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# Aspartic acid as an efficient and green catalyst for the one-pot synthesis of 2-amino-4*H*-chromene derivatives under thermal, solvent free conditions

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A high-yielding synthesis of 2-amino-4*H*-chromenes is described involving the reaction of 1-naphthol or 2-naphthol, with aryl aldehydes and malononitrile in the presence of a catalytic amount of aspartic acid under thermal, solvent-free conditions. The salient features of this protocol are: aerobic conditions, non-hazardous, green catalyst, short reaction times and mild reaction conditions.

**Keywords:** Aspartic acid, 2-Amino-4*H*-chromenes, Solvent-free, Green catalyst, Malononitrile, Multi-component reactions

## 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]. Moreover, functionalized chromenes have played an 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 cetyltrimethyl ammonium chloride [14], cetyltrimethyl ammonium 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]. The methods reported previously for the synthesis of chromene derivatives suffer from severe disadvantages such as long reaction times, hazardous organic solvents, complex work-up and purification, strongly acidic conditions, high temperatures and inadequate yields. Based on the above information and due to our interest in developing synthetic strategies for the construction of heterocyclic compounds, we have now used aspartic acid-catalyzed condensation as a new rapid method affording excellent yields for the synthesis of 2-amino-4*H*-chromenes under thermal solvent-free conditions.

## EXPERIMENTAL

### *Instruments*

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a FT-IR-JASCO-460 plus spectrometer.

The NMR spectra were obtained on a Bruker Avance DRX-400 FT spectrometer ($^1$H NMR at 400 Hz, $^{13}$C NMR at 100 Hz) using DMSO-$d_6$ as solvent with TMS as internal standard.

### *General experimental procedure*

Aspartic acid (5 mol%) was added to a mixture of 1-naphthol or 2-naphthol (1 mmol), aryl aldehyde (1 mmol), and malononitrile (1 mmol), the reaction mixture was heated to 100°C and maintained for the appropriate time (Table 2). The progress of the reaction was followed by TLC (hexane:ethylacetate).

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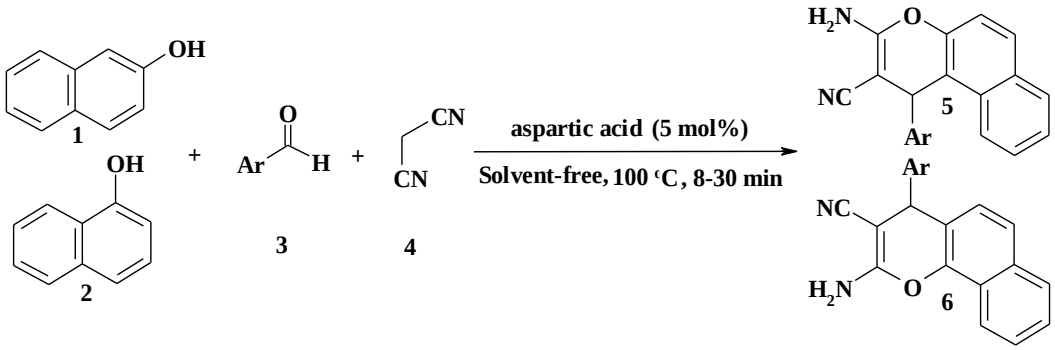


**Scheme 1.** Synthesis of 2-amino-4*H*-chromenes in the presence of aspartic acid under thermal, solvent-free conditions.

**Table 1.** Evaluation of the activity of different catalysts for synthesis of 2-amino-4*H*-chromene derivatives

| Entry | Catalyst | Conditions | Yield[a] /% |
|---|---|---|---|
| 1 | Tetrabutyl ammonium chloride | $H_2O$/reflux | 95 |
| 2 | Tetrabutyl ammonium fluoride | $H_2O$/reflux | 88 |
| 3 | $Fe(HSO_4)_3$ | $CH_3CN$/reflux | 86 |
| 4 | $H_{14}[NaP_5W_{30}O_{110}]$ | $H_2O$/reflux | 93 |
| 5 | Methanesulfonic acid | $CH_3CN$/reflux | 90 |
| 6 | Aspartic acid | Solvent-free/ 100°C | 85-97 [This work] |

[a] Yields of the isolated products

**Table 2.** Optimization of the reaction conditions for synthesis of **5a**

| Entry | Catalyst (amount, mol%) | T(˚C) | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | Aspartic acid (0) | 50 | 24 | - |
| 2 | Aspartic acid (0) | 100 | 24 | Trace |
| 3 | Aspartic acid (2.5) | 30 | 12 | 10 |
| 4 | Aspartic acid (2.5) | 65 | 5 | 45 |
| 5 | Aspartic acid (2.5) | 80 | 3 | 65 |
| 6 | Aspartic acid (2.5) | 100 | 1 | 75 |
| 7 | Aspartic acid (2.5) | 125 | 1 | 75 |
| 8 | Aspartic acid (5) | 100 | ½ (30 min) | 92 |
| 9 | Aspartic acid (10) | 100 | ½ (30 min) | 92 |
| 10 | Aspartic acid (15) | 100 | ½ (30 min) | 85 |

After the completion of the reaction, the mixture was washed with $H_2O$ (3×10 mL) and filtered to remove the catalyst. The crude product was recrystallized from hot ethanol to obtain the pure compound.

## RESULTS AND DISCUSSION

In continuation of our studies on MCRs [23-27] we report here the reaction between 2-naphthol **1** or 1-naphthol **2**, aryl aldehydes **3**, and malononitrile **4** in the presence of a catalytic amount of aspartic acid under thermal, solvent-free conditions. (Scheme 1). Aspartic acid was used for preparation of 2-amino-4*H*-chromenes. In order to establish the better catalytic activity of aspartic acid, we have compared the reaction using other catalysts. The results are listed in Table 1.

Initially, we began with the condensation of 2-naphthol (1 mmol), benzaldehyde (1 mmol) and malononitrile (1 mmol) in solvent-free conditions at 50°C for 24 h in the absence of catalyst, which led to very poor yield of 3-amino-1-phenyl-1H-benzo[*f*]chromene-2-carbonitrile. To enhance the yield of the desired product the temperature of the reaction was increased to 100˚C but no appreciable increment in the product yield was observed. Then, it was thought worthwhile to carry out the reaction in the presence of organocatalyst aspartic acid. We also evaluated the amount of catalyst required for this transformation and it was found that using 2.5 mol%, 5 mol%, 10 and 15 mol% catalyst, the maximum yield (92%) was obtained when the reaction mixture was loaded with 5 mol% of the catalyst (Table 2). Further increasing of the amount of catalyst loading affects the yield and slightly slows down the reaction. The detailed results obtained are given in Table 2.

**Table 3.** Reaction between 1-naphthol or 2-naphthol, aryl aldehydes and malononitrile in the presence of a catalytic amount of aspartic acid under thermal, solvent-free conditions.

| Product | Naphthol | Ar | Time (min) | Yield (%)[a] | m.p. (° C) |
|---|---|---|---|---|---|
| **6a** | 1-naphthol | $C_6H_5$ | 20 | 93 | 212-214 |
| **6b** | 1-naphthol | 4-Cl-$C_6H_4$ | 8 | 97 | 230-232 |
| **6c** | 1-naphthol | 3,4-$(CH_3O)_2C_6H_3$ | 25 | 89 | 211-213 |
| **6d** | 1-naphthol | 2-Cl-$C_6H_4$ | 10 | 95 | 237-239 |
| **6e** | 1-naphthol | 4-$NO_2$-$C_6H_4$ | 8 | 96 | 190-192 |
| **5a** | 2-naphthol | $C_6H_5$ | 30 | 92 | 279-281 |
| **5b** | 2-naphthol | 4-Cl-$C_6H_4$ | 10 | 95 | 208-210 |
| **5c** | 2-naphthol | 2-Cl-$C_6H_4$ | 10 | 94 | 262-264 |
| **5d** | 2-naphthol | 2,4-$(Cl)_2C_6H_3$ | 8 | 95 | 241-243 |
| **5e** | 2-naphthol | 4-Br-$C_6H_4$ | 8 | 97 | 243-245 |
| **5f** | 2-naphthol | 4-$CH_3$-$C_6H_4$ | 15 | 90 | 181-183 |
| **5g** | 2-naphthol | 3,4-$(CH_3O)_2C_6H_3$ | 30 | 85 | 143-145 |
| **5h** | 2-naphthol | 4-$CH_3O$-$C_6H$ | 15 | 87 | 181-183 |
| **5i** | 2-naphthol | 4-$NO_2$-$C_6H_4$ | 10 | 95 | 186-188 |
| **5j** | 2-naphthol | 3-$CH_3O$-$C_6H_4$ | 20 | 93 | 259-261 |
| **5k** | 2-naphthol | 3-HO-$C_6H_4$ | 25 | 91 | 282-284 |
| **5l** | 2-naphthol | 2-HO-4-$NO_2$-$C_6H_3$ | 15 | 88 | 225-227 |

[a] Yields refer to the pure isolated products

To study the scope of the reaction, a series of aromatic aldehydes, malononitrile and 1-naphthol or 2-naphthol catalyzed by aspartic acid under thermal, solvent-free conditions were examined. The results are shown in Table 3. In all cases, the aromatic aldehyde substituted with either electron-donating or electron-withdrawing groups underwent the reaction smoothly and gave products in excellent yields. Compound **5l** is new and its composition and structure were deduced by elemental and spectral analysis. The mass spectrum of compound **5l** showed a molecular ion peak at *m/z* 359. The $^1$H-NMR spectrum of compound **5l** exhibited a methine proton signal at 5.36 ppm. The OH proton was observed at 11.01 ppm and a singlet signal at δ 9.23 ppm for the $NH_2$ hydrogen atoms, which disappears after addition of some $D_2O$. Also observed were multiplets between 7.26 and 8.16 ppm which are related to aromatic protons. The $^{13}$C-NMR spectrum of compound **5l** showed 20 signals in agreement with the proposed structure, the IR spectrum also supported the suggested structure.

In summary, we have shown that aspartic acid has advantages in the preparation of 2-amino-4*H*-chromenes such as short reaction times, simple work-up, aerobic conditions, non-hazardous, green catalyst and affords excellent yield. The present method does not involve any hazardous organic solvent. Therefore, this procedure could be classified as green chemistry.

*3-Amino-1-(2-hydroxy-4-nitrophenyl)-1H-benzo[f]chromene-2-carbonitrile* **(5l).** Yellow solid; FTIR ($\nu_{max}$, cm$^{-1}$): 3422, 3346, 2197 1657 and

1590; $^{1}$H NMR (DMSO-$d_6$), δ: 11.01 (s, 1H, OH), 9.23 (s, 2H, $NH_2$), 7.26-8.16 (m, 9H, Ar-H), 5.36 (s, 1H, CH) ppm; $^{13}$C NMR (DMSO-$d_6$), δ: 58.4, 97.6, 106.5, 113.0, 119.4, 121.8, 122.1, 122.3, 122.6, 124.1, 126.6, 130.1, 131.3, 131.7, 133.9, 143.9, 149.3, 158.9 ppm; MS (m/z, %): 359 (7); Analyses: Calcd. for $C_{20}H_{13}N_3O_4$: C, 66.85; H, 3.65; N, 11.69. Found: C, 66.98; H, 3.80; N, 11.85%.

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