 & 3331 (OH and NH_2), 2188 (CN)	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).
4b	3459–3306 (OH and NH_2), 2166 (CN)	--
4c	3576 & 3333 (OH and NH_2), 2189 (CN)	--
4d	3574 & 3343 (OH and NH_2), 2227 (CN)	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	3573 & 3334 (OH and NH_2), 2206 (CN)	3.05 (6H), 2.50 (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).
4f	3413 & 3331 (OH and NH_2), 2190 (CN)	--
4g	3431 & 3325 (OH and NH_2), 2190 (CN)	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).
4h	3432 & 3329 (OH and NH_2), 2189 (CN)	--

4. Result and Discussion

Our synthesis starts 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), (Table 3). 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 conventional as well as ultrasound bath sonicator. The outcome is given in Table 5. The use of RS gives 75% yield (Table 5) under conventional conditions while US method gives 90% yield. Different catalytic amount of catalyst were used and gave best result with 0.30 gm of RS (Table 1). It is interesting while we increase temp of sonicator there is increase in yield upto 40^{o}C only (Table 2). 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 of aromatic aldehydes 4a-h were allowed to undergo multicomponent reaction with malononitrile and resorcinol in a molar ratio of 1:1:1 with RS in ethanol affording 2-amino-4H-chromenes 4a-h in excellent yields (Table 4). 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

1H 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 = 4.57–4.92ppm. The aromatic protons and other groups also show peaks in aromatic region (see Table 3). Hence we go though proposed structures for compounds 4a-h. All known compounds were identical in all physical and spectroscopic aspects with the others which are reported in literatures.

5. Conclusion

We have discovered a green and efficient synthetic route to synthesize some new chromenes, namely, 2-amino chromenes of expected biological interest, by using Rochelle salt as a catalyst and ultrasound bath sonicator. To the best of our knowledge, this is the first time for utilizing Rochelle salt as a catalyst and ultrasound bath sonicator 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 and environment friendly protocols.

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