Facile synthesis of chromeno[4,3-*b*]quinolin-6-ones from unexpected reactions of aryl isocyanides with 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde†

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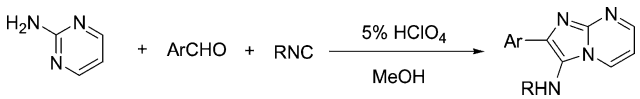
An unexpected reaction of aryl isocyanides with 4-chloro-2-oxo-*2H*-chromene-3-carbaldehyde leads to chromeno[4,3-*b*]quinolin-6-ones in good yields.

A goal of chemical genetics is to find small molecules that modulate the individual functions of gene products with high potency and high specificity.[1] Natural products and natural product-derived compounds provide many of the most striking examples, particularly in terms of their specificity. It seems unlikely that natural products alone will provide the hypothetical "complete" set of small molecules that would allow the functions of all proteins, as well as their individual domains, to be determined. For chemistry to have its maximal effect on biology, efficient methods for discovering natural product-like compounds are in great demand in the field of chemical genetics.[1] On the other hand, multicomponent reactions (MCR) have emerged as a powerful tool for delivering the molecular diversity needed in the combinatorial approaches for the preparation of bioactive compounds.[2] In 1998, Bienaymé reported a highly efficient and practical approach to fused 3-amino-imidazoles of high structural diversity[3] (Scheme 1). Its reliability, the ready availability of the starting materials, and the versatility of the resulting products make it a very important process for library generation.



Scheme 1 MCRs reported by Bienaymé.

As part of a program aimed at developing new approaches to construct natural product-like compound libraries, we are interested in isocyanide involved multicomponent reactions developed by Bienaymé,[3] based on 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde **1**, due to our ongoing research in coumarin chemistry.[4]

The reaction was initially studied with 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde **1a**, which was selected as suitable substrate for reaction development. During an attempt to prepare compound **A** or **B** from **1a**, 4-methoxyphenyl isocyanide **2a**, and 2-aminopyrimidine in MeOH, treated with 10 mol% of perchloric acid (Scheme 2), a white crystalline solid precipitated from the reaction mixture when left to stand overnight at room temperature (46% yield). After purification, however, the product of this reaction was not the expected one (**A** or **B**). From spectral characterization, it was found to be generated from 1 equiv. of **1a** and 1 equiv. of **2a**. Structure elucidation by ^{1}H, ^{13}C NMR and mass spectroscopy, as well as comparison of the standard ^{1}H NMR spectra of the compound we made from 4-(4-methoxyphenyl)amino coumarin and $POCl_3$,[5] revealed this precipitate to be 9-methoxychromeno[4,3-*b*]quinolin-6-one **3a**.

Following an extensive investigation, we found that, without any promoters, the reaction of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde **1a** with 4-methoxyphenyl isocyanide **2a** in MeOH also proceeded smoothly to give 9-methoxychromeno[4,3-*b*]quinolin-6-one **3a** at room temperature in high yield (87%). It is noteworthy that this reaction could be run under air without loss of efficiency. In contrast to the formation of **A** or **B**, which results from multicomponent reaction of the Bienaymé product,[3] the formation of **3a** is less easy to understand.

Although the mechanism is not clear, a possible mechanistic rationalization for the reaction is given in Scheme 3. The initial event is the formation of amine **a** from the isocyanide and methanol. The amine **a** can react with compound **1** *via* 1,4-addition and elimination resulting in the formation of **5**. After cyclization by attacking the aldehyde, intermediate **6** could be formed, which then delivers the primary adduct **7**. The latter then losses a molecule of H_2O to give the final product **3**. Evidence in support of this is now being investigated.

Further screening revealed that methanol is the solvent of choice. Other solvents, such as benzene and DMF, gave unsatisfactory results. To explore the scope of the reaction, a set of substrates were subjected to the reaction (Table 1). Complete conversion and moderate to good isolated yields were observed for all substituted coumarin substrates employed. Electronic effects both in the 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde **1** and in the aryl isocyanides **2** showed similar influences on the reaction. It is interesting that hydroxyl products **4a** and **4b** were obtained when 4-diethylaminophenyl isocyanide **2c** reacted with **1b** and **1d** (entries 5 and 9). This is maybe due to the isomerization *via* [1,3]-H shift from intermediate **7**. The operation process is very simple: after completion of reaction, the reaction mixture was filtered and precipitate was collected. The solid obtained could be used for spectra analysis directly without further purification in some cases.

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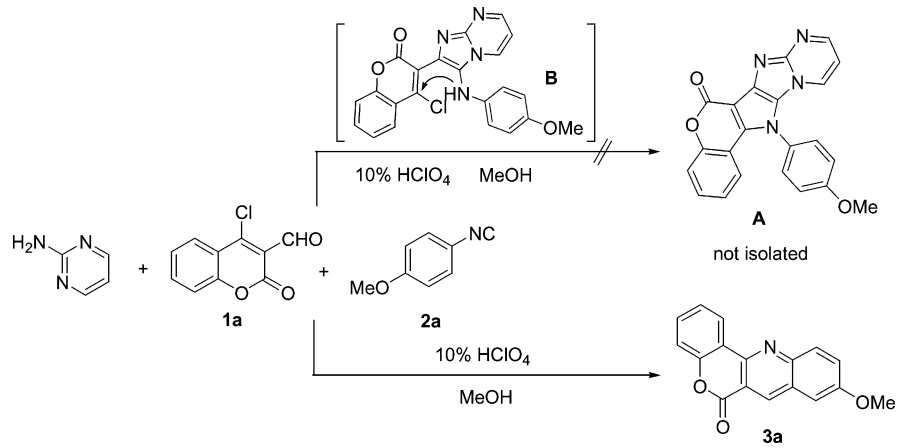
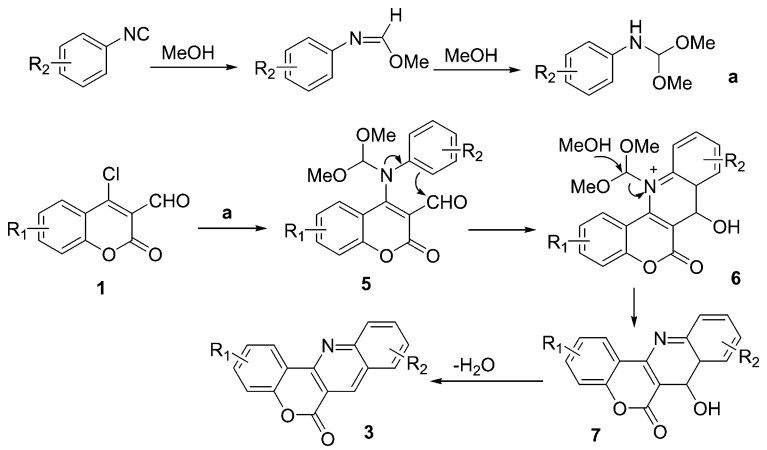
† Electronic Supplementary Information (ESI) available: ^{1}H and ^{13}C NMR spectra of compound **3f**. See DOI: 10.1039/b600540c



Scheme 2 Initial studies.



Scheme 3 Proposed possible mechanism.

Conclusions

In summary, the reaction described here represents a highly efficient and practical route to chromeno[4,3-*b*]quinolin-6-ones. It is likely that the efficiency and novelty of this method combined with the operational simplicity of the present process will make it potentially attractive for library construction. Mechanism studies and investigations aimed at exploring the scope of the reaction are currently under way.

Experimental

General procedure for the reaction of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde 1 with aryl isocyanide 2

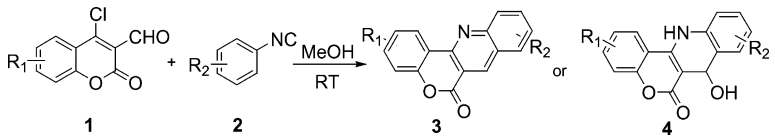
Aryl isocyanide (0.25 mmol) was added to a solution of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde **1** (0.25 mmol) in MeOH (4 mL). The reaction mixture was stirred at room temperature overnight. After the reaction was complete (monitored by TLC), the mixture was filtered. The precipitate was collected and purified by flash chromatography column (silica gel) to afford the corresponding product **3** or **4**. (The solid obtained could be used for spectral analysis directly without further purification in some cases.)

9-Methoxy-6*H*-chromeno[4,3-*b*]quinolin-6-one 3a[5]. White solid. Mp: 237–238 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.00 (s, 3H), 7.27 (s, 1H), 7.39–7.46 (m, 2H), 7.56–7.60 (m, 2H), 8.14 (d, J = 9.5 Hz, 1H), 8.75 (d, J = 8.0 Hz, 1H), 9.10 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 56.0, 105.8, 116.2, 117.5, 120.1, 125.0, 125.1, 127.3, 128.8, 131.2, 132.0, 139.2, 147.7, 147.9, 152.6, 158.6, 161.8. MS [$C_{17}H_{11}NO_3$], m/z (M^+ + 1): calcd 278.08, found 278.25. HRMS: Anal. Calcd. for $C_{17}H_{11}NO_3$, 277.0739. Found, 277.0742.

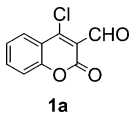
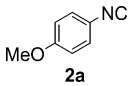
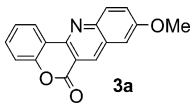
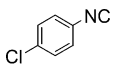
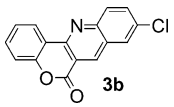
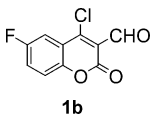
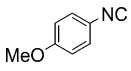
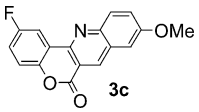
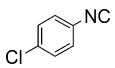
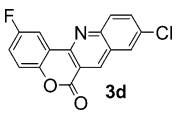
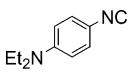
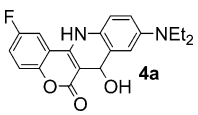
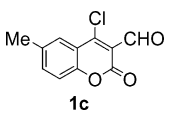
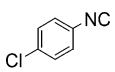
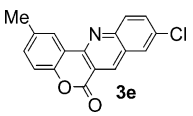
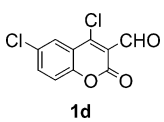
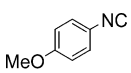
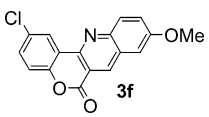
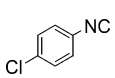
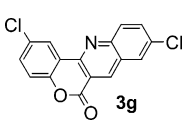
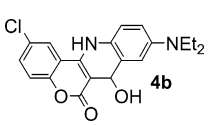
9-Chloro-6*H*-chromeno[4,3-*b*]quinolin-6-one 3b[5]. White solid. Mp: 246–247 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.38–7.46 (m, 2H), 7.58–7.63 (m, 1H), 7.84 (dd, J = 9.5, 2.5 Hz, 1H), 7.99 (d, J = 2.5 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 8.75 (dd, J = 8.0, 1.5 Hz, 1H), 9.13 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 116.7, 117.7, 119.6, 125.3, 125.5, 127.9, 128.0, 131.4, 132.9, 133.6, 134.5, 140.2, 149.7, 150.1, 152.9, 161.2. MS [$C_{16}H_8ClNO_2$], m/z (M^+ + 1): calcd 282.03, found 282.22. HRMS: Anal. Calcd. for $C_{16}H_8ClNO_2$, 281.0244. Found, 281.0237.

2-Fluoro-9-methoxy-6*H*-chromeno[4,3-*b*]quinolin-6-one 3c. White solid. Mp: 226–227 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.00 (s, 3H), 7.22–7.28 (m, 2H), 7.34–7.38 (m, 1H), 7.58 (dd, J = 9.5, 2.5 Hz, 1H), 8.13 (d, J = 9.0 Hz, 1H), 8.40 (dd, J = 8.0, 1.5 Hz, 1H), 9.08 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$)

Table 1 Reaction of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehydes with aryl isocyanides[a]



1 2 3 4

Entry	Aldehyde	Isocyanide	Product	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	77
2		 **2b**	 **3b**	79
3	 **1b**	 **2a**	 **3c**	82
4		 **2b**	 **3d**	80
5		 **2c**	 **4a**	63
6	 **1c**	 **2b**	 **3e**	78
7	 **1d**	 **2a**	 **3f**	75
8		 **2b**	 **3g**	76
9		 **2c**	 **4b**	61

[a] Reaction conditions: aryl isocyanide (0.25 mmol), 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde (0.25 mmol) in MeOH (4 mL) at room temperature, overnight. [b] Isolated yield.

δ (ppm): 56.0, 105.8, 110.8, 111.0, 115.9, 119.2, 121.4, 127.6, 129.1, 131.3, 139.2, 146.9, 147.8, 148.6, 158.9, 160.8, 161.5. MS [$C_{17}H_{10}FNO_3$], m/z ($M^+ + 1$): calcd 296.07, found 296.24. HRMS: Anal. Calcd. for $C_{17}H_{10}FNO_3$, 295.0645. Found, 295.0651.

9-Chloro-2-fluoro-6*H*-chromeno[4,3-*b*]quinolin-6-one 3d. White solid. Mp: 239–240 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.27–7.33 (m, 1H), 7.36–7.40 (m, 1H), 7.86 (dd, $J = 9.0$, 2.5 Hz, 1H), 8.01 (d, $J = 2.0$ Hz, 1H), 8.18 (d, $J = 9.0$ Hz, 1H), 8.40 (dd, $J = 8.0$, 1.5 Hz, 1H), 9.13 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 111.1, 111.3, 116.5, 119.3, 120.0, 120.9, 128.0, 128.2, 131.4, 134.0, 134.8, 140.4, 149.2, 149.6, 158.9, 160.8. MS [$C_{16}H_7ClFNO_2$], m/z ($M^+ + 1$): calcd 300.02, found 300.18. HRMS: Anal. Calcd. for $C_{16}H_7ClFNO_2$, 299.0149. Found, 299.0143.

9-Chloro-2-methyl-6*H*-chromeno[4,3-*b*]quinolin-6-one 3e. White solid. Mp: 252–253 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 2.51 (s, 3H), 7.24–7.27 (m, 1H), 7.37–7.40 (m, 1H), 7.82 (dd, J = 9.0, 2.5 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H), 8.13 (d, J = 8.5 Hz, 1H), 8.48 (s, 1H), 9.08 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 21.2, 115.6, 116.7, 117.4, 119.0, 125.1, 127.9, 131.2, 133.5, 133.8, 134.4, 135.1, 140.2, 149.6, 150.1, 151.0, 161.3. MS [$C_{17}H_{10}ClNO_2$], m/z (M^+ + 1): calcd 296.05, found 296.26. HRMS: Anal. Calcd. for $C_{17}H_{10}ClNO_2$, 295.0400. Found, 295.0396.

2-Chloro-9-methoxy-6*H*-chromeno[4,3-*b*]quinolin-6-one 3f. White solid. Mp: 247–248 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.00 (s, 3H), 7.22 (d, J = 3.0 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.50 (dd, J = 9.0, 2.0 Hz, 1H), 7.60 (dd, J = 9.5, 3.0 Hz, 1H), 8.13 (d, J = 9.0 Hz, 1H), 8.70 (d, J = 2.5 Hz, 1H), 9.08 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 56.0, 105.8, 115.9, 119.0, 121.4, 124.7, 127.6, 129.0, 130.8, 131.3, 131.8, 139.2, 146.5, 147.8, 150.9, 158.9, 161.2. MS [$C_{17}H_{10}ClNO_3$], m/z (M^+ + 1): calcd 312.04, found 312.20. HRMS: Anal. Calcd. for $C_{17}H_{10}ClNO_3$, 311.0349. Found, 311.0355.

2,9-Dichloro-6*H*-chromeno[4,3-*b*]quinolin-6-one 3g[6]. White solid. Mp: 272–273 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.48 (d, J = 9.0 Hz, 1H), 7.55 (dd, J = 9.0, 2.5 Hz, 1H), 7.88 (dd, J = 9.5, 3.0 Hz, 1H), 8.02 (s, 1H), 8.20 (d, J = 9.5 Hz, 1H), 8.72 (s, 1H), 9.14 (s, 1H). MS [$C_{16}H_7Cl_2NO_2$], m/z (M^+ + 1): calcd 316.00, found 316.17. HRMS: Anal. Calcd. for $C_{16}H_7Cl_2NO_2$, 314.9854. Found, 314.9851.

9-(Diethylamino)-2-fluoro-7-hydroxy-7*H*-chromeno[4,3-*b*]-quinolin-6(12*H*)-one 4a. White solid. Mp: 212–213 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.32 (t, J = 7.0 Hz, 6H), 3.20–3.80 (m, 5H), 6.55 (d, J = 9.0 Hz, 1H), 7.23–7.33 (m, 2H), 7.42 (d, J = 9.0 Hz, 2H), 7.88 (s, 2H), 10.24 (s, 1H). IR: 3350 cm^{-1}. MS [$C_{20}H_{19}FN_2O_3$], m/z (M^+ + 1): calcd 355.15, found 355.35. HRMS: Anal. Calcd. for $C_{20}H_{19}FN_2O_3$, 354.1380. Found, 354.1386.

2-Chloro-9-(diethylamino)-7-hydroxy-7*H*-chromeno[4,3-*b*]-quinolin-6(12*H*)-one 4b. White solid. Mp: 231–232 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.32 (t, J = 7.0 Hz, 6H), 3.20–3.80 (m, 5H), 6.94 (s, 1H), 7.26–7.30 (m, 2H), 7.40–7.49 (m, 3H), 7.60–7.90 (br, 1H), 10.24 (s, 1H). IR: 3400 cm^{-1}. MS [$C_{20}H_{19}ClN_2O_3$], m/z (M^+ + 1): calcd 371.12, found 371.31. HRMS: Anal. Calcd. for $C_{20}H_{19}ClN_2O_3$, 370.1084. Found, 370.1076.

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