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ZnO catalyzed condensation of salicylaldehyde derivatives and malononitrile

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ABSTRACT

Several novel derivatives of 2-imino-2*H*-chromen-3-carbonitrile were prepared by the direct condensation of malononitrile and derivatives of salicylaldehyde in the presence of ZnO or MgO (40 mol%) as new green catalyst and EtOH as solvent at room temperature. Also in this project, the effect of different basic catalysts was studied. The attractive features of this procedure are environmentally benign and biodegradable solvent, operational simplicity, high yields, short reaction times, more economic, mild reaction conditions and simple work-up of the products. The structure of the synthesized compounds was established on the basis of spectral data, IR, ^{1} H-NMR and ^{13}C-NMR data.

Keywords: *2-Imino-2H-chromen-3-carbonitrile, green chemistry, ZnO, salicylaldehyde, malononitril*.

1. INTRODUCTION

Chromene derivatives are an important class of compounds. These products are widely present in plants, including edible vegetables and fruits. So far, numerous bioactive natural products have been identified including chromene-based structures. The presence of the chromene-based structure in these products has been associated with the capacity to prevent disease [1]. This class of natural products should be considered further in the development of new and more potent drugs.

A detailed analysis of the reports on the reaction of salicylaldehyde and malononitrile indicates that a delicate control of solvent, temperature, and ratio of reagents are determinant for the incorporation of 1, 2, or 3 molar equiv of malononitrile in the aldehyde unit [2]. A more recent publication reports the preparation of 2-iminochromene 1 when a 1:1 mixture of the reagents was refluxed in ethanol in the presence of trimethylamine [3].

The application of new catalytic methods in the fine and specialty chemicals industry has increased in recent years in order to minimize both production cost and waste generation. Among recent catalytic systems, DBU [4], DABCO [5], piperidine [6], morpholine [7], triethyl amine [8], hexamethylenetetramine [9], ionic liquid [10], cetyltrimethylammonium chloride (CTAC) [11], triethylbenzylammonium chloride (TEBC) [12], PEG-400 [13], $Ca(OH)_2$ [14] and KF/Al_2O_3 [15] could be mentioned for this component reaction. However, almost all of these methods suffer from long reaction time, high temperature, use of solvents or expensive and hazardous catalysts, and problems associated with the reusability of the catalysts.

In the present work, we carried out a detailed study on the reaction of salicylaldehyde derivatives and malononitrile in an attempt to clarify the reaction speed, the structure of the isolated products and the corresponding reaction conditions. The synthetic approaches allowed the preparation of 2-imino-*2H*-chromen-3-carbonitrils in the presence of green catalysts. To the best of our knowledge, the effect of these types of catalyst has never been reported. In this contribution, the catalytic behavior of ZnO and MgO in the synthesis of 2-imino-*2H*-chromen-3-carbonitrile derivatives is studied. Comparison of these two catalysts with other catalysts and conditions are listed in the table and returns responses.

2. EXPERIMENTAL SECTION

2.1. General: The chemicals involved in the synthesis were purchased from Merck or Aldrich. Melting Points were determined using in open capillary tubes on an electro thermal digital apparatus and are uncorrected. The reactions were monitored with the help of TLC using pre-coated aluminum sheets with GF254 silica gel, 0.25mm layer thickness (E-Merck). IR spectra were recorded on a varian 5000 Galaxy series FT-IR spectrophotometer using KBr discs. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 25℃ and 500 MHz, in DMSO-d_6 using tetramethylsilane (TMS) as internal standard.

2.2. General procedure for the synthesis of 2-imino-2H-chromene-3-carbonitril (3a-i): Equivalent amounts (1mmol) of both reactants (salicylaldehyde (1a) and malononitrile (2)) were mixed in a pyrex flask with ZnO and C_2H_5OH as catalyst and solvent respectively. The mixture was stirred at room temperature. Within 5 min, a yellow solid started to precipitate from the reaction mixture which was stirred at room temperature for a further 1.5 to 2 h. The progress of the reaction was followed by TLC. After completion, the precipitate was filtered off and recrystallized by water and diethylether.

To analyze the influence of carrying out the reaction with MgO as catalyst, the reactants were mixed with MgO as catalyst and the reaction was carried out as described above.

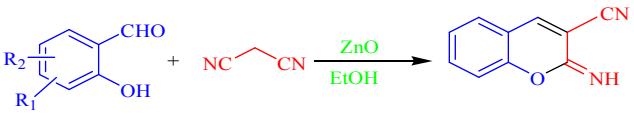
Spectral data for selected new products:

2-imino -*2H*-chromen-3-carbonitrile (3a): yellow solid, yield: 99%, m.p:150, IR(KBr) ν_{max}/cm^{-1}: 3459 (NH), 2225(CN); ^{1}H-NMR (500 MHz, DMSO-d_6) δ 3.88 (s, 3H), 7.33 (t, J = 2.1 Hz, 1H), 7.43 (t, J = 2.1 Hz, 1H), 8.25 (t, J = 1.8 Hz, 1H), 9,07 (d, J = 1.5 Hz, 1H); ^{13}C-NMR (MHz, DMSO-d_6) δ 56.5, 105.7, 114.9, 115.3, 119.0, 122.3, 137.7, 142.4, 145.8, 147.0.

2-imino-8-methyl-*2H*-chromen-3-carbonitrile (3h): White solid; yield: 95% (ZnO); mp: 201-203 °C; ^{1}H-NMR (500 MHz, DMSO-d_6) δ 3.68 (s, 3H), 6.83 (t, J = 2.1 Hz, 1H), 7.13 (t, J = 2.1 Hz, 1H), 7.75 (d, J = 1.8 Hz, 1H), 8,07 s, J = 1.5 Hz, 1H); ^{13}C-NMR (MHz, DMSO-d_6) δ 25.5, δ 56.5, 105.7, 114.9, 115.3, 119.0, 122.3, 137.7, 142.4, 145.8, 147.0.

3. RESULTS AND DISCUSSION

In continuation of our work [16], in this study, we wish to report a facile, component procedure for the synthesis of 2-imino-3-carbonitrile-*2H*-chromene derivatives (3a-i) using malononitrile (2), different aromatic aldehydes (1a-h) at 25-40℃ in the presence of ZnO or MgO under stirring conditions (Scheme 1).



1(a-i) 2 3(a-i)

85-100%

1a) R_1=H; R_2=H
1b) R_1=OMe; R_2=H
1c) R_1=Cl; R_2=H
1d) R_1=Br; R_2=OMe
1e) R_1=F; R_2=H
1f) R_1=NO_2; R_2=H
1g) R_1=H; R_2=NO_2
1h) R_1=Me; R_2=H
1i) R_1=Me; R_2=Me

Scheme 1. Synthesis of 2-imino- *2H*-chromene-3-carbonitriles.

First, in order to evaluate the synthetic potential of the proposed procedure and to optimize the general conditions, the condensation reaction of salicylaldehyde (1a) and malononitrile (2) was studied using different bases under conditions as the model reaction. The results have been summarized in (Table 1).

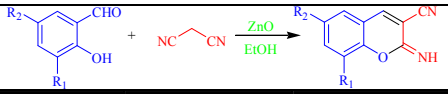
Table 1. Optimization of the reaction conditions for 2-imino-*2H* chromene-3-carbonitril

Entry [a]	Catalyst	Mol %	Time (h)	Yield (%) [b]
1[c]	-	-	5	-
2	$NaHCO_3$	20	5	89
3	Na_2CO_3	10	4	88
4	DABCO	30	4	75
5	Piperidine	20	7	76
6	$Ca(OH)_2$	30	4	90
7	*L*-Proline	10	6	90
8	MgO	50	2	98
9	ZnO	40	2	99
10	ZnO	10	2	80
11	ZnO	60	2	99
12	ZnO	20	2	85
13	MgO	65	2	98
14	MgO	20	2	80
15	MgO	30	2	85
16	K_2CO_3	25	2	90

[a]Reaction conditions: salicylaldehyde (1.0 mmol), malononitrile (1.0 mmol) and required amount of catalyst; [b] Isolated yield (average of at least 2 runs); [c] Reaction was performed at room temperature.

As can be seen ZnO afforded higher yield (99%) compared to other basic catalysts (Table 2, entries 2-16). After completion of the reaction, a simple work up afforded the desired product. It was also observed that the reaction did not proceed completely in the absence of a basic catalyst at room temperature (Table2, entry 1) [16]. We then turned our attention to optimize the amount of catalyst. It was discovered that 40 mol% of ZnO and 50 mol% of MgO were the optimum amount for this transformation at room temperature (Table 2, entries 9-16). Encouraged by these results, aromatic aldehydes bearing both electron-withdrawing and electron-donating groups were subjected to component condensation reactions under optimized reaction conditions (40 mol% ZnO and 50 mol% MgO at room temperature).

Table 2. Synthesis of 2-imino-*2H*-chromen-3-carbonitril derivatives catalyzed by ZnO.



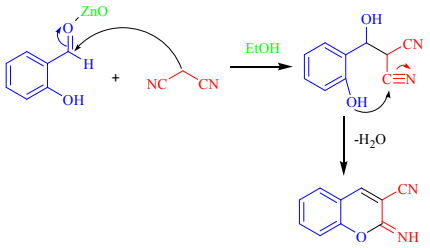
Entry	R_1	R_2	Product	Time (h)	Mp (°C)	mp [ref] (°C)	Yield (%)[b]	T (°C)
1	H	H	3a	1	150-152	142-145 [17]	100	r.t
2	OMe	H	3b	1	145-146	111-112 [17]	98	r.t
3	Cl	H	3C	2	160-162	163-164 [17]	89	r.t
4	Br	OMe	3d	2	200-202	201-203 [17]	85	r.t
5	F	H	3e	2	190-192	187-189 [17]	89	r.t
6	NO_2	H	3f	3	173-174	169-170 [15]	85	40
7	H	NO_2	3g	3	209-210	211-213 [15]	87	40
8	Me	H	3h	2	200-201	This work	95	r.t
9	Me	Me	3i	2	220-223	This work	96	r.t

[a] Reaction conditions: malononitrile (1mmol), salicylaldehyde (1mmol), ZnO or MgO (40 m0l%) in EtOH at r.t;
[b]All yields refer to isolated products.

The results have been summarized in Table 2. The reactions worked well with almost all salicylaldehydes with both electron-donating and electron-withdrawing substituents and excellent yields of the desired products 3a-i were obtained, selectively, in a simple procedure. Moreover, By-products, such as enaminonitrile, malononitrile, self-condensation adducts, and reduced products were not detected in the reaction mixture [4, 17]. Finally, the corresponding 2-imino-*2H*-chromene-3-carbonitril derivatives were isolated by crystallization from the crude filtrate. Interestingly, the condensations of 3-methoxcysalicylicaldehyde (3b), 3-methylsalicylicaldehyde (3h) and 3,4- dimethyl salicylaldehyde (3i) were completed at room temperature in relatively short reaction time (entries 2, 8 and 9). This would be

promising for large scale preparation of *2H*-chromene derivatives (3a-i).

Scheme 2. Proposed mechanism for the synthesis of 2-imino-*2H*-chromen-3-carbonitril.



It is also worth to mention that using industrial techniques such as ball-milling [18, 19], Aliphatic aldehydes such as isobutyraldehyde, dihydrocinnamaldehyde and cinnamaldehyde, produce mixtures of products in low yields under the above optimized conditions. This may be attributed to the undesired aldol condensation or Michael addition as the side reactions [19]. In the end of our work, we have compared the present protocol with some of those reported in the literature in order to show the advantages of the present method (Table 3). As is evident the present procedure gives the highest yield of the products. Taking into consideration the above result, the following mechanism can be proposed for the condensation of different salycilaldehydes (1a) and malononitrile (2) to afford 2-imino-3-carbonitril-2H-chromene derivatives (3a-I) catalyzed by ZnO or MgO (Scheme 2).

Table 3. Comparision of different methods in synthesis of 2-imino-*2H*-chromen-3-carbonitrile.

Entry	Solvent	Catalyst	T (°C)	Time (min)	Yield (%)
1	Ethanol	DABCO	r.t	120-240	75 [5]
2	----	Na_2CO_3	50	40	92 [11]
3	Ethanol	$Ca(OH)_2$	60	120	89 [14]
4	propanol	NaBr [b]	r.t	90	83 [12]
5	Ethanol	ZnO	r.t	90	99 [This work]
6	Ethanol	MgO	r.t	120	98 [This work]
7	H_2O	L-proline	75	120-240	90 [13]
8	H_2O	K_2CO_3	70	52	87 [14]
9	Solvent free	NaOAC/ KF	60	180	92 [15]
10	EtOH	ACOH	75	24h	89 [16]

[a] All yields are based on benzaldehyde; [b] NaBr was used as electrolyte

4. CONCLUSIONS

In summary, an efficient, rapid and simple procedure for the preparation of densely functionalized 2-imino-3-cyano-*2H*-chromene derivatives has been established. The attractive features of this procedure are environmentally benign, biodegradable solvent, operational simplicity, high yields, short reaction times, more economic, mild reaction conditions and simple work-up of the products.

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