A simple synthesis of functionalized 2-amino-3-cyano-4-chromones by application of the *N*-hydroxybenzotriazole methodology

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Abstract
A novel and simple method for the synthesis of functionalized 2-amino-3-cyano-4-chromones is reported. The title compounds were isolated after acylation of malononitrile with *N*-hydroxybenzotriazolyl acetylsalicylates, generated *in situ* by treating acetylsalicylic acid derivatives with *N*-hydroxybenzotriazole, followed by cyclization. The described one-pot methodology is characterized by short reaction times, high yields (68 to 77%), no side-products and provides chromones with a variety of substituents on the aromatic ring. The structure of the isolated compounds has been determined by means of $^{1}H/^{13}C$ NMR and FT-IR Spectroscopy.

Keywords: Chromones, *N*-hydroxybenzotriazole, acylation, cyclization

Introduction

Chromones (Figure 1) constitute one of the major classes of naturally occurring compounds, and interest in their chemistry continues unabated because of their usefulness as biologically active agents.[1]

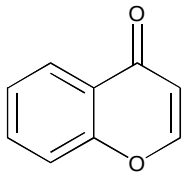


Figure 1. The chromone nucleus

Some of the biological activities attributed to chromone derivatives include cytotoxic (anticancer),[2-4] neuroprotective,[5] HIV-inhibitory,[6] antimicrobial,[7, 8] antifungal[9] and antioxidant

activity.[10] Due to their abundance in plants and their low mammalian toxicity, chromone derivatives are present in large amounts in the diet of humans.[11]

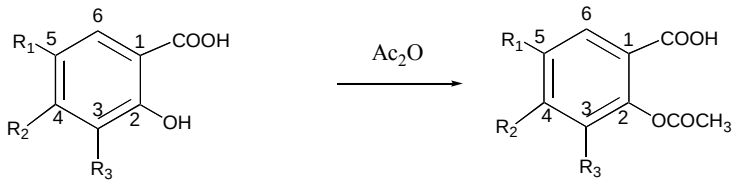
The synthesis of chromone derivatives is a research field of great interest and long history.[12] In general, chromones are synthesized by the cyclodehydration of 1-(*o*-hydroxyaryl)-1,3- diketones or equivalent intermediates catalyzed by strong acids or strong bases (Vilsmeier-Haack reaction).[13] They have been prepared on a large scale by the Allan-Robinson synthesis involving acylation-rearrangement, and subsequent cyclization.[14] This methodology has been followed in the synthesis of chromone derivatives with quaternary ammonium functionalities which show not only activity of cosmetic interest but also for hair sustainability, as well as in the asymmetric synthesis of optically active 4-chromone derivatives.[15] In the Baker-Venkataraman synthesis,[16] internal Claisen condensation of 2-aryloxy-1-acetylarenes is employed as a key step. More recently the synthesis of chromone derivatives was accomplished by intramolecular ester carbonyl olefination[17] or Pd-catalyzed regiospecific carbonylative annulation of *o*-iodophenol acetates and acetylenes.[1, 18] 3-Cyanochromones have been synthesized in a mild and facile method from oximes derived from 3-formyl chromones using dimethyl formamide/ thionyl chloride complex.[19] As for aminochromones, useful for the prevention of allergic and asthmatic reactions in mammals, as indicated by tests in rats, they have been synthesized either by rearrangement of isoxazoles[20] or from chlorinated salicylic acids and malononitrile in aqueous NaOH or NaH.[21]

During the last few years we have been involved in the one-step synthesis of heterocycles[22a, 22b] employing *N*-hydroxybenzotriazole esters of α-amino or α-hydroxy acids as acylating agents of active methylene compounds to produce a wide variety of γ-amino[22c] or γ-hydroxy butenoates,[22d] which can be converted to five-membered heterocycles with biological interest. As a consequence, we employed the *N*-hydroxybenzotriazole methodology in the synthesis of 4-hydroxycoumarins by using a number of substituted acetyl salicylic acids as the precursors.[22e]

Results and Discussion

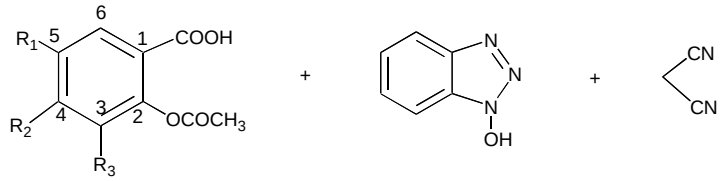
Having examined the reaction of substituted acetyl salicyclic acids with various active methylene compounds for the synthesis of 4-hydroxycoumarins, we decided to proceed with the use of malononitrile as the active methylene compound. In this case, we first acetylated the salicylic acids we used by a standard procedure.[22e] The products **2-7** were isolated in excellent yields and without need for further purification. We next proceeded with the synthesis of the *N*-hydroxybenzotriazole esters of the acetyl salicylic acids. Accordingly, the acetyl salicylic acid **1-7** and *N*-hydroxybenzotriazole were dissolved in anhydrous THF at 0^{o}C and then dicyclohexylcarbodiimide (DCC) dissolved in THF was added dropwise. The mixture was stirred at 0^{o}C for 1 hour and then refrigerated overnight. The precipitate was discarded and the filtrate containing the active ester was added to a slurry of sodium hydride and malononitrile in

anhydrous THF and stirred at room temperature for 2.5 hours. The solvent was then removed under reduced pressure, the residue was diluted with water, washed with Et_2O and the aqueous layer was acidified with 10% HCl solution to give an oily product after extractions with DCM. The oily product was treated with methanolic 10% HCl solution and stirred at room temperature for 24-48 hours to afford the desired chromones **10**-**16** as solids, which were collected by filtration and washed with dichloromethane and diethyl ether.



	R_1	R_2	R_3
	H	H	H
	Cl	H	H
	H	H	OCH_3
	H	H	CH_3
	CH_3	H	H
	OCH_3	H	H
	H	OCH_3	H

	R_1	R_2	R_3
1	H	H	H
2	Cl	H	H
3	H	H	OCH_3
4	H	H	CH_3
5	CH_3	H	H
6	OCH_3	H	H
7	H	OCH_3	H

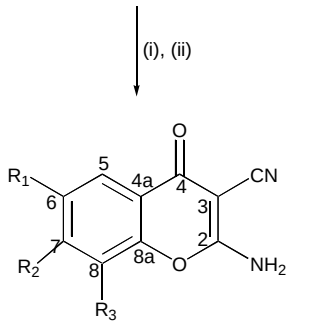


8 **9**

	R_1	R_2	R_3
1	H	H	H
2	Cl	H	H
3	H	H	OCH_3
4	H	H	CH_3
5	CH_3	H	H
6	OCH_3	H	H
7	H	OCH_3	H

(i): NaH, DCC, THF anhd.

(ii): 10%HCl, MeOH



	R_1	R_2	R_3
10	H	H	H
11	Cl	H	H
12	H	H	OCH_3
13	H	H	CH_3
14	CH_3	H	H
15	OCH_3	H	H
16	H	OCH_3	H

Scheme 1. Synthesis of functionalized 2-amino-3-cyano-4-chromones.

An important feature of the described methodology is the use of the *N*-hydroxybenzotriazole esters as useful precursors for the synthesis of compounds with potent

biological and pharmacological properties. The activation of the substituted salicylic acids as their hydroxybenzotriazole esters is an alternative route to other methods of activation[21] permitting mild reaction conditions. In addition, there is no need to isolate the intermediate esters, therefore the overall reaction time is reduced. Furthermore, the absence of active sites on the *N*-hydroxybenzotriazole molecule allows control of the chemoselectivity of the reaction. Finally, the reaction is simple, inexpensive and easily scaled-up.

In conclusion, we have synthesized a series of functionalized 2-amino-3-cyano-4-chromones **10-16** using a short-step synthesis. The described methodology makes use of the *N*-hydroxybenzotriazole esters of the functionalized acetyl salicylic acids as acylating agents and malononitrile as the active methylene compound. The reaction has the advantage of high yields and short reaction times. Work currently in progress includes the study of structure-activity relationships of chromones and the application of *N*-hydroxybenzotriazole in the synthesis of more complex molecules.

Experimental Section

General Procedures. All melting points were determined with Gallenkamp MFB-595 melting point apparatus and are uncorrected. FT-IR spectra were recorded on a Nicolet Magna IR 560. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian Gemini-2000 300 MHz spectrometer. Chemical shifts (δ) are given from $CDCl_3$ (7.26 ppm) or DMSO-d_6 (2.50 ppm) as internal standard for ^{1}H and DMSO-d_6 (39.50 ppm) for ^{13}C NMR spectra (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad); *J* values are given in Hz. Elemental analyses were obtained on a Euro EA3000 Series Euro Vector CHNS Elemental Analyser.

General procedure for the synthesis of the functionalized 2-acetoxy benzoic acids 2-7

In a typical reaction, the functionalized salicylic acid (10 mmol) was mixed with acetic anhydride (8 mL, 12 mmol) and a few drops of 85% phosphoric acid solution. The mixture was stirred under reflux for 2 hours whereupon water (3 mL) was added. The reaction continued for 5 minutes and the mixture was poured into cold water (20 mL) and brought to room temperature. The precipitate formed was filtered off, washed with water and dried *in vacuo*.

2-Acetoxy-5-chloro-benzoic acid (2). Colorless solid; yield 1.92 g, 90%; mp 150-151°C (lit.[22e] mp 153-154°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (3H, s, $OCOCH_3$), 7.18 (1H, s, H-6), 7.35 (1H, d, *J* = 8.1 Hz, H-4), 8.06 (1H, d, *J* = 8.1 Hz, H-3).

2-Acetoxy-3-methoxy-benzoic acid (3). Colorless solid; yield 1.85 g, 88%; mp 136-138°C (lit.[22e] mp 140-142°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (3H, s, $OCOCH_3$), 3.86 (3H, s, OCH_3), 7.19 (1H, dd, *J* = 1.8, 7.8 Hz, H-4), 7.26 (1H, t, *J* = 7.8 Hz, H-5), 7.65 (1H, dd, *J* = 1.8, 7.8 Hz, H-6).

2-Acetoxy-3-methyl-benzoic acid (4). Colorless solid; yield 1.70 g, 88%; mp 114-116°C (lit.[22e] mp 117-118.5°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (3H, s, $OCOCH_3$), 2.40 (3H, s, CH_3), 7.28 (1H, d, *J* = 6.9 Hz, H-5), 7.52 (1H, d, *J* = 6.9 Hz, H-4), 7.97 (1H, d, *J* = 6.9 Hz, H-6).

2-Acetoxy-5-methyl-benzoic acid (5). Colorless solid; yield 1.65 g, 85%; mp 144-146°C (lit.[22e] mp 148-151°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (3H, s, $OCOCH_3$), 2.40 (3H, s, CH_3), 7.02 (1H, d, *J* = 11.7 Hz, H-6), 7.42 (1H, dd, *J* = 2.7, 11.7 Hz, H-4), 7.92 (1H, d, *J* = 2.7 Hz, H-3).

2-Acetoxy-5-methoxy-benzoic acid (6). Colorless solid; yield 1.88 g, 90%; mp 151-153°C (lit.[23] mp 156-158°C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.32 (3H, s, $OCOCH_3$), 3.85 (3H, s, OCH_3), 7.04 (1H, d, *J* = 8.7 Hz), 7.14 (1H, d, *J* = 8.7 Hz), 7.59 (1H, s, H-6).

2-Acetoxy-4-methoxy-benzoic acid (7). Colorless solid; yield 1.80 g, 86%; mp 115-116°C; *Anal*. Calcd. $C_{10}H_{10}O_5$: C 57.14, H 4.76. Found: C 57.26, H 4.62,. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (3H, s, $OCOCH_3$), 3.85 (3H, s, OCH_3), 7.18 (1H, d, *J* = 8.4 Hz), 7.32 (1H, s, H-3), 7.60 (1H, d, *J* = 8.4 Hz).

General procedure for the synthesis of the functionalized chromones 10-16. In a typical reaction, the functionalized acetyl salicylic acid (5 mmol) **1-7** was treated with *N*-hydroxybenzotriazole (0.67 g, 5 mmol) **8** and DCC (1.03 g, 5 mmol) added dropwise in anhydrous THF (25 mL) at 0°C for 1 hour. The resulting suspension was refrigerated overnight at 3-5°C. The precipitated solid (DCCU) was filtered off and the filtrate was added to a solution of NaH (0.4 g, 10 mmol) and malononitrile (0.33 g, 5 mmol) **9** in anhydrous THF (40 mL). The resulting mixture was stirred at room temperature for 2.5 hours and then concentrated *in vacuo*. The obtained gummy solid was diluted with water and washed with Et_2O. The aqueous extract was acidified with 10% HCl in an ice water bath. The precipitated white solid (*N*-hydroxybenzotriazole) was filtered off and the aqueous filtrate was extracted with DCM (3 x15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford an oily product, which was dissolved in MeOH (5 mL) and treated with 10% HCl solution (5-10 mL) for 24-48 hours at room temperature to afford the corresponding 2-amino-3-cyano-4-chromones **10-16** as white solids. All solid products were filtered off, washed with DCM and Et_2O and dried *in vacuo*.

2-Amino-4-oxo-4*H*-chromene-3-carbonitrile (10). Beige solid; yield 1.4 g, 75%; mp 308-310°C (decomp.) (lit.[19] mp 310-311°C); *Anal*. Calcd. $C_{10}H_6N_2O_2$: C 64.52, H 3.23, N 15.05. Found: C 64.46, H 3.42, N 14.97. IR (KBr) cm^{-1}: 3138, 2226, 1661. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.38-7.43 (2H, m, H-6/H-8), 7.72 (1H, t, *J* = 8.1 Hz, H-7), 7.93 (1H, d, *J* = 8.1 Hz, H-5), 8.94 (2H, br s, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 73.5, 115.4, 117.0, 120.7, 125.0, 125.7, 134.2, 152.7, 167.0, 173.8.

2-Amino-6-chloro-4-oxo-4*H*-chromene-3-carbonitrile (11). Beige solid; yield 0.75 g, 68%; mp >320°C (lit.[21] mp 340°C); *Anal*. Calcd. $C_{10}H_5N_2O_2Cl$: C 54.42, H 2.27, N 12.70. Found: C 54.63, H 2.39, N 12.57. IR (KBr) cm^{-1}: 3131, 2232, 1657. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.49 (1H, dd, *J* = 3.3, 12 Hz, H-7), 7.59 (1H, d, *J* = 3.3 Hz, H-5), 7.92 (1H, d, *J* = 12 Hz, H-8), 9.06 (2H, br s, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 73.6, 115.0, 116.9, 119.6, 125.9, 126.6, 138.0, 152.8, 166.7, 172.8.

2-Amino-8-methoxy-4-oxo-4*H*-chromene-3-carbonitrile (12). Colorless solid; yield 0.73 g, 68%; mp 303-305°C (decomp.) (lit.[21] mp 300°C); *Anal*. Calcd. $C_{11}H_8N_2O_3$: C 61.11, H 3.70, N 12.96. Found: C 60.88, H 3.83, N 13.09. IR (KBr) cm^{-1}: 3130, 2222, 1655. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.91 (3H, s, OCH_3), 7.30-7.48 (3H, m, aromatic protons), 8.94 (2H, br s, NH_2); ^{13}C

NMR (75 MHz, DMSO-d_6): δ 56.2, 73.6, 115.2, 115.5, 115.9, 121.5, 125.2, 142.2, 147.2, 166.5, 173.5.

2-Amino-8-methyl-4-oxo-4*H*-chromene-3-carbonitrile (13). Beige solid; yield 0.72 g, 72 %; mp >290°C (decomp.) *Anal*. Calcd. $C_{11}H_8N_2O_2$: C 66.00, H 4.00, N 14.00. Found: C 66.20, H 3.89, N 13.87. IR (KBr) cm^{-1}: 3130, 2222, 1655. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.38 (3H, s, CH_3), 7.30 (1H, t, *J* = 11.1 Hz, H-6), 7.56 (1H, d, *J* = 11.1 Hz, H-7), 7.75 (1H, d, *J* = 11.1 Hz, H-5), 8.89 (2H, br s, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.8, 73.4, 115.4, 120.4, 122.4, 124.9, 126.1, 134.9, 150.9, 166.6, 173.9.

2-Amino-6-methyl-4-oxo-4*H*-chromene-3-carbonitrile (14): Colorless solid; yield 0.77 g, 77 %; mp 280-282°C (decomp.) (lit.[24] mp 282-284°C); *Anal*. Calcd. $C_{11}H_8N_2O_2$: C 66.00, H 4.00, N 14.00. Found: C 65.79, H 3.81, N 14.29. IR (KBr) cm^{-1}: 3131, 2223, 1656. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.38 (3H, s, CH_3), 7.31 (1H, d, *J* = 12 Hz, H-8), 7.52 (1H, d, *J* = 12 Hz, H-7), 7.72 (1H, s, H-5), 8.86 (2H, br s, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.9, 73.4, 115.5, 120.2, 122.5, 125.0, 126.0, 135.3, 151.1, 166.6, 173.7.

2-Amino-6-methoxy-4-oxo-4*H*-chromene-3-carbonitrile (15): Colorless solid; yield 0.79 g, 73 %; mp>320°C (lit.[21] mp 320°C); *Anal*. Calcd. $C_{11}H_8N_2O_3$: C 61.11, H 3.70, N 12.96. Found: C 60.89, H 3.56, N 13.02. IR (KBr) cm^{-1}: 3132, 2222, 1659. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.82 (3H, s, OCH_3), 7.25-7.40 (3H, m, aromatic protons), 8.85 (2H, br s, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 56.2, 72.3, 101.1, 113.0, 113.9, 115.2, 126.9, 154.8, 163.1, 166.7, 172.9.

2-Amino-7-methoxy-4-oxo-4*H*-chromene-3-carbonitrile (16): Beige solid; yield 0.75 g, 70 %; mp>300°C; *Anal*. Calcd. $C_{11}H_8N_2O_3$: C 61.11, H 3.70, N 12.96. Found: C 61.29, H 3.49, N 13.08. IR (KBr) cm^{-1}: 3130, 2223, 1661. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.87 (3H, s, OCH_3), 6.88 (1H, s, H-8), 7.00 (1H, d, *J* = 13.2 Hz, H-6), 7.83 (1H, d, *J* = 13.2 Hz, H-5), 8.83 (2H, br s, NH_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 56.0, 72.7, 100.6, 113.3, 113.9, 115.4, 126.3, 155.0, 163.6, 166.9, 173.1.

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