



2-Amino-5-hydroxy-4-phenyl-7-methyl-4H[1-chromeno-3-carbonitrile as a key precursor for the synthesis of several chromene based heterocyclic systems

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Abstract

Synthesis of 2-amino-5-hydroxy-4-phenyl-7-methylchromeno-3-carbonitrile. **1** obtained by the reaction of 5-methyl resorcinol and benzylidene malonitrile used in synthetic routes to several heterocyclic compounds containing pyrimidine, pyridine, chromene, oxazine, thiazine and pyrrol by reaction of **1** with various reagents such as formamide, formic acid, phenylisothiocyanate, urea, thiourea, semicarbazide thiosemicarbazide to give chromenopyrimidine derivatives **2, 3, 4, 9, 10_{a,b}, 11_{a,b}** respectively. The reaction of **1** with acetic anhydride under different conditions to give **5, 6, 7** followed by reactions with hydrazine hydrates, formamide, hydroxylamine hydrochloride to give chromenopyrimidine derivatives **8_{a-c}**. The interaction between **1** with cyclohexane, malonitrile, carbon disulfide gave **12, 13, 14** which was cyclised to give thiazine **15** and the O-alkylation of **1** by using ethylbromoacetate or chloroacetonitrile to give **16_{a,b}** and chromenopyrrol derivatives **17**.

Key words

Pyrimidinochromene, pyridinochromene, oxazinochromene, thiazinochromene, pyrrolochromene

Introduction

4H- chromene derivatives are an important class of heterocycles, which have attracted considerable interest due to their useful biological and pharmacological properties, examples including anticoagulant, spasmolytic, diuretic, anticancer^[1] and antianaphylactic characteristics.^[2] 4H-Pyrans are also structural features of various natural products^[3] and also possess useful photochemical properties.^[4] In view of these useful properties, it is not surprising that the development of synthetic approaches to these ring systems has attracted considerable interest over the years. Moreover, nitrogen-containing heterocycles are also of broad pharmaceutical interest and significance, which justifies our continuing efforts in exploring synthetic strategies which lead to structures formed from a combination of both types of heterocycle, an area which could also provide useful information regarding structural-activity relationships in this area.^[5] Herein, we report in full on synthetic approaches to several

heterocyclic systems derived from 4H-pyrans (chromenes), represented by the title compound **1**, which can subsequently be used as intermediates and building blocks for additional heterocycles.

Finally, alkylation of the initial chromene **1** was investigated, with the aim of setting up precursors suitable for pyrrole formation, for example. Unfortunately, such reactions occurred predominantly at the phenol hydroxy group: the *O*-alkylation products **16a,b** were formed when chromene **1** was exposed to either ethyl bromoacetate or chloroacetonitrile in acetone containing anhydrous potassium carbonate. As the 2-amino group in chromene **1** is, in effect, a vinylogous cyanamide, these outcomes are perhaps not so surprising. In the case of bromoacetate, the *O*-alkylation product **16a** was the sole product and there was no evidence for further alkylation, even when alternative conditions were used (sodium sulfite in DMF).^[10] However, in the case of chloroacetonitrile, both the *O*-alkylation product **16b** and the pyrrole **17** were isolated, in 48% and 47% yields respectively. All spectroscopic and analytical data were consistent with the structure **17** proposed. Presumably, if the more reactive phenol group were to be masked, then such a pyrrole synthesis could easily be extended and could be much more efficient.

Experimental Section

All melting points uncorrected and were determined on Stuart electric melting point apparatus. Elemental analyses were performed by the microanalytical center, Faculty of Science, Cairo University. Infrared spectra were recorded on Bruker or Satellite 2000 spectrometer using KBr discs. ¹H NMR spectra were recorded at Bruker DX400 (unless stated) at 400 MHz and ¹³C NMR spectra measured on the same instrument (unless stated) at 100.6MHz at School of Chemistry, Cardiff University. Mass spectra were determined on GC-MS (QP 1000 EX) SHIMADZU spectrometer. HRMS were determined by EPSRC mass spectrometry services, School of Chemistry, Cardiff University.

2-Amino-5-hydroxy- 4-phenyl-7-methyl-4H[1]chromene-3-carbonitrile (1)

To a stirred mixture of 5-methylresorcinol monohydrate (1.42 g, 10 mmol) and benzylidenemalonitrile (1.54 g, 10 mmol) in absolute ethanol (30 ml) was added anhydrous potassium carbonate (2 g) and stirring continued at room temperature for 3 h. The solvent was largely evaporated, the mixture diluted with cold water and left to stand at room temperature for 45 min. The precipitated solid collected by filtration, washed with cold water (3 x), then dried and crystallized from ethanol to afford the chromene **1** (2.44 g, 88%) as colorless crystals, m.p. 206 °C. Elemental analysis for C₁₇H₁₄N₂O₂, (Calc., C, 73.37, H, 5.07, N, 10.07), (Found, C, 72.68, H, 5.37, N, 10.16); IR, $\nu_{\max}/\text{cm}^{-1}$, 3427, 3367, 3288, 2194; ¹H NMR δ_{H} 1.92 (3H, s, CH₃), 4.53 (1H, s, 4-H), 6.40 (1H, d, J 2.0, 6- (or 8-) H), 6.71 (1H, s, 8- (or 6-) H), 6.80 (2H, d, NH₂), 7.07 (2H, d, J 7.3, 2 x Ar-H), 7.20 (1H, t, J 7.3, Ar-H), 7.34 (2H, t, J 7.3, 2 x Ar-H), 9.70 (1H, br s, OH); ¹³C NMR δ_{C} 19.2 (CH₃), 38.9 (4-CH), 58.4 (3-C), 100.7 (6- (or 8-) CH), 112.9 (8- (or 6-) CH), 114.3, 121.2 (both ArC), 126.8, 127.4, 129.0, (all ArCH), 138.4 (ArC), 146.0, 150.5, 157.3, 160.3 (all ArC); m/z [EI] 278 (M⁺, 14%), 201 (100), 77 (10), 51 (12).

4-Amino-8-methyl-5-phenyl-5H-chromeno[2,3-d]pyrimidin-6-ol (2)

The chromene **1** (2.78 g, 10 mmol.) dissolved in a mixture of DMF (10 ml) and formamide (20 ml). The mixture was heated at 110 °C for 22 h. After cooling, the mixture diluted with water (50

ml) and extracted with ethyl acetate (3 x 40 ml). The organic layer was separated, the aqueous layer washed with ethyl acetate many times. The combined organic solutions washed with water (2 x), then dried over magnesium sulphate, filtered, and the solvent evaporated. The solid obtained crystallized from methanol to furnish the *aminopyrimidine 2* (2.44 g, 80%) as a yellow solid, m.p. 237-240 °C; IR, $\nu_{\max}/\text{cm}^{-1}$, 3478, 3379, 3326, 3084, 2948, 2920, 1630; $^1\text{H NMR } \delta_{\text{H}}$ 2.15 (3H, s, CH₃), 5.21 (1H, s, 5-CH), 6.40 (1H, d, J 2.0, 7- (or 9-) H), 6.50 (1H, d, J 2.0, 9- (or 7-) H), 7.02 (2H, br s, NH₂), 7.12 (1H, t, J 7.2, 4-H-Ph), 7.22 (2H, t, J 7.7, 3- and 5-H-Ph), 7.32 (2H, d, J 7.7, 2- and 6-H-Ph), 8.02 (1H, s, 2-H), 9.61 (1H, s, OH); $^{13}\text{C NMR } \delta_{\text{C}}$ 19.2 (CH₃), 35.3 (5-CH), 98.2 (ArC), 101.5 (7- (or 9-) CH), 114.0 (9- (or 7-) CH), 115.0 (ArC), 126.9 (4-PhCH), 128.2 (2 x ArCH), 128.7 (2 x ArCH), 138.2, 144.2, 151.5 (all ArC), 156.6 (2-CH), 157.3, 162.6, 162.7 (all ArC); m/z [EI] 305 (M⁺, 11%), 228 (10), 201 (5), 186 (46), 77 (100).

6-Hydroxy-8-methyl-5-phenyl-3H-chromeno[2,3-d]pyrimidin-4(5H)-one (3) and 3,4-dihydro-5-hydroxy-7-methyl-2-oxo-4-phenyl-2H-chromene-3-carbonitrile (4)

A mixture of the chromene **1** (2.78 g, 10 mmol) and formic acid (15 ml, 88%) was refluxed for 5 h as a solid started to form. The mixture cooled and the precipitate filtered off, then washed with acetone and diethyl ether. The solid crystallized from methanol and afforded the *pyrimidinone 3* (1.59 g, 52%) as colorless crystals m.p. >300 °C. IR, $\nu_{\max}/\text{cm}^{-1}$, 3147, 2907, 1645, 1590, 1461, 1376; $^1\text{H NMR } \delta_{\text{H}}$ 7.30 (3H, s, CH₃), 5.05 (1H, s, 5-H), 6.45 (1H, d, J 2.1, 7- (or 9-) H), 6.55 (1H, d, J 2.1, 9- (or 7-) H), 7.10-7.30 (5H, m, 5 x Ar-H) 8.10 (1H, s, 2-H), 9.70 (1H, br s, NH), and 12.50 (1H, br s, OH); $^{13}\text{CNMR } \delta_{\text{C}}$ 19.2 (CH₃), 36.0 (5-CH), 101.3 (7- (or 9-) CH), 104.8, 113.7 (both ArC), 114.7 (9- (or 7-) CH), 126.8, 128.6, 128.8 (all Ar-CH), 138.4, 144.6 (both ArC), 149.1 (ArCH), 151.3, 157.3, 161.4, 161.7 (all ArC); HRMS [ES] [Found: [M⁺+H], 307.1085. C₁₈H₁₅N₂O₃ requires *M*, 307.1083]. The filtrate was concentrated and the solid formed collected by filtration, washed with water, dried, and crystallized from DCM furnishing the *dihydrocoumarin 4* (1.06 g, 38%) as colorless crystals, m. p. 217 °C; IR, 3307, 2907, 2280, 1760, 1613, 1595; $^1\text{H NMR } \delta_{\text{H}}$ 2.05 (3H, s, CH₃), 4.85 (H, d, J 3.4, 4-H), 5.30 (1H, d, J 3.4, 3-H), 6.51 (2H, app. s, 6- and 8-H), 7.15-7.45 (5H, m, 5 x Ar-H), 9.94 (1H, s, OH); $^{13}\text{C NMR } \delta_{\text{C}}$ 18.8 (CH₃), 40.5 (4-CH), 41.3 (3-CH), 101.7 (6- (or 8-) CH), 113.1 (ArC), 114.5 (8- (or 6-) CH), 115.5 (ArC), 128.2, 128.5, 129.5 (all ArCH), 137.5, 138.0, 151.8, 158.3 (all ArC), 162.4 (CO); HRMS [ES] [Found: [M⁺+H], 280.0967. C₁₇H₁₄NO₃ requires *M*, 280.0974].

4,5-Dihydro-2,8-dimethyl-4-oxo-5-phenyl-3H-chromeno[2,3-d]pyrimidin-6-yl acetate (5) and 3,4-dihydro-5-hydroxy-7-methyl-4-phenylchromen-2-one(6)

Acetic anhydride (15 ml) was added to the chromene **1** (2.78 g, 10 mmol), then orthophosphoric acid (15 ml) was added carefully and the resulting hot mixture refluxed for 12 h. After cooling, the mixture diluted with ice cold water when a solid formed which collected by filtration, washed several times with cold water and dried. On crystallization from dichloromethane the product was partially soluble. On filtration, the solid proved to be the *pyrimidinoacetate 5* and the *dihydrocoumarin 6* contained in the filtrate the filtrate.

Compound **5** crystallized from ethanol as pale yellow crystals (1.84 g, 51 %), m.p. 145 °C; IR, $\nu_{\max}/\text{cm}^{-1}$, 3254, 2923, 1738, 1644, 1583; H NMR δ_{H} 2.0 (3H, s, 8-CH₃), 2.10 (3H, s, 2-CH₃), 2.20 (3H, s, CH₃CO), 5.03 (1H, s, 9-H), 6.42 (1H, d, J 2.0, 5- (or 7-) H), 6.50 (1H, d, J 2.0, 7- (or 5-) H), 7.05-7.35 (6H, m, 5 x Ar-H + NH); $^{13}\text{C NMR } \delta_{\text{C}}$ 19.2 (8-CH₃), 21.3 (2-CH₃), 21.4

(CH₃CO) 35.9 (9-CH), 101.3, 114.6 (5-and 7-CH), 127.1, 128.2, 128.3 (all Ar-CH), 138.4, 144.9, 151.5, 157.3, 158.5, 161.3 (all ArC), 162.7, 167.9 (both CO). *m/z* [EI] 362 (M⁺, 15%), 320 (25), 285 (32), 77 (100).

Compound **6** crystallized from DCM as colorless crystals (0.82 g, 31 %), m.p. 198-200 °C; IR, $\nu_{\max}/\text{cm}^{-1}$, 3345, 2922, 2726, 1731, 1633, 1589, 1461; ¹H NMR δ_{H} 2.05 (3H, s, CH₃), 2.85 (1H, dd, J 1.6, 15.8, H_a), 3.20-3.30 (1H, dd, J 7.1, 15.8, H_b), 4.45 (1H, d, J 7.1, H_c) 6.41 (1H, d, J 2.3, 6- (or 8-) -H), 6.50 (1H, d, J 2.3, 8- (or 6-) H), 7.05-7.42 (5H, m, 5 x Ar-H), 9.75 (1H, s, OH); ¹³C NMR δ_{C} 18.9 (CH₃), 37.0 (4-CH), 38.1 (3-CH₂), 101.7 (ArCH), 113.8 (ArC), 114.3, 127.2, 127.4, 129.3 (all ArCH), 137.9, 142.0, 153.0, 157.8, 167.9 (all ArC); HRMS [EI] [Found: [M⁺], 254.0941. C₁₆H₁₄O₃ requires *M*, 254.0941].

4,5-Dihydro-2,8-dimethyl-4-oxo-5-phenylchromeno[2,3-d][1,3]oxazin-6-yl acetate (7)

To a solution of the chromene **1** (2.78 g, 10 mmol) in pyridine (10 ml) was added acetic anhydride (15 ml). The mixture was refluxed for 24 h then cooled, ethyl acetate (50 ml) was added and the whole mixture washed several times with copper sulphate solution. The organic layer was separated, washed with water, brine, then dried over sodium sulphate and filtered. The solvent evaporated and the product crystallized from ethyl acetate/ether mixture to give the *oxazinone 7* (2.60 g, 72 %) as colorless crystals, m.p. 307-309 °C; IR, $\nu_{\max}/\text{cm}^{-1}$, 2923, 1777, 1655, 1621, 1600; ¹H NMR δ_{H} 2.04 (3H, s, 8-CH₃), 2.25 (3H, s, 2-CH₃), 2.50 (3H, s, CH₃CO), 5.25 (1H, s, 9-H), 6.90 (1H, d, J 2.0, 5- (or 7-) H), 7.15 (1H, d, J 2.0, 7- (or 5-) H), 7.25-7.45 (5H, m, 5 x Ar-H); ¹³C NMR δ_{C} 19.1 (8-CH₃), 21.2 (2-CH₃), 25.3 (CH₃CO), 39.5 (9-CH), 94.2 (ArC), 108.8 (ArCH), 115.5, 117.6 (both ArC), 122.0, 128.3, 128.6, 129.5 (all ArCH), 139.4, 141.5, 150.1, 150.5, 151.5 (all ArC), 169.3, 170.8 (both CO); *m/z* [EI], 363 (M⁺, 10 %), 320 (5), 303 (18), 285 (10), 243 (100).

Reaction of compound(7) with nitrogen nucleophiles (amines) to afford compound(8a-c)

Method A for (8a)

To a solution of compound **7** (0.92 g, 2.5 mmol) in absolute ethanol (25 ml) was added hydrazine hydrate (0.5 ml (excess)). The reaction mixture was refluxed for 5 h. After cooling, the mixture poured into ice cold water with stirring while a solid precipitated out which was filtered, washed with water, then dried and crystallized from benzene furnishing the *aminopyrimidinone* derivative **8a** as a yellowish brown solid (0.51 g, 62 %), m.p. > 300 °C, IR, $\nu_{\max}/\text{cm}^{-1}$, 3600, 3136, 3022, 1663, 1630, 1600; *m/z* for C₁₉H₁₇N₃O₃ (EI), *m/z* [EI] 335 (M⁺, 16%), 244 (15), 243 (100), 201 (5), 77 (4).

Method B for compound (8b)

A mixture of compound **7** (0.2 g, 0.55 mmol) and formamide (15 ml), was refluxed for 5 h. The reaction mixture left at room temperature, the solid that crystallized out filtered, washed several times with ether and dried to give the *pyrimidinone 8b*. The filtrate diluted with cold water and the solid formed was collected by filtration, washed with cold water, dried to yield an additional amount of the product as colorless crystals (0.127 g, 73%), m.p. 255-257 °C, IR, $\nu_{\max}/\text{cm}^{-1}$, 3309, 3183, 2922, 2725, 1644, 1582; ¹H NMR (250 MHz), δ_{H} 2.02 (3H, s, CH₃), 2.25 (3H, s, CH₃), 5.02 (1H, s, 9-CH), 6.42 (1H, d, J 2.1, 5- (or 7-) H), 6.49 (1H, d, J 2.1, 7- (or 5-) H), 6.90 (1H, br s, NH), 7.10-7.29 (5H, m, 5 x Ar-H), 9.65 (1H, br s, OH); ¹³C NMR δ_{C} 19.2 (8-CH₃), 21.3 (2-

CH₃), 35.9 (9-CH), 101.3 (ArCH), 101.6, 113.9 (both ArC), 114.5, 126.7, 128.5, 128.6 (all ArCH), 138.4, 144.9, 151.5, 157.3, 158.5, 161.3, 162.7 (all ArC); *m/z* [EI] 320 (M⁺, 45%), 243 (100%).

Method C for compound (8c)

To a solution of compound **7** (0.2 g, 0.55 mmol) in pyridine (10 ml) was added hydroxylamine hydrochloride (0.075, 1.1 mmol, 2 equiv.). The mixture was refluxed for 12 h. After cooling, ethyl acetate (50 ml) was added, the mixture washed several times with copper sulphate solution, organic layer was separated, washed with water (3 x) then dried over sodium sulphate and filtered. The solvent was evaporated and the solid obtained crystallized from ethyl acetate/petrol mixture furnishing the *dihydroxypyrimidinone 8c* (0.106 g, 57%) as yellowish brown solid, m.p. > 300 °C, IR, $\nu_{\max}/\text{cm}^{-1}$, br to 3199, 2954, 2843, 1644, 1582; ¹H NMR (250 MHz) δ_{H} 2.0 (3H, s, CH₃), 2.62 (3H, s, CH₃), 5.08 (1H, s, 7- (or 9-) CH), 6.50 (2H, s, 5- and 9- (or 7-) H), 7.05-7.42 (5H, m, 5 x Ar-H), 9.65 (1H, br s, OH); ¹³C NMR δ_{C} 24.0 (8-CH₃), 26.0 (2-CH₃), 40.6 (9-CH), 106.0 (ArCH), 118.6 (ArC), 119.3 (ArCH), 121.9 (ArC), 131.4, 133.3 (both ArCH), 139.4, 143.1, 149.6, 156.2, 162.0, 163.3, 167.4 (all ArC); *m/z* [EI], 318 (M⁺-H₂O, 100%), 243 (55), 202 (92).

8-Hydroxy-4-imino-6-methyl-3,5-diphenyl-3,4-dihydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione (9)

A mixture of the chromene **1** (1.39 g, 5 mmol), and phenyl isothiocyanate (0.6 ml, 5 mmol) in pyridine (10 ml) was refluxed for one day, Then cooled, ethyl acetate (30 ml) was added and the yellow solid **9** obtained filtered, washed several times with ether and dried. The filtrate was washed several times with aqueous copper sulphate, dried over sodium sulphate and removal of the solvent recovered unreacted starting material.

Compound **9** crystallized from methanol as yellowish crystals (1 g, 48%), IR, $\nu_{\max}/\text{cm}^{-1}$, 3479, 3392, 3218, 3083, 3059, 2923, 1633, 1607; ¹H NMR δ_{H} 2.13 (3H, s, CH₃), 5.37 (1H, s, 5-H), 6.42 (1H, d, J 2.2, 7- (or 9-) H), 6.51 (1H, d, J 2.2, 9- (or 7-) H), 7.05 (1H, t, J 5.0, 4-H-Ph), 7.18 (1H, d, J 7.4, Ar-H), 7.20 (1H, d, J 7.9, Ar-H), 7.25 (2H, t, J 7.7, 3- and 5-H-Ph), 7.32 (2H, d, J 7.7, 2- and 6-H-Ph), 7.49 (2H, t, J 6.0, 2 x Ar-H), 7.55 (1H, t, J 5.36, Ar-H), 9.66 (1H, br s, OH); ¹³C NMR (125 MHz) δ_{C} 19.2 (CH₃), 34.8 (5-CH), 90.1 (ArC), 101.6, 114.4 (both ArCH), 114.7 (ArC), 127.1 (4-PhCH), 127.8 (2 x ArCH), 128.6 (4-CH-Ph-N), 128.9 (2 x ArCH), 129.3, 129.6, 130.5, 130.8 (all ArCH), 138.0, 139.1, 144.2, 151.3, 156.3, 157.4, 160.6 (all ArC), 179.4 (CS); HRMS, [Found: [M⁺+H], 413.1198. C₂₄H₂₀N₃O₂S requires *M*, 413.1198].

Reaction of compound 1 with urea and thiourea to give compound (10a,b)

A mixture of the chromene **1** (2.78 g, 10 mmol) and urea or thiourea (12 mmol) was fused under dry conditions. The fused mixture was dissolved in methanol (15 ml) and the resulting solution refluxed for 2 h. After cooling, the precipitate formed collected by filtration and the filtrate further worked up by diluting with cold water to give an additional amount of the product which washed with water, dried and purified by crystallization to furnish compounds **10a, b**.

4-Amino-8-hydroxy-6-methyl-5-phenyl-1H-chromeno[2,3-d]pyrimidin-2(5H)-one (10a)

Crystallized from methanol as a yellow solid (2.20 g, 68%), m.p.>300 °C, IR, $\nu_{\max}/\text{cm}^{-1}$, 3451, 3332, 3175, 2954, 2858, 1654, 1624, 1608; Elemental analysis for $\text{C}_{18}\text{H}_{15}\text{N}_3\text{O}_3$, (Calc., C, 67.28; H, 4.71; N, 13.08), (Found, C, 66.65; H, 4.93; N, 13.26).

4-Amino-8-hydroxy-6-methyl-5-phenyl-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione (10b)

Crystallized from ethyl acetate as a yellow solid (2.56 g, 80%), m.p. 210-212 °C, IR, $\nu_{\max}/\text{cm}^{-1}$, 3565, 3337, 3208, 3061, 3028, 2923, 1625, 1559; ^1H NMR δ_{H} 2.17 (3H, s, CH_3), 5.10 (1H, br s, NH), 5.20 (1H, s, 5-H), 5.88 (2H, s, NH_2), 5.97 (1H, d, J 2.0, 7- (or 9-) H), 6.06 (1H, d, J 2.0, 9- (or 7-) H), 7.05 (1H, t, J 7.7, 4-H-Ph), 7.14 (2H, t, J 7.7, 3- and 5-H -Ph), 7.21 (2H, d, J 7.7, 2- and 6-H-Ph), 8.90 (1H, br s, OH); m/z [EI] 337 (M^+ , 13%). Using the same procedure, chromene **1** (10 mmol) was reacted with thiosemicarbazide and semicarbazide (10 mmol) to give compound **11a,b**

3-Amino-8-hydroxy-4-imino-6-methyl-5-phenyl-3,4-dihydro-1H-chromeno[2,3-d]pyrimidine-2(5H)-thione (11a)

Crystallized from methanol as a yellow solid (2.787 g, 82%), m.p. 235-237 °C, IR, $\nu_{\max}/\text{cm}^{-1}$, 3329, 3210, 3060, 3027, 2924, 1681, 1624, 1598.

3-Amino-8-hydroxy-4-imino-6-methyl-5-phenyl-3,4-dihydro-1H-chromeno[2,3-d]pyrimidin-2(5H)-one (11b)

Crystallized from methanol as an orange-red solid (2.97 g, 84%), m.p.> 300 °C; IR $\nu_{\max}/\text{cm}^{-1}$, 3354, 3200, 3089, 2956, 2852, 1619, 1598; Elemental analysis for $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_2\text{S}$, (Calc., C, 61.35; H, 4.58; N, 15.90; S, 9.10), (Found, C, 60.60; H, 4.83; N, 15.21; S, 9.27); ^1H NMR δ_{H} 2.02 (3H, s, CH_3), 5.05 (1H, s, 5-H), 6.40 (1H, app s, 7- (or 9-) H), 6.47 (1H, app s, 9- (or 7-) H), 7.23 (1H, d, J 6.50, Ar-H), 7.20 (2H, d, J 6.5, Ar-H), 7.25 (2H, t, J 6.5, Ar-H), 7.41 (2H, s, NH_2), 7.50 (1H, br s, NH), 7.29 (1H, br s, NH), 8.01 (1H, s, OH).

11-Amino-1-methyl-12-phenyl-8,9,10,12-tetrahydro-7H-chromeno[2,3-b]quinolin-3-ol (12)

A mixture of the chromene **1** (1.39 g, 5 mmol), cyclohexanone (5 ml) and anhydrous zinc chloride (1 g, 5 mmol) was refluxed under dry conditions for 16h. The reaction mixture cooled, then treated with 2M aqueous sodium hydroxide (10 ml), ethyl acetate (40 ml) was added and the precipitated solid removed by filtration. The filtrate washed many times with water and brine, then dried over magnesium sulphate, filtered, the solvent was evaporated and the solid obtained purified by crystallization from DCM to give the *pyridine derivative* **12** (1.09 g, 61%) as a colorless solid, m.p.> 300 °C, IR, $\nu_{\max}/\text{cm}^{-1}$, 3336, 3182, 2962, 1661, 1628, 1573; ^1H NMR δ_{H} 1.70 (4H, t, H_a), 2.18 (3H, s, CH_3), 2.52 (2H, t, J 1.6, H_b), 2.62 (2H, t, H_c), 5.37 (1H, s, 12-CH), 6.42 (1H, d, J 2.2, 2- (or 4-) H), 6.50 (1H, d, J 2.2, 4- (or 2-) H), 6.70 (2H, br s, NH_2), 7.11 (1H, t, J 7.3, 4-H-Ph), 7.20 (2H, t, J 7.4, 3- and 5-H-Ph), 7.38 (2H, d, J 7.4, 2- and 6-H-Ph), 9.64 (1H, br s, OH); ^{13}C NMR δ_{C} 24.0 (CH_3), 26.5, 26.6, 27.8, 34.4 (all CH_2), 40.2 (12-CH), 105.4 (ArC), 105.9 (ArCH), 117.4 (ArC), 118.8 (ArCH), 119.7 (ArC), 131.6, 133.0, 133.4 (all ArCH), 134.9,

143.0, 148.9, 156.0, 158.0, 158.8, 162.0 (all ArC); HRMS [ES] [Found: $[M^+ + H]$], 359.1751. $C_{23}H_{23}N_2O_2$ requires M , 359.1751].

2-Amino-8-hydroxy-6-methyl-4-oxo-5-phenyl-4,5-dihydro-1H-chromeno[2,3-b]pyridine-3-carbonitrile (13)

To a mixture of the chromene **1** (1.39 g, 5 mmol) and malononitrile (0.33 g, 5 mmol) in DMF (10 ml) was added a few drops of piperidine and the resulting mixture refluxed for 24 h. The mixture allowed to cool to room temperature, diluted with cold water, a few drops of concentrated HCl were added, the resulting solid filtered off, washed several times with cold water, then dried and crystallized from DCM, furnishing the *pyridinone* **13** (1.29 g, 75%) as grey solid, m.p. > 300 °C, IR, ν_{max}/cm^{-1} , 3441, 3362, 3217, 2220; 1H NMR δ_H 2.20 (3H, s, CH₃), 4.55 (1H, s, 5-CH), 6.39 (2H, s, 7- and 9-H), 6.88 (2H, s, NH₂), 7.06-7.31 (5H, m, 5 x Ar-H), 9.69 (1H, s, OH); ^{13}C NMR (125 MHz) δ_C 21.3 (CH₃), 36.9 (5-CH), 107.3 (CH), 108.9 (ArC), 112.1 (ArCH), 112.9, 121.2 (both ArC), 126.7, 127.5, 128.6 (all ArCH), 138.5, 146.3, 150.3, 154.8, 157.3, 160.9; m/z [EI] 345 (M^+ , 33%).

3-Cyano-7-hydroxy-5-methyl-4-phenyl-4H-chromen-2-ylcarbamodithioic acid (14) and 8-hydroxy-4-imino-6-methyl-5-phenyl-4,5-dihydrochromeno[2,3-d][1,3]thiazine-2(1H)-thione (15)

Carbon disulfide (2 ml, excess) was dropped to a solution of compound **1** (1.39 g, 5 mmol) in pyridine (15 ml) and the mixture was heated carefully at reflux temperature for 24 h. The reaction mixture cooled, poured into ice/conc. HCl mixture, the resin formed was allowed to solidify with strong stirring and standing. The product collected by filtration, washed with cold water, dried and crystallized from toluene and gave the *carbamodithioic acid* **14** (1.4 g, 79%) as yellow solid, m.p. 167-169 °C, IR, ν_{max}/cm^{-1} , 3428, 3264, 2971, 2914, 2861, 2185, 1628, 1572.

Compound **14** (0.5 g, 1.41 mmol.), was further heated in pyridine for 10 h, Cooled, and worked up as above to afford the *thiazinethione* **15** (0.25 g, 50%) as a yellow solid, m.p. 2238-240 °C, IR, ν_{max}/cm^{-1} , 3380, 3135, 2925, 1631, 1551; m/z [EI] 354 (M^+ , 88%), 321 (1), 295 (12), 277 (100), 211 (62), 201 (69), 129 (9), 77 (16).

General procedure for alkylation of the title compound(1) with β -haloacetic acid derivatives to give compound (16a,b)

To a stirred solution of the chromene **1** (1.39 g, 5 mmol) in anhydrous acetone (40 ml) containing anhydrous potassium carbonate (1g, 7.2 mmol) was added an alkylating agent (10 mmol, 2 equiv.). The reaction mixture was refluxed overnight. The solvent was evaporated at room temperature, the residue treated with a mixture of cold water and acetic acid, the solid obtained collected by filtration, washed with cold water, dried and crystallized from a suitable solvent.

Ethyl 2-(2-amino-3-cyano-5-methyl-4-phenyl-4H-chromen-7-yloxy)acetate (16a)

Using the general procedure, chromene **1** reacted with ethyl bromoacetate (0.6 ml) followed by crystallization from dichloromethane gave the *acetate* **16a** (1.68 g, 92%) as colorless crystals,

m.p. 193-194 °C, IR, $\nu_{\max}/\text{cm}^{-1}$, 3410, 3333, 3026, 2982, 2907, 2194, 1746, 1660, 1620; ^1H NMR δ_{H} 1.20 (3H, t, J 7.1, CH_3CH_2), 1.80 (3H, s, 5- CH_3), 4.20 (2H, q, J 7.1, CH_2O), 4.60 (1H, s, 4-H), 4.80 (2H, s, COCH_2O), 6.50 (1H, d, J 2.5, 6- (or 8-) H), 6.61 (1H, d, J 2.5, 8- (or 6-) H), 6.87 (2H, s, NH_2), 7.08 (2H, d, J 7.2, 2- and 6-H-Ph), 7.20 (1H, t, J 7.4, 4-H-Ph), 7.30 (2H, t, J 7.6, 3- and 5-H-Ph); ^{13}C NMR (125 MHz) δ_{C} 14.5 (CH_3), 19.3 (5- CH_3), 38.9 (4-CH), 61.1 (CH_2O), 65.2 (COCH_2O), 100.1 (6- (or 8-) CH), 113.7 (ArC), 115.3 (8- (or 6-) CH), 121.0 (ArC), 127.0 (4-PhCH), 127.5 (2 x ArCH), 129.0 (2 x ArCH), 138.6, 145.8, 150.4, 157.4, 160.2 (all ArC), 169.0 (CO); m/z [EI] 364 (M^+ , 11%), 291 (2), 287 (23), 213 (3), 200 (11), 91 (12), 78 (100).

2-Amino-7-(cyanomethoxy)-5-methyl-4-phenyl-4H-chromene-3-carbonitrile(16b)

Using the general procedure, the chromene **1** reacted with chloroacetonitrile (0.315 ml) followed by crystallization from dichloromethane gave the *acetonitrile derivative* **16b** (0.76 g, 48%) as colorless crystals, m.p. 180 °C, IR, $\nu_{\max}/\text{cm}^{-1}$, 3387, 3322, 3085, 3027, 2921, 2188, 1657, 1618, 1578; ^1H NMR (250 MHz) δ_{H} 2.31 (3H, s, CH_3), 4.62 (1H, s, 4-H), 5.05 (2H, s, CH_2), 6.70 (1H, app. s, 6- (or 8-) H), 6.75 (1H, app. s, 8- (or 6-) H), 6.90 (2H, s, NH_2), 7.15 (2H, d, J 6.8, 2- and 6-H-Ph), 7.23 (1H, d, J 7.1, 4-H-Ph), 7.30 (2H, t, J 7.4, 3- and 5-H-Ph); ^{13}C NMR (125 MHz) δ_{C} 21.5 (CH_3), 36.9 (4-CH), 54.2 (CH_2), 109.5, 111.0 (6- and 8-CH), 116.6, 120.9 (both ArC), 127.0 (4-PhCH), 127.4 (2 x ArCH), 128.8 (2 x ArCH), 139.4, 145.7, 150.0, 153.6, 160.7 (all ArC); m/z [EI], 317 (M^+ , 8%), 276 (1), 240 (100), 200 (50), 171 (29), 128 (6), 102 (9), 77 (76).

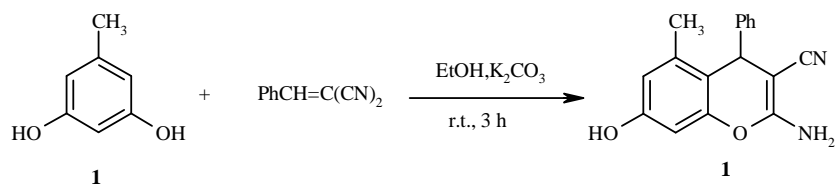
3-Amino-7-(cyanomethoxy)-5-methyl-4-phenyl-1,4-dihydrochromeno[2,3-b]pyrrole-2-carbonitrile (17)

While crystallizing compound **16b** from dichloromethane, a part was insoluble and was subsequently crystallized from dioxane and identified as the pyrrole **17** (0.831 g, 47%), as colorless crystals m.p. 250 °C, IR, $\nu_{\max}/\text{cm}^{-1}$, 3434, 3336, 3082, 3056, 2963, 2924, 2189, 1647, 1624, 1580; ^1H NMR (250 MHz) δ_{H} 2.01 (3H, s, CH_3), 4.68 (1H, s, 4-H), 5.72 (2H, s, CH_2), 6.71 (2H, app. s, 6- and 8-H), 6.86 (2H, s, NH_2), 7.22 (2H, d, J 15.0, 2- and 6-H-Ph), 7.25 (1H, d, J 8.2, 4-H-Ph), 7.32 (2H, t, J 7.4, 3- and 5-H-Ph); ^{13}C NMR δ_{C} 19.3 (CH_3), 38.8 (4-CH), 54.1 (CH_2), 100.3 (6- (or 8-) CH), 113.9 (8- (or 6-) CH), 116.5, 116.6, 117.0, 120.9 (all ArC), 127.0 (4-PhCH), 127.5 (2 x ArCH), 129.1 (2 x ArCH), 139.1, 145.6, 150.5, 153.6, 156.0, 160.1 (all ArC); m/z [EI] 356 (M^+ , 13%), 317 (67), 240 (100%), 200 (94).

Results and Discussion

The synthesis of 2-aminochromenes has been previously reported from reactions between relatively activated nucleophilic phenols and an arylidenemalononitrile under basic conditions [piperidine, potassium carbonate and cetyltrimethylammonium chloride (CTACI)], either in an organic solvent or in water.^[6,7] The title compound **1** is new and was readily obtained in 88% isolated yield when a mixture of 5-methylresorcinol and benzylidenemalononitrile was allowed to react in absolute ethanol containing anhydrous potassium carbonate at room temperature for 3 hours (Scheme 1). Structural confirmation of chromene **1** was obtained from spectroscopic data and microanalysis: infrared spectra showed strong absorbances for both OH and NH_2 groups at 3427, 3367 and 3288 cm^{-1} and for the nitrile group at 2194 cm^{-1} . The ^1H NMR spectrum showed

a singlet at δ_{H} 4.53, characteristic of H-4, together with two aromatic methine resonances. A correct combustion analysis was accompanied by the observation of a molecular ion at m/z 278.

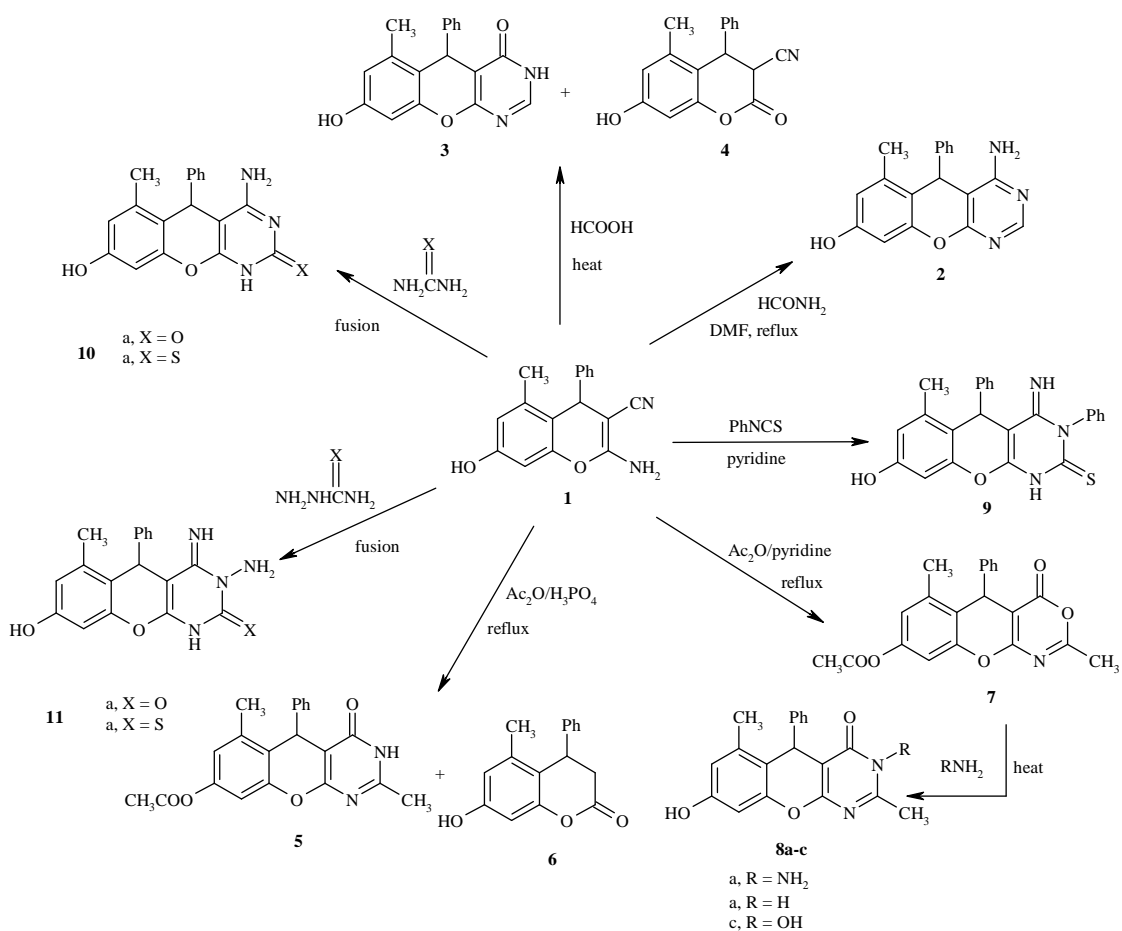


The cyano and amino substituents, in combination with chromene double bond, provide a rich opportunity for heterocyclic construction. In a first experiment, reaction between chromene **1** and formamide in refluxing dimethylformamide (DMF) furnished the aminopyrimidine **2** in 80% yield (Scheme 2). The IR spectrum of compound **2** is devoid of an absorption band for the cyano group but does show two bands for an amino group at 3379 and 3326 cm^{-1} . The ^1H NMR data revealed a new resonance at δ_{H} 8.02, assigned to the pyrimidine 2-H. The structure **2** was also consistent a molecular ion at m/z (EI) 305.

In contrast, a cyclocondensation of compound **1** with hot formic acid resulted in the formation of a separable mixture of the pyrimidinone **3** and the dihydrocoumarin **4**, in 52 and 38% yields respectively (Scheme 2). The expected pyrimidinone **3**, presumably formed by partial nitrile hydrolysis, amine formylation and cyclodehydration, showed a characteristic C=O stretch at 1645 cm^{-1} and a resonance at δ_{H} of 8.02 for the 2-H, along with exchangeable protons at δ_{H} 9.70 and 12.50 (NH and OH) and the anticipated molecular ion at m/z (EI) 306. A logical explanation for the formation of the dihydrocoumarin **4**, which was isolated as a single stereoisomer, is acid-induced hydrolysis of the enamine function in chromene **1**. Supporting evidence for the suggested structure comes from its infrared spectrum (1760 cm^{-1} for a β -lactone and 2280 cm^{-1} for the cyano group), along with two doublets centred on δ_{H} 4.85 and 5.30 ($J = 3.4$ Hz), assigned to H-3 and H-4. In addition, the compound was evidently devoid of an amino group and showed a correct molecular ion [m/z (ES) $M + H = 278$] corresponding to the proposed structure.

The reaction between the chromene **1** and acetic anhydride was conducted under both acidic and basic conditions. Thus, refluxing compound **1** in a mixture of acetic anhydride and phosphoric acid for several hours resulted in formation of the pyrimidine **5**, together with, once again, an enamine hydrolysis product, the dihydrocoumarin **6** (Scheme 2). However, under these more vigorous conditions, the nitrile group had evidently also been hydrolysed to the corresponding carboxylic acid which, being now effectively a malonic acid derivative, underwent facile decarboxylation to give the observed product **6**.

The identity of pyrimidine **5** was deduced from the close similarity of much of its spectroscopic data with those of its desmethyl relative, the pyrimidine **3**, but with the additional acetate carbonyl and methyl groups. Dihydrocoumarin **6** showed a strong stretching vibration at 1731 cm^{-1} and no band for a nitrile group, along with the expected proton coupling patterns in the aliphatic region. All other data were also consistent with the proposed structure, which was finally confirmed by X-ray analysis. The ORTEP diagram is shown in Figure 1.



Scheme 2

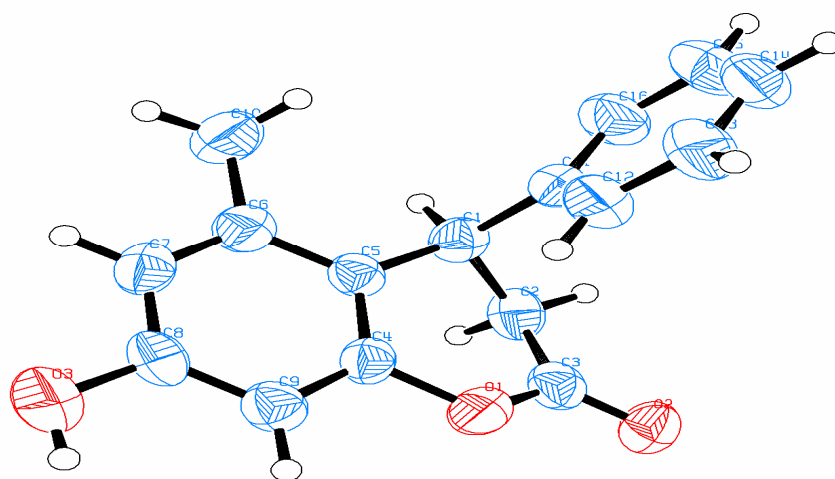


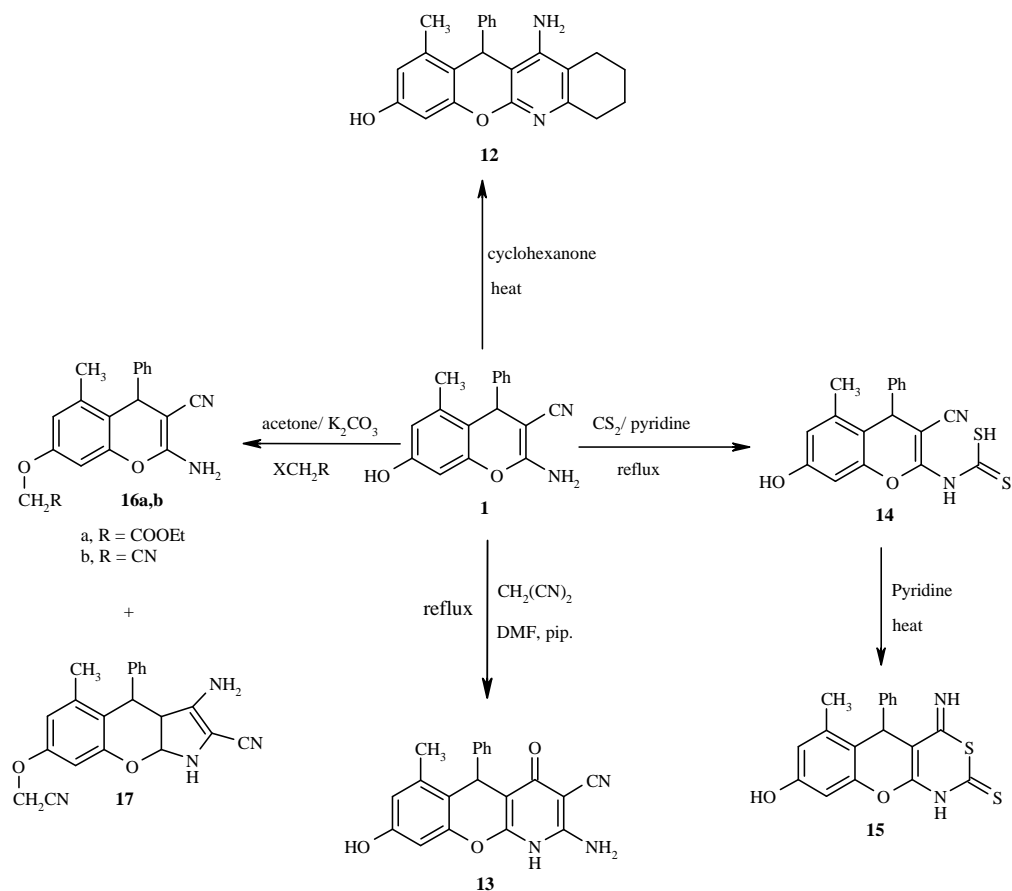
Figure 1: X-ray Crystallographic Analysis of compound 6

In contrast, heating chromene **1** in a mixture of acetic anhydride and pyridine gave the oxazinone **7** (Scheme 2). A carbonyl absorption at 1777 cm^{-1} was consistent with the proposed structure, as was the absence of any exchangeable protons, precluding the presence of either OH or NH functions. Three methyl groups were clearly present according to NMR data, as were two separate carbonyl groups according to ^{13}C data. Presumably, chromene **1** undergoes rapid *N*-acetylation under these conditions; subsequent hydrolysis of the nitrile group to the corresponding carboxylic acid is followed by cyclodehydration to the observed product **7**.

A facile synthetic method for converting an oxazinone into the corresponding pyrimidinone is by reactions with amines. Thus, heating oxazinone **7** with hydrazine hydrate, formamide or hydroxylamine delivered around 60% isolated yields of the corresponding pyrimidinones **8a-c**. Again, infrared spectra were useful in identifying the presence of a conjugated cyclic amide function in each product ($1644\text{-}1663\text{ cm}^{-1}$).

The interaction between the chromene **1** and phenyl isothiocyanate allowed for the introduction of sulphur into the substrate. When the two reactants were heated together in pyridine at reflux for 24 hours, the pyrimidinethione **9** was formed in around 50% yield (Scheme 2). The IR spectrum showed no absorption for the nitrile group, while there had been a marked change in the chemical shifts displayed in the ^1H NMR spectrum: the benzylic proton (H-5) has moved from δ_{H} 4.53 to 5.37 and in the ^{13}C NMR spectrum, a resonance at 179.4 ppm suggested the presence of a thiocarbonyl function. Mechanistically, it is presumed that the amino group of chromene **1** reacts with the isothiocyanate to give the corresponding thiourea, which can then undergo cyclisation onto the cyano function. Quite similar chemistry was involved in the formation of the aminopyrimidines **10a,b** and the closely related *N*-amino derivatives **11a,b** by the fusion of chromene **1** with, respectively urea, thiourea, semicarbazide and thiosemicarbazide (Scheme 2). All spectroscopic and analytical data was consistent with the structures proposed.

A number of other heterocyclic residues can be built onto the initial chromene **1**, by reason of the presence of the cyano enamine functional group combination. For example, condensation of the chromene **1** and cyclohexanone in the presence of the Lewis acid zinc chloride proceeded smoothly to give a 61% isolated yield of the pyridine derivative **12** (Scheme 3).^[8] This reaction represents a useful way for the preparation of Tacrine analogues,^[9] a class of compounds known to exhibit bioactivities. The proposed structure was deduced from IR data [no CN group; absorbances at $3336, 3182$ and 1629 cm^{-1} (NH_2 and $\text{C}=\text{N}$ groups)], appropriate resonances in the aliphatic region of the ^1H NMR spectrum to account for the presence of the cyclohexyl residue, along with ^{13}C NMR and MS data. Mechanistically, the reaction probably involves formation of an imine-enamine tautomer between the ketone and the 2-amino group of chromene **1**. Lewis acid-catalysed addition of the enamine to the cyano group then completes carbon-carbon bond formation. Heating chromene **1** with malononitrile in refluxing DMF containing piperidine causes a reaction in a reverse sense, but one which produces a similar product, the 4-pyridinone **13**, in 75% isolated yield. Presumably, ionized malononitrile attacks the cyano group in chromene **1** before the 2-amino group of the latter attacks one of the malononitrile cyano groups resulting in ring formation (Scheme 3). In contrast, heating the chromene **1** with carbon disulfide in alcoholic potassium hydroxide for 24 hours resulted in formation of the dithionocarbamate **14** in good yield, which was cyclised in turn by heating in pyridine to finally give the thiazine **15** in reasonable yield (Scheme 3).



Scheme 3

Rererences

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