Sodium saccharin Mediated one-pot Synthesis of 2-amino-4H-Chromene Derivatives in Aqueous Media

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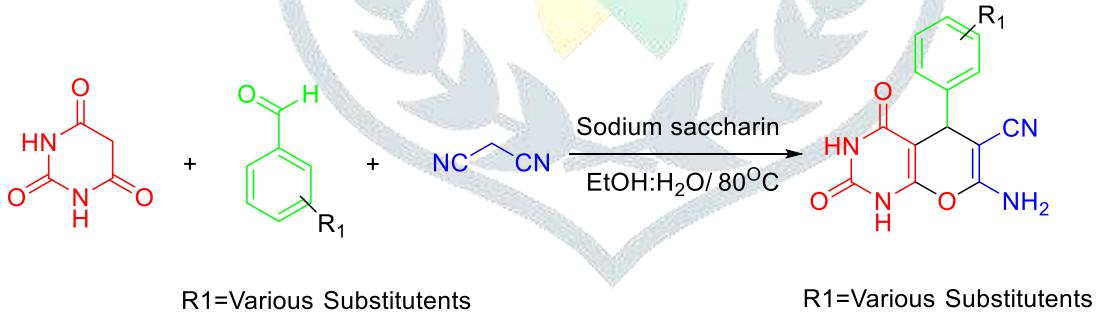
Abstract : In the present protocol Sodium saccharin catalyst was utilized for the one-pot three-component cyclo condensation reaction of Aromatic Aldehyde, Barbituric acid, and dimedone, in water as environmentally benign water as a green medium at 80°C temperature within 30 minutes of reaction time in ethanol: water solvent system. The current method has major advantages like mild reaction conditions with simple operation process, high yields, by using a less toxic and lower costlier catalyst.

IndexTerms - Sodium saccharin, Barbituric acid, Malononitrile, Substituted Aromatic aldehydes.

I. INTRODUCTION

Owing to worth mentioning, diverse and potential biological activities, that includes notably vasodilator, cardiotonic, antibacterial, antihypertensive, analgesics, bronchodilators atoprotective, antiallergic herbicidal antitumor, antifungal and antimalarial properties[1-2] has allured the scientific community across the globe to carry out the facile synthesis of pyrano-pyrimidinones[3] based heterocycles and their derivatives. Hence a good deal of numerous approaches were reported in the recent times ranging from thermal, ultrasonic, microwave and other catalytic methods that includes mainly use of catalysts[4-5] like L-proline, N-methyl-morpholine, $H_{14}[NaP_5W_{30}O_{110}]$, triethylamine, (SBA-Pr-SO_3H), [BMIm]BF_4, [$KAl(SO_4)_2$] under heating and diammonium hydrogen phosphate (DAHP), *etc*.

Although the reported methods have their own merits and demerits in an attempt to provide a feasible route which not only satisfies the criteria of environmentally benign approach but also can lead the foundation for building a sustainable healthy environment, we thought of utilizing a cheap, green and environmentally benign catalyst[6]. It is well known that Saccharin[7] is an artificial sweetener having no food energy but utilized mainly in a variety of beverages and foods including soft drinks, cookies, medicines, juices, toothpaste, gelatin, cosmetics, nutritive and pharmaceutical products. Apart from these utilities recently sodium saccharin[8] is used as a basic green and easily available compound that is used as a catalyst in some organic synthesis and transformation reactions. Inspired by all these findings, we also thought of exploring its synthetic utility in some transformation reactions. In this regard, after careful literature survey, we revealed that literature is devoid of the use of Sodium



Scheme 1

saccharin in above said transformation and there is as such no report on the synthesis of 2-amino-4H-Chromene Derivatives compound and their derivatives in aqueous media. Herewith we report a new efficient and simple synthetic method, for the synthesis of 2-amino-4H-Chromene Derivatives in ethanol: water by the cyclo condensation reaction of substituted aromatic aldehyde, malononitrile and barbituric acid within a very short reaction time at 80 °C.

Results and discussion

To standardize and set the reaction conditions we carried out various optimization protocols in terms of the amount of Sodium Saccharin (10 % mole), time, solvent and temperature. To set the conditions we carried out a model reaction of between benzaldehyde (1 mmol), malononitrile (1.0 mmol) and barbituric acid (1.0 mmol). The product was formed in a trace amount of yield when the reaction was carried out without the aid of any catalyst and solvent which indicated the need for the solvent to proceed with the reaction. We have studied various solvent system and after studying various reactions on different solvent system, Dichloromethane, Chloroform, water, ethanol, and ethanol: water system, but we are happy to know that we

ended the reaction giving the product in 11%, 14%, 44%, 64%, and 88 % yield respectively, proving that ethanol: water (1:1) system will be more efficient to yield the product in 8 hrs.

Table 1. Screening of Solvents

Entry	Solvent	Time	Yield
1	No Solvent	8 Hrs	Trace
2	No Catalyst	8 Hrs	Trace
3	Dichloromethane	8 Hrs	11 %
4	$CHCl_3$	8 Hrs	14 %
5	Water	8 Hrs	44 %
6	Ethanol	8 Hrs	64 %
7	Ethanol: Water	8 Hrs	88%

Further, we have checked and examined the effect of mole % Sodium Saccharin catalyst in aforesaid reaction protocol and as expected we ended the reaction yielding trace, 52 %, 88 %, 85 % of the product when 0%, 5 %, 10 % and 20 % of catalyst was utilized. Further, we have carried out standardization of reaction on the

Table 2. % Mole of Catalyst

Entry	Catalyst	Time	Yield
1	No Catalyst	8 Hrs	Trace
2	5 %	8 Hrs	52%
3	10%	8 Hrs	88 %
4	20%	8 Hrs	85 %

temperature of the reaction and as per expectation at room temperature, 30^{O}C, 50^{O}C 80^{O}C, and 100^{O}C it yielded 15%, 36% 88% and 90% of the product within 8 hrs. Thus from the above observation, it is clear that a 10% mole of the catalyst was sufficient to carry out the reaction at 80^{O}C utilizing ethanol: water solvent system. Finally, to set reaction time, we have performed the reaction under the set reaction conditions for 30 min, 120 min, 180 min, and 240 min. To our surprise, the reaction was good enough to give the expected product in 30 min of reaction time in 88% yield. Extended reaction time doesn't yield a major amount of product which indicated that to obtain the maximum amount of product yield only 30 minutes of reaction time was sufficient

Table 3. Screening of Temperature in Solvent System

Entry	Solvent	Time	Yield
1	Ethanol: Water	8 Hrs, RT	66%

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2	Ethanol: Water	30 min/ 80^{O}C	88%
3	Ethanol:Water	60 min/80^{O}C	90%
4	Ethanol: Water	120 Min/ 80^{O}C	91%

Experimental

Chemicals were purchased from commercial suppliers and used without further purification. Yields refer to isolated products. Melting points were determined by an Electrothermal 9100 apparatus and are uncorrected. The IR spectra were obtained on an FT-IR Hartman- Bomen spectrophotometer as KBr disks, or neat. The ^{1}H NMR (400 MHz) spectra were recorded on a Bruker Avance NMR spectrometer in $CDCl_3$ solution. The progress of the reaction was monitored by TLC using silica-gel SILG/UV 254 plates. All products are known and were characterized by comparing their physical and spectral data with those of the authentic samples.

General procedure:

A mixture of aldehyde (1 mmol), barbituric acid (1 mmol), and malononitrile (1 mmol), was taken in a round bottom flask which was dissolved in ethanol: water (10 ml), to which 10 mole % of Sodium Saccharin was added at room temperature which was vigorously stirred at room temperature for 10 min. Further, the reaction was subjected to heating in ethanol: water system at 80 °C for 20 minutes. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured on crushed ice. Further, it was filtered off and washed

with cold H_2O (3×10 mL). Finally, the crude product was recrystallized from hot ethanol to give the pure product in 88 % yield.

Table 3. Synthesis of various pyrano [2, 3-*d*] pyrimidine derivative

Entry	Compound	Ar	Time (Min)	Yield (%)	M.P. (°C)
1.	a	Ph	**30**	**88**	204-206[a]
2.	b	4-Me-Ph	**30**	**88**	162-164[a]
3.	c	4-Me_2N-Ph	**20**	**82**	180-182[a]
4.	d	4-NO_2-Ph	**20**	**70**	230-232[a]
5.	e	3-NO_2-Ph	**20**	**72**	258-260[a]
6.	f	2-Cl-Ph	**30**	**70**	207-209[a]
7.	g	3-Cl-Ph	**30**	**76**	210-212[a]
8.	h	4-Cl-Ph	**25**	**84**	230-232[a]
9.	i	4-MeO-Ph	**30**	**85**	277-279[a]

Analytical data of selected compounds: ***7-amino-2, 4-dioxo-5-phenyl-2, 3, 4, 5-tetrahydro-1H-pyrano [2, 3-d] pyrimidine-6-carbonitrile*** **(1a): M. P.** 204-206^{O}C, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.24 (s, 1H) 7.51-7.67 (m, 5H), 7.79 (s, 2H), 7.90 (s, 1H), 7.92 (s, 1H). IR (KBr, cm^{-1}): *ν* 3392, 3064, 2223, 1718, 1677, 1565, 676.

7-Amino-6-cyano-5-(4-chlorophenyl)-4-oxo-2- thioxo-5H-pyrano[2,3-d]pyrimidinone (8h): M. P. 230-232 ^{O}C, ^{1}H NMR (400 MHz, DMSO–d_6) δ: 4.26 (1H, s, H-5), 7.04 (2H, br s, NH_2), 7.21 (2H, d, J = 47.10; H, 2.64; N, 8.3 Hz, H–Ar), 7.29 (2H, d, J = 8.2 Hz, H–Ar) 11.07 (1H, br s, NH), 12.04 (1H, br s, NH) ppm; IR (KBr) 3389, 3305, 3187, 3073, 2196, 1718, 1674, 1600, 1410, 1280 cm^{-1}.

Conclusion:

In conclusion, we have identified a new protocol by recruiting the Sodium Saccharin catalyst for carrying out multicomponent synthesis of diverse Pyrano [2, 3-d] pyrimidinone derivatives. in ethanol: water solvent system following the path of green chemistry and environment benign protocol. The current has some major advantages that include easy work procedure, cheap and nontoxic catalyst, explored nicely the unknown synthetic applicability of Sodium Saccharin as a commercially available, mild, straightforward, simple, environmentally friendly basic catalyst for the efficient synthesis of diverse Pyrano [2, 3-d] pyrimidinone derivatives. in ethanol: water system.

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