Green chemical approach for the synthesis of chromenes derivatives in presence of novel green catalyst (Rochelle salt) and their biological activity

Preeti Bansal[1], Gajanand Sharma[2]

[1]ph.d in chemistry, Suresh Gyan Vihar University, Jaipur, Rajasthan (India)

[2]Assistant Professor, chemistry department, Suresh Gyan Vihar University, Jaipur, Rajasthan (India).

Abstract- **Biological active 4H- chromenes derivatives were synthesized by a one pot efficient, green, practical and environment friendly multicomponent reaction of aromatic aldehyde (1), Malononitrile (2) and carbonyl derivatives (3). Compounds (1), (2), (3) react to each other in presence of Rochelle salt which is a novel green and reusable catalyst. The method is very rapid, safe and avoids the use of hazardous and expensive reagents and solvents so this is a simple green and efficient protocol for synthesis of 4H-Chromenes derivatives. Chromenes derivatives are important scaffold of many biologically active compounds. The synthesize chromenes derivatives possess important biological activities such as antimicrobial, antifungal, and herbicidal activities.**

Keywords— 4H-chromenes, multicomponent reaction, Rochelle salt, biological activity

I. INTRODUCTION

The chromenes are biological active compound with a wide spectrum of activities such as (a) antimicrobial (b) mutagenicitical (c) antitumoral (d) antiviral (e) antifungal (f) antiproliferative (g) antibacterial (h) hypotensive (I) antileishmanial activities. (1-11) Chromenes is one of the privileged medicinal pharmacophore. Lipophilic nature of the benzopyran derivatives help to cross the cell membrane easily (12).

Chromenes derivatives are also play an important role in the production of highly effective fluorescent dyes for synthetic fibres, daylight fluorescent pigment and electro photographic and electroluminescent devices (13).vitamin E was an evident example for the naturally search chromenes, which possess antioxidant activities (14). Chromenes derivatives were also used as biodegradable agrochemicals and component of many natural products (15).In recent years, significant consideration has been focused on MCRs because of their valuable features such as high efficiency, mild conditions, simplistic completion and environment friendliness (16-18).

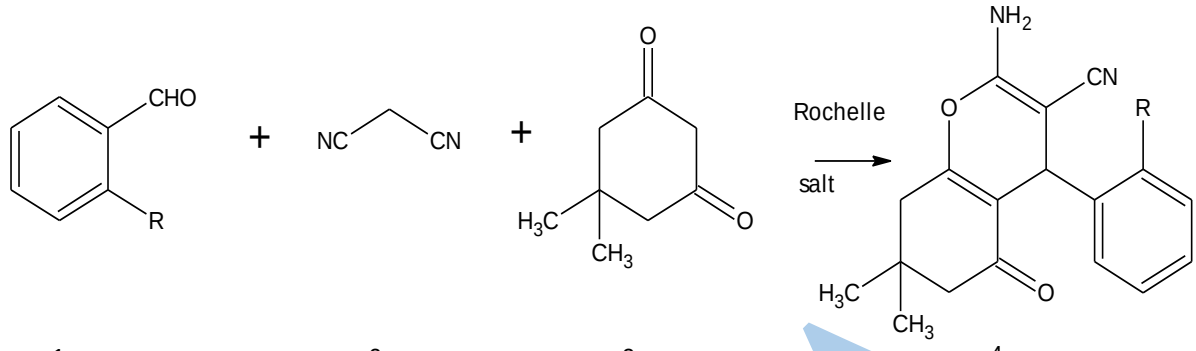
MCRs provide maximum structural complexity and diversity with a minimum number of synthetic steps to assemble compounds with interesting properties (19).That is one of the challenges in modern organic synthesis (20).as such processes avoid time- consuming and costly purification processes. As well as protection-deportation steps, they are inherently more environmentally benign and atom-economic (21).

Water is one of the best solvents due to its features such as being environment friendly, cheep, safe, non-flammable, clean, green, inexpensive, readily available and risk free (22).multicomponent reaction in water are of outstanding value in organic synthesis and green chemistry (23-24).chromenes have been prepared by heating a mixture of malononitrile, aromatic aldehyde and aromatic phenol in the presence of hazardous organic bases.

The drawbacks of these reactions are prolonged reaction time; tadius work-up procedure, organic solvents as well as the requirement of special apparatus. So we report here in our result on the utility of Rochelle salt as a novel green catalyst in the three component condensation b/w aromatic aldehyde, malononitrile and activated phenols.

II. RESULT AND DISCUSSING ON:-

In a representative experiment, aromatic organic compound aldehyde (1), malononitrile (2), and aromatic phenol (3) in refluxing ethanol containing a catalytic amount of Rochelle salt to give aminochromenes derivatives. The employment of novel green, Rochelle salt is catalytically economical, rapid, simple, green procedure for the synthesis of the organic molecules.



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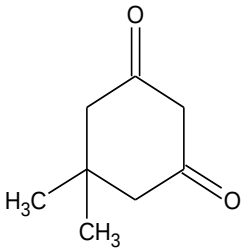
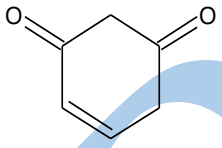


3(a)



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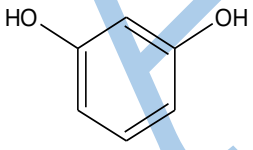


3(c)

Table-1

Entry	*Products* M.F	*R*	*3*	*Reaction time (h)*	*Isolated yield (%)*	*Mp. (°c)*
1	$C_{17}H_{17}N_3O_4$	o-NO_2	3a	2-4	90%	220-222
2	$C_{20}H_{23}N_3O_2$	p-$N(CH_3)_2$	3a	2-4	92%	209-201
3	$C_{18}H_{16}N_2O_3$	p-CH_3CO	3b	2-4	90%	198-200
4	$C_{16}H_{12}N_2O_2Cl_2$	o-Cl, p-Cl	3b	2-4	88%	192-194
5	$C_{18}H_{14}N_2O_4$	p-OH, m-CH_3CO	3c	2-4	95%	240-242
6	$C_{16}H_{12}N_2O_3$	m-OH	3c	2-4	90%	224-226

Table-2 Synthesis of 1, 4 dihydropyridine derivatives:-

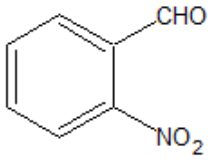
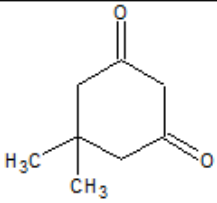
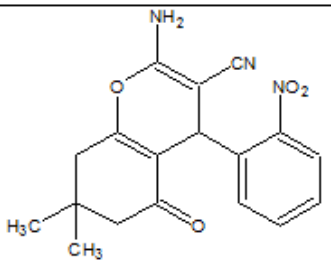
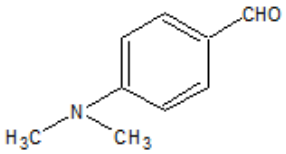
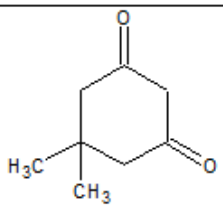
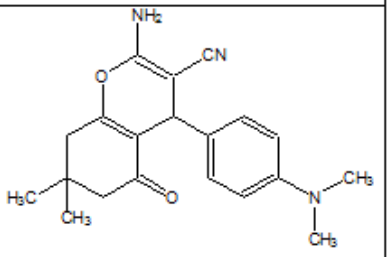
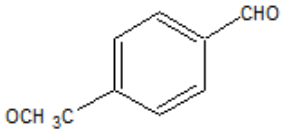
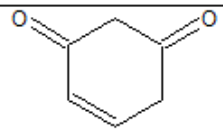
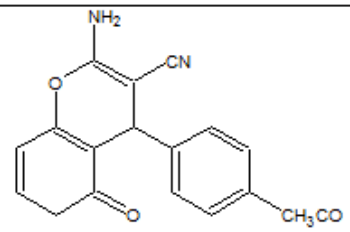
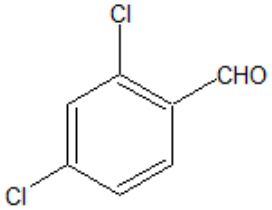
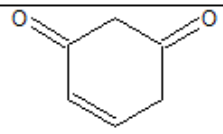
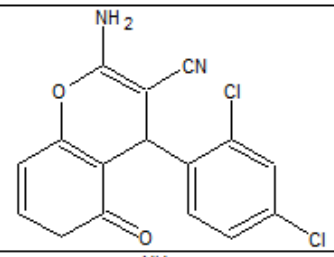
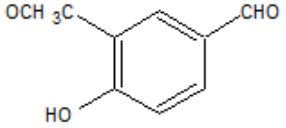
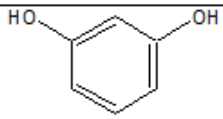
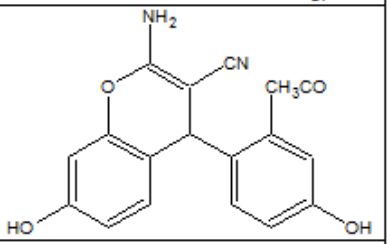
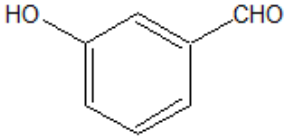
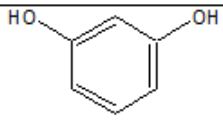
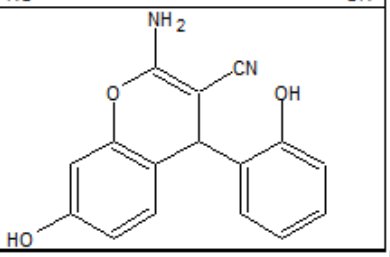
Entry	Reactant			Product
	(1)	(2)	(3)	
1				
2				
3				
4				
5				
6				

Table: - 3

Antibacterial activity of compounds (newly synthesized chromenes derivatives (1a-1f)) (disk diameter 7 c.m.)

Compound	*Vibreocholerae*	*E.Coli*	*B.subtillus*	*S.aureus*
1(a)	22	16	14	15
1(b)	30	16	7	9
1(c)	22	17	18	13
1(d)	12	15	15	25
1(e)	12	25	14	13
1(f)	-	27	16	15
ciprofloxacin	32	27	21	24

Table-4

Antifungal activity of compounds (newly synthesized chromenes derivatives (1a-1f)) disk diameter-7 c.m.

Compound	*Chrysosporium sp.*	*Trichoderma sp.*	*A.niger*	*A.Parasitica*
1a	15	10	13	17
1b	9	-	10	8
1c	24	11	17	20
1d	15	15	22	16
1e	20	20	24	16
1f	15	15	26	18
Clomatrimazole	25	27	24	27

The structure assigned for the reaction product is established from analytical data.

Antibacterial screening:-

The bacterial zones of inhibition values (mm) are given in table-3. The antimicrobial activities of compounds vibreocholerae, E.Coli, B.subtillus, S.aureus were screened. Ciprofloxacin were used as a standard at 100 µgmL-1.

Compounds 1a-1f were screened .Vibreocholerae for compound 1b was found to be highly active compared with the standard ciprofloxacin. On the other hand, for compound 1a, 1c; 1d had low activity compared with the ciprofloxacin. And for 1f show no activity. E.Coli for compound 1f was found to be highly active, on the other hand for compound 1a-1e had low activity compared with the standard ciprofloxacin. B.subtillus for compound 1c was found to be highly active compared with the ciprofloxacin. On the other hand for 1a, 1b, 1d, 1e, 1f had low activity compared with the ciprofloxacin. S.aureus for compound 1d was found to be highly active compared with ciprofloxacin on the other hand for compound 1a, 1b, 1c, 1e; 1f had low activity compared with the ciprofloxacin.

Antifungal screening:-

The fungal zones of inhibition values (mm) are given in table-4. The antifungal activity of compounds Chrysosporium sp., Trichoderma sp., A. Niger, A.Parasitica were screened. Clomatrimazole were used as a standard at a 100 µgmL-1.Compound 1a-1f were screened. Chrysosporium sp. for compound 1c was found to be highly active compared with

Clomatrimazole while on the other hand for compound 1a, 1b, 1d, 1e, 1f had low activity compared with standard Clomatrimazole.

Trichoderma sp. for compound 1e was found to be highly active on the other hand for compound 1a, 1c, 1d; 1f had low activity compared with standard Clomatrimazole. While for compound 1b had no activity with Clomatrimazole. A.niger for compound 1e was found to be highly active compared with standard Clomatrimazole. On the other hand for 1a, 1b, 1c, 1d, 1f had low activity compared with standard Clomatrimazole. A.Parasitica for compound 1c was found to be highly active compared with standard Clomatrimazole. On the other hand for 1a, 1b, 1d, 1e, 1f had low activity compared with Clomatrimazole.

III. CONCLUSION

We have been able to introduce associate economical and environmentally friendly approach for the synthesis of biologically active chromenes derivatives by the reaction of aromatic organic compound aldehyde, malononitrile and carbonyl compounds in presence of novel green catalyst Rochelle salt.

High yields, straight forward work-up, purification of products by non chromatographic technique (crystallization only) are the key advantages of this method. Most of the compounds showed higher antibacterial activity, further optimization and development is required in designing more potent antibacterial and antifungal agents for therapeutic use.

It is mentioning that minor amendment in molecular configuration of these compounds deeply influences the activity. The products were characterized by IR and 1H NMR spectral information, and their melting points were compared literature reports.

IV. EXPERIMENTAL METHOD

Solvent used were of analytical grade. All melting Spoints were taken in open capillaries and are uncorrected. Thin layer chromatography (TLC, aluminium plates precoated with silica gel , 60F254, 0.25 mm thickness)(Merck, Darmstadt, Germany) was used for monitoring the progress of all reactions, purity and homogeneity of the synthesized compounds, eluent-hexane: ethyl acetate 6:4. UV radiation and /or iodine were used as the visualizing agents. Elemental analysis (% C, H, N) was carried out by a Perkin – Elmer 2400 series-ii elemental analyzer (Perkin-Elmer, USA) and all compounds were within + or – 0.4% of calculation. The IR spectra were recorded in KBr pellet on a Perkin- Elmer spectrum GXFT-IR spectrophotometer. (Perkin-Elmer, USA) and only the characteristic peaks were recorded in c.m.-1. 1H NMR and 13C-NMR spectra were recorded in DMSO on a Bruker Advance 400F (MHz) spectrometer (Bruker scientific corporation Ltd., Switzerland) using solvent peak as internal standard at 400MHz and 100MHz respectively. Chemical shifts were reported in parts per million (ppm).

V. EXPERIMENT

To a mixture of equimolar amounts of aromatic aldehyde 1a-1f (5m mol), malononitrile (5m mol) and 5, 5 dimethyl1,3 cyclohexanedione or 1,3 cyclohexanedione or resorcinol (5m mol) in ethanol/water mixture(1:1) (10ml), Rochelle salt (.30g) was added. The reaction mixture was heated at reflux temp. For 2-4 h. After cooling to room temp. , the resulting solid products were collected by filtration, dried.

For spectral studies and elemental analyses, a compound (1a-1f) was further recrystallized from ethyl alcohol to give chromenes.

(5a) yield 90%, mp. 220-2220c, reaction time- 2-4 h. , Anal. Found: C, 62.36; H, 5.23; N, 12.84, Calc. C17H17N3O4: C, 62.50; H, 5.21; N, 12.87. IR (KBr) max 3076(aromatic C-H), 2669(aliphatic C-H), 1890(C=O), 1690(C=C), 1HNMR (CDCl3) (ppm); 6.90-7.12(4H, Ar-H), 2.31(S, 6H, (CH3)2), 3.45-3.20(S, 4H, (CH2)2), 6.6(S, 2H, NH2), 7.5(m, 1H, CH)

(5b) yield 92%, mp. 209-2010c, reaction time 2-4 h., Anal. Found: C, 71.17; H, 6.87; N, 12.45, Calc. C20H23N3O2: C, 71.26; H, 6.82; N, 12.47. IR (KBr) max 3083 (aromatic C-H), 2580(aliphatic C-H), 1760(C=O), 1685(C=C), 1HNMR (CDCl3) (ppm) 6.90-7.12 (m, 4H, ArH), 6.6(S, 2H, NH2), 2.32(S, 6H, (CH3)2), 3.35-3.10(S, 4H, (CH2)2), 7.4 (m, 1H, CH)

(5C) yield 90%, mp. 198-2000c, reaction time – 2-4 h., Anal. Found: C, 70.10; H, 5.23; N, 9.08, Calc. C18H16N2O3: C, 70.21; H, 5.21; N, 9.16. IR (KBr) max 3080 (aromatic C-H), 2680 (aliphatic C-H), 1785 (C=O), 1670 (C=C), 1HNMR (CDCl3) (ppm) 6.59-7.78 (m, 4H, ArH), 6.3(S, 2H, NH2), .3(t, 1H, CHO), 5.8(m, 1H, CH), 7.9(m*/, 2H, (CH)2),8.45(m, 2H, CH2),

(5D) yield 88%, mp. 192-1940c, reaction time 2-4 h., Anal. Found: C, 57.46; H, 3.61; N, 8.38, Calc. C16H12N2O2Cl2: C, 57.60; H, 3.57; N, 8.42. IR (KBr) max3076 (aromatic C-H), 2670 (aliphatic C-H), 1890 (C =O), 1720(C=C), 1HNMR (CDCl3), (ppm); 6.70-7.80 (m, 3H, ArH), 6.39 (S, 2H, NH2), 7.6(m, 2H, (CH) 2), 8.35(m, 2H, CH2), 5.6(m, 1H, CH)

(5e) yield 95%, mp. 240-2420c, reaction time 2-4 h., Anal. Found: C, 67.06; H, 4.38; N, 8.69, Calc. C18H14N2O4; C, 67.15; H, 4.32; N, 8.74. IR (KBr) max 3079(aromatic C-H), 2569 (aliphatic C-H), 1875(C=O), 1735(C=C), 1HNMR (CDCl3), (ppm), 6.72-7.60 (m, 6H, ArH), 6.40(S, 2H, NH2), .3 (t, 1H, CHO), 8.45(m, 2H, CH2), 5.65(m, 1H, CH), 7.7(S, 1H, OH)

(5f) yield 90%, mp. 224-2260c, reaction time 2-4 h., Anal. Found: C, 68.55; H, 4.31; N, 9.99, Calc. C16H12N2O3: C, 68.70; H, 4.28; N, 9.97. IR (KBr) max 3095(aromatic C-H), 2680 (aliphatic C-H), 1850(C=O), 1660(C=C), 1HNMR (CDCl3), (ppm), 6.69-7.13 (m, 7H, ArH), 6.38 (S, 2H, NH2), 7.6 (S, 1H, OH), 5.8(m, 1H, CH)

In vitro antibacterial screening:-

The compounds 1a-1f was evaluated for their in vitro antibacterial activity against vibreocholerae, E.Coli, B.subtillus, S.aureus by the agar diffusion method, using Mueller-Hinton Agar (Hi-media) medium. Each compound was tested at a concentration of 100 µgmL-1 in DMSO. Ciprofloxacin was used as the standard .the zone of inhibition (mm) was measured after 24 h incubation at 370c.

In vitro antifungal screening:-

The compound 1a-1f were evaluated for their in vitro antifungal activity against Chrysosporium sp., Trichoderma sp., A. Niger, A.Parasitica by the agar diffusion method, using Sabouraud's dextrose agar (Hi-media) media. Each compound was tested at a concentration of 100 µgmL-1 in DMSO.

Clomatrimazole was used as the standard .the zone of inhibition (mm) was measured after 24 h incubation at 370c

VI. ACKNOWLEDGMENT

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VII. REFERANCE

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