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New approach to synthesis of 4-arylcoumarin derivatives

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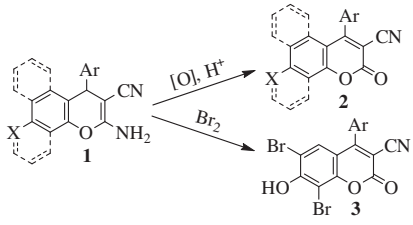
ABSTRACT

A simple and highly efficient new approach for the synthesis of 4-aryl-2-oxo-2*H*-chromene-3-carbonitriles based on the oxidation and hydrolysis of 2-amino-4-aryl-4*H*-chromene-3-carbonitriles is described.

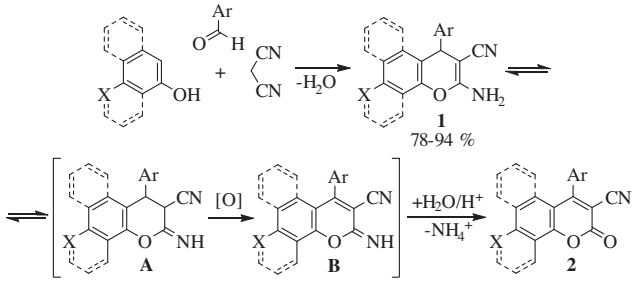
Coumarins are an important class of oxygen-containing heterocycles. The 2*H*-chromen-2-one (coumarin) fragment is known to be a part of many biologically active compounds,[1] possessing anti-inflammatory,[1a,b] antioxidant,[1c–e] antimicrobial,[1f] antiviral,[1g–i] anticancer,[1j,k] and antiproliferative[1l] activities. Additionally, good photochemical properties, chemical stability, and ease of synthesis make coumarin derivatives an important class of fluorescent probes for biological studies.[2] Coumarin chromophores, which can be used as light removable protecting groups in caged compounds, have been used as light-removable protecting groups, so-called 'caging groups', and applied in the optical control of biological processes.[3] Generally, coumarins are synthesized utilizing the Perkin, Pechmann, Wittig, and Reformatsky reactions,[4a–g] Knoevenagel condensation reactions,[4h,i] as well as other cyclization reactions.[4j,k] The most common method for the synthesis of cyano-containing 4-arylcoumarin derivatives is the Knoevenagel condensation between substituted benzophenones and cyanoacetic acid or its esters[4h,i] or the reaction between 3-aryl-2-cyanoacrylic acid esters and phenols with subsequent oxidation.[5]

In this Letter, we describe a new approach to 4-arylcoumarin derivatives based on the oxidation and hydrolysis of 4-aryl-2-amino-4*H*-chromenes **1**, leading to formation of 4-aryl-2-oxo-2*H*-chromene-3-carbonitriles **2a–o**[6] and **3a–c**[7] (Scheme 1).

2-Amino-4-aryl-4*H*-chromene-3-carbonitriles (**1a–o**) were synthesized according to literature procedures via the three-



Scheme 1. Oxidation of 2-amino-4*H*-chromenes **1a–o** into coumarin derivatives **2a–o** and **3a–c**.



Scheme 2. Oxidation and hydrolysis of 2-amino-4*H*-chromenes **1a–o** into coumarin derivatives **2a–o**.

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0040-4039/

Table 1
Synthesis of 4-aryl-2-oxo-2*H*-chromene-3-carbonitriles **2a–o**[a]

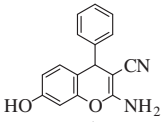
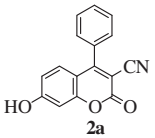
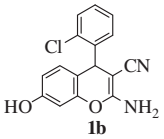
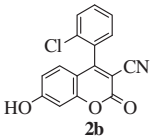
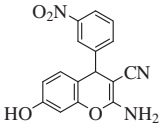
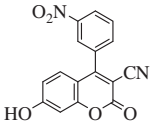
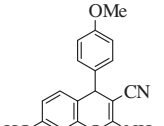
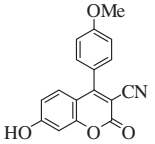
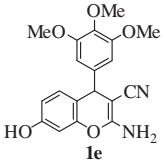
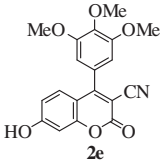
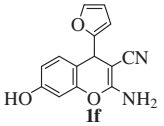
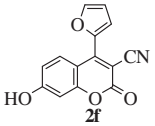
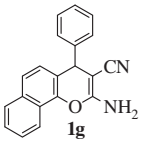
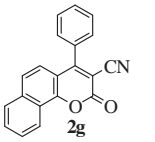
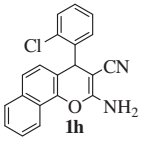
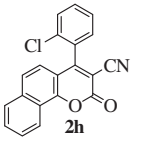
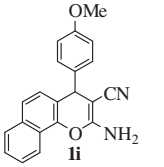
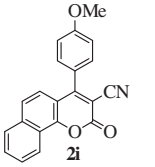
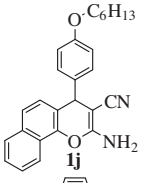
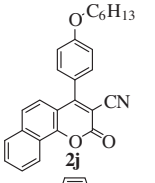
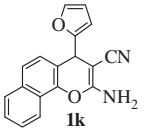
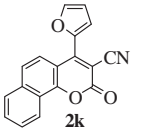
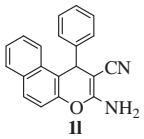
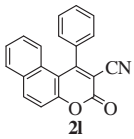
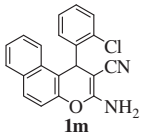
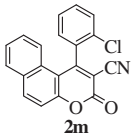
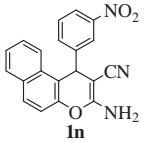
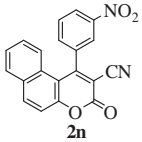
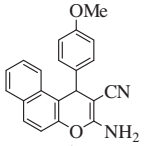
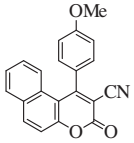
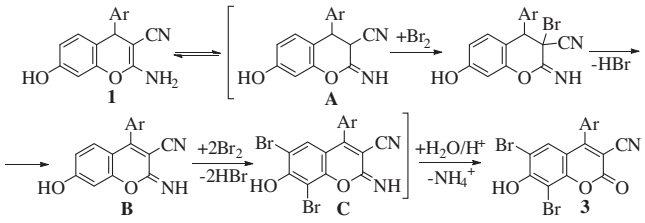
Entry	Substrate	Product	Yield[b] (%)
1	 **1a**	 **2a**	62
2	 **1b**	 **2b**	73
3	 **1c**	 **2c**	81
4	 **1d**	 **2d**	71
5	 **1e**	 **2e**	73
6	 **1f**	 **2f**	57
7	 **1g**	 **2g**	76
8	 **1h**	 **2h**	64
9	 **1i**	 **2i**	68
10	 **1j**	 **2j**	70
11	 **1k**	 **2k**	51

Table 1 (*continued*)

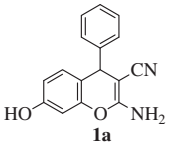
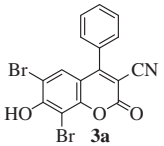
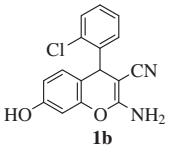
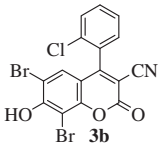
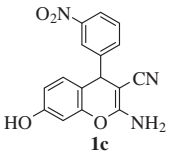
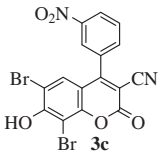
Entry	Substrate	Product	Yield[b] (%)
12	 **1l**	 **2l**	82
13	 **1m**	 **2m**	75
14	 **1n**	 **2n**	80
15	 **1o**	 **2o**	82

[a] Reaction conditions: compound **1** (10 mmol), I_2O_5 (2 mmol), CH_3COOH (15 mL), H_2O (5 mL), 70 °C, 20 min.
[b] Yield of isolated product.



Scheme 3. Synthesis of 4-aryl-6,8-dibromo-7-hydroxy-2-oxo-2*H*-chromene-3-carbonitriles **3a**–**c**.

Table 2
Synthesis of 4-aryl-6,8-dibromo-7-hydroxy-2-oxo-2*H*-chromene-3-carbonitriles **3a**–**c**[a]

Entry	Substrate	Product	Yield[b] (%)
1	 **1a**	 **3a**	85
2	 **1b**	 **3b**	82
3	 **1c**	 **3c**	78

[a] Reaction conditions: compound **1** (10 mmol), Br_2 (30 mmol), CH_3COOH (20 mL), 60 °C, 1 h.
[b] Yield of isolated product.

component condensation reaction of various phenols, arylaldehydes, and malononitrile in ethanol under basic conditions.[8] Hydrogen peroxide, selenium dioxide, chromium trioxide, oxygen, bromine and iodine pentoxide were all examined as oxidants for the synthesis of coumarin derivatives **2a**–**o**, with the best results being obtained using iodine pentoxide. The reaction was postulated to involve tautomerization of **1** into intermediate **A** followed by oxidation to give iminopyran **B**, which upon acid-catalyzed hydrolysis

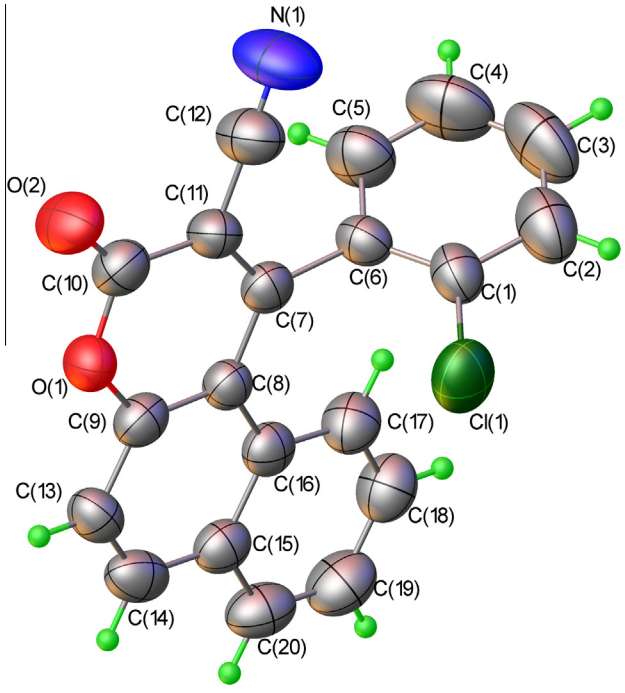


Figure 1. ORTEP diagram of 1-(2-chlorophenyl)-3-oxo-3*H*-benzo[*f*]chromene-2-carbonitrile (**2m**).

formed the 4-aryl-2-oxo-2*H*-chromene-3-carbonitriles **2a–o** in 51–82% yields (Scheme 2 and Table 1).

Using bromine as the oxidizing agent caused dibromination of the phenyl ring during oxidation leading to the formation of compounds **3a–c**. This reaction was proposed to involve the bromination of intermediate **A** and subsequent dehydrohalogenation to iminopyran **B**. Following electrophilic bromination, intermediate **C** can be hydrolysed to yield 4-aryl-6,8-dibromo-7-hydroxy-2-oxo-2*H*-chromene-3-carbonitriles **3a–c** in 78–85% yields (Scheme 3 and Table 2).

The structures of compounds **2a–o** and **3a–c** were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry[6,7] and by single crystal X-ray diffraction analysis of compound **2m** (Fig. 1).[9]

In conclusion, there are several articles in the literature that describe the synthesis of 4-arylchromene-3-carbonitriles from 4-aryl-2-amino-4*H*-chromenes,[10] but detailed research in this area has not been carried out. In this Letter, we report a novel, operationally simple approach for the synthesis of coumarin derivatives. Future work regarding the expansion of this reaction is currently in progress.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.111.

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6. *Typical procedure for the preparation of 4-aryl-2-oxo-2H-chromene-3-carbonitriles* **2**: 2-Amino-4*H*-chromenes **1** (10 mmol) and I_2O_5 (2 mmol) in a mixture of CH_3COOH (15 mL) and H_2O (5 mL) was stirred at 70 °C for 20 min. After cooling, H_2O (40 mL) was added, and the precipitate was filtered and washed with H_2O (20 mL). Compound **2a**. Mp 175–176 °C (dec); ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 6.84–6.88 (2H, m, 2CH), 7.12 (1H, d, J = 8.7 Hz, CH), 7.52–7.55 (2H, m, C_6H_5), 7.63–7.65 (3H, m, C_6H_5), 11.38 (1H, br s, OH). ^{13}C NMR (125.76 MHz, DMSO-d_6): 96.03 (C^3), 102.75 (C^8), 110.49, 114.78 ($C^{4'}$, C^6), 114.62 (CN), 128.29, 128.70, 128.78, 130.45, 132.38 (C^5, C_6H_5), 155.87, 157.66 ($C^{8'}$, C^2), 163.56, 164.60 (C^7, C^4). IR (mineral oil, cm^{-1}): 2221 (CN), 1695 (C=O). MS (EI, 70 eV): m/z (%) 263 $[M]^+$ (100), 235 $[M-28]^+$ (80). Anal. Calcd for $C_{16}H_9NO_3$: C, 73.00; H, 3.45; N, 5.32. Found: C, 73.09; H, 3.46; N, 5.40.

7. *Typical procedure for the preparation of 4-aryl-6,8-dibromo-7-hydroxy-2-oxo-2H-chromene-3-carbonitriles* **3**: Br_2 (30 mmol) was added to 2-amino-4*H*-chromenes **1** (10 mmol) in CH_3COOH (20 mL) and heated at 60 °C for 1 h. After cooling, H_2O (20 mL) was added, and the precipitate was filtered and washed with a mixture of H_2O (15 mL) and *i*-PrOH (5 mL). Compound **3a**. Mp 290–291 °C (dec); ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 4.40 (1H, br s, OH), 7.22 (1H, s, CH), 7.51–7.54 (2H, m, C_6H_5), 7.65–7.68 (3H, m, C_6H_5). ^{13}C NMR (125.76 MHz, DMSO-d_6): 98.22 (C^3), 100.45 (C^6), 109.07, 112.97 ($C^{4'}$, C^8), 114.77 (CN), 128.75, 129.48, 130.76, 131.27, 132.23 (C^5, C_6H_5), 152.04 ($C^{8'}$), 157.30, 158.20 (C^2, C^7), 162.55 (C^4). IR (mineral oil, cm^{-1}): 2225 (CN), 1691 (C=O). MS (EI, 70 eV): m/z (%) 423 $[M]^+$ (44), 421 $[M]^+$ (82), 419 $[M]^+$ (43), 393 $[M-28]^+$ (40). Anal. Calcd for $C_{16}H_7Br_2NO_3$: C, 45.64; H, 1.68; N, 3.33. Found: C, 45.59; H, 1.76; N, 3.40.

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9. Crystallographic data (excluding structure factors) for the structure **2l** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1058585. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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