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

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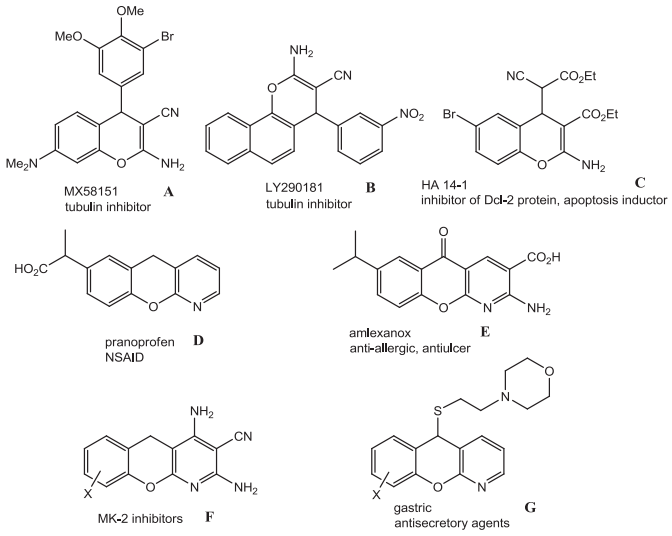
1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)

ABSTRACT

We have reported DBU catalyzed synthesis of 4-unsubstituted 2-amino-4*H*-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. 5*H*-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.

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-4*H*-chromenes are of particular utility as they belong to privileged medicinal scaffolds serving for generation of small-molecule ligands with highly pronounced spasmolitic-, diuretic-, anticoagulant-, antibacterial- and antianaphylactic activities.[1] Substituted 2-amino-4*H*-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-4*H*-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 4*H*-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-4*H*-chromene-2-carbonitriles is still of current interest.



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

The chromeno[2,3-*b*]pyridine scaffold also is of significant medicinal relevance. The examples of approved therapeutic agents incorporating this molecular framework include pranoprofen **D** and

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amlexanox **E** (Scheme 1).[9] In addition, many of these compounds possess anti-bacterial, anti-proliferative, anti-myopic, hypotensive, anti-histaminic, anti-rheumatic and anti-asthmatic activities.[10] 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 TNFα.[11] Compound **G** has reported to inhibit histamine-stimulated gastric acid secretion.[12]

A number of methods have been reported for the syntheses of 2-amino-4*H*-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 alumina) 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-4*H*-chromene-2-carbonitriles have been synthesized in two steps.[4–6,8] The first step consisted in preparing and isolating benzylidenmalononitrile. The second step involved the reaction of these compounds with the corresponding phenol or naphthol. It should be noted that only 4-arylsubstituted 2-amino-4*H*-chromene-2-carbonitriles can be prepared by these methods. Several 4-unsustituted 2-amino-4*H*-chromene-2-carbonitriles were prepared from salicylic aldehydes, malononitrile and Hantzsch dihydropyridine ester using a catalytic amount of $InCl_3$.[19] 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] thiols,[10,21] anion of malononitrile[11]). Besides, chromeno[2,3-*b*]pyridines were prepared from resorcinol and arylmethylidene derivatives of malononitrile dimer,[22] quaternary ammonium salt and malononitrile dimer.[11]

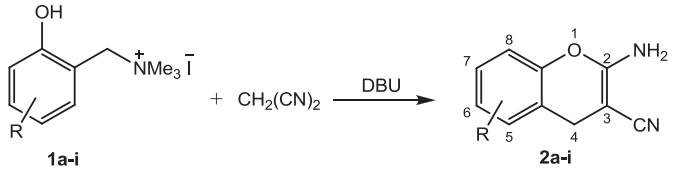
As part of our current studies[23] on the development of new routes to heterocyclic systems from *o*-quinone methides (*o*-QMs), we now report an efficient synthetic route to 2-amino-4*H*-chromene-2-carbonitriles and 5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles from quaternary ammonium salts.

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-4*H*-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,



R = 6-CH_3O (**2a**); 6-Ad (**2b**); 6-CH_3-8-Ad (**2c**); 6-$(CH_3)_3C$ (**2d**); 6-CH_3O_2C (**2e**); 7-CH_3O_2C (**2f**); 6,7-$(CH_3)_2$ (**2g**); 6-Bn (**2h**); 6-Cl (**2i**).

Scheme 2.

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-4*H*-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 (pK_a=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
Effect of quantity of DBU on the synthesis of **2a**[a]

Entry	Quantity (equiv)	Yield[b] (%)
1	0.1	42
2	0.5	83
3	1.0	88
4	1.5	77
5	2.0	54

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

Next, the reaction was attempted at different temperatures ranging from 25 to 100 °C (Table 2). It was found that below 80 °C the yield of the product significantly decreased. Below 50 °C, only traces of **2a** were detected. The reaction worked best at 100 °C. However, we succeeded in carrying out this reaction at room temperature under solvent-free condition.

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-4*H*-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.

Table 2
Effect of temperature and time on the synthesis of **2a** in the presence of DBU[a]

Entry	Temperature (°C)	Time	Yield[b] (%)
1	25	24 h	0
2	25	15 min	63[c]
3	50	5 min	6
4	50	15 min	22
5	50	1 h	19
6	80	15 min	73
7	100	1 min	88
8	100	5 min	89
9	100	15 min	90
10	100	1 h	90

[a] Reaction conditions: Compound **1a** (1.5 mmol), malononitrile (1.5 mmol), DBU (1.5 mmol), 12 mL of water.
[b] Isolated yields.
[c] Reaction was carried out under solvent-free condition.

Table 3
The results of the optimization of bases[a]

Entry	Base	p*Ka*[26]	Yield[b] (%)	Ratio of **2a**/**3b**
1	NaOH	15.74	83	95:5
2	TMG	13.6	69	94:6
3	DBU	12.0	88	96:4
4	DIPEA	11.4	71	92:8
5	TEA	10.75	67	91:9
6	K_2CO_3	10.38	62	88:12
7	DMAP	9.2	64	97:3
8	TMEDA	8.97	74	95:5
9	DABCO	8.82	52	89:11
10	*N*-Methylimidazole	7.4	43	96:4
11	Py	5.25	41	97:3

[a] Reaction conditions: Compound **1a** (1.5 mmol), malononitrile (1.5 mmol), base (1.5 mmol), 12 mL of water, 100 °C, 1 min.
[b] Isolated yields.

Table 4
DBU catalyzed synthesis of 2-amino-4*H*-chromene-2-carbonitriles **2a**–**i**

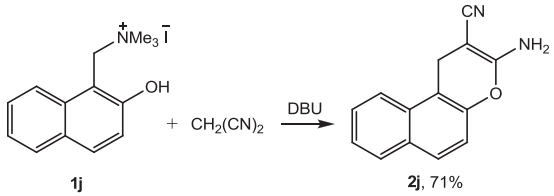
Entry	R	Solvent	Time (min)	Yield[a] (%)
2a	6-CH_3O	H_2O	1	88
2b	6-Ad	EtOH	1	80
2c	6-CH_3-8-Ad	EtOH	20	69
2d	6-$(CH_3)_3C$	EtOH	1	82
2e	6-CH_3O_2C	H_2O	10	76
2f	7-CH_3O_2C	H_2O	5	74
2g	6,7-$(CH_3)_2$	H_2O	1	82
2h	6-Bn	EtOH	1	85
2i	6-Cl	H_2O	5	61

[a] Isolated yields.

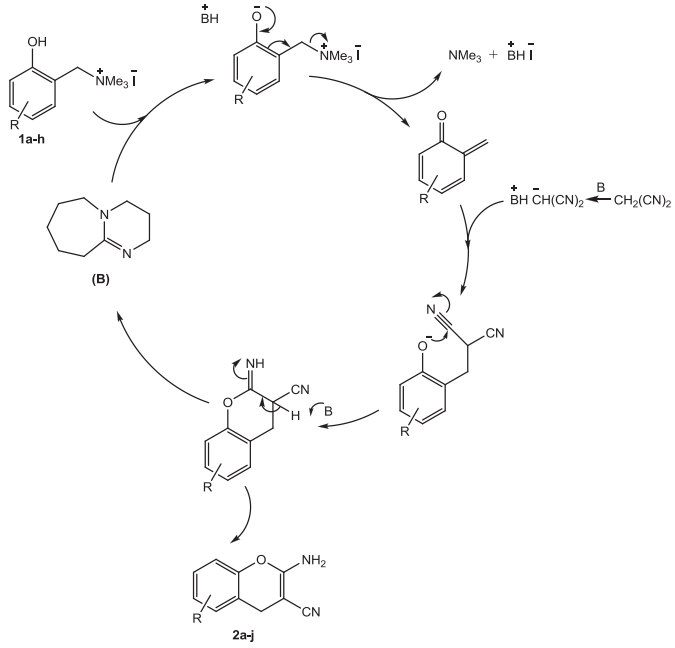
The reactions of quaternary salts containing electron-withdrawing (such as CO_2CH_3, Cl) or bulky (adamantyl) groups show a slightly slower reaction rate and lower yields than those containing electron-donating groups (such as methoxy group, alkyl group). Products can be easily purified from impurities 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 naphthaline derivative. When a mixture of quaternary salt **1j**, malononitrile and DBU (each 1 equiv) in ethanol was refluxed for 4 h, the corresponding 2-aminochromene derivative **2j** was obtained in 71% yield (Scheme 3).

A mechanistic rationale portraying the probable sequence of events is given in Scheme 4. We suppose that the reaction proceeds via the *o*-QM intermediate, which is formed by the thermal decomposition of the quaternary ammonium salts. Subsequent



Scheme 3.

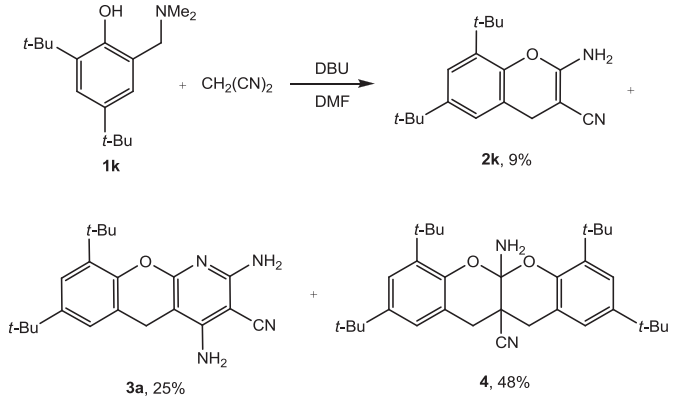


Scheme 4. Plausible mechanism for the synthesis of 2-amino-4*H*-chromene-2-carbonitriles **2a**–**j.**

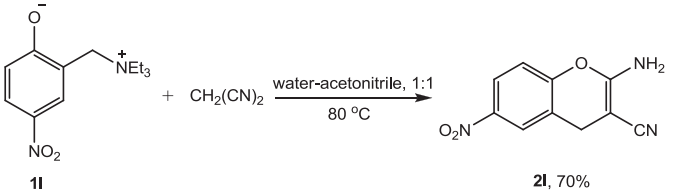
a Michael-type addition of the deprotonated malononitrile to the *o*-QM affords the 2-hydroxybenzylmalononitrile. The driving force of the reaction is the resulting rearomatization of the molecule. The intramolecular nucleophilic addition reaction, involving the hydroxyl group and the cyano group (Pinner reaction[27]), 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.[28] 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*-butyl-5*H*-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 may be 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).



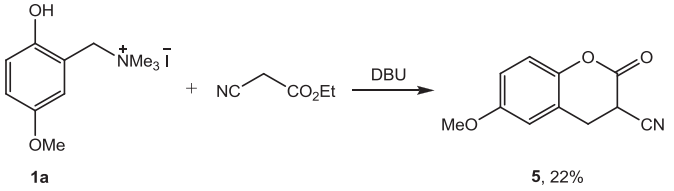
Scheme 5.



Scheme 6.

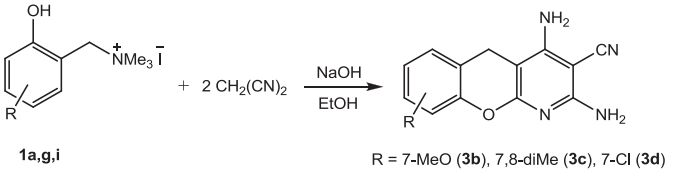
The structures of all products were determined on the basis of their analytical data. The ^{1}H NMR spectra of products (**2a**–**l**) show characteristic 2-H singlets at δ 3.31–3.48 ppm for benzylic protons. A distinguishing resonance at 23.8–24.9 ppm for C-4, 49.0–49.7 ppm for C-3 and 161.1–161.6 ppm for C-2 are observed in the ^{13}C NMR spectra. Enamine NH_2 signal appears as a singlet at 6.64–6.90 ppm (D_2O exchangeable). The IR spectra show NH_2 stretch at ν 3468–3406, 3337–3318 and 3233–3194 cm^{-1}, strong CN stretch at 2218–2183 cm^{-1}, C=C vinylnitrile stretch at 1674–1638 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).



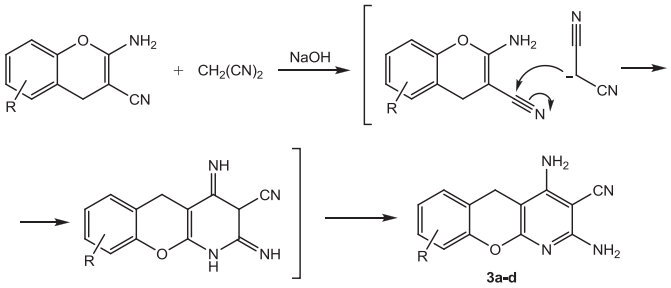
Scheme 7.

When the quaternary ammonium salts **1a**,**g**,**i** and excess of malononitrile were heated in ethanolic solution in the presence of NaOH, the 2,4-diamino-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **3b**–**d** were formed in moderate yields (30–52%) (Scheme 8).



Scheme 8.

Probably, the reaction proceeds via the intermediate formation of 2-amino-4*H*-chromene-2-carbonitriles, which react with another equivalent of malononitrile to form chromeno[2,3-*b*]pyridines **3a**–**d** (Scheme 9).



Scheme 9.

The ^{1}H NMR spectra of products **3a**–**d** show characteristic singlet peaks at δ 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_2O exchangeable). The IR spectra show NH_2 stretch at ν 3472–3129 cm^{-1}, CN stretch at ν 2203–2191 cm^{-1}.

3. Conclusions

We have described a general and highly efficient procedure for the preparation of 4-unsubstituted 2-amino-4*H*-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 F_{254}) 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-4*H*-chromene-2-carbonitriles

A mixture of a quaternary ammonium salt **1a**–**i** (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

appropriate time (Table 4). After completion of the reaction, the mixture was cooled to 0 °C, solid was filtered off and washed with H_2O or ethanol. The crude products were purified by recrystallization from ethanol.

*4.2.1. 2-Amino-6-methoxy-4H-chromene-2-carbonitrile (**2a**).* Creamy solid; mp 193–194 °C; IR ν_{max} (KBr): 3406, 3337, 3221 (NH_2), 2841 (CH_3O), 2193 (CN), 1659 (C=C, vinylnitrile), 1622, 1587 (C=C, aromatic), 1501, 1435, 1410, 1265, 1211, 1184, 1152, 1040, 872, 800, 696 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.38 (s, 2H, CH_2), 3.67 (s, 3H, CH_3O), 6.65 (s, 2H, NH_2), 6.69 (d, 1H, J=2.8 Hz, H-5), 6.72 (dd, 1H, J=8.7, 2.8 Hz, H-7), 6.84 (d, 1H, J=8.7 Hz, H-8) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.7 (CH_2-4), 49.0 (C-3), 55.9 (CH_3O), 113.2 (CH), 114.1 (CH), 117.3 (CH), 120.9 (C), 121.7 (C), 143.7 (C), 156.1 (C), 161.6 (C-2) ppm. Anal. Calcd (%) for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found (%): C, 65.26; H, 5.07; N, 13.80.

*Synthesis of **2a** under solvent-free condition*

Malononitrile (0.20 g, 3 mmol), quaternary ammonium salt **1a** (0.65 g, 2 mmol) and DBU (0.45 mL, 3 mmol) were stirred at room temperature for 15 min. The crude solid was washed with cold water and purified by crystallization from ethanol. Yield 0.25 g (63%).

*4.2.2. 6-(1-Adamantyl)-2-amino-4H-chromene-2-carbonitrile (**2b**).* White solid; mp 241–243 °C (decomp.); IR ν_{max} (KBr): 3418, 3327, 3208 (NH_2), 2911, 2847 (CH Ad), 2187 (CN), 1647 (C=C, vinylnitrile), 1609, 1585 (C=C, aromatic), 1501, 1420, 1271, 1233, 1215, 1157, 1032, 808 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.67 (br s, 6H, Ad), 1.78 (br s, 6H, Ad), 2.00 (br s, 3H, Ad), 3.42 (s, 2H, CH_2), 6.71 (s, 2H, NH_2), 6.85 (d, 1H, J=8.7 Hz, H-8), 7.10 (d, 1H, J=2.3 Hz, H-5), 7.16 (dd, 1H, J=8.7, 2.3 Hz, H-7) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.5 (CH_2-4), 28.8 (CH Ad), 35.9 (C Ad), 36.6 (CH_2 Ad), 43.1 (CH_2 Ad), 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 $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found (%): C, 78.49; H, 7.19; N, 9.22.

*4.2.3. 8-(1-Adamantyl)-6-methyl-2-amino-4H-chromene-2-carbonitrile (**2c**).* White solid; mp 275–276 °C (decomp.); IR ν_{max} (KBr): 3468, 3337 (NH_2), 2905, 2851 (CH Ad), 2195 (CN), 1667 (C=C, vinylnitrile), 1597 (C=C, aromatic), 1454, 1400, 1315, 1211, 1157, 1038, 856 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.63 (d, 3H, J=11.7 Hz, Ad), 1.82 (d, 3H, J=11.7 Hz, Ad), 1.95–1.97 (m, 9H, Ad), 3.06 (s, 3H, CH_3), 3.33 (s, 2H, CH_2), 6.64 (s, 2H, NH_2), 6.77 (s, 1H, Ar), 6.85 (s, 1H, Ar) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.0 (CH_3), 24.7 (CH_2-4), 28.9 (CH Ad), 36.7 (CH_2 Ad), 36.8 (C Ad), 40.9 (CH_2 Ad), 49.7 (C-3), 120.5 (C), 121.7 (C), 126.3 (CH), 127.1 (CH), 133.2 (C), 137.2 (C), 146.9 (C), 161.3 (C-2) ppm. Anal. Calcd (%) for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found (%): C, 78.65; H, 7.64; N, 8.68.

*4.2.4. 2-Amino-6-tert-butyl-4H-chromene-2-carbonitrile (**2d**).* White solid; mp 153–154 °C; IR ν_{max} (KBr): 3426, 3325, 3210 (NH_2), 2959, 2862 (CH_3, CH_2), 2191 (CN), 1651 (C=C, vinylnitrile), 1612, 1589 (C=C, aromatic), 1504, 1412, 1273, 1234, 1180, 1126, 1037 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.21 (s, 9H, $C(CH_3)_3$), 3.40 (s, 2H, CH_2), 6.71 (br s, 2H, NH_2), 6.84 (d, 1H, J=8.7 Hz, H-8), 7.14 (d, 1H, J=2.3 Hz, H-5), 7.19 (dd, 1H, J=8.7, 2.3 Hz, H-7) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.5 (CH_2), 31.7 (CH_3), 34.6 (C), 49.4 (C-3), 115.9 (CH), 119.3 (C), 121.7 (C), 125.3 (CH), 125.8 (CH), 147.3 (C), 147.7 (C), 161.5 (C-2) ppm. Anal. Calcd (%) for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found (%): C, 73.70; H, 7.01; N, 12.32.

*4.2.5. Methyl 2-amino-3-cyano-4H-chromene-6-carboxylate (**2e**).* White solid; mp 211–212 °C; IR ν_{max} (KBr): 3414, 3327, 3213 (NH_2), 2193 (CN), 1711 (CO), 1661 (C=C, vinylnitrile), 1614, 1585 (C=C, aromatic), 1501, 1441, 1400, 1308, 1265, 1194, 1175, 1126, 1040, 766 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.48 (s, 2H, CH_2), 3.79 (s, 3H, CH_3), 6.90 (s, 2H, NH_2), 7.03 (d, 1H, J=9.2 Hz, H-8), 7.75–7.77 (m, 2H, H-5,7) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.9 (CH_2), 49.5 (C-3), 52.7 (CH_3), 117.0 (CH), 120.7 (C), 121.2 (C), 126.1 (C), 129.8 (CH), 130.8 (CH), 153.2 (C), 160.8 (C-2), 165.9 (CO) ppm. Anal. Calcd (%) for $C_{12}H_{10}N_2O_3$: 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 ν_{max} (KBr): 3410, 3333, 3210 (NH_2), 2189 (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-d_6) δ: 3.48 (s, 2H, CH_2), 3.80 (s, 3H, CH_3), 6.88 (s, 2H, NH_2), 7.28 (d, 1H, J=7.8 Hz, H-5), 7.36 (d, 1H, J=1.4 Hz, H-8), 7.61 (dd, 1H, J=7.8, 1.4 Hz, H-6) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.3 (CH_2), 49.1 (C-3), 52.9 (CH_3), 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 $C_{12}H_{10}N_2O_3$: 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 ν_{max} (KBr): 3453, 3333, 3217 (NH_2), 2187 (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-d_6) δ: 2.10 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 3.31 (s, 2H, CH_2), 6.68 (s, 1H, Ar), 6.69 (s, 2H, NH_2), 6.87 (s, 1H, Ar) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.1 (CH_3), 19.6 (CH_3), 23.8 (CH_2-4), 49.4 (C-3), 116.6 (C), 117.0 (CH), 121.8 (C), 129.7 (CH), 132.7 (C), 136.5 (C), 147.6 (C), 161.5 (C-2) ppm. Anal. Calcd (%) for $C_{12}H_{12}N_2O$: 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 ν_{max} (KBr): 3418, 3318, 3194 (NH_2), 2195 (CN), 1659 (C=C, vinylnitrile), 1612, 1589 (C=C, aromatic), 1497, 1435, 1404, 1312, 1269, 1223, 1207, 1038 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.38 (s, 2H, 4-CH_2), 3.83 (s, 2H, CH_2Ph), 6.73 (s, 2H, NH_2), 6.84 (d, 1H, J=8.2 Hz, H-8), 7.00–7.03 (m, 2H, Ar), 7.12–7.19 (m, 3H, Ar), 7.22–7.26 (m, 2H, Ar) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.2 (CH_2-2), 40.8 (CH_2Ph), 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 $C_{17}H_{14}N_2O$: 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 ν_{max} (KBr): 3418, 3331, 3208 (NH_2), 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-d_6) δ: 3.42 (s, 2H, CH_2), 6.84 (br s, 2H, NH_2), 6.95 (d, 1H, J=8.7 Hz, H-8), 7.23 (dd, 1H, J=8.7, 2.3 Hz, H-7), 7.26 (d, 1H, J=2.3 Hz, H-5) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.1 (CH_2), 49.1 (C-3), 118.3 (CH), 121.3 (C), 122.5 (C), 128.3 (CH), 128.4 (C), 128.8 (CH), 148.6 (C), 161.2 (C-2) ppm. Anal. Calcd (%) for $C_{10}H_7ClN_2O$: C, 58.13; H, 3.41; N, 13.56. Found (%): C, 58.21; H, 3.37; N, 13.65.

*4.2.10. 3-Amino-1H-benzo[f]chromene-2-carbonitrile (**2j**).* A mixture of 1 g (2.9 mmol) of quaternary ammonim salt **1h**,[33] 0.19 g (2.9 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 ν (KBr): 3441, 3333 (NH_2), 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-d_6) δ: 3.73 (s, 2H, CH_2), 6.86 (br s, 2H, NH_2), 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), 7.82 (d, 1H, *J*=9.0 Hz, H-6), 7.89 (d, 1H, *J*=8.0 Hz, Ar) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 22.2 (CH_2), 49.8 (C-2), 112.3 (C), 117.2 (CH), 121.8 (C), 123.5 (CH), 125.6 (CH), 127.8 (CH), 128.8 (CH), 129.2 (CH), 130.7 (C), 131.3 (C), 146.7 (C), 160.7 (C-3) ppm. Anal. Calcd (%) for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found (%): C, 75.73; H, 4.47; N, 12.63.

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 (3.8 mmol) of malononitrile in DMF (2 mL) was added for 15 min under an Ar atmosphere. Afterwards, the reaction mixture was refluxed for 1 h, cooled, poured into 50 mL of cold water to yield the cream solid, which was filtered, washed with water, dried and separated by column chromatography (silica gel, EtOAc/dichloroethane/1:3) to give **4** (0.46, 48%), **2k** (0.10 g, 9%) and **3a** (0.33 g, 25%).

*4.3.1. 2-Amino-6,8-di-tert-butyl-4H-chromene-2-carbonitrile (**2k**).* White solid; mp 195–196 °C (from EtOH); IR ν_{max} (KBr): 3460, 3321, 3287, 3233, 3186 (NH_2), 2967, 2870 (CH_3, CH_2), 2195 (CN), 1663 (C=C, vinylnitrile), 1605, 1593 (C=C, aromatic), 1477, 1404, 1315, 1234, 1204, 1165, 1179, 1030 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.21 (s, 9H, $C(CH_3)_3$), 1.32 (s, 9H, $C(CH_3)_3$), 3.37 (s, 2H, CH_2), 6.76 (br s, 2H, NH_2), 6.98 (d, 1H, *J*=2.3 Hz, Ar), 7.10 (d, 1H, *J*=2.3 Hz, Ar) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.9 (CH_2), 30.6 ($3CH_3$), 31.7 ($3CH_3$), 34.7 (C), 35.1 (C), 49.3 (C-3), 120.3 (C), 121.7 (C), 122.1 (CH), 123.8 (CH), 136.6 (C), 146.2 (C), 146.6 (C), 161.5 (C-2) ppm. Anal. Calcd (%) for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found (%): C, 75.97; H, 8.47; N, 9.90.

*4.3.2. 2,4-Diamino-7,9-di-tert-butyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile (**3a**).* White solid; mp 262–264 °C (decomp.) (from EtOH/DMF); IR ν_{max} (KBr): 3464, 3372, 3252, 3306, 3156 (NH_2), 2959, 2905, 2870 (CH_2, CH_3), 2191 (CN), 1639, 1574, 1485, 1439, 1404, 1331, 1227, 1204, 1169 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.22 (s, 9H, $C(CH_3)_3$), 1.36 (s, 9H, $C(CH_3)_3$), 3.63 (s, 2H, CH_2), 6.40 (br s, 2H, NH_2), 6.46 (br s, 2H, NH_2), 6.94 (d, 1H, *J*=2.3 Hz, Ar), 7.10 (d, 1H, *J*=2.3 Hz, Ar) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.8 (CH_2), 30.3 ($3CH_3$), 31.8 ($3CH_3$), 34.6 (C), 35.2 (C), 70.6 (C-3), 86.4 (C-4a), 117.3 (C), 120.1 (C), 122.1 (CH), 123.9 (CH), 136.5 (C), 145.4 (C), 147.7 (C), 157.4 (C), 159.4 (C), 160.2 (C) ppm. Anal. Calcd (%) for $C_{21}H_{26}N_4O$: C, 71.97; H, 7.48; N, 15.99. Found (%): C, 72.05; H, 7.51; N, 16.09.

*4.3.3. 5a-Amino-2,4,7,9-tetra-tert-butyl-5a,11,11a,12-tetrahydrochromeno[2,3-b]chromene-11a-carbonitrile (**4**).* White solid; mp 208–209 °C (from MeOH); IR ν_{max} (KBr): 3395, 3325 (NH_2), 2963, 2909, 2870 (CH_3, CH_2), 2241 (CN, weak), 1605, 1477, 1362, 1223, 1200, 980 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.24 (s, 18H, $C(CH_3)_3$), 1.33 (s, 18H, $C(CH_3)_3$), 2.70 (br s, 2H, NH_2), 3.07 (d, 2H, *J*=16.5 Hz, CH_2), 3.37 (d, 2H, *J*=16.5 Hz, CH_2), 6.86 (d, 2H, *J*=2.3 Hz, Ar), 7.16 (d, 2H, *J*=2.3 Hz, Ar) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 29.9 ($6CH_3$), 31.6 ($6CH_3$), 34.3 ($2CH_2$), 34.4 (2C), 35.0 (2C), 35.9 (C-11a), 102.0 (C-5a), 116.6 (2C), 121.0 (CN), 122.9 (2CH), 123.6 (2CH), 137.2 (2C), 144.1 (2C), 147.2 (2C) ppm. MS (EI, 70 eV): *m*/*z* (%)=402 (M^+, 11), 283 (100), 269 (18), 203 (12). Anal. Calcd (%) for $C_{33}H_{46}N_2O_2$: C, 78.84; H, 9.22; N, 5.57. Found (%): C, 79.05; H, 9.18; N, 5.65.

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

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 ν_{max} (KBr): 3468, 3329 (NH_2), 2218 (CN), 1638 (C=C, vinylnitrile), 1578, 1502 (NO_2), 1378 (NO_2), 1164, 823 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.55 (s, 2H, CH_2), 7.03 (br s, 2H, NH_2), 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*=2.8 Hz, H-5) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.0 (CH_2), 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. Calcd (%) for $C_{10}H_7N_3O_3$: C, 55.30; H, 3.25; N, 19.35. Found (%): C, 55.40; H, 3.19; N, 19.41.

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

A mixture of 3 mmol of quternary ammonim salt (**1a,j** 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.

*4.5.1. 2,4-Diamino-7-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (**3b**).* Yield 0.41 g (51%). White solid; decomposed >325 °C; IR ν_{max} (KBr): 3441, 3356, 3260, 3129 (NH_2), 2199 (CN), 1655, 1639, 1609, 1578, 1501, 1481, 1435, 1404, 1339, 1258, 1215, 1142, 1119, 1034, 795, 768 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.61 (s, 2H, CH_2), 3.69 (s, 3H, CH_3O), 6.28 (br s, 2H, NH_2), 6.47 (br s, 2H, NH_2), 6.63 (d, 1H, *J*=2.8 Hz, H-6), 6.76 (dd, 1H, *J*=9.2, 2.8 Hz, H-8), 6.91 (d, 1H, *J*=9.2 Hz, H-9) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.6 (CH_2), 55.9 (CH_3), 70.5 (C-3), 85.7 (C-4a), 113.7 (CH), 114.0 (CH), 117.3 (C), 117.7 (CH), 120.8 (C), 144.8 (C), 155.7 (C), 157.6 (C), 159.2 (C), 160.0 (C) ppm. Anal. Calcd (%) for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.88. Found (%): C, 62.75; H, 4.44; N, 20.91.

*4.5.2. 2,4-Diamino-7,8-dimethyl-5H-chromeno[2,3-b]pyridine-3-carbonitrile (**3c**).* Yield 0.34 g (43%). Pink solid; decomposed >330 °C; IR ν_{max} (KBr): 3472, 3364, 3233 (NH_2), 2199 (CN), 1628, 1605, 1570, 1477, 1404, 1323, 1308, 1204, 1180, 1157, 1076 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 2.12 and 2.14 (s, 6H, $2CH_3$), 3.53 (s, 2H, CH_2), 6.26 (br s, 2H, NH_2), 6.46 (br s, 2H, NH_2), 6.64 and 6.86 (s, 2H, H-6,9) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 19.1 (CH_3), 19.6 (CH_3), 22.8 (CH_2), 70.5 (C-3), 86.3 (C-4a), 116.6 (C), 117.3 (C), 117.4 (CH), 130.0 (CH), 132.0 (C), 136.4 (C), 148.8 (C), 157.6 (C), 159.2 (C), 159.9 (C) ppm. Anal. Calcd (%) for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found (%): C, 67.72; H, 5.21; N, 20.98.

*4.5.3. 2,4-Diamino-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile (**3d**).* Yield 0.25 g (30%). White solid; decomposed >310 °C; IR ν_{max} (KBr): 3429, 3360, 3294, 3252, 3171 (NH_2), 2203 (CN), 1647, 1628, 1605, 1570, 1477, 1423, 1400, 1331, 1261, 1223, 1192 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.64 (s, 2H, CH_2), 6.34 (br s, 2H, NH_2), 6.52 (br s, 2H, NH_2), 7.00 (d, 1H, *J*=8.7 Hz, H-9), 7.14 (d, 1H, *J*=2.5 Hz, H-6), 7.23 (dd, 1H, *J*=8.7, 2.5 Hz, H-8) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.2 (CH_2), 70.8 (C-3), 85.5 (C-4a), 117.1 (C), 118.7 (CH), 122.4 (C), 127.7 (C), 128.3 (CH), 128.9 (CH), 149.9 (C), 157.6 (C), 158.7 (C), 160.0 (C) ppm. Anal. Calcd (%)

for $C_{13}H_9ClN_4O$: C, 57.26; H, 3.33; N, 20.55. Found (%): C, 57.36; H, 3.28; N, 20.62.

4.6. Synthesis of 6-methoxy-2-oxochromane-3-carbonitrile (5)

Ethyl cyanoacetate (0.32 mL, 3 mmol), quaternary ammonium salt **1a** (1 g, 3 mmol) and DBU (0.45 mL, 3 mmol) were stirred at 80 °C for 10 min. The crude solid was washed with water, dried, purified by column chromatography (silica gel, dichloroethane) and recrystallized from methanol. Yield 0.14 g (22%). White solid; mp 153–155 °C; IR ν_{max} (KBr): 2264 (CN), 1767 (CO), 1597, 1501, 1443, 1358, 1292, 1250, 1207, 1192, 1180, 1150, 1026, 1003, 880, 864, 829 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.29 (dd, 1H, J=15.1, 6.0 Hz, CH_2), 3.53 (dd, 1H, J=15.1, 13.3 Hz, CH_2), 3.71 (s, 3H, CH_3), 4.76 (dd, 1H, J=13.3, 6.0 Hz, H-3), 6.85 (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, H-8) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ: 27.7 (CH_2), 33.1 (CH_3), 56.1 (CH-3), 113.6 (CH), 114.5 (CH), 117.0 (C), 117.9 (CH), 122.2 (C), 145.2 (C), 156.5 (C), 162.9 (C) ppm. Anal. Calcd (%) for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found (%): C, 64.97; H, 4.53; N, 6.96.

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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.

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