Convenient one-step synthesis of 4-unsubstituted 2-amino-4H-chromene-2-carbonitriles and 5-unsubstituted 5H-chromeno[2,3-b]pyridine-3-carbonitriles from quaternary ammonium salts

Vitaly A. Osyanin *, Dmitry V. Osipov, Yuri N. Klimochkin
Department of Organic Chemistry, Samara State Technical University, 244 Molodogvardeiskaya St., 443100 Samara, Russian Federation

Abstract
We have reported DBU catalyzed synthesis of 4-unsubstituted 2-amino-4H-chromene-2-carbonitriles in water under reflux. The attractive features of this process are mild reaction conditions, short reaction times, easy isolation of products and good yields. 5H-chromeno[2,3-b]pyridine-3-carbonitriles were obtained by refluxing excess of malononitrile and quaternary ammonium salts in ethanol in the presence of NaOH as catalyst. The mechanisms of these reactions are believed to involve the formation of the o-quinone methide intermediate.

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1. Introduction
One of the main objectives of organic and medicinal chemistry is the design and synthesis of molecules having value as human therapeutic agents. 2-Amino-4H-chromenes are of particular utility as they belong to privileged medicinal scaffolds serving for generation of small-molecule ligands with highly pronounced spasmodilic-, diuretic-, anticoagulant-, antibacterial- and antianaphylactic activities.1 Substituted 2-amino-4H-benzochromenes were proposed for the treatment of immune system diseases and diabetic complications resulted from an increase in permeability of blood vessels and a change in blood pressure.2 The current interest in 2-amino-4H-chromenes arises from their application in the treatment of human inflammatory TNFα-mediated diseases, such as rheumatoid and psoriatic arthritis and in cancer therapy (compounds A–C, Scheme 1).1,3 Besides, β-enaminonitrile derivatives of 4H-chromenes are useful synthetic intermediates for the preparation of heterocyclic systems having potential biological activity.4–8 That is why the development of novel, highly efficient methods for the synthesis of 4-unsubstituted 2-amino-4H-chromene-2-carbonitriles is still of current interest.

Scheme 1. 2-Amino-4H-chromenes and chromeno[2,3-b]pyridines as privileged medicinal scaffolds.

* Corresponding author. Tel./fax: +7 846 332 2122; e-mail address: VOsyanin@mail.ru (V.A. Osyanin).
amlexanox E (Scheme 1). In addition, many of these compounds possess anti-bacterial, anti-proliferative, anti-myopic, hypotensive, anti-histaminic, anti-rheumatic and anti-asthmatic activities. For example, chromeno[2,3-b]pyridine F has reported to inhibit mitogen activated protein kinase-activated protein kinase 2 and attenuate the production of pro-inflammatory TNF-α. Compound 2 has reported to inhibit histamine-stimulated gastric acid secretion. 12

A number of methods have been reported for the syntheses of 2-amino-4H-chromene-2-carbonitriles. These compounds are generally prepared by the three-component condensation of malononitrile, an aromatic aldehyde and an activated phenol in the presence of a catalyst (organic bases, ammonium salts, basic aluminas) in an organic solvent (i.e., acetonitrile, ethanol). 7,13,18 However, phenols with electron-withdrawing substituents in the ring are inert under the reaction conditions, which considerably limits the scope of accessible structures. Besides, 2-amino-4H-chromene-2-carbonitriles have been synthesized in two steps. 4,6 The first step consisted in preparing and isolating benzylidenomalononitrile. The second step involved the reaction of these compounds with the corresponding phenol or napththol. It should be noted that only 4-aryl-substituted 2-amino-4H-chromene-2-carbonitriles can be prepared by these methods. Several 4-unsubstituted 2-amino-4H-chromene-2-carbonitriles were prepared from salicylic aldehydes, malononitrile and Hantzsch dihydropryanidine ester using a catalytic amount of InCl3. However, the resulting products must be purified by column chromatography from Hantzsch pyridine ester. A few methods have been reported for the synthesis of chromeno[2,3-b]pyridine derivatives by multi-component reactions of malononitrile dimer or 2 equiv of malononitrile with salicylic aldehydes and different nucleophiles (secondary amines, 20 thiol, 10,21 anion of malononitrile11). Besides, chromeno[2,3-b]pyridines were prepared from resorcinol and arylmethylidene derivatives of malononitrile dimer, 22 quaternary ammonium salt and malononitrile dimer. 11

As part of our current studies 23 on the development of new routes to heterocyclic systems from o-quinone methides (o-QMs), we now report an efficient synthetic route to 2-amino-4H-chromene-2-carbonitriles and 5H-chromeno[2,3-b]pyridine-3-carbonitriles from quaternary ammonium salts. o-QMs are important intermediates in many chemical and biological processes. These reactive species are efficient DNA alkylating and cross-linking agents, play a key role in the biological action of several antibiotics, such as mitomycin and anthracyclines. o-QMs act as heterodienes in inter- and intramolecular cycloadditions with olefins to give various substituted chromanes. Like vinyl ketones, o-QMs also act as Michael acceptor. 24

2. Results and discussion

Herein, we report a simple, efficient method for the synthesis of 4-unsubstituted 2-amino-4H-chromene-2-carbonitriles 2a–i from quaternary ammonium salts 1a–i and malononitrile in high yields using water or ethanol as the reaction medium (Scheme 2). The use of water as a solvent has many advantages in organic processes and reactions, both in industry and in green chemistry applications. It is economical, non-toxic and environmentally friendly. The hydrophobic products produced when using water as the solvent are separable by extraction with an organic solvent or filtration. It should be noted that the synthetic potential of the Mannich bases for an o-QM formation has remained largely underestimated in relation to the high temperature needed for the thermal elimination of the amine. The formation of quaternary ammonium salts by alkylation of the Mannich adducts is a way to induce easier removal of the amino residue and, therefore, trapping of the transient electrophilic species at lower temperature. Furthermore, elimination of the tertiary amines as an ammonium salt makes the process irreversible. 25

In order to evaluate the efficiency of this method the synthesis of 2-amino-6-methoxy-4H-chromene-2-carbonitrile 2a, via reaction of 2-hydroxy-5-methoxybenzyl(trimethyl)ammonium iodide 1a and malononitrile as a model system, was carried out in water using DBU as a catalyst. DBU is an organic base (pKb=12) and +M effect of the adjacent nitrogen stabilizes the protonated species. DBU is an effective catalyst for Michael addition. 18

First, we investigated the effect of quantity of DBU on the synthesis of 2a. The reaction was investigated in the presence of 0.1, 0.5, 1.0, 1.5 and 2.0 equiv of DBU. In all cases, the reaction times were 1 min. It was observed that the use of 1 equiv of DBU in aqueous medium under reflux yielded the desired product in 88% yield in 1 min (Table 1, entry 3). A stoichiometric amount of DBU is required to generate the phenolate and to keep the system basic. Increasing of the catalyst to 1.5 and 2 equiv results in decreasing the reaction yields to 77% and 54%, respectively. When this reaction was repeated at room temperature, no desired product formation was observed. Refluxing in ethanol was also found to be a successful procedure in the preparation of the 2a. The product is separated from the reaction mixture and isolated by filtration. Besides, the model reaction was carried out simply by stirring equimolar amounts of malononitrile, quaternary salt 1a and DBU at 25 °C for 15 min without any solvent to afford the product 2a in 63% yield. Conventional chromatographic purification was not required.

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Quantity (equiv)</th>
<th>Yield (%)</th>
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<tbody>
<tr>
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<tr>
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<td>0.5</td>
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<td>3</td>
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<tr>
<td>5</td>
<td>2.0</td>
<td>54</td>
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</tbody>
</table>

* Reaction conditions: Compound 1a (1.5 mmol), malononitrile (1.5 mmol), DBU, 12 mL of water, 100 °C, 1 min.

In order to evaluate the effect of the base on the reaction, a range of both organic and inorganic bases were examined (Table 3). Among the different catalysts tested, DBU and NaOH were the most effective, whereas weaker bases, such as pyridine, N-methylimidazole and DABCO, led to lower yields. In the absence of any catalyst, no reaction was observed.

The scope of this method for the synthesis of other 2-amino-4H-chromene-2-carbonitriles using the optimized conditions was studied (Table 4). In each case good yields of products were obtained and no by-products were found.

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The reactions of quaternary salts containing electron-withdrawing (such as CO₂CH₃, Cl) or bulky (adamantyl) groups show a slightly slower reaction rate and lower yields than those containing electron-donating groups (such as methoxy group, alkyl group). Products can be easily purified from impurities by single recrystallization. The reaction was repeated on several different scales (up to 20 mmol), all with comparable yields.

In order to broaden the scope of the present method, we attempted the present protocol for the naphthalene derivative. This procedure showed some limitations. We could not prepare the chromene 2k from the quaternized 2-dimethylaminomethyl-4,6-di-tert-butylphenol because the obtain of pure salt is very complicated. However, compound 2k has been prepared in low yield (9%) from the Mannich base 1k just in the case of slow addition of the malononitrile to a mixture of 1k and DBU in a boiling DMF. This reaction proceed along with formation of 2,4-diamino-7,9-di-tert-buty1-5H-chromeno[2,3-b]pyridine-3-carbonitrile 3a (25%) and unexpected product of formal Diels–Alder reaction between compound 2k and corresponding o-QM as a major product 4 (48%) (Scheme 5). It should be noted that the formation of chromene 2k assumed to be a limiting stage. This assumption was confirmed by the reaction of Mannich base 1k with malononitrile in presence of DBU — only pyridine 3a and by-product 4 has been obtained. It means that steric factors for ortho-substituted o-QM precursors can significantly reduce the reaction yield.

Attempts to extend this reaction to the quaternized 2-dimethylaminomethyl-4-nitrophenol also failed due to the relatively greater thermal stability of this quaternary salt and consequent difficulty in generating the o-QM intermediate. This reaction proceeds via the o-QM intermediate, which is formed by the thermal decomposition of the quaternary ammonium salts. Subsequent a Michael-type addition of the deprotonated malononitrile to the o-QM affords the 2-hydroxybenzylmalononitrile. The driving force of the reaction is the resulting rearomatization of the molecule. The intramolecular nucleophilic addition reaction, involving the hydroxyl group and the cyano group (Pinner reaction), takes place and the imine is generated. The chromene is afforded through tautomerization of imine.

This procedure showed some limitations. We could not prepare the chromene 2k from the quaternized 2-dimethylaminomethyl-4,6-di-tert-butylphenol because the obtain of pure salt is very complicated. However, compound 2k has been prepared in low yield (9%) from the Mannich base 1k just in the case of slow addition of the malononitrile to a mixture of 1k and DBU in a boiling DMF. This reaction proceed along with formation of 2,4-diamino-7,9-di-tert-buty1-5H-chromeno[2,3-b]pyridine-3-carbonitrile 3a (25%) and unexpected product of formal Diels–Alder reaction between compound 2k and corresponding o-QM as a major product 4 (48%) (Scheme 5). It should be noted that the formation of chromene 2k assumed to be a limiting stage. This assumption was confirmed by the reaction of Mannich base 1k with malononitrile in presence of DBU — only pyridine 3a and by-product 4 has been obtained. It means that steric factors for ortho-substituted o-QM precursors can significantly reduce the reaction yield.

Attempts to extend this reaction to the quaternized 2-dimethylaminomethyl-4-nitrophenol also failed due to the relatively greater thermal stability of this quaternary salt and consequent difficulty in generating the o-QM under the conditions mentioned in this paper. Nevertheless, in the reaction with ammoniophenolate 1l,29 which is more reactivity precursor of o-QM corresponding chromene 2l was prepared in 70% yield (Scheme 6).

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**Table 2**

<table>
<thead>
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<th>Entry</th>
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</tr>
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<td>3</td>
<td>50</td>
<td>5 min</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>15 min</td>
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<td>5</td>
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<td>10</td>
<td>100</td>
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*Reaction conditions: Compound 1a (1.5 mmol), malononitrile (1.5 mmol), DBU (1.5 mmol), 12 mL of water.*

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**Table 3**

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<td>11</td>
<td>Py</td>
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*Reaction conditions: Compound 1a (1.5 mmol), malononitrile (1.5 mmol), base (1.5 mmol), 12 mL of water, 100 °C, 1 min.*

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**Table 4**

<table>
<thead>
<tr>
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<td>82</td>
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<td>EtOH</td>
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<td>9</td>
<td>6-Cl</td>
<td>H₂O</td>
<td>5</td>
<td>61</td>
</tr>
</tbody>
</table>

*Reaction conditions: Compound 1a (1.5 mmol), malononitrile (1.5 mmol), DBU (1.5 mmol), 12 mL of water.*

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The structures of all products were determined on the basis of their analytical data. The $^1$H NMR spectra of products (2a–l) show characteristic 2-H singlets at $\delta$ 3.31–3.48 ppm for benzylic protons. A distinguishing resonance at $\delta$ 23.8–24.9 ppm for C-4, 49.0–49.7 ppm for C-3 and 161.1–161.6 ppm for C-2 are observed in the $^{13}$C NMR spectra. Enamine NH$_2$ signal appears as a singlet at $\delta$ 6.64–6.90 ppm (D$_2$O exchangeable). The IR spectra show NH$_2$ stretch at $\nu$ 3468–3406, 3337–3318 and 3233–3194 cm$^{-1}$.

In an effort to expand the scope of the method, the replacement of malononitrile with ethyl cyanoacetate was examined. It was observed that with ethyl cyanoacetate, which is a less reactive methylene component compared with malononitrile, the yield of the chromene derivative 5 significantly decreased (Scheme 7).

The $^1$H NMR spectra of products 3a–d show characteristic singlet peaks at $\delta$ 3.53–3.64 ppm for benzylic protons. The $^{13}$C NMR spectra of 3a–d exhibit a specific peak in the region of 70.5–70.8 ppm, that is, related to C-3. A signal in the region of 85.5–86.4 ppm was assigned to C-4a. Protons of NH$_2$ groups appear as two broad singlets in the region of 6.26–6.52 ppm (D$_2$O exchangeable). The IR spectra show NH$_2$ stretch at $\nu$ 3472–3129 cm$^{-1}$, CN stretch at $\nu$ 2203–2191 cm$^{-1}$.

3. Conclusions

We have described a general and highly efficient procedure for the preparation of 4-unsubstituted 2-amino-4H-chromene-2-carbonitriles catalyzed by DBU under refluxing water. The reaction is easily carried out, and the reaction products are directly crystallized from the reaction mixture. Access to these heterocyclic compounds may prove to be of some therapeutic interest in the future including highly pronounced anticancer activities. The direct use of inexpensive reagents, short reaction times and mild reaction conditions make this domino Michael–Pinner reaction very attractive and practical.

4. Experimental

4.1. Materials and methods

FTIR-spectra were taken on a Shimadzu FTIR-8400S spectrophotometer in KBr pellets. $^1$H, $^{13}$C and DEPT NMR spectra were recorded on a JEOL JNM-ECX400 spectrometer (400 and 100 MHz, respectively) in DMSO-d$_6$ solutions with TMS as internal standard. Chemical shifts and coupling constants were recorded in units of parts per million and hertz, respectively. Mass spectra were obtained on a Finnigan Trace DSQ instrument, energy of ionizing electrons was 70 eV. Melting points were determined on Electrothermal melting point apparatus and are uncorrected. Elemental analysis was carried out on an Euro Vector EA-3000 automatic CHNS-analyzer. Thin-layer chromatography was carried out on aluminium-backed silica gel plates (Merck 60 F254) with visualisation of components by UV light (254 nm) or exposure to I$_2$. Non-commercial Mannich bases and their quaternary ammonium salts were prepared according to the well known methods.$^{23a,30–32}$

4.2. General procedure for the synthesis of 2-amino-4H-chromene-2-carbonitriles

A mixture of a quaternary ammonium salt 1a–l (3 mmol), malononitrile (0.20 g, 3 mmol) and DBU (0.45 mL, 3 mmol) in water (20 mL) or ethanol (10 mL) was heated under reflux for the
3.06 (s, 3H, CH₃), 3.33 (s, 2H, CH₂), 6.64 (s, 2H, NH₂), 6.77 (s, 1H, Ar), 6.71 (s, 2H, NH₂), 6.85 (s, 2H, NH₂) ppm; 1H NMR (400 MHz, DMSO-d₆) δ: 2.34 (s, 2H, CH₂), 3.79 (s, 3H, CH₃), 6.90 (s, 2H, NH₂), 7.03 (d, 1H, J=9.2 Hz, H-8), 7.57–7.77 (m, 2H, H-5, H-7) ppm; 13C NMR (100 MHz, DMSO-d₆) δ: 23.9 (CH₂), 49.5 (C-3), 52.7 (CH₂), 117.0 (CH), 120.7 (C), 121.2 (C), 126.1 (C), 129.8 (CH), 130.8 (CH), 153.2 (CH), 160.8 (C-2), 165.9 (CO) ppm. Anal. Calcd (%) for C₁₂H₁₉N₃O₂: C, 62.60; H, 4.38; N, 12.17. Found (%): C, 62.70; H, 4.43; N, 12.12.

4.2.6. Methyl 2-amino-3-cyano-4H-chromene-7-carboxylate (2f). White solid; mp 216–217 °C (decomp.): IR (KBr): 3410, 3333, 3210 (NH₂), 2819 (CN), 1703 (CO), 1655 (C=C, vinylnitrile), 1612, 1578 (C=C, aromatic), 1441, 1425, 1412, 1308, 1292, 1250, 1096, 1040, 903, 760 cm⁻¹; 1H NMR (400 MHz, DMSO-d₆) δ: 3.48 (s, 2H, CH₂), 3.80 (s, 3H, CH₃), 6.88 (s, 2H, NH₂), 7.28 (d, 1H, J=7.8 Hz, H-5), 7.36 (d, 1H, J=1.4–1.8 Hz, H-6), 7.61 (dd, 1H, J=7.8, 1.8 Hz, H-6) ppm; 13C NMR (100 MHz, DMSO-d₆) δ: 24.3 (CH₃), 49.1 (C-3), 52.9 (CH₂), 116.8 (CH), 121.3 (C), 125.4 (CH), 126.0 (C), 129.8 (CH), 129.9 (C), 149.8 (C), 161.1 (C-2), 165.8 (CO) ppm. Anal. Calcd (%) for C₁₂H₁₅NO₂: C, 62.60; H, 4.38; N, 12.17. Found (%): C, 62.65; H, 4.36; N, 12.21.

4.2.7. 2-Amino-6,7-dimethyl-4H-chromene-2-carbonitrile (2g). Light yellow solid; mp 242–244 °C (decomp.) (from DMF): IR (KBr): 3453, 3333, 3217 (NH₂), 2817 (CN), 1659 (C=C, vinylnitrile), 1612, 1578 (C=C, aromatic), 1501, 1454, 1412, 1300, 1223, 1180, 1099, 1030, 991, 872 cm⁻¹; 1H NMR (400 MHz, DMSO-d₆) δ: 2.10 (s, 3H, CH₃), 2.12 (s, 3H, CH₃), 2.03 (s, 3H, CH₃), 6.52 (s, 2H, NH₂), 6.72 (s, 2H, NH₂), 7.08 (d, 1H, J=1.8–2.0 Hz, H-8), 7.05 (d, 1H, J=7.2 Hz, H-5) ppm; 13C NMR (100 MHz, DMSO-d₆) δ: 24.2 (CH₂), 28.8 (CH₃), 35.9 (CH₃), 36.6 (CH₂), 43.1 (CH₃), 49.4 (C-3), 115.9 (CH), 119.4 (C), 121.7 (C), 124.8 (CH), 125.5 (CH), 147.6 (C), 147.7 (C), 161.5 (C-2) ppm. Anal. Calcd (%) for C₁₂H₁₂N₂O: C, 71.98; H, 6.04; N, 13.99. Found (%): C, 72.03; H, 6.09; N, 14.05.

4.2.8. 2-Amino-6-benzyl-4H-chromene-2-carbonitrile (2h). White solid; mp 156–157 °C: IR (KBr): 3418, 3318, 3194 (NH₂), 2195 (CN), 1659 (C=C, vinylnitrile), 1612, 1589 (C=C, aromatic), 1497, 1435, 1404, 1312, 1269, 1223, 1073, 1038 cm⁻¹; 1H NMR (400 MHz, DMSO-d₆) δ: 3.38 (s, 2H, 4-CH₂), 3.83 (s, 2H, CH₂Ph), 6.73 (s, 2H, NH₂), 6.84 (d, 1H, J=8.2–8.4 Hz, H-7), 7.00–7.03 (m, 2H, Ar), 7.12–7.19 (m, 3H, Ar), 7.22–7.26 (m, 2H, Ar) ppm; 13C NMR (100 MHz, DMSO-d₆) δ: 24.2 (CH₂), 40.8 (CH₂Ph), 49.3 (C-3), 54.9 (C-4), 116.5 (CH), 120.0 (C), 121.7 (C), 126.5 (CH), 128.7 (CH), 129.0 (CH), 129.2 (CH), 137.9 (C), 141.7 (C), 148.1 (C), 161.5 (C-2) ppm. Anal. Calcd (%) for C₁₇H₁₄N₂O: C, 77.84; H, 5.38; N, 10.68. Found (%): C, 77.78; H, 5.31; N, 10.73.

4.2.9. 2-Amino-6-chloro-4H-chromene-2-carbonitrile (2i). Light yellow solid; mp 213–215 °C: IR (KBr): 3418, 3331, 3208 (NH₂), 2183 (CN), 1661 (C=C, vinylnitrile), 1609, 1580 (C=C, aromatic), 1481, 1450, 1422, 1406, 1308, 1261, 1233, 1180, 1036, 812 cm⁻¹; 1H NMR (400 MHz, DMSO-d₆) δ: 3.42 (s, 2H, CH₂), 6.84 (br s, 2H, NH₂), 6.95 (d, 1H, J=8.7 Hz, H-7), 7.23 (dd, 1H, J=8.7, 2.3 Hz, H-7), 7.26 (d, 1H, J=2.3–2.4 Hz, H-5), 7.19 (dd, 1H, J=8.7, 2.3 Hz, H-7) ppm; 13C NMR (100 MHz, DMSO-d₆) δ: 24.5 (CH₃), 31.7 (CH₂), 49.4 (C-3), 319.3 (C), 117.1 (CH), 125.3 (CH), 125.8 (CH), 147.3 (C), 147.7 (C), 161.5 (C-2) ppm. Anal. Calcd (%) for C₁₇H₁₂ClN₂O: C, 73.66; H, 7.06; N, 12.27. Found (%): C, 73.70; H, 7.01; N, 12.32.

4.2.10. 1H-benzo[f]chromene-2-carbonitrile (2j). A mixture of 1 g (2.9 mmol) of quaternary ammonium salt 1h, 0.19 g (2.94 mmol) of malononitrile and 0.43 mL (2.9 mmol) of DBU in ethanol (20 mL) was refluxed for 4 h and then stored at −10 °C overnight. The precipitate formed was then filtered, washed ice-
cold ethanol and recrystallized from ethanol. Yield 0.46 g (71%). Light yellow solid; mp 209–211 °C; IR (KBr): 3441, 3333 (NH2), 2187 (CN), 1674 (C=C, vinylnitrile), 1589 (C=C, aromatic), 1408, 1296, 1234, 1177, 1080, 1026, 945, 806, 741 cm⁻¹; 1H NMR (400 MHz, DMSO-d6): 6.57 (s, 1H, CH), 6.76 (br s, 2H, NH2), 7.14 (d, 1H, J=9.0 Hz, H-5), 7.47 (dd, 1H, J=8.0, 6.9 Hz, Ar), 7.57 (dd, 1H, J=8.0, 6.9 Hz, Ar), 7.79 (d, 1H, J=8.0 Hz, Ar). 13C NMR (100 MHz, DMSO-d6): 142.2 (CH), 141.2 (CH), 127.9 (CH), 112.3 (C), 121.1 (C), 125.8 (C), 127.3 (C), 127.2 (C), 127.3 (C), 127.7 (C), 131.2 (C), 146.7 (C), 160.6 (C-3) ppm. Anal. Calc’d (%) for C18H24N2O: C, 76.02; H, 8.51; N, 9.85. Found (%): C, 76.01; H, 8.73; N, 9.78.

4.3. Reaction of Mannich base 1k with malononitrile in presence of DBU

To a boiling solution of 1 g (3.8 mmol) of Mannich base 1l and 0.57 mL (3.8 mmol) of DBU in DMF (10 mL) a solution of 0.25 g (25%) of 2-amino-6,8-di-tert-butyl-4H-chromene-2-carbonitrile (0.33 g, 2.5%) was added. The reaction mixture was stirred for 1.5 h under an Ar atmosphere. Afterwards, the reaction mixture was cooled to room temperature, filtered, washed with water, dried and recrystallized from DMF.

4.3.1. 2-Amino-6,8-di-tert-butyl-4H-chromene-2-carbonitrile (2k)

White solid; mp 262–264 °C (decomp.) (from EtOH); IR νmax (KBr): 3460, 3395, 3325, 3280 (NH2), 2967, 2870 (CH3, CH2), 2195 (CN), 1663 (C=C, vinylnitrile), 1693, 1593 (C=C, aromatic), 1477, 1404, 1315, 1234, 1204, 1169, 1179, 1030 cm⁻¹; 1H NMR (400 MHz, DMSO-d6): 6.12 (s, 1H, CH), 1.32 (s, 9H, C(CH3)3), 3.37 (s, 2H, CH2), 6.76 (br s, 2H, NH2), 6.98 (d, 1H, J=2.3 Hz, Ar), 7.10 (d, 1H, J=2.3 Hz, Ar) ppm; 13C NMR (100 MHz, DMSO-d6): 24.9 (CH2), 30.6 (3CH3), 33.7 (1CH3), 34.0 (2CH2), 35.2 (2C), 35.9 (C-11a), 71.7 (C), 112.3 (C), 123.8 (CH), 136.6 (C), 141.2 (C), 146.5 (C), 161.5 (C-2) ppm. Anal. Calc’d (%) for C14H21N2O: C, 75.73; H, 4.47; N, 12.63.

4.3.2. 2,4-Diamino-7,9-di-tert-butyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile (2i)

A mixture of 0.15 g (0.6 mmol) of 4-nitro-2-[(triethylammonio)methyl]phenolate,29 0.04 g (0.6 mmol) of malononitrile, 1 mL of water and 1 mL of acetonitrile was refluxed for 1.5 h and then stored at 0 °C overnight. The precipitate formed was then filtered and recrystallized from ethanol. Yield 0.09 g (70%). Yellow solid; mp 211–212 °C (decomp.); IR νmax (KBr): 3468, 3329 (NH2), 2218 (CN), 1638 (C=C, vinylnitrile), 1578, 1502 (NO2), 1378 (NO2), 1164, 823 cm⁻¹; 1H NMR (400 MHz, DMSO-d6): 3.55 (s, 2H, CH2), 7.03 (br s, 2H, NH2), 7.16 (d, 1H, J=8.9 Hz, H-8), 8.06 (dd, 1H, J=8.9, 2.8 Hz, H-7), 8.13 (d, 1H, J=8.0 Hz, H-5) ppm; 13C NMR (100 MHz, DMSO-d6): 24.0 (CH3), 49.3 (C-3), 117.8 (CH), 120.9 (C), 122.0 (C), 124.4 (CH), 125.3 (CH), 144.0 (C), 154.4 (C), 160.6 (C-2) ppm. Anal. Calc’d (%) for C18H18N4O2: C, 76.60; H, 6.69; N, 20.25.

4.4. Synthesis of 2-amino-6-nitro-4H-chromene-2-carbonitrile (2l)

A mixture of 3 mmol of quaternary ammonium salt (1aJ or i), 2 g (30 mmol) of malononitrile and 0.12 g (3 mmol) of NaOH in ethanol (10 mL) was refluxed for 4 h and then stored at –10 °C overnight. The precipitate formed was then filtered, washed ice-cold ethanol and recrystallized from DMF.

4.5. General procedure for synthesis of 2,4-diamino-5H-chromeno[2,3-b]pyridine-3-carbonitrile

A mixture of 3 mmol of quaternary ammonium salt (1aJ or i), 2 g (30 mmol) of malononitrile and 0.12 g (3 mmol) of NaOH in ethanol (10 mL) was refluxed for 4 h and then stored at –10 °C overnight. The precipitate formed was then filtered, washed ice-cold ethanol and recrystallized from DMF.
6.0 Hz, CH2), 3.53 (dd, 1H, J = 8.7, 2.8 Hz, H-7), 6.89 (d, 1H, J = 2.8 Hz, H-5), 7.03 (d, 1H, J = 8.7, 2.8 Hz, H-7), 6.85 (dd, 1H, J = 13.3, 6.0 Hz, H-3), 6.85 (dd, 1H, J = 15.1, 3.3 Hz, CH2). 3.53 (dd, 1H, J = 15.1, 13.3 Hz, CH2), 3.71 (s, 3H, CH3). 4.76 (dd, 1H, J = 13.3, 6.0 Hz, H-3), 6.85 (dd, 1H, J = 15.1, 3.3 Hz, CH2).

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Supplementary data
Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.04.065. These data include MOL files and InChIKeys of the most important compounds described in this article.

References and notes