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A green protocol for synthesis of pyran annulated heterocyclic systems using Na_2SO_4 as an efficient catalyst

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ABSTRACT

Na_2SO_4 as an inexpensive and effective catalyst has provided a green protocol for the synthesis of tetrahydrobenzo[b]pyran, pyrano[2,3-d]pyrimidinone and dihydropyrano[3,2c]chromene derivatives from the three-component domino reaction of aromatic aldehydes and malononitrile with 4-hydroxycoumarin/ dimedone/ barbituric acid in ethanol/water as a mixture of solvent that, this mixture entirely is green solvent. Products could simply be separated from the catalyst. Using neutral and mild conditions, short reaction time, environmentally benign procedure, high to excellent yields of the products and easy work-up without using column chromatography are the advantages of this method.

***Keywords**: Pyran annulated heterocyclic systems; Na_2SO_4; Green protocol; Barbituric acid; 4-hydroxycoumarin.*

1. Introduction

The development of new methodologies for the synthesis of chromenes and their derivatives are interesting subjects in synthetic and medicinal chemistry. Because their derivatives have versatile biological and medicinal properties [1–3], they are widely used in various biologically active natural products [4]. Some 4H-chromene derivatives bearing a nitrile functionality, especially 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3 carbonitriles, are synthetic precursors in medical synthesis [5] and display potent in vitro antileishmanial activity [6].

Recently, there have been many methods reported for the preparation of chromenes and their derivatives by three-component condensations including the use of sodium bromide [7], molecular iodine [8], KF-Alumina [9], diammonium hydrogen phosphate [10], fluoride ion [11], magnesium oxide [12], sodium selenate [13], iodine [14], $H_6[P_2W_{12}O_{62}].H_2O$ [15], tetrabutylammo-nium bromide [16], lithium bromide [17], amberlite IRA-40 (OH) [18], acidic ionic liquids [19], ZnO-beta Zeolite [20], trisodium citrate [21], and basic ionic liquids [22]. Na_2SO_4 is an inexpensive, neutral salt, water-soluble, non-toxic and commercially available compound that can be used in the laboratory without special precautions. As part of our work on one-pot multicomponent reactions for the synthesis of various heterocyclic compounds of biological importance [23-26]. Herein, we wish to report a general and highly efficient procedure for the preparation of these kinds of compounds. It was achieved via a one-pot three-component tandem Knoevenagel-cyclocondensation reaction using Na_2SO_4 as a catalyst (Scheme 1).

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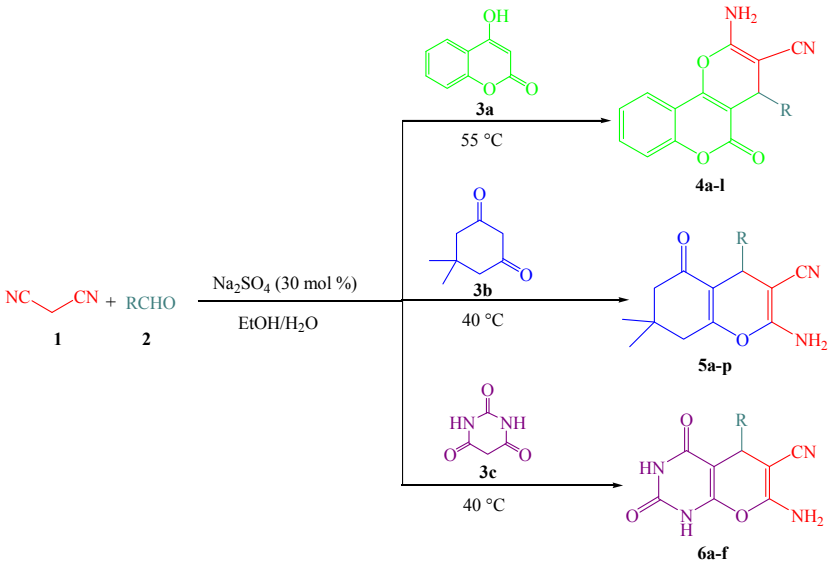
2. Experimental

2.1. General

Melting points and FT-IR spectra of all compounds were measured on an Electrothermal 9100 apparatus and a FT/IR-460 plus JASCO spectrometer, respectively. The 1H NMR spectra were obtained on BRUKER DRX-400 AVANCE instruments with acetone and DMSO as solvent. All reagents and solvents obtained from Fluka and Merck were used without further purification.



Scheme 1. Na_2SO_4 catalyzed synthesis of pyran annulated heterocyclic systems.

2.2. General procedure for the synthesis of tetrahydrobenzo[b]pyran or pyrano[2,3-d] pyrimidinone or dihydropyrano[3,2-c]chromene

A mixture of a malononitrile 1 (1 mmol), aldehyde 2 (1 mmol), 4-hydroxycoumarin 3a (1 mmol), dimedone 3b (1 mmol) or barbiturice acid 3c (1 mmol) and 30 mol % of Na_2SO_4 in ethanol/water (1:1) was stirred at 40-55 °C for a suitable time (Table 1). The reaction was monitored by thin-layer chromatography (TLC) using ethyl acetate/petroleum benzene (1:3) as eluent. After completion of the reaction, solid product was separated from catalyst by filtration, and after recrystallization from ethanol, the corresponding pure products were obtained.

Selected spectral data

Table 2, entry 1:

White solid; IR (KBr): $\bar{\nu}$ = 3377, 3284, 3255, 3179, 2198, 1708 cm^{-1}. ^1H NMR (400 MHz, Acetone-d_6) δ= 4.57 (1H, s), 6.70 (2H, br s), 7.26-8.0 (9H, m) ppm.

Table 2, entry 13:

White solid; IR (KBr): $\bar{\nu}$ = 3395, 3323, 3027, 2960, 2199, 1680 cm^{-1}. ^{1}HNMR (400 MHz, Acetone-d_6) δ= 1.04 (3H, s), 1.13 (3H, s), 2.16 (1H, d, *J*= 16.0 HZ), 2.28 (1H, d, *J*= 16.0 HZ), 2.58 (2H, s), 4.30 (1H, s), 6.25 (2H, br s), 7.19 (1H, m), 7.28 (4H, m) ppm.

Table 2, entry 29:

Dark yellow solid; IR (KBr): $\bar{\nu}$ = 3415, 3311, 3203, 3102, 3022, 2193, 1710 cm^{-1}. ^{1}HNMR (400 MHz, DMSO-d_6) δ= 4.48 (1H, s), 7.30 (2H, s), 7.60 (1H, t), 7.70 (1H, d), 8.0 (2H, t), 11.12 (1H, s), 12.18(1H, s) ppm.

3. Results and Discussion

In order to optimize the conditions, the reaction between benzaldehyde, dimedone and malononitrile was chosen as a simple model reaction. The model reaction under 10 mol% of different catalysts and at different temperature in ethanol/water (1:1) was first attempted (Table 1). After systematic screening, 30 mol % of the Na_2SO_4 in EtOH/H_2O at 40 °C was found to be the best (Table 1, entry 7). As shown in Table 1, the same model reaction was carried out in water, ethanol and mixture of them at different temperatures to assess the effect of temperature on the reaction yield. It was observed that the reaction yield was a function of temperature, since the yield increased as the reaction temperature increased at 40 °C, the product 5a was obtained in an excellent yield and higher temperature did not increase the reaction yield (Table 1, Entry 8). The effect of the amount of the catalyst on these reactions was also investigated. As a result, with the mixture of benzaldehyde, malononitrile, and dimedone in the presence of 3, 10 and 20 mol% Na_2SO_4, the product 5a was obtained in 63, 67 and 86% yield at 40 °C in EtOH/H_2O (1:1), respectively (Table 1, entries 4-6). Increasing the amount of catalyst to 40 mol%, yield of 95% was obtained. Therefore, the use of 30 mol% Na_2SO_4 is sufficient to push the reaction forward.

To explore the scope of the procedure, we extended this reaction to various aromatic aldehydes in the presence of electron-withdrawing or electron-releasing substituents (Table 2). To estimate the generality and versatility of the catalyst, the same reactions were applied for the synthesis of pyrano[2,3-*d*]pyrimidine and 3,4-dihydropyrano[c]chromene derivatives by replacing dimedone with barbituric acid and

Table 1. Optimization of various parameters for the synthesis of **5a**.

Entry	Catalyst	mol (%)	Time (min)	Solvent	Temp. (°C)	Yield (%) [a]
1	$HONH_3Cl$	15	60	$EtOH/H_2O$ (1:1)	60	-
2	Fumaric acid	10	60	$EtOH/H_2O$ (1:1)	60	90
3	Fumaric acid	10	720	$EtOH/H_2O$ (1:1)	r.t	91
4	Na_2SO_4	5	30	$EtOH/H_2O$ (1:1)	40	63
5	Na_2SO_4	10	16	$EtOH/H_2O$ (1:1)	40	67
6	Na_2SO_4	20	9	$EtOH/H_2O$ (1:1)	40	86
7	**Na_2SO_4**	**30**	**5**	**$EtOH/H_2O$ (1:1)**	**40**	**95**
8	Na_2SO_4	30	10	$EtOH/H_2O$ (1:1)	80	85
9	Na_2SO_4	30	300	$EtOH/H_2O$ (1:1)	r.t	95
10	Na_2SO_4	30	35	H_2O	60	89
11	Na_2SO_4	30	25	EtOH	40	85
12	Na_2SO_4	40	5	$EtOH/H_2O$ (1:1)	40	95

[a]Yield refers to the pure isolated products.

Table 2. Synthesis of chromenes and their derivatives with various aldehydes in the presence of Na_2SO_4 as a catalyst.

Entry	R	1,3-dicabonyl	Product	Time (min)	Yield (%)[a]	m.p.(°C)		Ref.
						Found	Reported	
1	C_6H_5	3a	**4a**	5	93	258-260	258-259	[27]
2	4-ClC_6H_4	3a	**4b**	16	87	261-263	261-262	[28]
3	2,4-$Cl_2C_6H_3$	3a	**4c**	15	95	255-257	258-259	[29]
4	4-$O_2NC_6H_4$	3a	**4d**	7	94	261-263	261-262	[28]
5	3-$O_2NC_6H_4$	3a	**4e**	23	90	263-264	261-262	[28]
6	4-MeC_6H_4	3a	**4f**	25	84	251-253	253-255	[29]
7	2-MeC_6H_4	3a	**4g**	25	88	262-264	260-261	[28]
8	4-$MeOC_6H_4$	3a	**4h**	20	80	223-225	222-224	[28]
9	2,5-$(MeO)_2C_6H_3$	3a	**4i**	8	91	226-228	230-233	[28]
10	3-MeO-4-HOC_6H_3	3a	**4j**	25	83	254-256	253-254	[27]
11	4-$(CH_3)_2NC_6H_4$	3a	**4k**	18	94	221-223	224-225	[29]
12	4-HOC_6H_4	3a	**4l**	14	79	260-263	264-266	[27]
13	C_6H_5	3b	**5a**	5	95	229-231	227-229	[28]
14	4-ClC_6H_4	3b	**5b**	15	94	207-209	207-209	[30]
15	3-ClC_6H_4	3b	**5c**	5	96	228-230	228-229	[30]
16	4-$O_2NC_6H_4$	3b	**5d**	14	87	180-182	180-182	[30]
17	3-$O_2NC_6H_4$	3b	**5e**	15	90	211-213	210-212	[30]
18	2-$O_2NC_6H_4$	3b	**5f**	10	85	225-227	227-230	[31]

Table 2. (*Continued*).

19	4-MeC_6H_4	3b	**5g**	5	94	213-216	212-215	[28]
20	4-$MeOC_6H_4$	3b	**5h**	10	93	200-202	203	[13]
21	3-HOC_6H_4	3b	**5i**	15	89	227-229	223	[13]
22	4-NCC_6H_4	3b	**5j**	15	93	224-226	227-230	[32]
23	4-$(Me)_2NC_6H_4$	3b	**5k**	20	85	199-201	198-200	[33]
24	3-MeO-4-HOC_6H_3	3b	**5l**	12	89	229-230	227-228	[34]
25	4-FC_6H_4	3b	**5m**	10	85	190-192	191-193	[19]
26	2-Furyl	3b	**5n**	12	92	223-225	222-224	[30]
27	2-Thienyl	3b	**5o**	12	90	210-212	210-212	[35]
28	$CH_3(CH_2)_5$	3b	**5p**	10	91	181-183	185-187	[36]
29	4-ClC_6H_4	3c	**6a**	7	96	242-244	241-242	[37]
30	2-ClC_6H_4	3c	**6b**	20	85	214-216	213-215	[37]
31	2,4-$Cl_2C_6H_3$	3c	**6c**	10	90	240-242	239-241	[31]
32	4-$O_2NC_6H_4$	3c	**6d**	10	94	237-239	238-239	[37]
33	3-$O_2NC_6H_4$	3c	**6e**	5	91	272-274	271-272	[31]
34	4-NCC_6H_4	3c	**6f**	8	88	249-251	252-253	[31]

[a]Yield refers to the pure isolated products.
[b]All known products were characterized from their spectral data (IR and NMR) and compared with those reported in the literature.

4-hydroxycoumarin. In each case, the products were obtained in excellent yields. For synthesizing of 3,4-dihydropyrano[c]chromene derivatives, when aromatic aldehydes containing electron-withdrawing groups were employed (Table 2, 4b-k) the obtained yield were better than those encountered with electron donating groups on aromatic rings (Table 2, 4f-l). In preparing tetrahydrobenzo[*b*]pyrans, no significant substituent effect was observed on the yields of the products (Table 2, 5a-p). Encouraged by these results, we also studied the cyclocondensation of heterocyclic aldehyde, such as furfuraldehyde and 2-thiophen carbaldehyde with malononitrile and dimedone to obtain the corresponding tetrahydrobenzo[*b*]pyran (Table 2, 5n-o) in a better yield. Also, using aromatic aldehydes including electron-withdrawing groups, Pyrano[2,3-*d*]pyrimidinone derivatives were obtained in good yields (Table 2, 6a-f). By studying these findings, we suggested a mechanism for the synthesis of pyran derivatives. For example, compound 5 is synthesized by a Knoevenagel condensation and Michael addition which is shown in Scheme 2. The reaction occurs via initial formation of the cyanoolefin 6 from the condensation of malononitrile 1 and aldehyde 2 which reacts with 7 to give the intermediates 8 and subsequently the desired compound 5 is formed by a cyclization reaction. Na_2SO_4 can be a suitable catalyst for this method because sodium cation (Na^+) is oxophilic, hence it will make a strong co-ordinate bond with oxygen atom (O) of 1,3-diketone to form its enolate ion 7. Sulfate anion (SO_4^{-2}) as a counter anion is sufficiently basic for the formation of cyanoolefin 6 and subsequent Michael addition of enolate of 1,3-diketone 7 on cyanoolefin 6, followed by cyclocondensation to form corresponding tetrahydrobenzo[*b*]pyran 5.

4. Conclusions

Na_2SO_4 is efficient, non-toxic, neutral salt, safe and inexpensive catalyst. Moreover, the experimental procedure was remarkably simple without the use of hazarded and/or expensive organic solvents. Therefore, sodium sulfate can be used as catalyst in the organic transformations.

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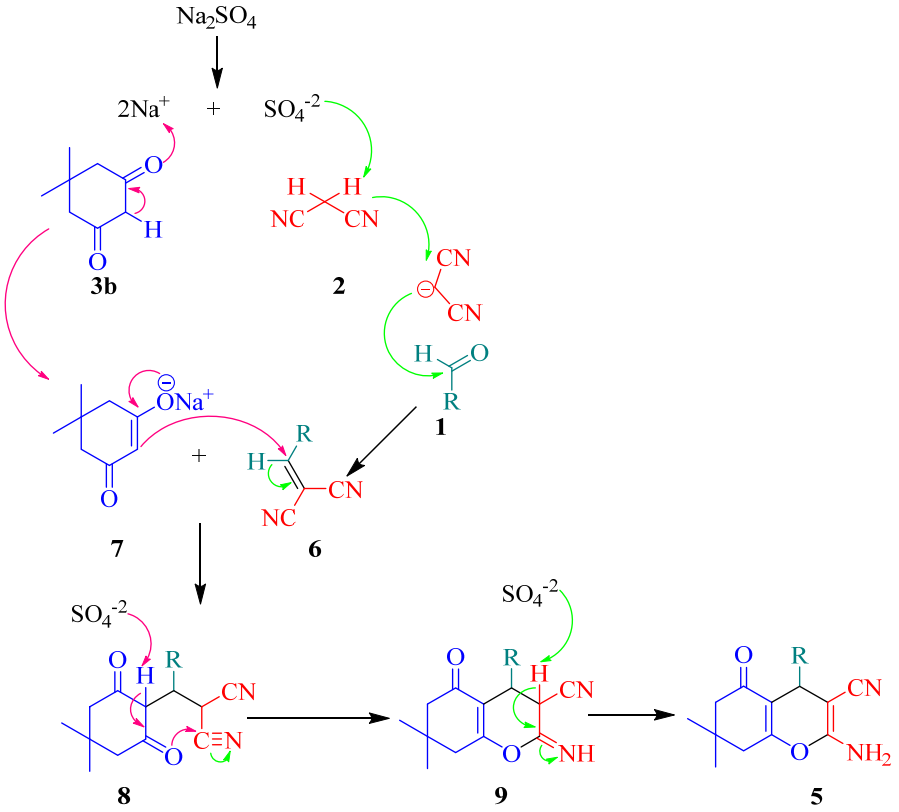

Scheme 2. Mechanistic pathway for three-component one-pot reaction leading to tetrahydrobenzo[b]pyran derivatives.

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