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A green and efficient one-pot three-component synthesis of dihydropyrano[3,2-c]chromenes using NaCl in hydroalcoholic media

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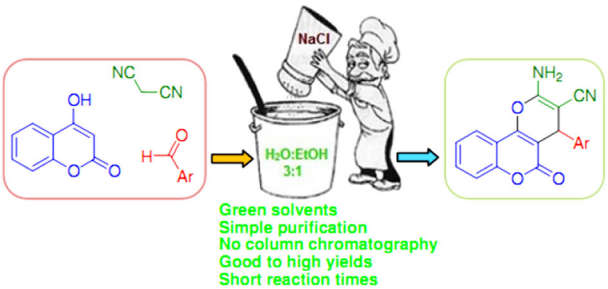
Abstract An ecofriendly and efficient one-pot procedure for the preparation of dihydropyrano[3,2-c]chromene derivatives via NaCl-catalyzed three-component reaction of aromatic aldehydes, malononitrile and 4-hydroxycoumarin in hydroalcoholic media at ambient temperature has been reported. Greenness of the process was well established, as a mixture of water–ethanol was used as reaction media. Furthermore, the presented methodology offers several advantages such as inexpensive catalyst, high to excellent yields, short reaction times, simple procedure and lack of need for column chromatography.

Graphical abstract



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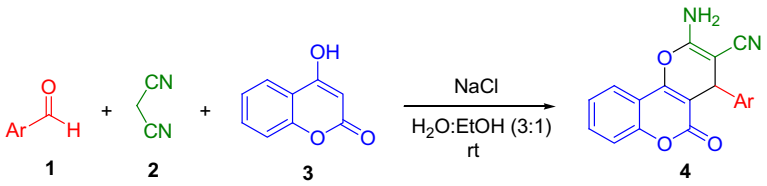
Keywords Dihydropyrano[3,2-c]chromene · Sodium chloride · Three-component reaction · Malononitrile · 4-hydroxycoumarin

Introduction

The development of efficient, practical and eco-friendly methodologies for the preparation of compounds with biological significance is one of the main priorities for green chemistry [1]. Among the several aspects of green chemistry, the replacement of volatile organic solvents with green solvents such as water and ethanol is of greatest concern. One of the most useful tools for the synthesis of chemically and biologically important compounds is multicomponent reactions (MCRs), which combine three or more substrates, either simultaneously, leading to domino processes, or through the sequential addition of one or more reactants without isolating intermediate species or changing the solvent. MCRs offer remarkable advantages including operational simplicity, facile automation and minimized waste generation due to the reduction in the number of work-up, extraction and purification steps [2–4].

Dihydropyrano[3,2-c]chromenes are very interesting compounds due to their biological and pharmaceutical activities, such as anti-HIV, antimicrobial, antibacterial, anticancer, spasmolytic and anticoagulant [5–8]. Dihydropyrano[3,2-c]chromene derivatives have also been reported as potential drugs for the treatment of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, AIDS-associated dementia, Down's syndrome, and Huntington's disease as well as schizophrenia and myoclonus [8]. As a result, considerable efforts have been made for the synthesis of this important class of compounds. These heterocycles are generally prepared by means of reaction between aldehydes, activated methylene compounds and phenol derivatives in the presence of catalysts such as piperidine [9, 10], cetyltrimethylammonium chloride (CTAC) [11], and cetyltrimethylammonium bromide (CTAB) coupled with ultrasound [12], γ-alumina [13], K_2CO_3 under microwave irradiation [14], MgO nanoparticles [15], heteropolyacid [16], hexadecyltrimethylammonium bromide (HTMAB) [17], triethylbenzylammonium chloride (TEBA) [18], $TiCl_4$ [19], $(NH_4)_2HPO_4$, (*S*)-proline [20], sodium carbonate [21], NaOAc/KF [22], NaBr coupled with electrochemical technique [23], indium with NaI [24], sodium dodecyl sulfate (SDS) [25], tetrabutylammonium chloride [26], and 3-hydroxypropanaminium acetate (HPAA) [27]. However, some of these methods have displayed drawbacks, such as environmental pollution caused by utilization of toxic solvents, long reaction times, moderate yields, and using stoichiometric amounts of catalyst. Therefore, it is necessary to further develop an efficient and convenient method to construct such a significant scaffold.

In continuation of our ongoing research to develop mild and efficient catalyst systems for the synthesis of heterocycle compounds [28–31], we wish to report commercially available NaCl, as an inexpensive catalyst for the one-pot synthesis of dihydropyrano[3,2-c]chromene derivatives **4** via three-component reaction of aromatic aldehydes **1**, malononitrile **2** and 4-hydroxycoumarin **3** in water–ethanol media (3:1) at ambient temperature (Scheme 1).



Scheme 1 Synthesis of dihydropyrano[3,2-c]chromenes **4**

Experimental

General procedure for the synthesis of dihydropyrano[3,2-c]chromene

A mixture of aromatic aldehyde (1 mmol), malononitrile (1 mmol), 4-hydroxy-coumarin (1 mmol) and NaCl (5 mol%) in water:ethanol (3:1, 5 mL) was stirred at ambient temperature for the appropriate time (Table 3). The progress of the reaction was monitored by TLC. After completion, the solid precipitate was filtered off and washed with ethanol and purified by recrystallization from hot ethanol, if necessary. Spectral data of selected products are represented below.

2-Amino-4,5-dihydro-5-oxo-4-phenylpyrano[3,2-c]chromene-3-carbonitrile (**4a**)

IR (KBr, cm^{-1}): 3,375, 3,285 (NH_2), 2,197 (CN), 1,708 (C=O), 1,674, 1,605, 1,380. ^1H NMR (400 MHz, DMSO-d_6): δ, 4.57 (1H, s, CH), 6.70 (2H, brs, NH_2), 7.25–7.50 (7H, m, ArH), 7.69–7.73 (1H, m, ArH), 7.97–8.00 (1H, m, ArH) ppm.

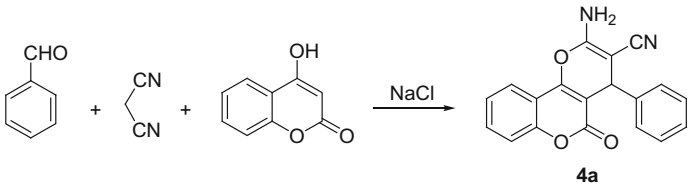
2-Amino-4,5-dihydro-5-oxo-4-p-tolylpyrano[3,2-c]chromene-3-carbonitrile (**4b**)

IR (KBr, cm^{-1}): 3,388, 3,310 (NH_2), 2,194 (CN), 1,715 (C=O), 1,675, 1,610, 1,375. ^1H NMR (400 MHz, DMSO-d_6): δ 2.42 (3H, s, CH_3), 4.49 (1H, s, CH), 7.27 (2H, d, $J = 8.0$ Hz, ArH), 7.33 (2H, brs, NH_2), 7.38–7.41 (2H, m, ArH), 7.45 (1H, d, $J = 7.8$ Hz, ArH), 7.61–7.76 (3H, m, ArH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.1, 33.4, 58.1, 102.4, 116.2, 118.5, 119.86, 122.7, 126.7, 127.9, 131.0, 131.8, 134.9, 143.8, 152.5, 153.7, 157.8, 159.4 ppm.

2-Amino-4,5-dihydro-4-(3-nitrophenyl)-5-oxopyrano[3,2-c]chromene-3-carbonitrile (**4g**)

IR (KBr, cm^{-1}): 3,402, 3,322 (NH_2), 2,202 (CN), 1,703 (C=O), 1,670, 1,606, 1,538, 1,380. ^1H NMR (400 MHz, DMSO-d_6): δ 4.70 (1H, s, CH), 7.35–7.44 (3H, m, NH_2 and ArH), 7.53–7.80 (7H, m, ArH) ppm.

Table 1 Investigation of solvent effects on the model reaction



4a

Entry	Solvent (ratio)	Time (min)	Yield (%)[a]
1	H_2O	120	65
2	EtOH	200	48
3	H_2O:EtOH (1:1)	60	70
4	H_2O:EtOH (2:1)	45	82
5	H_2O:EtOH (3:1)	20	91
6	H_2O:EtOH (5:1)	40	73
7	H_2O:EtOH (10:1)	90	51

Experimental conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), 4-hydroxycoumarin (1 mmol), NaCl (5 mol%) in solvent (5 mL) at ambient temperature

[a] Isolated yield

Table 2 Optimization of catalyst effects in the synthesis of compound **4a**

Entry	Catalyst (mol %)	Time (min)	Yield (%)[a]
1	NaCl (2.5)	50	84
2	NaCl (5)	20	91
3	NaCl (10)	35	88
4	NaCl (20)	30	80
5	NaCl (30)	35	82
6	NaCl (40)	30	79
7	NaBr (5)	90	55
8	NaOH (5)	40	84
9	LiCl (5)	120	25
10	LiBr (5)	120	24
11	KCl (5)	120	37
12	AgCl (5)	6 h	61
13	Na_2SO_4 (5)	180	58
14	$CaSO_4$ (5)	180	74
15	No catalyst	24 h	18

Experimental conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), 4-hydroxycoumarin (1 mmol) in 5 mL of H_2O:EtOH (3:1) solvent at room temperature

[a] Isolated yield

2-Amino-4,5-dihydro-4-(3,4-dimethoxyphenyl)-5-oxopyrano[3,2-c]chromene-3-carbonitrile (**4l**)

IR (KBr, cm^{-1}): 3,401, 3,320 (NH_2), 2,199 (CN), 1,711 (C=O), 1,670, 1,605, 1,524, 1,381. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (3H, s, OCH_3), 3.73 (3H, s, OCH_3),

Table 3 Synthesis of dihydropyrano[3,2-c]chromenes **4a–l**

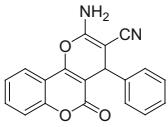
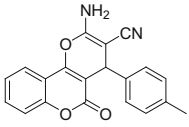
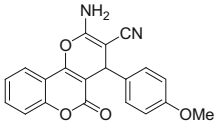
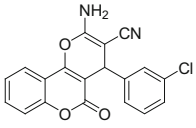
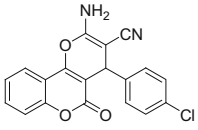
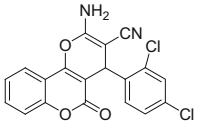
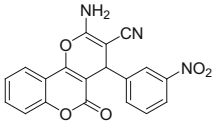
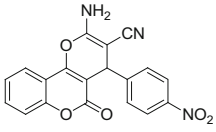
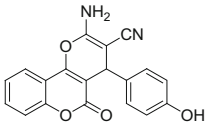
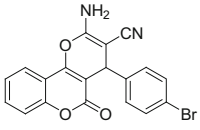
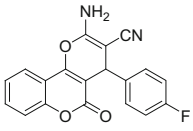
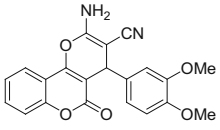
Entry	Ar	Product	Time (min)	Yield (%)[a]	M.p. (°C)	Lit. M.p. (°C)[b]
1	Ph	 **4a**	20	91	257–259	256–258 [25]
2	4-Me-C_6H_4	 **4b**	15	84	249–251	251–253 [25]
3	4-MeO-C_6H_4	 **4c**	15	90	235–237	229–230 [27]
4	3-Cl-C_6H_4	 **4d**	12	89	244–246	243–244 [27]
5	4-Cl-C_6H_4	 **4e**	10	92	260–262	263–265 [20]
6	2,4-Cl_2-C_6H_3	 **4f**	10	90	257–259	257–259 [20]
7	3-NO_2-C_6H_4	 **4g**	10	89	261–263	262–264 [20]
8	4-NO_2-C_6H_4	 **4h**	10	91	254–256	258–260 [20]

Table 3 continued

Entry	Ar	Product	Time (min)	Yield (%)[a]	M.p. (°C)	Lit. M.p. (°C)[b]
9	4-HO-C_6H_4	 **4i**	20	83	258–260	259–260 [27]
10	4-Br-C_6H_4	 **4j**	20	89	250–252	247–249 [25]
11	4-F-C_6H_4	 **4k**	25	91	256–258	260–262 [25]
12	3,4-MeO_2-C_6H_3	 **4l**	25	85	222–224	228–230 [25]

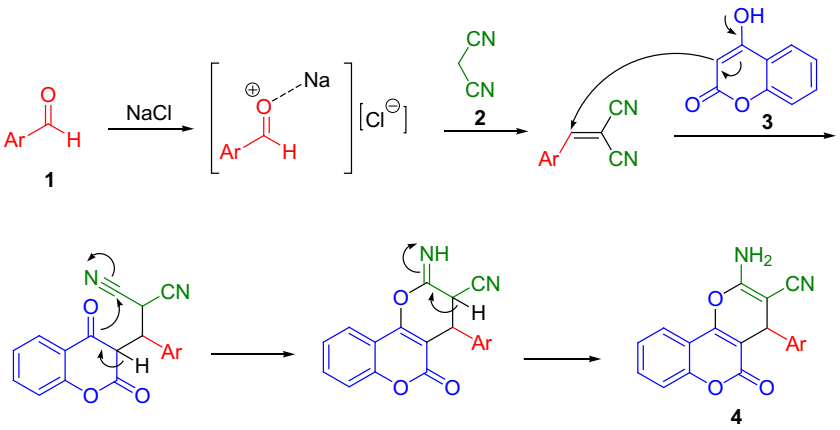
[a] Isolated yield

[b] The known products were characterized by comparison of their IR and NMR spectra and melting points with those of authentic samples

4.45 (1H, s, CH), 6.72 (1H, m, ArH), 6.90 (2H, d, $J = 8.2$ Hz, ArH), 7.35 (2H, brs, NH_2), 7.38–7.45 (2H, m, ArH), 7.63–7.66 (1H, m, ArH), 7.90 (1H, $J = 7.8$ Hz, ArH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.1, 55.4, 55.5, 58.0, 103.5, 110.9, 111.5, 112.7, 115.9, 119.5, 119.8, 122.2, 122.5, 124.6, 132.5, 136.0, 148.4, 152.1, 153.3, 157.5, 159.5 ppm.

Results and discussion

Initially, the mixture of benzaldehyde (1 mmol), malononitrile (1 mmol) and 4-hydroxycoumarin (1 mmol) in water (5 mL) was treated with 5 mol% of NaCl at ambient temperature. The corresponding dihydropyrano[3,2-c]chromene **4a** was obtained in 65 % yield after 2 h. This reaction was chosen as a model and was carried out in ethanol and mixtures of water and ethanol, and the results are summarized in Table 1. The best result was obtained in the mixture of water:ethanol (3:1).



Scheme 2 The proposed mechanism for the synthesis of dihydropyrano[3,2-c]chromenes

Next, to find out the optimum quantity of catalyst, the model reaction was performed in the presence of different amounts of NaCl. Increasing the catalyst loading to 40 mol% did not improve the reaction yield. Notably, when the reaction was examined in the absence of the catalyst, a low yield (18 %) of the target product was obtained. Some potential catalysts such as NaBr, NaOH, LiCl, LiBr, KCl, AgCl, Na_2SO_4 and $CaSO_4$ were also tested for the synthesis of product **4a**, and the results are listed in Table 2.

With the above optimized reaction conditions, a series of the dihydropyrano[3,2-c]chromenes **4a–l** were synthesized (Table 3). As shown in Table 3, the reaction was found to be compatible with various functional groups such as F, Cl, Br, NO_2, OH, Me and OMe. In all cases, the reaction proceeded smoothly to produce the corresponding product in good to high yield.

In general, at the beginning of the reaction, the chemicals themselves were dissolved completely in the reaction medium to form a homogeneous mixture. But, at the end of the reaction, the system became a suspension and finally the product was precipitated. The products were obtained through simple filtration and washed with ethanol and recrystallized in hot ethanol to afford pure products. The structure of the products **4a–l** was characterized by IR, ^1H and ^{13}C NMR spectral data and by comparison of their melting points with those of authentic samples.

As reported in the literature [20, 21, 27], a possible mechanism for the formation of dihydropyrano[3,2-c]chromene **4** is shown in Scheme 2.

Conclusion

In conclusion, we have developed a green and efficient synthesis of dihydropyrano[3,2-c]chromene derivatives via a one-pot three-component reaction using NaCl as an inexpensive catalyst. The noteworthy features of this methodology are mild

reaction conditions, operational simplicity, readily available starting materials and catalyst, short reaction times and good to high yields. Moreover, all products were obtained through simple filtration with no need for column chromatography, which reduces the waste as well as environmental pollution.

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