DOI: 10.1002/ejoc.200500495

# Preparation of 2-Amino-4*H*-chromene Derivatives from Coumarins in Basic Media

**Massimo Curini,*[a] Ornelio Rosati,*[a] Maria Carla Marcotullio,[a] Francesca Montanari,[a] Valerio Campagna,[a] Vittorio Pace,[a] and Giancarlo Cravotto[b]**

**Keywords:** Carbanions / Chromenes / Coumarins / Michael additions / Rearrangements

The reaction of coumarin with cyanoacetate derivatives in the presence of a nucleophilic base (alkoxides or piperidine) follows an interesting pathway that involves both a coumarin skeletal rearrangement and a Michael addition, via a coumaric acid derivative, to afford a substituted 4*H*-chromene skeleton. The particular behavior of this process influences the performance and the type of compounds that can be obtained. We demonstrate that the use of an excess of cyanoacetate affords the 4*H*-chromene derivative in high yield. An explanation of the mechanism involved in this process is proposed.



## Introduction

The coumarin fragment occurs in many synthetic and natural products that are used as drugs[1] as well as anticoagulants[2] and in the preparation of pesticides.[3] These important applications have generated considerable interest in the functionalization of the coumarin skeleton for the preparation of derivatives with potential biological activity.

During our studies in the field of coumarins,[4] we discovered that coumarin **1** can be easily transformed into the 2-amino-4*H*-chromene derivative **4** or a 2-chromanone derivative **5**. This transformation occurs when coumarin reacts with cyanoacetates in the presence of a nucleophilic base such as an alkoxide (or piperidine).

## Results and Discussion

The process takes place through the initial formation of coumaric derivative **2** and the subsequent Michael-type addition of the cyanoacetate carbanion to **2** to give the intermediate **3**. In the final step, the intermediate **3** is converted into the 2-amino-4*H*-chromene derivative **4** and the 2-chromanone derivative **5** (Scheme 1).

Compounds **4** and **5** were easily separated during the workup, and structural determination was made on the basis of analytical and spectroscopic data. The alkyl (3-cyano-2-oxo-3,4-dihydro-2*H*-chromen-4-yl) acetate **5** was obtained as an inseparable mixture of two diastereoisomers. A NOESY experiment on the diastereomeric mixture of **5** allowed definitive assignment of the structures and identification of a *syn* configuration for the more abundant diastereomer (Figure 1).

Furthermore, we discovered the possibility of shifting the reaction towards the formation of either **4** or **5** by using an appropriate molar ratio of cyanoacetate and alkoxide (see Table 1). In particular, an excess of cyanoacetate (Table 1, entries 4 and 5) affords the 4*H*-chromene derivative in high yield.

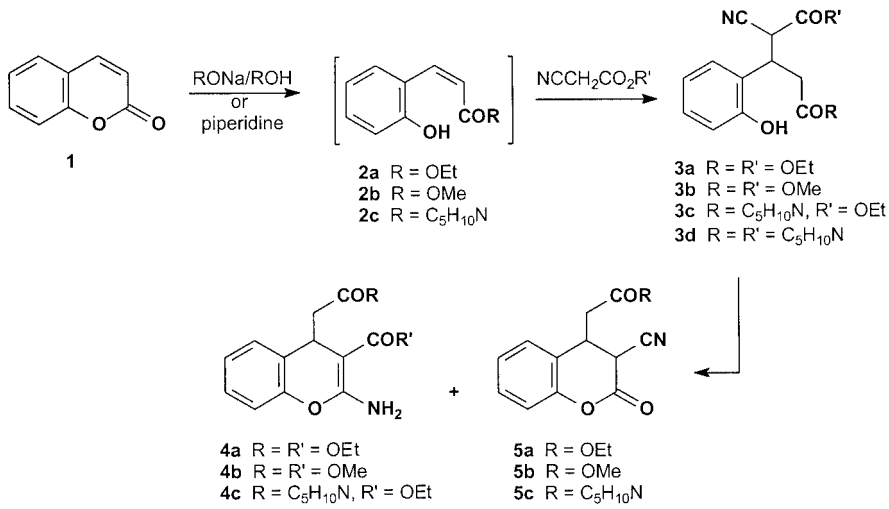
To explain the complex behavior of this reaction, we need to consider the existence of various acid–base equilibria (Scheme 2). In particular, intermediate **3** contains two acidic protons whose ionization depends on the basic conditions in the reaction mixture (p$K_a$ EtOH $\approx$ 16; p$K_a$ $NCCH_2CO_2R \approx 9$).

When an excess of ethyl cyanoacetate is used, the predominant basic species in the reaction mixture is the carbanion of the cyanoacetate. The strength of this base should be such that it is unable to extract the phenolic proton from the intermediate **3**. The neutral compound **3** seems to be the intermediate that more favorably leads to the 2-amino-4*H*-chromene **4** as the main compound (Scheme 2).

When an excess of sodium alkoxide is used, the intermediate **3** should principally exist in an anionic form that remains in solution as such. Following acidification in the workup step, it is possible to isolate compounds **3** or **5** (Scheme 2).

[a] Dipartimento di Chimica e Tecnologia del Farmaco, Università degli Studi,
Via del Liceo 1, 06123 Perugia, Italy
Fax: +39-075-585-5116
E-mail: curmax@unipg.it
ornros@unipg.it
[b] Dipartimento di Scienza e Tecnologia del Farmaco, Università degli Studi,
Via P. Giuria 9, 10125 Torino, Italy




Scheme 1.

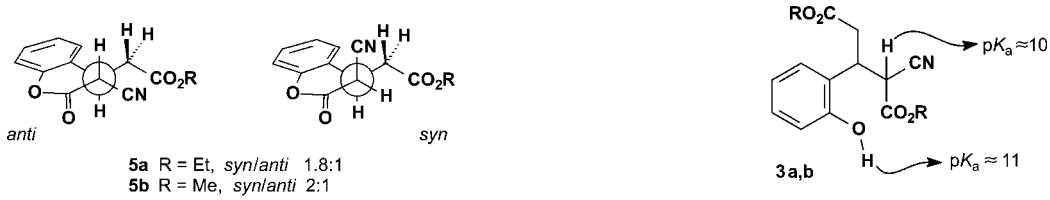


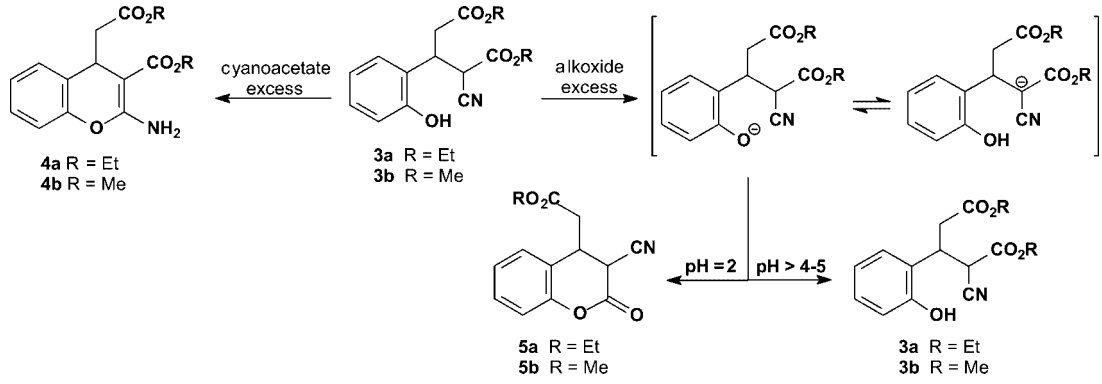

Figure 1. Diastereomeric ratio (*syn*/*anti*) of the 2-chromanone derivatives.

Table 1. Reaction of coumarin using different ratios of cyanoacetate and alkoxide (workup: acidification with 1 N HCl).

| Entry | NaOR [equiv.] | $CNCH_2CO_2R$ [equiv.] | *t* [h] | Yield [%] 4a | 4b | 5a | 5b |
|---|---|---|---|---|---|---|---|
| 1 | 1.4 | 1.2 | 24 | 17 | 32 | 41 | 40 |
| 2 | 2.0 | 1.2 | 24 | 7 | 10 | 76 | 66 |
| 3 | 2.0 | 2.2 | 24 | 24 | 27 | 45 | 53 |
| 4 | 1.2 | 2.4 | 24 | 85 | 79 | 10 | 16 |
| 5 | 1.2 | 2.4 | 2 | 81 | 72 | 11 | 27 |

Compound **5** was obtained as the exclusive lactone system after acidification at pH 2 with 1 N HCl solution. The milder acidification conditions obtained by using glacial acetic acid (pH 4–5) allowed isolation of compound **3** as a mixture of diastereoisomers. Thus, **3** is the key intermediate in this process (Table 2).

The solubility of compound **3** in an alkaline aqueous solution was successfully exploited to separate the chromene derivative **4** from opened derivative **3** or lactone derivative **5** without further purification.




Scheme 2. Chemical behavior of **3** under different reaction conditions.

Table 2. Reaction of coumarin using different ratios of cyanoacetate and alkoxide (workup: acidification with conc. acetic acid).

| Entry | NaOR [equiv.] | $CNCH_2CO_2R$ [equiv.] | *t* [h] | Yield [%] 4a | 4b | 3a | 3b |
|---|---|---|---|---|---|---|---|
| 1 | 1.1 | 1.1 | 2 | 11 | 16 | 35 | 49 |
| 2 | 2.0 | 1.2 | 2 | 9 | 12 | 47 | 51 |
| 3 | 1.2 | 2.4 | 2 | 59 | 75 | 27 | 18 |

The use of a non-nucleophilic base such as sodium *tert*-butoxide, lithium diisopropylamide, TEA, or $Zr(KPO_4)_2$[5] in this type of process did not afford any reaction product, and the starting coumarin was always recovered. This result confirms that the reaction takes place through a coumaric intermediate, and that the nucleophilic base plays an important role.

Following this idea, we decided to use piperidine as the nucleophilic base as it is known to be a useful base for the synthesis of 2-amino-4*H*-pyran derivatives from α-CH-acidic nitriles and Michael acceptors.[6] It is also used in the conversion of functionalized coumarins accompanied by opening and recyclization of the lactone ring.[7]

The reaction was carried out by allowing coumarin to react with ethyl cyanoacetate (1.2 equiv.) in the presence of piperidine (2.0 equiv.) in ethanol. After workup, chromatography on silica gel was required to purify the reaction products and eliminate by-products. Although the reaction mechanism should be the same as above (Scheme 1), only compounds **4c** and **4a** were obtained − no opened intermediate (**3c**) or 2-chromanone derivative (**5c**) was observed (Table 3).

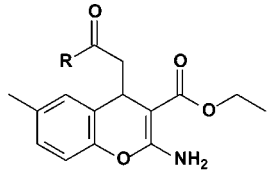
Table 3. Reaction of coumarin with ethyl cyanoacetate using piperidine as base.

| Entry | Piperidine [equiv.] | $CNCH_2CO_2R$ [equiv.] | Time [h] | Yield [%] 4c | 4a | Solvent |
|---|---|---|---|---|---|---|
| 1 | 1.2 | 2.4 | 20 | 34 | 34 | EtOH |
| 2 | 2.0 | 2.0 | 18 | 31 | 38 | EtOH |
| 3 | 2.4 | 1.2 | 22 | 51 | 22 | EtOH |
| 4 | 2.4 | 1.2 | 20 | 39 | – | THF |
| 5 | 2.4 | 1.2 | 20 | 41 | – | benzene |

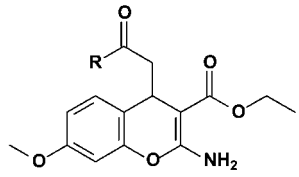
The formation of compound **4a** shows that ethanol and piperidine are competing. To avoid this problem, THF or benzene was used as reaction solvent, resulting in the formation of the chromene derivative only. The use of these solvents rather than ethanol did not increase the reaction yield, and by-products such as the opened system **3d** and the piperidinyl cyanoacetate were observed.

To extend the applicability to other models, we considered the possibility of using functionalized coumarins such as 6-methylcoumarin and 7-methoxycoumarin. Surprisingly, these compounds did not react when using an alkoxide as base, and unreacted starting material was recovered exclusively. At the moment we are unable to explain why functionalized coumarins do not react at all, since substitution with a methyl or methoxy group should not dramatically affect the reactivity of the coumarin skeleton.

In contrast, the use of piperidine in ethanol was found to be effective in the reaction of functionalized coumarins with cyanoacetates, affording the 2-amino-4*H*-chromene derivatives **6** (**a** = 30%; **b** = 45%) and **7** (**a** = 11%, **b** = 57%).

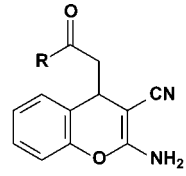



**6a** R = OEt
**6b** R = $C_5H_{10}N$

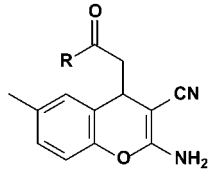



**7a** R = OEt
**7b** R = $C_5H_{10}N$

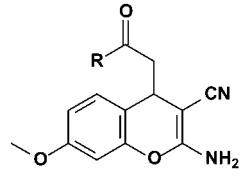
Since the presence of a carboxy ester group in cyanoacetates also leads to the formation of a lactone skeleton when alkoxides are used as a base, we decided to use a reagent such as malononitrile to drive the reaction towards exclusive formation of the 2-amino-4*H*-chromene derivative. When the reaction was carried out in the presence of malononitrile as a Michael donor, and sodium ethoxide in ethanol, only ethyl (2-amino-3-cyano-4*H*-chromen-4-yl)acetate (**8a**) was obtained, with a yield of 68%.




**8a** R = OEt
**8b** R = $C_5H_{10}N$




**9a** R = OEt
**9b** R = $C_5H_{10}N$




**10a** R = OEt
**10b** R = $C_5H_{10}N$

Piperidine in ethanol was also applied in the reaction of malononitrile with coumarin as well as functionalized coumarins (6-methylcoumarin and 7-methoxycoumarin), affording 2-amino-4*H*-chromene derivatives **8b**, **9b**, and **10b** and their corresponding ethyl esters **8a**, **9a**, and **10a** (Table 4).

Table 4. Reaction of coumarins with ethyl cyanoacetate using piperidine in ethanol as a base.

| Entry | Substrate | Time [h] | Chromene derivative | Yield [%] |
|---|---|---|---|---|
| 1 | coumarin | 20 | **8a** | 8 |
| | | | **8b** | 51 |
| 2 | 6-methylcoumarin | 22 | **9a** | 20 |
| | | | **9b** | 43 |
| 3 | 7-methoxycoumarin | 20 | **10a** | 9 |
| | | | **10b** | 47 |

The interest in this class of compounds is due to the ability of some 2-amino-4*H*-chromene derivatives to bind Bcl-

2 protein and induce apoptosis in tumor cells.[8] The discovery of this Bcl-2 binding compound has provided a promising lead for the development of potential anti-cancer agents, although a survey of the literature reveals that the synthesis of these derivatives has received little attention. To the best of our knowledge, 2-amino-4*H*-chromene derivatives can be prepared from salicylaldehydes[5,8–10] or from the reaction between alkyl isocyanides and DMAD in the presence of poly(hydroxybenzene)s.[11]

## Conclusions

In summary, we have reported the first example of the preparation of a 2-amino-4*H*-chromene derivative from coumarin. This process presents an interesting flexibility depending on the reaction conditions. The alkoxide/alcohol/cyanoacetate system is preferable to convert coumarin into 2-amino-4*H*-chromene derivatives or a 2-chromanone derivative with good yield. Although the piperidine/ethanol (or benzene/THF) system leads to a moderate reaction yield, it should be used to convert functionalized coumarins into 2-amino-4*H*-chromene derivatives.

Further experiments using other Michael donors are currently in progress in order to prepare more complex molecules with potential biological activity.

## Experimental Section

**General Remarks:** All chemicals were purchased from the major chemical suppliers as highest purity grade and used without any further purification. Column chromatography was performed with Merck silica gel 60 (70–230 mesh ASTM), with hexane/ethyl acetate mixture. $^1$H and $^{13}$C NMR spectra were recorded in $CDCl_3$ with a Bruker Avance DRX 200 spectrometer at a frequency of 200.1 and 50 MHz, respectively, or a Bruker Avance DPX 400 spectrometer at a frequency of 400.13 and 100.62 MHz, respectively. Chemical shifts ($\delta$) are reported in ppm relative to TMS; $J$ values are given in Hertz. FT-IR spectra were recorded with a Jasco model 410 spectrometer with ATR sampling. GC-MS analysis was performed with an HP-6890 gas chromatograph (dimethyl silicone column, 12.5 m) equipped with an HP-5973 mass-selective detector at an ionizing voltage of 70 eV. Melting points are uncorrected. Elemental analysis was carried out with a Carlo–Erba 1106 elemental analyzer. Yields reported are for isolated compounds judged pure by NMR analysis.

**Typical Reaction Procedure of Coumarin with Ethyl (or Methyl) Cyanoacetate and Alkoxide:** A solution of ethyl (or methyl) cyanoacetate in ethanol (or methanol; 1 mL) was added to a solution of sodium ethoxide (or methoxide) in ethanol (or methanol; 2 mL) at room temperature under nitrogen (see Tables 1 and 2 for the appropriate ratios). After 30 min, a solution of coumarin (1 mmol) in ethanol (or methanol; 2 mL) was added and the reaction mixture kept at room temp. for the appropriate time. The mixture was concentrated to half volume then poured into water and extracted with dichloromethane. The organic solution was dried over $Na_2SO_4$ then concentrated under vacuum to afford chromene derivative **4**. The remaining aqueous solution was acidified with 1 N HCl to pH 2, then extracted with dichloromethane. The organic solution was dried over $Na_2SO_4$ then concentrated under vacuum to afford lactone derivative **5**. Alternatively, the remaining aqueous solution was acidified with conc. acetic acid to pH 4–5 then extracted with dichloromethane. The organic solution was dried with $Na_2SO_4$ then concentrated under vacuum to afford derivative **3**.

**Ethyl 2-Amino-4-(2-ethoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate (4a):** White solid; m.p. 71–73 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.13 (t, $J$ = 7.2 Hz, 3 H, $CH_3$), 1.30 (t, $J$ = 7.1 Hz, 3 H, $CH_3$), 2.59 (dd, $J$ = 14.8, 7.2 Hz, 1 H, $CH_2$), 2.66 (dd, $J$ = 14.8, 4.4 Hz 1 H, $CH_2$), 3.82 (q, $J$ = 7.1 Hz, 2 H, $OCH_2$), 4.14 (q, $J$ = 7.1 Hz, 2 H, $OCH_2$), 4.20 (dd, $J$ = 7.2, 4.4 Hz, 1 H, 4-H), 6.35 (br. s, 2 H, $NH_2$), 6.96 (dd, $J$ = 8.6, 1.2 Hz, 1 H, 8-H), 7.07 (dt, $J$ = 8.6, 7.5, 1.2 Hz, 1 H, 6-H), 7.19 (dt, $J$ = 7.6, 7.5, 1.6 Hz, 1 H, 7-H), 7.25 (dd, $J$ = 7.6, 1.6 Hz, 1 H, 5-H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 14.5, 15.0, 31.6, 44.1, 59.9, 60.6, 77.0, 116.2, 124.7, 126.0, 128.0, 128.8, 150.3, 162.0, 169.5, 172.2 ppm. GC-MS: $m/z$ (%) = 305 [$M^+$], 276, 232, 218, 190, 172, 159, 128, 116. IR (neat): $\tilde{\nu}$ = 3414, 3310, 1731, 1674, 1620 cm$^{-1}$. $C_{16}H_{19}NO_5$ (305.33): calcd. C 62.94, H 6.27, N 4.59; found C 62.79, H 6.38, N 4.65.

**Methyl 2-Amino-4-(2-methoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate (4b):** Amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 2.47 (dd, $J$ = 14.8, 7.6 Hz, 1 H, $CH_2$), 2.56 (dd, $J$ = 14.8, 4.6 Hz, 1 H, $CH_2$), 3.51 (s, 3 H, $CH_3$), 3.68 (s, 3 H, $CH_3$), 4.20 (dd, $J$ = 7.6, 4.6 Hz, 1 H, 4-H), 6.29 (br. s, 2 H, $NH_2$), 6.89 (d, $J$ = 8.1 Hz, 1 H, 8-H), 6.99 (t, $J$ = 7.4 Hz, 1 H, 6-H), 7.12 (m, 7-H+5-H) ppm. $^{13}$C NMR: δ (100 MHz, $CDCl_3$): $\delta$ = 31.9, 44.5, 51.4, 51.9, 76.7, 116.3, 124.9, 125.9, 128.2, 128.7, 150.3, 162.2, 169.9, 172.7 ppm. GC-MS: $m/z$ (%) = 277 [$M^+$], 244, 218, 204, 186, 172, 145. IR (neat): $\tilde{\nu}$ = 3422, 3312, 1731, 1679, 1621 cm$^{-1}$. $C_{14}H_{15}NO_5$ (277.28): calcd. C 60.64, H 5.45, N 5.05; found C 60.51, H 5.53, N 5.11.

**Methyl (3-Cyano-2-oxo-3,4-dihydro-2*H*-chromen-4-yl)acetate (5b, *anti* + *syn*):** Amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ (*anti*) = 2.91 (dd, $J$ = 6.1, 17.4 Hz, 1 H, HC*H*), 3.01 (dd, $J$ = 6.1, 17.4 Hz, 1 H, *H*CH), 3.74 (s, 3 H, $OCH_3$), 3.83 (m, 1 H, 4-H), 4.39 (d, $J$ = 8.4 Hz, 1 H, 3-H), 7.15–7.46 (m, 4 H, PhH) ppm; $\delta$ (*syn*) = 2.72 (dd, $J$ = 9.4, 16.4 Hz, 1 H, HC*H*), 3.01, (dd, $J$ = 4.4, 16.4 Hz, 1 H, *H*CH), 3.69 (s, 3 H, $OCH_3$), 3.94 (m, 1 H, 4-H), 4.14 (d, $J$ = 5.7 Hz, 1 H, 3-H), 7.15–7.46 (m, 4 H, PhH) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (*anti*) = 34.7, 35.2, 37.3, 52.4, 113.8, 117.5, 121.6, 125.9, 126.6, 130.1, 150.3, 160.2, 170.4 ppm; $\delta$ (*syn*) = 35.2, 36.4, 38.1, 52.2, 113.5, 117.6, 122.0, 125.6, 128.5, 130.1, 150.2, 160.2, 170.2 ppm. GC-MS: $m/z$ (%) = 245 [$M^+$], 230, 218, 184, 172, 158, 147, 128, 118. IR (neat): $\tilde{\nu}$ = 2256, 1769, 1729 cm$^{-1}$. $C_{13}H_{11}NO_4$ (245.23): calcd. C 63.67, H 4.52, N 5.71; found C 63.81, H 4.41, N 5.66.

**Dimethyl 2-Cyano-3-(2-hydroxyphenyl)pentanedioate (3b, mixture of diastereoisomers):** Amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 2.90–3.20 (m, 4 H, $CH_2CO$ [**3b$_1$**/**3b$_2$**]), 3.61 (s, 3 H, $CH_3$ [**3b$_1$**]), 3.64 (s, 3 H, $CH_3$ [**3b$_2$**]), 3.70 (s, 3 H, $CH_3$ [**3b$_1$**]), 3.72 (s, 3 H, $CH_3$ [**3b$_2$**]), 4.07–4.22 (m, 3 H, Ph-CH [**3b$_1$**/**3b$_2$**] + CNCH [**3b$_1$**]), 4.35 (d, $J$ = 7.3 Hz, 1 H, CNCH [**3b$_2$**]), 6.61–7.53 (m, 8 H, PhH [**3b$_1$**/**3b$_2$**]), 9.37 (br. s, 1 H, PhOH [**3b$_2$**]), 9.50 (br. s, 1 H, PhOH [**3b$_1$**]) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ (**3b$_1$**) = 36.5, 36.9, 41.3, 52.3, 53.6, 115.6, 116.3, 120.7, 123.4, 128.9, 129.4, 154.0, 166.3, 172.4 ppm; $\delta$ (**3b$_2$**) = 35.2, 37.1, 41.5, 52.3, 53.5, 115.5, 116.0, 120.6, 123.8, 128.5, 129.3, 153.9, 166.0, 172.4 ppm. IR (neat): $\tilde{\nu}$ = 3407, 2254, 1736, 1608, 1595 cm$^{-1}$. $C_{14}H_{15}NO_5$ (277.28): calcd. C 60.64, H 5.45, N 5.05; found C 60.57, H 5.51, N 5.09.

**Typical Reaction Procedure of Coumarins with Ethyl Cyanoacetate and Piperidine in Ethanol:** A solution of ethyl cyanoacetate in ethanol (1 mL) was added to a solution of piperidine in ethanol (2 mL) at room temperature under nitrogen (see Table 3 for the appropriate ratio). After 10 min a solution of coumarin (1 mmol) in ethanol

(2 mL) was added and reaction mixture kept at room temp. for the appropriate time. The mixture was then concentrated to half volume, poured into water, and then extracted with dichloromethane. The organic solution was dried over $Na_2SO_4$ then concentrated under vacuum. Chromatography of the crude product over silica gel was required in all instances to separate the reaction products (**4c** and **4a**, **6a** and **6b**, **7a** and **7b**).

**Ethyl 2-Amino-4-[2-oxo-2-(1-piperidinyl)ethyl]-4*H*-chromene-3-carboxylate (4c):** White solid, m.p. 112–114 °C. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 1.32 (t, $J$ = 7.1 Hz, 3 H, $CH_3$), 1.35–1.88 (m, 6 H, 3×$CH_2$), 2.50 (dd, $J$ = 13.8, 9.3 Hz, 1 H, HC*H*CO), 2.66 (dd, $J$ = 13.8, 4.7 Hz, 1 H, *H*CHCO), 3.07–3.46 (m, 2 H, $CH_2N$), 3.54 (m, 2 H, $CH_2N$), 4.22 (q, $J$ = 7.1 Hz, 2 H, $OCH_2$), 4.33 (dd, $J$ = 9.3, 4.7 Hz, 1 H, 4-H), 6.30 (br. s, 2 H, $NH_2$), 6.99 (dd, $J$ = 7.8, 1.3 Hz, 1 H, 8-H), 7.09 (dt, $J$ = 9.0, 7.5, 1.3 Hz, 1 H, 6-H), 7.21 (dt, $J$ = 9.0, 7.8, 1.8 Hz, 1 H, 7-H), 7.31 (dd, $J$ = 7.5, 1.8 Hz, 1 H, 5-H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 15.0, 24.5, 25.7, 26.3, 31.6, 42.2, 42.7, 46.5, 59.1, 75.6, 115.9, 124.5, 126.5, 128.0, 129.6, 150.1, 162.5, 168.4, 168.5 ppm. IR (neat): $\tilde{\nu}$ = 3389, 3278, 2856, 1675, 1622 cm$^{-1}$. $C_{19}H_{24}N_2O_4$ (344.41): calcd. C 66.26, H 7.02, N 8.13; found C 66.38, H 6.90, N 8.09.

**Ethyl 2-Amino-4-(2-ethoxy-2-oxoethyl)-6-methyl-4*H*-chromene-3-carboxylate (6a):** Oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.18 (t, $J$ = 7.1 Hz, 3 H, $CH_3$), 1.33 (t, $J$ = 7.1 Hz, 3 H, $CH_3$), 2.30 (s, 3 H, $CH_3$), 2.58 (dd, $J$ = 14.7, 7.2 Hz, 1 H, HC*H*CO), 2.64 (dd, $J$ = 14.7, 4.5 Hz, 1 H, *H*CHCO), 4.05 (q, $J$ = 7.1 Hz, 2 H, $OCH_2$), 4.23 (q, $J$ = 7.1 Hz, 2 H, $OCH_2$), 4.26 (m, 1 H, 4-H), 6.34 (br. s, 2 H, $NH_2$), 6.86 (d, $J$ = 8.2 Hz, 1 H, 8-H), 6.99 (dd, $J$ = 8.2, 1.7 Hz, 1 H, 7-H), 7.04 (d, $J$ = 1.7 Hz, 1 H, 5-H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 14.1, 14.6, 20.8, 31.3, 43.7, 59.4, 60.2, 76.6, 115.5, 125.2, 128.2, 128.6, 133.7, 147.8, 161.7, 169.1, 171.8 ppm. IR (neat): $\tilde{\nu}$ = 3417, 3309, 2980, 1725, 1669, 1616 cm$^{-1}$. $C_{17}H_{21}NO_5$ (319.36): calcd. C 63.94, H 6.63, N 4.39; found C 63.87, H 6.54, N 4.48.

**Ethyl 2-Amino-6-methyl-4-[2-oxo-2-(1-piperidinyl)ethyl]-4*H*-chromene-3-carboxylate (6b):** White solid, m.p. 115–117 °C. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 1.31 (t, $J$ = 7.1 Hz, 3 H, $CH_3$), 1.30–1.68 (m, 6 H, 3×$CH_2$), 2.27 (s, 3 H, $CH_3$), 2.49 (dd, $J$ = 13.9, 8.9 Hz, 1 H, HC*H*CO), 2.62 (dd, $J$ = 13.9, 4.8 Hz, 1 H, *H*CHCO), 3.03–3.48 (m, 2 H, $CH_2N$), 3.54 (m, 2 H, $CH_2N$), 4.21 (q, $J$ = 7.1 Hz, 2 H, $OCH_2$), 4.28 (dd, $J$ = 8.9, 4.8 Hz, 1 H, 4-H), 6.31 (br. s, 2 H, $NH_2$), 6.83 (d, $J$ = 8.1 Hz, 1 H, 7-H), 6.97 (d, $J$ = 8.1 Hz, 1 H, 8-H), 7.03 (s, 1 H, 5-H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 14.6, 20.8, 24.5, 25.5, 26.2, 31.9, 42.2, 42.6, 46.9, 59.5, 77.8, 115.4, 125.7, 128.1, 129.2, 133.7, 147.9, 161.8, 169.2, 169.4 ppm. IR (neat): $\tilde{\nu}$ = 3385, 3278, 2937, 2855, 1669, 1624 cm$^{-1}$. $C_{20}H_{26}N_2O_4$ (358.44): calcd. C 67.02, H 7.31, N 7.82; found C 67.17, H 7.38, N 7.65.

**Ethyl 2-Amino-4-(2-ethoxy-2-oxoethyl)-7-methoxy-4*H*-chromene-3-carboxylate (7a):** Oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.19 (t, $J$ = 7.1 Hz, 3 H, $CH_3$), 1.34 (t, $J$ = 7.1 Hz, 3 H, $CH_3$), 2.55 (dd, $J$ = 14.8, 7.4 Hz, 1 H, HC*H*CO), 2.63 (dd, $J$ = 14.8, 4.2 Hz, 1 H, *H*CHCO), 3.79 (s, 3 H, $OCH_3$), 4.05 (q, $J$ = 7.1 Hz, 2 H, $OCH_2$), 4.23 (m, 3 H, 4-H, $CH_2O$), 6.34 (br. s, 1 H, $NH_2$), 6.52 (d, $J$ = 2.3 Hz, 1 H, 8-H), 6.66 (dd, $J$ = 8.4, 2.3 Hz, 1 H, 6-H), 7.15 (d, $J$ = 8.4 Hz, 1 H, 5-H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 14.4, 14.8, 30.9, 44.0, 55.7, 59.8, 60.4, 77.5, 101.5, 110.9, 117.9, 129.2, 150.8, 159.4, 161.7, 169.4, 172.2 ppm. IR (neat): $\tilde{\nu}$ = 3416, 3311, 2982, 1727, 1683, 1617 cm$^{-1}$. $C_{17}H_{21}NO_6$ (335.36): calcd. C 60.89, H 6.31, N 4.18; found C 60.78, H 6.27, N 4.25.

**Ethyl 2-Amino-7-methoxy-4-[2-oxo-2-(1-piperidinyl)ethyl]-4*H*-chromene-3-carboxylate (7b):** White solid, m.p. 139–140 °C. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 1.29 (t, $J$ = 7.1 Hz, 3 H, $CH_3$), 1.25–1.68 (m, 6 H, 3×$CH_2$), 2.45 (dd, $J$ = 13.9, 9.4 Hz, 1 H, HC*H*CO), 2.65 (dd, $J$ = 13.9, 4.3 Hz, 1 H, *H*CHCO), 3.09–3.65 [m, 4 H, $(CH_2)_2N$], 3.79 (s, 3 H, $OCH_3$), 4.23 (m, 3 H, 4-H, $CH_2O$), 6.31 (br. s, 1 H, $NH_2$), 6.51 (d, $J$ = 2.5 Hz, 1 H, 8-H), 6.63 (dd, $J$ = 8.5, 2.5 Hz, 1 H, 6-H), 7.16 (d, $J$ = 8.5 Hz, 1 H, 5-H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 14.6, 24.5, 25.5, 26.3, 31.0, 42.6, 42.7, 46.8, 55.4, 59.5, 78.1, 101.3, 110.3, 118.0, 129.5, 150.5, 159.1, 161.5, 169.2, 169.4 ppm. IR (neat): $\tilde{\nu}$ = 3385, 3282, 2932, 2855, 1674, 1607 cm$^{-1}$. $C_{20}H_{26}N_2O_5$ (374.44): calcd. C 64.16, H 7.00, N 7.48; found C 64.22, H 7.09, N 7.31.

**Typical Reaction Procedure of Coumarin with Malononitrile and Alkoxide:** A solution of the malononitrile (2 mmol) in ethanol (1 mL) was added to a solution of sodium ethoxide (1.2 mmol) in ethanol (2 mL) at room temperature under nitrogen. After 30 min, a solution of coumarin (1 mmol) in ethanol (2 mmol) was added, then the reaction was kept at room temp. for 4 h. The reaction was concentrated to half volume then poured into water and extracted with dichloromethane. The organic solution was dried over $Na_2SO_4$ then concentrated under vacuum to afford 4*H*-chromene derivative **8a** (68%).

**Ethyl (2-Amino-3-cyano-4*H*-chromen-4-yl)acetate (8a):** Amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.27 (t, $J$ = 7 Hz, 3 H, $CH_3$), 2.65 (dd, $J$ = 1.8, 6.0 Hz, 2 H, $CH_2CO$), 4.01 (br. t, $J$ = 6.0 Hz, 1 H, 4-H), 4.08 (q, $J$ = 7.1 Hz, 2 H, $OCH_2$), 4.67 (br. s, 2 H, $NH_2$), 6.93 (d, $J$ = 6.9 Hz, 1 H, 8-H), 7.02–7.23 (m, 3 H, 5,6,7-H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 14.0, 31.9, 43.5, 57.4, 60.7, 116.4, 119.9, 122.5, 125.0, 128.0, 128.3, 149.3, 161.1, 170.9 ppm. GC-MS: $m/z$ (%) = 258 [M$^+$], 229, 184, 171, 156, 116. IR (neat): $\tilde{\nu}$ = 3455, 3332, 2982, 2185, 1731, 1652 cm$^{-1}$. $C_{14}H_{14}N_2O_3$ (258.28): calcd. C 65.11, H 5.46, N 10.85; found C 65.03, H 5.52, N 10.91.

**Typical Reaction Procedure of Coumarin with Malononitrile and Piperidine:** A solution of the piperidine (2.2 mmol) in ethanol (1 mL) was added to a solution of malononitrile (1.1 mmol) and coumarin (1 mmol) in ethanol (2 mL) at room temperature and under nitrogen. After 20 h at room temp. the reaction was concentrated to half volume then poured into water and extracted with dichloromethane. The organic solution was dried over $Na_2SO_4$ then concentrated under vacuum. The crude product was purified by chromatography over silica gel to afford 4*H*-chromene derivative **8b** (51%). When benzene was used as solvent rather than ethanol the reaction was complete in 4 h (yield of **8b**: 57%).

**2-Amino-4-[2-oxo-2-(1-piperidinyl)ethyl]-4*H*-chromene-3-carbonitrile (8b):** White solid, m.p. 161–162 °C. $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ = 1.29–1.72 (m, 6 H, 3×$CH_2$), 2.73 (m, 2 H, $CH_2CO$), 3.31 (m, 2 H, $NCH_2$), 3.58 (m, 2 H, $NCH_2$), 4.23 (br. t, $J$ = 6.5 Hz, 1 H, 4-H), 4.67 (s, 2 H, $NH_2$), 7.01 (dd, $J$ = 1.1, 8.1 Hz, 1 H, 8-H), 7.13–7.33 (m, 3 H, 5,6,7-H) ppm. $^{13}$C NMR (50.4 MHz, $CDCl_3$): $\delta$ = 24.4, 25.4, 26.3, 31.9, 42.1, 42.8, 46.8, 58.5, 116.2, 120.1, 123.6, 124.9, 128.1, 128.4, 149.2, 161.0, 168.3 ppm. IR (neat): $\tilde{\nu}$ = 3496, 3304, 3144, 2176, 1656, 1608 cm$^{-1}$. $C_{17}H_{19}N_3O_2$ (297.36): calcd. C 68.67, H 6.44, N 14.13; found C 68.77, H 6.41, N 14.03.

**Ethyl (2-Amino-3-cyano-6-methyl-4*H*-chromen-4-yl)acetate (9a):** Oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.24 (t, $J$ = 7.1 Hz, 3 H, $CH_3$), 2.31 (s, 3 H, $CH_3$), 2.67 (dd, $J$ = 15.2, 6.0 Hz, 1 H, HC*H*CO), 2.72 (dd, $J$ = 15.2, 6.0 Hz, 1 H, *H*CHCO), 4.02 (t, $J$ = 6 Hz 1 H, 4-H), 4.13 (q, $J$ = 7.1 Hz, 2 H, $OCH_2$), 4.63 (br. s, 2 H, $NH_2$), 6.87 (d, $J$ = 8.2 Hz, 1 H, 8-H), 7.01 (br. s, 1 H, 5-H), 7.03 (d, $J$ = 8.2 Hz, 1 H, 7-H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 14.1, 20.8, 31.9, 43.4, 57.7, 60.7, 116.1, 119.9, 122.1, 128.2, 128.9, 134.6, 147.2, 161.0, 170.9 ppm. IR (neat): $\tilde{\nu}$ = 3334, 2981 2924, 2187, 1645 cm$^{-1}$.

$C_{15}H_{16}N_2O_3$ (272.30): calcd. C 66.16, H 5.92, N 10.29; found C 66.24, H 5.87, N 10.23.

**2-Amino-6-methyl-4-[2-oxo-2-(1-piperidinyl)ethyl]-4*H*-chromene-3-carbonitrile (9b):** White solid, m.p. 209–210 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.27–1.65 (m, 6 H, 3×$CH_2$), 2.30 (s, 3 H, $CH_3$), 2.69 (m, 2 H, $CH_2CO$), 3.29 (m, 2 H, $CH_2N$), 3.53 (m, 1 H, CHN), 3.64 (m, 1 H, CHN), 4.15 (t, $J$ = 6.2 Hz, 1 H, 4-H), 4.64 (br. s, 2 H, $NH_2$), 6.86 (d, $J$ = 8.3 Hz, 1 H, 8-H), 7.01 (dd, $J$ = 8.3, 1.6 Hz, 1 H, 7-H), 7.08 (d, $J$ = 1.6 Hz, 1 H, 5-H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 21.1, 24.7, 25.7, 26.5, 32.3, 42.2, 43.2, 47.2, 58.9, 116.2, 120.4, 123.4, 128.9, 129.0, 134.7, 147.5, 161.4, 168.7 ppm. IR (neat): $\tilde{\nu}$ = 3370, 3155, 2937, 2183, 1659 cm$^{-1}$. $C_{18}H_{21}N_3O_2$ (311.38): calcd. C 69.43, H 6.80, N 13.49; found C 69.31, H 6.74, N 13.61.

**Ethyl (2-Amino-3-cyano-7-methoxy-4*H*-chromen-4-yl)acetate (10a):** Oil. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.24 (t, $J$ = 7.1 Hz, 3 H, $CH_3$), 2.65 (dd, $J$ = 15.4, 6.1 Hz, 1 H, HC*H*CO), 2.71 (dd, $J$ = 15.4, 6.1 Hz, 1 H, *H*CHCO), 3.80 (s, 3 H, $CH_3O$), 4.02 (t, $J$ = 6.1 Hz, 1 H, 4-H), 4.14 (q, $J$ = 7.1 Hz, 2 H, $OCH_2$), 4.63 (br. s, 2 H, $NH_2$), 6.53 (d, $J$ = 2.6 Hz, 1 H, 8-H), 6.70 (dd, $J$ = 8.6, 2.6 Hz, 1 H, 6-H), 7.12 (d, $J$ = 8.6 Hz, 1 H, 5-H) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 14.7, 31.3, 43.4, 55.5, 60.7, 60.9, 101.5, 111.4, 114.4, 119.8, 128.6, 149.8, 159.5, 160.7, 170.9 ppm. IR (neat): $\tilde{\nu}$ = 3345, 2920, 2848, 2189, 1698 cm$^{-1}$. $C_{15}H_{16}N_2O_4$ (288.30): calcd. C 62.49, H 5.59, N 9.72; found C 62.56, H 5.74, N 9.65.

**2-Amino-7-methoxy-4-[2-oxo-2-(1-piperidinyl)ethyl]-4*H*-chromene-3-carbonitrile (10b):** White solid, m.p. 156–157 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.37–1.70 (m, 6 H, 3×$CH_2$), 2.64 (dd, $J$ = 15.1, 7.5 Hz, 1 H, HC*H*CO), 2.71 (dd, $J$ = 15.1, 5.1 Hz, 1 H, *H*CHCO), 3.30 (m, 2 H, $CH_2N$), 3.57 (m, 2 H, $CH_2N$), 3.79 (s, 3 H, $OCH_3$), 4.13 (dd, $J$ = 7.5, 5.1 Hz 1 H, 4-H), 4.70 (br. s, 2 H, $NH_2$), 6.51 (d, $J$ = 2.6 Hz, 1 H, 8-H), 6.67 (dd, $J$ = 8.6, 2.6 Hz, 1 H, 6-H), 7.22 (d, $J$ = 8.6 Hz, 1 H, H-5) ppm. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 24.7, 25.7, 26.6, 31.5, 42.4, 43.1, 47.1, 55.8, 59.4, 101.9, 111.4, 115.8, 120.3, 129.5, 150.1, 159.6, 161.0, 168.7 ppm. IR (neat): $\tilde{\nu}$ = 3322, 3191, 2934, 2856, 2185, 1621 cm$^{-1}$. $C_{18}H_{21}N_3O_3$ (327.38): calcd. C 66.04, H 6.47, N 12.84; found C 66.13, H 6.38, N 12.72.

## Acknowledgments

Financial support from MIUR, National Project "Sviluppo di processi ecocompatibili nella sintesi organica", is gratefully acknowledged.

[1] a) G. Feuer, *Prog. Med. Chem.* **1974**, *10*, 85–158; b) O. Obaseki, W. R. Porter, *J. Heterocycl. Chem.* **1982**, *19*, 385–390; c) A. K. Das Gupta, R. M. Chatterjee, K. R. Das, *Indian J. Chem. Sect. B* **1981**, *20*, 511–512; d) R. O. Kennedy, R. D. Thornes, *Coumarins: Biology, Application and Mode of Action*; **1997**, J. Wiley & Sons, Chichester.
[2] a) F. Kazmier, *Mayo Clin. Proc.* **1974**, *49*, 918–922; b) T. Kralt, V. Classen, in *Drug Design* (Ed.: E. J. Ariens), Academic Press: New York, **1972**; Vol. 3, p. 189; c) R. A. O'Reilly, *Annu. Rev. Med.* **1976**, *27*, 245–261; d) L. A. Singer, N. P. Kong, *J. Am. Chem. Soc.* **1966**, *88*, 5213–5219.
[3] M. A. Hermodson, W. M. Barker, K. P. Link, *J. Med. Chem.* **1971**, *14*, 167–169.
[4] a) M. Curini, F. Epifano, F. Maltese, M. C. Marcotullio, S. Prieto Gonzales, J. C. Rodriguez, *Aust. J. Chem.* **2003**, *56*, 59–60; b) M. Curini, F. Epifano, F. Maltese, M. C. Marcotullio, S. Prieto Gonzales, J. C. Rodriguez, A. Tubaro, G. Altinier, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2241–2243.
[5] M. Curini, F. Epifano, S. Chimichi, F. Montanari, M. Nocchetti, O. Rosati, *Tetrahedron Lett.* **2005**, *46*, 3497–3499.
[6] a) D. Heber, E. V. Stoyanov, *Synthesis* **2003**, *2*, 227–232; b) M. Z. Piao, K. Imafuku, *Tetrahedron Lett.* **1997**, *38*, 5301–5302; c) R. A. Mekheimer, N. H. Mohamed, K. U. Sadek, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1625–1630; d) N. Martín, M. Quinteiro, C. Seoane, A. Albert, F. H. Cano, R. A. Abramovitch, *Tetrahedron* **1992**, *48*, 1581–1584.
[7] M. P. Nemeryuk, V. D. Dimitrova, O. S. Anisimova, A. L. Sedov, N. P. Solov'eva, V. F. Traven, *Chem. Heterocycl. Comp.* **2003**, *39*, 1454–1465.
[8] N. Yu, J. M. Aramini, M. W. Germann, Z. Huang, *Tetrahedron Lett.* **2000**, *41*, 6993–6996.
[9] A. Fujimoto, A. Sakurai, *Synthesis* **1977**, 871–872.
[10] J. F. Roudier, A. Foucaud, *Synthesis* **1984**, 159–160.
[11] I. Yavari, H. Djahaniani, F. Nasiri, *Tetrahedron* **2003**, *59*, 9409–9412.

Received: July 5, 2005
Published Online: November 17, 2005