Triton B Catalyzed Three-Component, One-Pot Synthesis of 2-Amino-2-chromenes at Ambient Temperature

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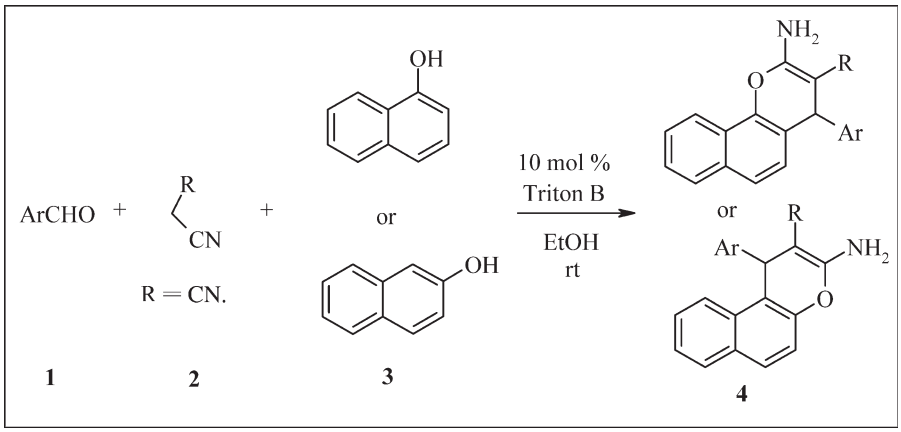

A one-pot, three-component synthesis of 2-amino-2-chromenes is described at ambient temperature by the reaction of an aldehyde and malononitrile or ethyl cyanoacetate with α-naphthol or β-naphthol in ethanol in presence of a catalytic amount of Triton B.

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INTRODUCTION

Multicomponent reactions are gaining importance both in academia and industry [1–4] due to their atom economy, simple procedure, selectivity, time and energy saving as well as environmental friendliness. 2-amino-chromenes are widely employed as pigments [5], cosmetics, and potential biodegradable agrochemicals [6] and represent an important class of compounds being the main components of many natural products. These compounds have been of interest to the medicinal chemist for many years [7]. Fused chromenes are biologically active compounds with a wide spectrum of activities such as antimicrobial [8a], mutagenicitical [8b], antiviral [9,10] antiproliferative [11] sex pheromonal [12], antitumora [13], and central nervous system activities [14]. The most straight forward synthesis of this heterocyclic nucleus involves the multicomponent reactions of an aldehyde, malononitrile and an activated phenol in the presence of piperidine [15] using acetonitrile or ethanol as solvent. Several methods with modified procedures have been reported [16] but, most of the reported methods require prolonged reaction times at reflux temperature, reagents in stoichiometric amounts, works only with α-naphthol, and generate moderate yields of the product. Therefore there is a still demand for the development of an effective catalyst for the synthesis of 2-aminochromenes, which equally works with α-and β-naphthol.

Initially we tried the reaction of aromatic aldehyde with malononitrile and α-naphthol using proline as a catalyst in aq. ethanol, but trace amounts of the product was isolated at reflux temperature. Then we screened other catalysts such as $CeCl_3.7H_2O/NaI$, PMA/SiO_2, which were failed to give the desired products.

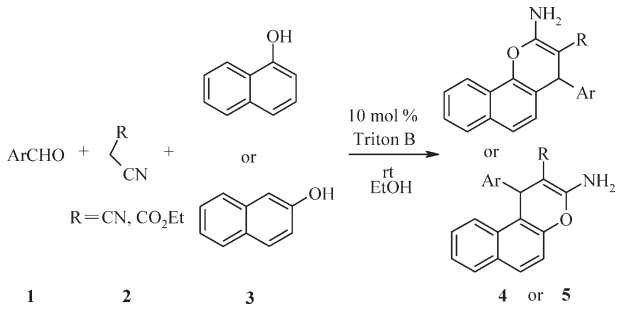
Benzyltrimethylammonium hydroxide (Triton B) has been used in the preparation of dithiocarbamates using alcoholic tosylates [17], dihydroxy-dithioethers [18] and in alkylation of mono Michael products [19].

RESULTS AND DISCUSSION

When *p*-nitro benzaldehyde **1b**, ethyl cyanoacetate **2**, α-naphthol **3**, and 10 mol % Triton B were added together and stirred at ambient temperature in EtOH, the reaction proceeded rapidly and was complete within 1 h to give the corresponding product **4b** in 92% yield (Scheme 1).

The structure of the product was confirmed by spectral data and compared with the authentic sample. To study the generality of this method the optimized

Scheme 1



procedure was used for the synthesis of a variety of 2-amino-2-chromenes. Aromatic aldehydes having electron-withdrawing groups reacted fast with malononitrile and α-naphthol giving high yields of products when compared to aldehydes containing electron-donating groups. It should be noted that under similar conditions, ethyl cyanoacetate also found to give better yields (Table 1, entries a-e). Encouraged by these results, we carried out the reaction of aromatic aldehyde and malononitrile with β-naphthol, which was found to react equally as α-naphthol giving high yields of products. The results of the study are shown in Table 2. The structures of all compounds were confirmed by IR, ^{1}H NMR and mass spectroscopy. The ^{1}H NMR of **4** displayed a singlet at δ 5.20 (H-4) and a broad singlet due to —NH_2 at δ 6.40 (D_2O exchangeable). Signals at δ 40 (C-4) and at 160 (C-2) in the ^{13}C NMR spectrum confirmed the formation of the product.

The change in mol% of Triton B did not much alter the yield of product. Also, when the reaction was run in EtOH/H_2O mixture, at room temperature the intermediate was isolated and at 100°C a 30% yield of the product formation was observed. The present reaction was studied with other catalysts such as ammonium molybdate and amberlite 400. The reaction using ammonium molybdate as catalyst in different media gives low yields of products and requires longer reaction time. However using amberlite 400, the reaction does not proceed at r. t., but gives low yield of product at higher temperature and results are shown in Table 3.

Mechanism of the reaction. As the mechanism for the formation of the product is well known that it represents a cascade reaction in which the benzylidene malononitrile is produced by Knoevenagel condensation of malononitrile to the aromatic aldehyde by loss of water. The second step requires a catalyst which involves the phenol ortho C-alkylation by reaction with the electrophilic C=C double bond and the nucleophilic addition of the phenolic OH group on the CN moiety [16l].

In conclusion, we have developed a highly efficient reaction protocol at room temperature for the synthesis of a variety of 2-amino-2-chromenes via Triton B catalyzed three component coupling of α- or β-naphthol, aromatic aldehyde and malononitrile or ethyl cyanoacetate.

EXPERIMENTAL

All reactions were monitored by thin layer chromatography (TLC) using silica-coated plates. Evaporation of solvents was performed at reduced pressure, using a Buchi rotary evaporator. ^{1}H NMR spectra were recorded on Varian FT-200 MHz (Gemini) and Bruker UXNMR FT-300 MHz (Avance) in $CDCl_3$. Chemical shift values were reported in parts per million (δ) relative to tetramethylsilane (δ 0.0) as an internal standard. Mass spectra were recorded under electron impact at 70eV on LC-MSD (Agilent Technologies). Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical, India. Thin-layer chromatography was performed on Merck 60 F-254 silica gel plates.

General procedure. A mixture of aldehyde (1.0 mmol), ethyl cyanoacetate /malononitrile (1.0 mmol) and α-naphthol/ β-naphthol (1.0 mmol) and Triton B (10 mol %) stirred in EtOH at room temperature for specified time (tables). Precipitated solid was filtered and recrystallized from MeOH.

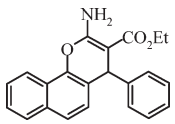
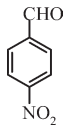
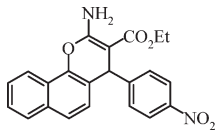
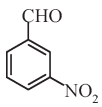
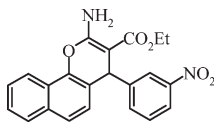
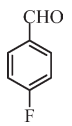
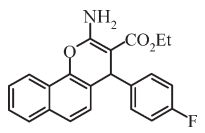
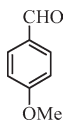
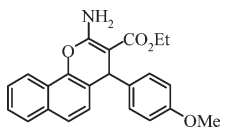
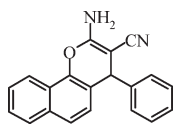
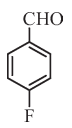
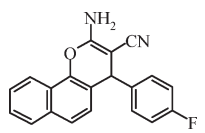
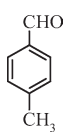
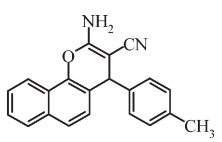
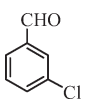
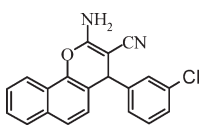
Spectral data. ***Ethyl 2-amino-4-(3-nitrophenyl)-4H-benzo[h]chromene-3-arboxylate (4c).*** Yellow solid, mp: 198–200°C; IR (KBr): 3416.0, 3289.9, 3084.4, 2924.3, 2854.7, 1672.4, 1603.6 and 1522.8 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz) δ: 8.26-8.22 (m, 2H, Ar-**H**), 8.03 (dd, J = 8.3, 2.2 Hz, 1H, Ar-**H**), 7.78 (d, J = 8.3 Hz, 1H, Ar-**H**), 7.61-7.48 (m, 4H, Ar-**H**), 7.38 (t, J = 8.3 Hz, 1H, Ar-**H**), 7.09 (d, J = 8.3 Hz, 1H, Ar-**H**), 6.52 (brs, 2H, -N**H**$_2$), 5.20 (s, 1H, -C**H**-), 4.12 (m, 2H, -OC**H**$_2$-), 1.23 (t, J = 6.8 Hz, 3H, -C**H**$_3$); ^{13}C NMR ($CDCl_3$, 100MHz) δ: 168.8, 159.9, 149.5, 147.9, 143.3, 134.2, 133.1, 129.0, 127.6, 126.6, 126.5, 126.1, 124.4, 123.2, 122.9, 121.3, 120.8, 118.9, 78.1, 59.7, 40.8, 14.4.; ESMS m/z: 413.0; HRMS m/z calc.: 413.1113; found: 413.1099 (M^++Na).

Ethyl 2-amino-4-(4-fluorophenyl)-4H-benzo[h]chromene-3-carboxylate (4d). Pale yellow solid, mp: 206–208°C.; IR (KBr): 3385.5, 3288.7, 3050.8, 2980.3, 2904.9, 1671.3, 1603.1 and 1505.1 cm^{-1}.; ^{1}H NMR ($CDCl_3$, 300MHz) δ: 8.17 (d, J = 8.0 Hz, 1H, Ar-**H**), 7.72 (dd, J = 7.3, 2.2 Hz, 1H, Ar-**H**), 7.55-7.39 (m, 3H, Ar-**H**), 7.24-7.14 (m, 2H, Ar-**H**), 7.07 (d, J = 8.8 Hz, 1H, Ar-**H**), 6.86 (t, J = 8.8 Hz, 2H, Ar-**H**), 6.45 (brs, 2H, -N**H**$_2$), 5.00 (s, 1H, -C**H**-), 4.08 (dq, J = 6.6, 2.2 Hz, 2H, -OC**H**$_2$-), 1.18 (t, J = 6.6 Hz, 3H, -C**H**$_3$).; ^{13}C NMR ($CDCl_3$, 75MHz) δ: 162.9, 159.9, 159.6, 143.4, 143.3, 143.1, 132.9, 129.4, 129.3, 127.6, 126.5, 126.3, 124.1, 123.3, 120.7, 120.4, 115.0, 114.7, 79.0, 59.5, 40.1, 14.3.; ESMS m/z: 386.0; HRMS m/z calc.: 386.1168; found: 386.1172 (M^++Na).

Ethyl 3-amino-1-phenyl-1H-benzo[f]chromene-2-carboxylate (5a). Pale yellow solid, mp: 166–168°C.; IR (KBr): 3402.3, 3295.5, 3052.9, 2991.8, 2963.2, 1671.5 and 1616.7 cm^{-1}.; ^{1}H NMR ($CDCl_3$, 200MHz) δ: 7.98 (d, J = 8.0 Hz, 1H, Ar-**H**), 7.76-7.67 (m, 2H, Ar-**H**), 7.46-6.98 (m, 8H, Ar-**H**), 6.30 (brs, 2H, -N**H**$_2$), 5.53 (s, 1H, -C**H**-), 4.30-4.12 (m, 2H, -OC**H**$_2$-), 1.37 (t, J = 7.3 Hz, 3H, -C**H**$_3$).; ^{13}C NMR ($CDCl_3$, 75MHz) δ: 169.1, 160.0, 159.9, 147.1, 146.4, 131.1, 131.0, 128.6, 128.3, 128.0, 127.9, 126.8, 126.1, 124.6, 123.5, 119.2, 119.1, 116.6, 80.3, 59.6, 37.1, 14.5.; ESMS m/z: 368.0; HRMS m/z calc.: 368.1262; found: 368.1260 (M^++Na).

Table 1

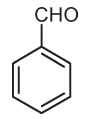
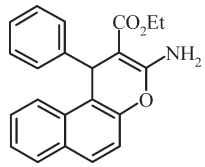
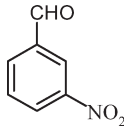
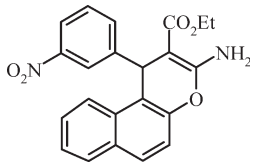
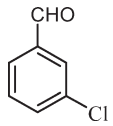
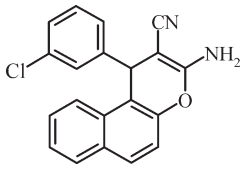
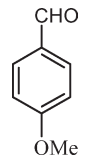
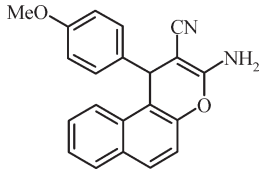
Triton B catalyzed synthesis of 2-amino-2-chromenes.[a,b,c]

Entry	Aldehyde **3**	*R*	Product **4**	Time (h)	Yield (%)
a		CO_2Et		1.50	88
b		CO_2Et		1.00	92
c		CO_2Et		1.00	92
d		CO_2Et		1.25	90
e		CO_2Et		3.00	80
f		CN		1.25	87[16c]
g		CN		1.00	90[16j]
h		CN		3.00	80[16j]
i		CN		1.25	90[16l]

[a] New products were characterized by IR, ^1H NMR, ^{13}C and mass spectral data.
[b] Known products were compared with authentic samples.
[c] Isolated pure products.

Table 2

Triton B catalyzed synthesis of 2-amino-2-chromenes.[a,b,c]

Entry	Aldehyde **3**	*R*	Product **5**	Time (h)	Yield (%)
a		CO_2Et		1.50	87
b		CO_2Et		1.00	92
c		CN		1.00	90
d		CN		3.00	80[16d]

[a] New products were characterized by IR, ^1H NMR, ^{13}C and mass spectral data.
[b] Known compounds were compared with authentic samples.
[c] Isolated pure products.

Table 3

Comparsion of various catalysts at various temperature.

Entry	Catalyst	Solvent	Temp.	Time (h)	Yield (%)
a	Triton B(10 mol%)	EtOH	r. t.	1.0	92
b	”	EtOH:H_2O (1:1)	r. t.	6.0	–[b]
c	”	”	100°C	3.0	30
d	$(NH_4)_2MoO_4$(10 mol %)	EtOH	r. t.	3.0	85
e	”	EtOH:H_2O (1:1)	r. t.	6.0	–[a]
f	”	”[b]	100°C	0.5	88
g	”	H_2O[b]	”	3.0	62
h	”	”	r. t.	12.0	–[a]
i	”	DMF	”	12.0	10
j	”	”	100°C	3.0	30
k	”	PEG 400	”	2.0	74
l	”	”	r. t.	6.0	35
m	Amberlite 400 (10 mol %)	EtOH	”	6.0	–[a]
n	”	”	100°C	3.0	68

[a] Intermediate was formed.
[b] Catalytic amount of TBAI was used.

Ethyl 3-amino-1-(3-nitrophenyl)-1H-benzo[f]chromene-2-carboxylate (5b). Yellow solid, mp: 188–190°C.; IR (KBr): 3463.0, 3312.7, 3072.7, 2976.6, 2930.0, 1675.7, 1595.5 and 1523.4 cm-^{1}.; ^{1}H NMR ($CDCl_3$, 300MHz) δ: 8.28 (s, 1H, Ar-**H**), 7.94 (dd, J = 8.3, 1.5 Hz, 1H, Ar-**H**), 7.85 (d, J = 8.3 Hz, 1H, Ar-**H**), 7.76 (d, J = 9.0 Hz, 2H, Ar-**H**), 7.48-7.24 (m, 5H, Ar-**H**), 6.37 (brs, 2H, -N**H**$_2$), 5.66 (s, 1H, -C**H**-), 4.30-4.14 (m, 2H, -OC**H**$_2$-), 1.40 (t, J = 7.5 Hz, 3H, -C**H**$_3$).; ^{13}C NMR ($CDCl_3$, 75MHz) δ: 168.2, 159.9, 148.4, 147.9, 147.0, 134.2, 131.2, 130.5, 129.4, 129.0, 128.6, 127.1, 124.9, 123.0, 122.9, 121.2, 117.3, 116.6, 79.06, 59.8, 37.0, 14.4.; ESMS *m*/*z*: 413.0; HRMS *m*/*z* calc.: 413.1113; found: 413.1124 (M^++Na).

3-amino-1-(3-chlorophenyl)-1H-benzo[f]chromen-2-yl cyanide (5c). Yellow solid, mp: 202–204°C; IR (KBr): 3410.3, 3302.5, 2924.0, 2853.7, 2187.5, 1655.2 cm^{-1}.; ^{1}H NMR ($CDCl_3$, 200MHz) δ: 7.85-7.76 (m, 2H, Ar-**H**), 7.68-7.61 (m, 2H, Ar-**H**), 7.42-7.34 (m, 2H, Ar-**H**), 7.31-7.17 (m, 2H, Ar-**H**), 7.15-7.06 (m, 2H, Ar-**H**), 6.32 (s, 2H, -N**H**$_2$), 5.18 (s, 1H, -C**H**-).; ^{13}C NMR ($CDCl_3$, 75MHz) δ: 160.0, 149.5, 143.2, 133.8, 133.0, 129.4, 129.1, 128.2, 127.8, 127.6, 126.4, 126.3, 126.2, 126.0, 124.2, 123.3, 120.8, 119.8, 59.5, 40.7.; ESMS *m*/*z*: 355.0; HRMS *m*/*z* calc.: 355.0614; found: 355.0609 (M^++Na).

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