Iranian Journal of Organic Chemistry Vol. 11, No. 1 (2019) 2525-2530

Synthesis of 2-amino-4*H*-chromene derivatives by three-component condensation using an amino acid as a suitable and useful catalyst under solvent-free and thermally conditions

Khatereh Khandan-Barani*, Somayeh Arzani

Department of Chemistry, Zahedan Branch, Islamic Azad University, Zahedan, Iran

Received: November 2018; Revised: December 2018; Accepted: January 2019

Abstract: An efficient, clean and one-pot procedure for the synthesis of 2-amino-4*H*-chromenes has been developed by three-component condensation of aldehyde derivatives, malononitrile, and 1- or 2-naphthol in the presence of aspartic acid as an amino acid and efficient catalyst under solvent-free and thermally conditions. Aspartic acid is one of two acidic amino acids. Aspartic acid is alanine with one of the β hydrogens replaced by a carboxylic acid group. The solvent-free conditions, a simple, efficient, and eco-friendly method, short reaction time and excellent yields of the products make this methodology highly significant.

Keywords: 2-Amino-4*H*-chromenes, Aspartic acid, Malononitrile, Solvent-free conditions, Amino acid.

Introduction

The discovery of novel synthetic methodologies to facilitate the preparation of compound libraries is a focal point of research activity in the field of modern medicinal and combinatorial chemistry [1]. One approach to address this challenge involves the development of multicomponent reactions (MCRs), in which three or more reactants are combined together in a single reaction flask to generate a product with the most of the atoms contained in the starting materials [2]. The rapid assembly of molecular diversity utilizing MCRs has received a great deal of attention, especially for the design and construction of elaborate heterocyclic frameworks possessing enhanced "drug-like" properties [3-5]. The chromene derivatives are widely present in natural alkaloids, flavonoids, tocopherols, and anthocyanins [6].

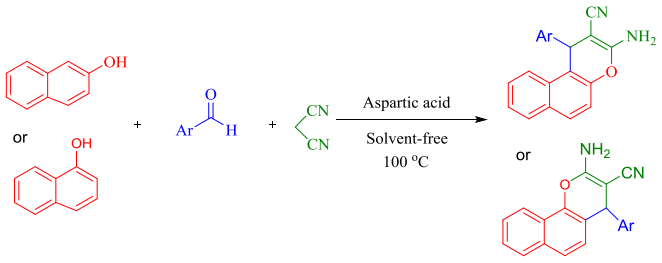
*Corresponding author: Tel: (+98) 5433443600, Fax: (+98) 5433441099, E-mail: kh_khandan_barani@yahoo.com

Moreover, functionalized chromenes have played in ever-increasing role in the synthetic approaches to promising compounds in the field of medicinal chemistry [7]. Among the different types of chromene systems, 2-amino-4*H*-chromenes are of particular utility as they belong to preferential medicinal scaffolds serving for generation of small-molecule ligands with highly pronounced anticoagulant-, diuretic-, spasmolitic- and antianaphylactic activities [8-10]. 2-Amino-4*H*-chromenes are generally produced by refluxing active methylene compounds (e.g., malononitrile and cyanoacetic acid esters), with an aldehyde and an activated phenol in organic solvents such as ethanol and acetonitrile, and in the presence of catalyst for several hours [11–13].

Various modified catalysts were used such as cetyltrimethylammonium chloride [14], cetyltrimethylammonium bromide under ultrasound irradiation [15], KSF clay [16], KF/Al_2O_3 [17], $TiCl_4$ [18], triethylamine [19], basic γ-alumina [10], MgO [9], heteropolyacids [20], basic ionic liquids [21],

iodine/K_2CO_3 [22]. However, some of these catalysts require long reaction times, difficult workup procedures and afford only moderate yields**.**

Recently, we have reported the Synthesis of tetrahydrobenzo[b]pyran and 3,4 dihydropyrimidinone derivatives using glutamic acid as an amino acid [23]. In our continuing interest in the development of one-pot multi-component reactions [24-27], we reported herein our results for the synthesis of 2-amino-4*H*-chromene scaffold using aspartic acid as an efficient and desirable catalyst for the three-component solvent-free condensation of aromatic aldehydes, malononitrile and 1- or 2-naphthol in thermally conditions with excellent yields (Scheme **1**).



Scheme 1: Three-component condensation between aromatic aldehydes, malononitrile and 1- or 2-naphthol in the presence of aspartic acid under solvent-free conditions

Aspartic acid and glutamic acid play important roles as general acids in enzyme active centers, as well as in maintaining the solubility and ionic character of proteins, aspartic acid is not an essential amino acid, which means that it can be synthesized from central metabolic pathwayintermediates in humans. The pKa of the β carboxyl group of aspartic acid in a polypeptide is 3.9 [28, 29]. Aspartic acid was first discovered in 1827 by Auguste-Arthur Plisson and Étienne Ossian Henry by hydrolysis of asparagine, which had been isolated from asparagus juice in 1806 [30]. Aspartic acid has an α-keto homolog, oxaloacetate, just as pyruvate is the α-keto homolog of alanine [31].

Result and Discussion

We have selected the reaction between benzaldehyde, 2-naphthol and malononitrile as a pattern. The reaction was carried out in various temperature and amount of catalyst. As can be seen in Table **1**, the best conclusions were gotten in the presence of 5 mol% of catalyst at 100 ^{o}C.

Table 1. Optimization of the reaction conditions and amount of catalyst for the synthesis of 2-amino-4*H*-chromene derivatives

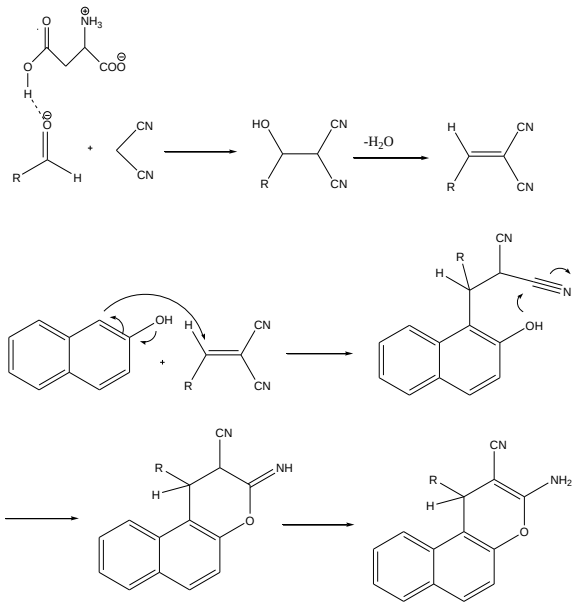
Entry	Catalyst (mol %)	T (˚C)	Time (h)	Yield (%)
1	-	50	24	-
2	-	100	24	Trace
3	2.5	rt	12	10
4	2.5	65	5	45
5	2.5	80	3	65
6	2.5	100	1	75
7	2.5	125	1	75
8	**5**	**100**	**1/2**	**92**
9	10	100	1/2	92
10	15	100	1/2	85

We used several aldehyde derivatives and 1- or 2-naphthol for the synthesis of 2-amino-4*H*-chromene. The desired products were obtained in excellent yields using a catalytic amount of the catalyst and the results are shown in Table **2**.

Table 2. Synthesis of 2-amino-4*H*-chromene derivatives catalyzed by aspartic acid

Entry	R	Naphthol	Time (min)	Isolated Yield (%)	m.p (°C)	Lit. m.p (°C)
1	C_6H_5	2-naphthol	30	92	279-281	278-280 [15]
2	4-Cl-C_6H_4		10	95	208-210	208 [10]
3	2-Cl-C_6H_4		10	94	262-264	259-261 [14]
4	2,4-$(Cl)_2$-C_6H_3		8	95	242	239-240 [32]
5	4-Br-C_6H_4		8	97	243-245	241-243 [15]
6	4-CH_3-C_6H_4		15	90	181-182	182-184 [33]
7	3,4-$(OCH_3)_2$-C_6H_3		30	85	143-145	141-143 [34]
8	4-OCH_3-C_6H_4		15	87	181-183	182-183 [15]
9	4-NO_2-C_6H_4		10	95	186-187	188 [21]
10	3-OCH_3-C_6H_4		20	93	259-261	262-263 [32]
11	3-OH-C_6H_4		25	91	282-284	280-282 [35]
12	2-OH-4-NO_2-C_6H_3		15	88	225-227	-
13	C_6H_5	1-naphthol	20	93	212-214	210-211 [15]
14	4-Cl-C_6H_4		8	97	230-232	232 [10]
15	3,4-$(OCH_3)_2$-C_6H_3		25	89	211-213	209-210 [36]
16	2-Cl-C_6H_4		10	95	238	236-237 [15]
17	4-NO_2-C_6H_4		8	96	190-192	188-189 [9]

Interestingly, a variety of aryl aldehydes including electron withdrawing or releasing substituents (ortho-, meta-, and para-substituted) participated well in this reaction and gave the 2-amino-4*H*-chromene derivatives in good to excellent yields. As reported in literature,[36] a possible mechanism for the formation of 2-amino-4*H*-chromene derivatives is shown in Scheme **2**.



Scheme 2: Proposed mechanism for synthesis of 2-amino-4*H*-chromene derivatives

The accessibility of the present work in comparison with the reported consequences in the literature, some of the results has been collected in Table **3**. The results show that aspartic acid is a remarkable catalyst with respect to the reaction time exhibits broad applicability in similar yield.

Table 3. The synthesis of 2-amino-4*H*-chromene derivatives using variety of catalysts was compared with aspartic acid as a catalyst in this work

Entry	Catalysts	Conditions	Yield (%)	Ref
1	Tetrabutyl ammonium chloride	water; reflux	95	37
2	Tetrabutyl ammonium fluoride	water; reflux	88	38
3	$Fe(HSO_4)_3$	CH_3CN; reflux	86	39
4	$H_{14}[NaP_5W_{30}O_{110}]$	water; reflux	93	40
5	Methanesulfonic acid	CH_3CN; reflux	90	20
6	Aspartic acid	Solvent-free; 100°C	85-97	This work

Conclusion

In summary, we report an eco-friendly and straightforward one-pot condensation for the synthesis of 2-amino-4*H*-chromene derivatives in the presence of aspartic acid as a highly effective, green, natural, advantageous, and biodegradable catalyst. Aspartic acid is clean, easy access, safe and nontoxic. Moreover, this method has several other advantages such as, operational simplicity, ecofriendly, high yields, and solvent-free conditions, which makes it a

useful and attractive process for the synthesis of a wide variety of biologically active compounds.

Experimental

All reagents were purchased from Merck (Darmastadt, Germany) and Fluka (Buchs, Switzerland) and used without further purification. Melting points and IR spectra of all the compounds were measured on an Electro Thermal 9100 apparatus and FT-IR-JASCO-460 plus spectrometer. ^{1}H and ^{13}C NMR spectra of known compounds were recorded on a Bruker DRX-400 Avance instrument in DMSO at 400 MHz and 100 MHz. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer.

General procedure for synthesis of 2-amino-4H-chromenes:

A mixture of malononitrile (1 mmol), benzaldehyde derivatives (1 mmol), 2-naphthol (1 mmol), and catalytic amount of aspartic acid (5 mol%) was heated to 100^{o}C under solvent-free conditions and maintained for an appropriate time (Table 2). After completion of the reaction as indicated by TLC, the residue was washed with water (3 × 10 mL) and recrystallized from ethanol to afford 2-amino-4*H*-chromene derivatives in exellent yields. The pure product was characterized by conventional spectroscopic methods. Spectral data for the selected compounds are given below:

3-Amino-1-phenyl-1H-benzo[f]chromene-2-carbonitrile (4a):

Yellow Solid; *FT–IR (KBr) (ν_{max}, cm^{-1}): 3430 and 3336 (NH_2), 2183 (C≡N), 1650* (C=C, vinylnitrile), 1589 (C=C, aromatic); ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 7.14-7.92 (m, 11H, Ar-H), 6.88 (br, s, 2H, NH_2), 5.21 (s, 1H, CH).

3-Amino-1-(4-chlorophenyl)-1H-benzo[f]chromene-2-carbonitrile (4b):

White Solid; FT–IR (KBr) (ν_{max}, cm^{-1}): 3458 and 3350 (NH_2), 2180 (C≡N), 1660 (C=C, vinylnitrile), 1564 (C=C, aromatic); ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 7.25-7.89 (m, 10H, Ar-H), 7.18 (d, 2H, J=8.1 Hz, Ar-H), 7.12 (d, 2H, J=8.1 Hz, Ar-H), 7.01 (s, 2H, NH_2), 5.11 (s, 1H, CH).

3-Amino-1-(4-methoxyphenyl)-1H-benzo[f] chromene -2-carbonitrile (4h):

Pale yellow solid; FT–IR (KBr) (ν_{max},cm^{-1}): 3415 and 3365 (NH_2), 2168 (C≡N), 1636 (C=C, vinylnitrile), 1554 (C=C, aromatic); ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 7.05-7.92 (m, 10H, Ar-H), 6.98 (br, s, 2H, NH_2), 4.89 (s, 1H, CH), 3.84 (s, 3H, OCH_3).

3-Amino-1-(2-hydroxy-4-nitrophenyl)-1*H*-benzo[*f*] chromene-2-carbonitrile (4l):

yellow solid; FT–IR (KBr) (ν_{max}, cm^{-1}): 3422 and 3346 (NH_2), 2197 (C≡N), 1657(C=C, vinylnitrile), 1590 (C=C, aromatic); ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 11.01 (s, 1H, OH), 7.49-8.16 (m, 6H, Ar-H), 7.23 (s, 2H, NH_2), 7.26-7.41 (m, 3H, Ar-H), 5.36 (s, 1H, CH_2). ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): 58.36, 97.61, 106.52, 113.01, 119.45, 121.86, 122.09, 122.13, 122.64, 124.07, 126.56, 130.14, 131.27, 131.72, 133.90, 143.88, 149.32, 158.92. Anal.Calcd for $C_{20}H_{13}N_3O_4$ (359.34): C, 66.85; H, 3.65; N, 11.69%; Found: C, 66.92; H, 3.67; N, 11.73%.

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