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Envirocat EPZG Mediated Synthesis of 3,4-Dihydropyrano[*c*]chromene Derivatives Under Microwave Irradiation in Solvent-free Conditions

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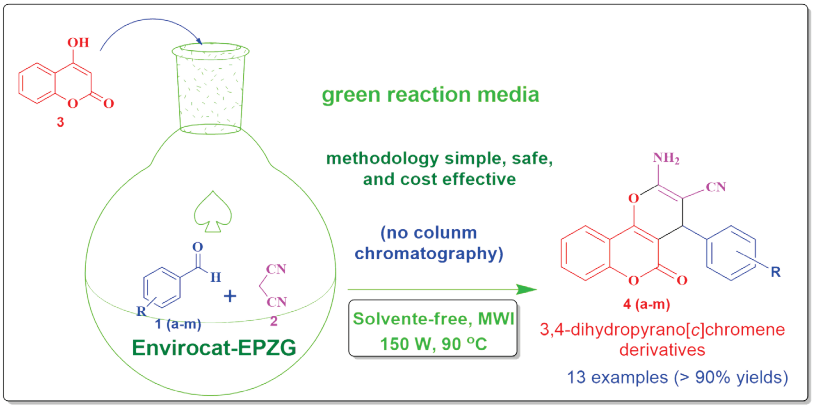
A Envirocat EPZG mediated method is developed for the synthesis of 3,4-dihydropyrano[*c*]chromene derivatives under microwave irradiation by three component cyclocondensation of 4-hydroxycoumarin, malononitrile and aromatic aldehydes. The process has been carried out under solvent-free conditions in the presence of very small amount of Envirocat EPZG. Use of ecofriendly readily available catalyst and green reaction media makes this methodology simple, safe, and cost effective. Mild reaction conditions, easy workup procedure, excellent yields and short reaction times are some remarkable features of this work.

Graphical abstract



Keywords

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1. Introduction

Multicomponent reactions (MCRs) allow assembly of several flexible, readily available integrant in a single step reaction to give highly functionalized organic molecules [1-3]. Over the past several years, chemists have been aware of the human health and environment, so they are trying to develop new synthetic methods, reaction conditions in the context of green chemistry. The reactions carried out under solvent-free conditions have many advantages such as high efficiency and selectivity, operational simplicity, low costs, mild reaction conditions and reduced pollution [3-5]. These factors are beneficial to industry as well as to the environment.

Dihydropyrano[*c*]chromenes and its derivatives are a class of important heterocycles because they possess a wide range of biological and pharmacological activities such as analgesic [6], anti-HIV [7], anticancer [8], antituberculosis agents [9], anticoagulant [10], antibacterial [11], anti-Alzheimer [12], antimalarial [6], antimicrobials [8], antifungal [13], molluscidal [14], acetylcholinesterase inhibitor [15] and anti-inflammatory [16]. Moreover, they have been used as cognitive enhancers for the treatment of neurodegenerative diseases, including Alzheimer's disease, amyotrophic lateral

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sclerosis, Parkinson's disease and AIDS associated dementia [13]. In addition, derivatives of dihydropyrano[2,3-c]chromene can also be employed as cosmetic pigment and utilized as potential biodegradable agrochemical [17].

In literature, few methods have been reported for the synthesis of dihydropyrano[*c*]chromene derivatives. Some recent methodologies include use of diammonium hydrogen phosphate (DAHP) [18], SiO_2PrSO_3H [17], K_2CO_3 under microwave irradiation [19], TBAB [20], MgO [21], $H_6P_2W_{18}O_{62}{\cdot}18H_2O$ [22], hexamethylene tetramine [23], TMGT [24], 3-hydroxypropanaminium acetate (HPAA) [25], 2-hydroxyethylammonium formate [26], potassium phthalimide-*N*-oxyl [27] and CuO nanoparticles [28] catalysts. However, many of these methodologies are associated with disadvantages such as harsh reaction condition, poor yields, prolonged reaction times and use of hazardous organic solvent. Hence, it is desirable to develop rapid, efficient and ecofriendly protocol for the synthesis of dihydropyrano[*c*]chromenes.

Microwave-assisted rapid organic reactions are extremely attractive to synthetic organic chemists due to reducing reaction times, getting cleaner reactions, improving yields, simplifying work-up and designing energy-saving protocols [29-32]. These reactions also attract research interest because these reactions exhibit some particular unexpected reactivity's and significant usefulness in green chemistry [33, 34]. Envirocat EPZG is a solid supported heterogeneous catalyst which exhibits both Bronsted and Lewis acid characteristics. This catalyst is nontoxic and used normally in non-polar or solvent-free reaction systems [35].

In continuation of our interest to develop greener methodologies for the synthesis of biologically active compounds, herein we report an Envirocat EPZG mediated one-pot synthesis of dihydropyrano[*c*]chromene derivatives by the reaction of aromatic aldehydes, malononitrile, and 4-hydroxycoumarin in solvent-free conditions under microwave irradiation.

2. Material and Methods

All the chemicals used are of commercial grade and were used without further purification. All reactions were prosecuted by thin layer chromatography (TLC). The uncorrected melting points of compounds were taken in an open capillary in a paraffin bath. ^{1}H NMR spectra were recorded on a Bruker Avance 400 and ^{13}C NMR was recorded on a Bruker DRX-300 instrument using TMS as an internal reference. Mass spectra were recorded on Waters UPLC-TQD Mass spectrometer using electrospray ionization technique. For the microwave irradiation experiments described below, a microwave oven equipped with a turntable was used (LG Smart Chef MS255R operating at 2450 MHz having maximum output of 900 W) for reaction.

General procedure for the Envirocat EPZG mediated synthesis of 3,4-dihydropyrano[c]chromenes

Aromatic aldehyde **1** (1 mmol), malononitrile **2** (1.2 mmol), 4-hydroxycoumarin **3** (1 mmol) and EPZG (0.10 g) were mixed thoroughly and kept in microwave irradiation at 150 W and 90 ºC for appropriate time. The progress of reaction was monitored by TLC (ethyl acetate: hexane 3:7). After completion of the reaction, the mixture was cooled at room temperature. The solid product was filtered washed with water dried and recrystallized from ethanol to give the pure crystals of 3,4-dihydropyrano[c]chromene derivatives.

Spectral data of selected 3,4-dihydropyrano[c]chromene derivatives

2-Amino-4-(furan-2-yl)-4, 5-dihydro-5-oxopyrano[3,2-*c*]chromene-3-carbonitrile (**4h**, Table 5) m.p.: 250-252 °C (lit. [36] m.p.: 251-254°C); ^{1}H NMR (DMSO, 300 MHz, Me_4Si) δ (ppm): 4.62(s, 1H, CH), 6.37 (brs, 2H, NH_2), 7.46-7.89 (m, 7H, Ar); ^{13}C NMR ($CDCl_3$, 75.46 MHz, Me_4Si) : 30.58, 55.26, 101.61, 106.42, 110.64, 112.88, 116.66, 118.99, 122.39, 124.77, 133.17, 142.40, 152.14, 153.96, 154.17, 158.75, 159.37; MS (EI): m/z 308.07 (M^+).

2-amino-4, 5-dihydro-4-(1H-indol-3-yl) pyrano [3, 2-c] chromene-3-carbonitrile (**4l**, Table 5) m.p.: 178-180 °C; ^{1}H NMR (DMSO, 300 MHz, Me_4Si) δ(ppm): 2.49 (s, 1H, NH), 4.73(s, 1H, CH) 6.91-8.69 (m, 9H, Ar), 10.99 (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$, 75.46 MHz, Me_4Si) : 28.73, 58.26, 69.26, 104.10, 110.95, 111.85, 113, 115.9, 116.45, 117.85, 118.99, 119.58, 120.89, 122.52, 123.91, 124.55, 126.66, 132.61, 133.22, 136.56, 151.45, 158.06, 159.44; MS (EI): m/z 341.36 (M^+)

3. Results and Discussion

To optimize the reaction conditions, the reaction of benzaldehyde (1.0 mmol), malononitrile (1.2 mmol), and 4-hydroxycoumarin (1.0 mmol) was used as a as a model reaction in presence of different catalysts in order to establish the effectiveness of the catalyst under solvent-free conditions (Table 1). According to the results that provided in Table 1, Envirocat- EPZG showed better catalytic activity among these catalysts (Table 1, entries 1-5). Most excitingly, when Envirocat EPZG was used, the reaction proceeded very smoothly and gave the product **4a** in 95% yield (Table 1, entry 5).

Table 1. Screening of catalysts.

Entry	Catalyst	Amount of Catalyst (g)	Time (min)	Yield (%)
1	EPZ10	0.15	45	58
2	EPIC	0.15	40	68
3	EPZE	0.15	35	72
4	EPAD	0.15	32	76
5	EPZG	0.15	05	95

[a]Reaction condition: Aromatic aldehyde **1a** (1 mmol), malononitrile **2** (1.2 mmol), 4-hydroxycoumarin **3** (1mmol), under solvent-free conditions in microwave irradiation at 150 W and 90 ºC.[b]Isolated yield.

Then, we examined the effect of catalyst concentration over the above model reaction and obtained results are summarized in Table 2. It was found that the yield of product 4a was strongly affected by the catalyst concentration. It is found that the yield of product is increased by increasing catalyst concentration and best result was obtained with 0.10 gm of EPZG catalyst (Table 2, entry 5). Therefore, 0.10 gm of EPZG catalyst was sufficient and excessive amount of catalyst did not increase the yields significantly (Table 2, entries 5 and 6).

In addition, the effect of solvent on model reaction was explored and obtained results are shown in Table 3. The results of Table 3 indicate that the use of solvent retards the rate of reaction which leads to decrease in yield of product. However, the best results were obtained under solvent-free

conditions (Table 3, entry 5).

Table 2. Optimization of catalyst concentration.

Entry	Amount of Catalyst (g)	Time (min)	Yield[b] (%)
1	0.02	25	65
2	0.04	22	72
3	0.06	20	80
4	0.08	16	85
5	0.10	05	95
6	0.15	05	95

[a]Reaction condition: Aromatic aldehyde **1a** (1 mmol), malononitrile **2** (1.2 mmol), 4-hydroxycoumarin **3** (1 mmol), and EPZG under solvent-free conditions in microwave irradiation at 150W and 90 °C. [b]Isolated yields.

Table 3. Optimization of different solvents.

Entry	Solvent	Time (min)	Yield[b] (%)
1	CH_3CN	12	72
2	Toluene	15	80
3	THF	16	85
4	H_2O	15	95
5	Solvent-free	05	95

[a]Reaction condition: Aromatic aldehyde **1a** (1 mmol), malononitrile **2** (1.2 mmol), 4-hydroxycoumarin **3** (1 mmol), and EPZG (0.10 g) under solvent-free conditions in microwave irradiation at 150W and 90 °C. [b]Isolated yields.

Moreover, the effect of reaction temperature on model reaction was investigated in the presence of EPZG (0.10 gm) under solvent free condition (Table 4). The obtained results revealed that percent yield was increased by increasing reaction temperature from 60 to 90 °C (Table 4, entries 1- 4). Therefore, higher yield of product was obtained at 90 °C in shorter reaction time. The yield of product and reaction time show no significant change with further rise in reaction temperature. Hence, 90 °C was selected as the optimum temperature for all the reactions.

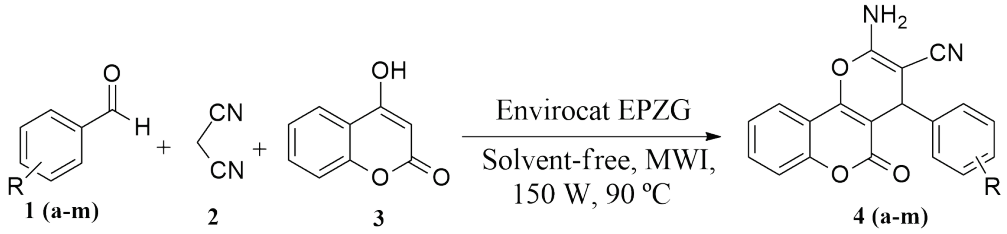
Table 4. Optimization of reaction temperature

Entry	Temperature (°C)	Microwave power	Time (min.)	Yield[b] %
1	60	150	18	62
2	70	150	12	62
3	80	150	10	74
4	**90**	**150**	**05**	**95**
5	100	150	05	95

[a]Reaction condition: Aromatic aldehyde **1a** (1 mmol), malononitrile **2** (1.2 mmol), 4-hydroxycoumarin **3** (1 mmol), and EPZG (0.10 g) under solvent-free conditions, in microwave irradiation at 150W and 90 [0]C. [b]Isolated yields.

With the optimized conditions in hand, to explore the scope of this procedure, we extended our study with wide range of aryl aldehydes containing either electron-withdrawing or electron-donating substituent's (Table 5). However, the electronic nature of the aryl substituents in the aldehydes did not show strong effects in terms of yields. Thus, the electron withdrawing substituted aromatic aldehydes and the aromatic aldehydes bearing electron-donating groups on the aromatic ring underwent clean conversion under the reaction conditions to produce the corresponding products in good yields. The reaction is equally good with heteroaromatic aldehyde (Table 5, entries h, I, and l), resulting in good yields of 3,4-dihydropyrano[c]chromenes.

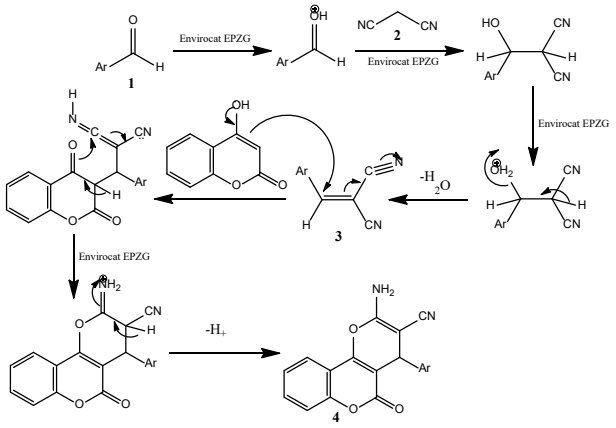
Table 5. Synthesis of 3,4-dihydropyrano[c]chromene **5(a-m).**



Product	R	Time (min)	Yield[b] %	Melting Point (°C)		Ref.
				Found	Reported	
4a	H	5	95	255-257	256-258	[18]
4b	4-Me	4	93	251-252	252–254	[36]
4c	4-MeO	4	93	241-243	240-242	[18]
4d	3,4(CH_3O)$_2$	5	93	231-232	230-232	[37]
4e	4-Cl	5	95	261-263	263-265	[18]
4f	4-OH	5	94	263-264	262-266	[17]
4g	4-NO_2	5	93	256-258	258-260	[18]
4h	2-furyl	5	94	250-252	251–254	[36]
4i	2-thiophene	5	91	230-231	228-230	[36]
4j	4-Br	4	92	247-248	247-250	[36]
4k	4-F	5	91	259-260	260-262	[37]
4l	3-indolyl	4	92	178-180	---------	
4m	4-CN	5	90	280-281	280-282	[37]

[a]Reaction condition: Aromatic aldehyde **1** (1 mmol), malononitrile **2** (1.2 mmol), 4- hydroxycoumarin **3** (1 mmol), and EPZG (0.10g) under solvent-free, conditions, in microwave irradiation at150 W and 90 [0]C. [b]Isolated yields.

A reasonable mechanism for the formation of 3,4-dihydropyrano[c]chromene (**4**) is proposed in (Scheme 1). Firstly, the Knoevenagel reaction occurs in the presence of catalyst between benzaldehyde **1** and malononitrile **2,** followed by dehydration to produce the 2-benzylidenemalononitrile **3**. Then, Michael addition of intermediate with 4-hydroxycoumarin followed by cyclization and tautomerization provides desired products.



Scheme 1. Proposed mechanism for the synthesis of 3,4-dihydropyrano[c]chromenes.

4. Conclusions

In summary, we have described Envirocat EPZG mediated facile and environmentally benign methodology for the synthesis of 3,4-dihydropyrano[c]chromene derivatives via one-pot, three-component condensation reaction of 4-hydroxycoumarin, malononitrile and aromatic aldehydes. The reactions were carried out in solvent-free conditions under MW irradiation with short reaction time and produced the corresponding products in good to excellent yields. The simplicity of procedure, mild reaction conditions, high atom-economy, eco-friendly standards and easy isolation of products are the advantages of these methods.

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Author Contributions

Conceptualization, S.N.D. and M.S.S; Methodology, S.N.D., and L.D.C.; Investigation, S.N.D.; Writing – Original Draft, S.N.D. and L.D.C.; Writing – Review & Editing, S.N.D. and L.D.C.; Resources, S.N.D. and L.D.C.; Supervision, M.S.S.

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