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Abstract
Cyclocondensation of 2-(3-amino-2-cyano-1H-benzo[f]chromen-1-yl)-malononitrile (1) with β-dicarboxyldiethanes 2a-d, benzoylacetonitrile 2e, malononitrile 2f, and 3-aminocrotononitrile (9) gave the benzo[5,6]chromeno[4,3,2-de][1,6]naphthyridines (4a-e, 6 and 11). Refluxing 1 with ammonium acetate in ethanol gave pyridine-3,5-dicarbonitrile 12 that converted in the presence of HCl into 5H-benzo[5,6]chromeno-[3,4-c]pyridine 14. The structures of the products were proved by elemental analyses, IR, MS, 1H and 13C NMR spectroscopy.

Keywords: Heterocyclic α-aminonitriles, chromenes, 1,6-naphthyridines

Introduction
Condensed heterocyclic systems are of considerable interest not only because of their potential biological activity but also because of their versatility as synthons in organic transformation. Thus, heterocyclic α-aminonitrile derivatives are useful substrates for the preparation of various condensed pyridine heterocyclic systems.1-7 A series of 1,6-naphthyridines have been demonstrated as anti-human cytomegalovirus (HCMV) activity.8-11 Furthermore, chromenes and their fused heterocyclic derivatives have attracted a great deal of interest due to their wide applications in the field of pharmaceuticals.12-17 In view of the above mentioned benefits and in continuation of our previous work in developing syntheses of polyfunctionally substituted heterocyclic compounds with potential biological activity,18-27 we report here the utility of the 2-(3-amino-2-cyano-1H-benzo[f]chromen-1-yl)-malononitrile (1) as a building block for the synthesis of benzo[5,6]chromeno[4,3,2-de][1,6]naphthyridines and benzo[5,6]chromeno[3,4-c]pyridine with the purpose of investigating in the future their possible biological activity.
Results and Discussion

The formation of the trinitrile 1 (from the reaction of 2-hydroxynaphthaldehyde with malononitrile in 1:2 ratio) was reported in 1984. Scheme 1 illustrates on the synthesis of benzo[5,6]chromeno[4,3,2-de][1,6]naphthyridines 4a-d from the reaction of the trinitriles 1 with β-dicarbonyles 2a-d. For example, the reaction of compound 1 with ethyl benzoylacetate (2a) in equimolar proportions in ethanol and in the presence of piperidine afforded a solid with the empirical formula C_{28}H_{18}N_{4}O_{3} (M^+ = 458) (Scheme 1). The structural assignment of 4a was confirmed on the basis of its spectroscopic data. Thus, the IR spectrum of 4a showed absorption bands at 3452-3240 (NH_2), 2222 (CN) and 1720 cm^{-1} (ester CO group). The \( ^1H \) NMR spectrum of 4a revealed characteristic signals due to the ethyl ester group as a triplet at δ 1.30 ppm for the CH_3 group and quartet at δ 4.29 ppm for the OCH_2 group, a singlet at δ 6.54 for the amino group and a multiplet at δ 7.38-8.42 due to the phenyl protons. Moreover, the \( ^{13}C \) NMR spectrum agreed with the proposed structure 4a.

Similarly, compound 1 was condensed with different active methylene reagents such as methyl 3-oxobutanoate (2b), 2,4-pentanedione (2c) and 1,3-diphenyl-1,3-propanedione (2d) to give the corresponding pentacyclic compounds 4b-d (Scheme 1). The molecular formula of compounds 4b-d is supported by elemental analyses and mass spectra that gave the expected molecular ion peaks and their corresponding fragmentation patterns. The IR, \( ^1H \) NMR as well as the \( ^{13}C \) NMR spectra agreed with the proposed structures 4b-d.
According to the literature results,\textsuperscript{7,29-31} the heterocycles obtained in the reaction between aminonitriles and β-dicarboxyls is formed via the intermediate β-enaminodiones A. These intermediates have never been isolated possibly due to their fast intramolecular cyclization to heterocyclic rings. Therefore, the structure of 4a-d is rationalized in terms of the initial formation of the intermediate 3, which on subsequent intramolecular cyclization followed by elimination of a water molecule and partial dehydrogenation under the reaction conditions affords the final product (Scheme 1).
In a similar manner, compound 1 condensed with benzoylacetonitrile (2e) under the previous reaction conditions to yield a product formulated as 4e (Scheme 1). The structure of 4e was elucidated on the same lines as 4a-d. Moreover, a mixture of equimolar amounts of compound 1 and malononitrile (2f) reacted in refluxing ethanol and in the presence of a catalytic amount of piperidine to yield a solid product of molecular formula $\text{C}_{20}\text{H}_{10}\text{N}_6\text{O} (\text{M}^+ = 350)$ which may be formulated as napthyridine 6 (route A) or pyridopyrimidine 8 (route B) (Scheme 1). The structure of 8, which was previously prepared from the condensation of 2-hydroxynaphthaldehyde with malononitrile in 1:2 ratios and in the presence of ammonium acetate, was ruled out on the basis of the spectral data of the isolated product. Thus, the $^1$H and $^{13}$C NMR spectra of compound 6 revealed the absence of signals attributable to the methylene protons of 8. With the results on hand the proposed napthyridine structure 6 is identified as shown in Scheme 1. Thus it appears that the dicyanomethyl anion attacks the cyano group of 1 yielding the intermediate 5 (route A) which by intramolecular cyclization between amino and cyano groups with partial dehydrogenation under the reaction conditions gives compound 6 (Scheme 1).

As described in Scheme 2, the 2-amino-5-methyl-benzo[5,6]chromeno[4,3,2-de]-[1,6]napthyridine-1,4-dicarbonitrile (11) was obtained when 1 was heated under reflux with 3-amino-crotononitrile (9) in boiling ethanol. Depending upon the spectroscopic data the structure of compound 11 is undoubtedly confirmed. The formation of 11 can be described in terms of the initial formation of the intermediate 10 followed by its cyclization to the final product 11.
Scheme 2

In a different type of reaction, the trinitriles 1 reacted with ammonium acetate in molar ratio 1:2 to afford 2,6-diamino-4-(2-hydroxy-1-naphthyl)-3,5-pyridine-dicarbonitrile (12). Compound 12 was converted, in the presence of hydrochloric acid, into 2,4-diamino-5-oxo-5H-benzo[5,6]chromeno[3,4-c]pyridine-1-carbonitrile (14); presumably the imino group in the postulated intermediate 13 is hydrolysed during formation of 14 (Scheme 2). The structures of 12 and 14 were deduced from their elemental analyses and their IR, MS, 1H, and 13C NMR data.

Experimental Section

General Procedures. All Mps were recorded on a Gallenkamp apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 880 spectrophotometer, using KBr pellets. The 1H NMR spectra were measured in DMSO-d6 with a JOEL Lambda 400 (400 MHz) spectrometer using TMS as an internal standard; the 13C NMR spectra were recorded at 100 MHz. The chemical shifts are expressed as δ values (ppm). Mass spectra were determined on a Shimadzu QP 5050 A mass spectrometer operating at 70 eV. The Microanalytical Unit at Chemistry Department, University of Hull, UK performed microanalytical analysis. Compound 1 was prepared according to the procedure mentioned in reference 28 and the starting materials were commercially available.

General procedures for the synthesis of benzo[5,6]chromeno[4,3,2-de][1,6]naphthyridines 4a-e and 6. A solution of equimolar amounts (5 mmol) of trinitriles 1, and either ethyl benzoylacetate (2a) methyl 3-oxobutanoate (2b), 2,4-pentanedione (2c) 1,3-diphenyl-1,3-propanedione (2d) benzoylacetonitrile (2e) or malononitrile (2f) in ethanol (50 ml) containing a
catalytic amount of piperidine was heated under reflux for 1 h. The solid product formed was collected by filtration, dried and recrystallized from DMF/EtOH to give yellow crystals.

**Ethyl 2-amino-1-cyano-5-methylbenzo[5,6]chromeno[4,3,2-de][1,6]naphthyridine-4-carboxylate (4a).** Yield: 81 %, mp >300 °C. IR (υ, cm⁻¹): 3452-3240 (NH₂), 3053 (Ar-H), 2222 (CN), 1720 (CO). ¹H NMR (DMSO-d₆) δ (ppm) 1.30 (t, 3H, J = 8.9 Hz, CH₃), 4.29 (q, 2H, J = 8.9 Hz, OCH₂), 6.54 (brs, 2H, NH₂), 7.38-8.42 (m, 11H, Ar-H). ¹³C NMR (DMSO-d₆) δ (ppm) 13.6 (CH₃), 59.2 (CH₂), 90.1 (C-4), 101.4 (C-13d), 116.8 (CN), 119.3 (C-8), 119.8 (C-13b), 121.4 (C-1), 124.3(C-11), 126.4 (C-12), 126.8 (C-13), 127.1 (C-4’), 127.2 x 2 (C-2’, C-6’), 128.2 (C-10), 129.1 (C-9a), 129.4 x 2 (C-3’, C-5’), 130.2 (C-9), 133.2 (C-13a), 139.7 (C-1’), 146.2 (C-3a), 149.3 (C-13c), 152.1 (C-7a), 157.6 (C-2), 162.5 (C-5), 167.2 (C-6a), 169.4 (CO). MS [m/z (% rel. int.): 458 [M⁺, 55%]. Anal. Calcd. for C₂₈H₁₈N₄O₃ (458.48): C, 73.35; H, 3.96; N, 12.22%; Found: C, 73.24; H, 3.83; N,12.12.

**Methyl 2-amino-1-cyano-5-methylbenzo[5,6]chromeno[4,3,2-de][1,6]naphthyridine-4-carboxylate (4b).** Yield: 78 %, mp > 300 °C. IR (υ, cm⁻¹): 3440-3200 (NH₂), 3051 (Ar-H), 2220 (CN), 1718 (CO). ¹H NMR (DMSO-d₆) δ (ppm) 2.55 (s, 3H, CH₃), 3.88 (s, 3H, OCH₃), 6.25 (brs, 2H, NH₂), 7.10 (d, 1H, J = 9.0 Hz, H-8), 7.24 (t, 1H, J = 8.0 Hz, H-11), 7.47 (t, 1H, J = 8.0 Hz, H-12), 7.61 (d, 1H, J = 9.0 Hz, H-13), 7.71 (d, 1H, J = 9.0 Hz, H-9), 7.76 (d, 1H, J = 8.5 Hz, H-10). ¹³C NMR (DMSO-d₆) δ (ppm) 21.4 (CH₃), 50.4 (OCH₃), 90.0 (C-4), 101.4 (C-13d), 116.1 (CN), 118.6 (C-8), 119.3 (C-13b), 122.2 (C-1), 124.2 (C-11), 126.4 (C-12), 126.8 (C-13), 128.3 (C-10), 129.2 (C-9a), 130.4 (C-9), 133.3 (C-13a), 146.2 (C-3a), 148.6 (C-13c), 152.2 (C-7a), 158.4 (C-2), 162.5 (C-5), 167.1 (C-6a), 169.4 (CO). MS [m/z (% rel. int.): 382 [M⁺, 62%]. Anal. Calcd. for C₂₂H₁₄N₄O₃ (382.38): C, 69.11; H, 3.69; N; 14.65%; Found: C, 69.22; H, 3.78; N, 14.56.

**4-Acetyl-2-amino-5-methylbenzo[5,6]chromeno[4,3,2-de][1,6]naphthyridine-1-carbonitrile (4c).** Yield: 79 %, mp > 300 °C. IR (υ, cm⁻¹): 3453-3212 (NH₂), 3050 (Ar-H), 2200 (CN), 1720 (CO). ¹H NMR (DMSO-d₆) δ (ppm) 2.52 (s, 3H, CH₃), 2.62 (s, 3H, CH₃), 6.22 (brs, 2H, NH₂), 7.13 (d, 1H, J = 9.0 Hz, H-8), 7.31 (t, 1H, J = 8.0 Hz, H-11), 7.44 (t, 1H, J = 8.0 Hz, H-12), 7.65 (d, 1H, J = 9.0 Hz, H-13), 7.74 (d, 1H, J = 9.0 Hz, H-9), 7.78 (d, 1H, J = 8.5 Hz, H-10). ¹³C NMR (DMSO-d₆) δ (ppm) 21.6 (CH₃), 24.4 (CH₃), 90.1 (C-4), 101.4 (C-13d), 116.6 (CN), 118.5 (C-8), 119.2 (C-13b), 122.2 (C-1), 124.2 (C-11), 126.4 (C-12), 126.8 (C-13), 128.4 (C-10), 129.7 (C-1), 130.5 (C-9), 133.4 (C-13a), 146.2 (C-3a), 147.8 (C-13c), 152.2 (C-7a), 158.4 (C-2), 162.5 (C-5), 167.2 (C-6a), 196.5 (CO). MS [m/z (% rel. int.): 366 [M⁺, 66%]. Anal. Calcd. for C₂₂H₁₄N₄O₂ (366.38): C, 72.12; H, 3.85; N, 14.56%.

**2-Amino-4-benzoyl-5-phenylbenzo[5,6]chromeno[4,3,2-de][1,6]naphthyridine-1-carbonitrile (4d).** Yield: 64 %, mp > 300 °C. IR (υ, cm⁻¹): 3450-3244 (NH₂), 3050 (Ar-H), 2200 (CN), 1725 (CO). ¹H NMR (DMSO-d₆) δ (ppm) 7.54-8.48 (m, 16H, Ar-H). ¹³C NMR (DMSO-d₆) δ (ppm) 90.2 (C-4), 101.6 (C-13d), 116.0 (CN), 119.4 (C-8), 119.8 (C-13b), 124.4 (C-11), 126.4 (C-12), 126.8 (C-13), 127.1 (C-4’), 127.2 x 2 (C-2’, C-6’), 128.3 (C-10), 128.6 x 2 (C-3’` C-5’`), 128.8 (C-1), 129.1 (C-9a), 129.3 x 2 (C-3’, C-5’), 129.5 x 2 (C-2’, C-6’), 130.4 (C-9), 133.0 (C-1’`), 132.4 (C-4’`), 133.3 (C-13a), 139.7 (C-1’), 146.2 (C-3a), 150.6 (C-13c), 152.2 (C-7a), 158.9 (C-2), 162.6 (C-5), 167.2 (C-6a), 187.2 (CO). MS [m/z (% rel. int.): 366 [M⁺, 66%]. Anal. Calcd. for C₂₂H₁₄N₄O₂ (366.38): C, 72.12; H, 3.85; N, 15.29%; Found: C, 72.22; H, 3.95; N, 15.18.

2-Amino-5-phenylbenzo[5,6]chromeno[4,3,2-de][1,6]naphthyridine-1,4-dicarbonitrile (4e).
Yield: 68 %, mp > 300 °C. IR (υ, cm⁻¹): 3440-3243 (NH₂), 3050 (Ar-H), 2218 (CN). ¹H NMR (DMSO-d₆) δ (ppm) 6.34 (brs, 2H, NH₂), 7.42-8.22 (m, 11H, Ar-H). ¹³C NMR (DMSO-d₆) δ (ppm) 89.8 (C-4), 101.8 (C-13d), 106.6 (C-1), 116.8 (CN), 118.6 (CN), 119.2 (C-8), 119.8 (C-13b), 124.2 (C-11), 126.3 (C-12), 126.6 (C-13), 127 (C-4'), 127.2 x 2 (C-2’, C-6’), 128.3 (C-10), 129.0 (C-9a), 129.2 x 2 (C-3’, C-5’), 130.3 (C-9), 133.2 (C-13a), 139.7 (C-1'), 146.2 (C-3a), 152.2 (C-7a), 153.7 (C-13c), 162.7 (C-5), 163.4 (C-2), 167.2 (C-6a). MS [m/z (% rel. int.)]: 411 [M⁺, 65%]. Anal. Calcd. for C₂₆H₁₃N₅O (411.43): C, 75.90; H, 3.18; N, 17.02%; Found: C, 75.78; H, 3.28; N, 17.11.

2,5-Diaminobenzo[5,6]chromeno[4,3,2-de][1,6]naphthyridine-1,4-dicarbonitrile (6).
Yield: 84 %, mp >300 °C. IR (υ, cm⁻¹): 3440, 3354, 3243, 3188 (NH₂), 3053 (Ar-H), 2220, 2207 (CN). ¹H NMR (DMSO-d₆) δ (ppm) 6.12 (brs, 4H, 2NH₂), 7.14 (d, 1H, J = 9.0 Hz, H-8), 7.21 (t, 1H, J = 8.0 Hz, H-11), 7.37 (t, 1H, J = 8.0 Hz, H-12), 7.58 (d, 1H, J = 9.0 Hz, H-9), 7.69 (d, 1H, J = 8.5 Hz, H-10). ¹³C NMR (DMSO-d₆) δ (ppm) 89.6 (C-4), 93.3 (C-1), 101.5 (C-13d), 116.1 (CN), 118.1 (CN), 118.8 (C-8), 119.6 (C-13b), 124.2 (C-11), 126.1 (C-12), 126.2 (C-13), 128.1 (C-9a), 130.3 (C-9), 133.2 (C-13a), 146.1 (C-3a), 152.2 (C-7a), 154.8 (C-13c), 162.6 (C-5), 163.2 (C-2), 165.5 (C-6a). MS [m/z (% rel. int.): 350 [M⁺, 84%]. Anal. Calcd. for C₂₀H₁₀N₆O (350.34): C, 68.57; H, 2.88; N, 23.99%; Found: C, 68.51; H, 2.75; N, 23.84.

A solution of equimolar amounts (5 mmol) of compound 1 and 3-amino-crotononitrile (9) in ethanol (50 ml) were heated under reflux for 1 h. The mixture, set a side at room temperature for 1 h, afforded a pure product. This was collected by filtration, dried and recrystallized from DMF/EtOH to give 11 as a crystalline yellow (yield: 65 %), mp > 300 °C. IR (υ, cm⁻¹): 3400-3200 (NH₂), 3050 (Ar-H), 2222, 2200 (CN). ¹H NMR (DMSO-d₆) δ (ppm) 2.55 (s, 3H, CH₃), 6.13 (s, 2H, NH₂), 7.10 (d, 1H, J = 9.0 Hz, H-8), 7.23 (t, 1H, J = 8.0 Hz, H-11), 7.40 (t, 1H, J = 8.0 Hz, H-12), 7.60 (d, 1H, J = 9.0 Hz, H-9), 7.66 (d, 1H, J = 9.0 Hz, H-10). ¹³C NMR (DMSO-d₆) δ (ppm) 13.9 (CH₃), 93.1 (C-1), 101.5 (C-13d), 104.2 (C-4), 116.4 (CN), 118.1 (CN), 118.8 (C-8), 119.4 (C-13b), 124.2 (C-11), 126.4 (C-12), 126.8 (C-13), 128.4 (C-10), 129.2 (C-9a), 130.2 (C-9), 133.2 (C-13a), 143.9 (C-3a), 152.4 (C-7a), 154.8 (C-13c), 160.0 (C-5), 165.1 (C-2), 167.5 (C-6a). MS [m/z (% rel. int.): 350 [M⁺, 100%]. Anal. Calcd. for C₂₁H₁₁N₅O (349.35): C, 72.20; H, 3.17; N, 20.05%; Found: C, 72.29; H, 3.28; N, 20.15.

Synthesis of 2,6-diamino-(2-hydroxy-1-naphthyl)-3,5-pyridinedicarbonitrile (12).
A mixture of 1 (1.43g, 5 mmol) and ammonium acetate (0.77g, 10 mmol) in ethanol (30 ml) was heated under reflux for 30 minutes, then cooled to room temperature, and the product which had separated was collected by filtration, dried and recrystallized from dioxane to give 12 as a pale yellow needles (yield: 63 %), mp 266-268 °C. IR (υ, cm⁻¹): 3440, 3352, 3152, (NH₂), 3050 (Ar-H), 2200 (CN). ¹H NMR (DMSO-d₆) δ (ppm) 7.00 (d, 1H, J = 9.0 Hz, H-3’), 7.12 (brs, 4H,
2NH₂), 7.36 (t, 1H, J = 8.0 Hz, H-6’), 7.43 (t, 1H, J = 8.0 Hz, H-7’), 7.52 (d, 1H, J = 9.0 Hz, H-8’), 7.60 (d, 1H, J = 9.0 Hz, H-4’), 7.74 (d, 1H, J = 8.5 Hz, H-5’), 9.9 (brs, 1H, OH). ¹³C NMR (DMSO-d₆) δ (ppm) 83.1 x 2 (C-3, C-5), 116.2 x 2 (2 CN), 118.2 (C₃’), 121.1 (C₁’), 124.2 (C₆’), 126.1 (C₇’), 126.3 (C₈’), 128.3 (C₅’), 129.0 (C₄’a), 131.1 (C₈’a), 130.1 (C₄’), 152.2 (C₂’), 161.6 (C-4), 168.4 x 2 (C-2, C-6). MS [m/z (% rel. int.)]: 301 [M⁺, 64%]. Anal. Calcd. for C₁₇H₁₁N₅O (301.31): C, 67.77; H, 3.68; N, 23.24%; Found: C, 67.68; H, 3.76; N, 23.33.


Compound 1₂ (100 mg) was suspended in conc. hydrochloric acid (3 ml) at room temperature for 3 days. The product 1₄, collected by filtration, washed with methanol and dried, had mp > 300 °C (65 mg, 67%). IR (υ, cm⁻¹): 3396, 3330, 3184 (NH₂), 3050 (Ar-H), 2200 (CN), 1690 (CO). ¹H NMR (DMSO-d₆) δ (ppm) 7.12 (d, 1H, J = 9.0 Hz, H-7), 7.23 (t, 1H, J = 8.0 Hz, H-10), 7.39 (t, 1H, J = 8.0 Hz, H-11), 7.45 (brs, 4H, 2NH₂), 7.60 (d, 1H, J = 9.0 Hz, H-12), 7.66 (d, 1H, J = 9.0 Hz, H-8), 7.72 (d, 1H, J = 8.5 Hz, H-9). ¹³C NMR (DMSO-d₆) δ (ppm) 82.6 (C-1), 99.8(C-4a), 118.2 (CN), 118.3 (C-7), 119.4 (C-12b), 124.2 (C-10), 126.3 (C-11), 126.5 (C-12), 128.2 (C-9), 129.1 (C-8a), 130.2 (C-8), 133.4 (C-12a), 152.4 (C-6a), 158.6 (C-12c), 164.1 (C-5), 164.8 (C-4), 167.2 (C-2). MS [m/z (% rel. int.]): 302 [M⁺, 52%]. Anal. Calcd. for C₁₇H₁₀N₄O₂ (302.29): C, 67.55; H, 3.33; N, 18.53%; Found: C, 67.46; H, 3.44; N, 18.61.

Conclusions

We have demonstrated that the cyclocondensation of the trinitriles 1 with active methylene reagents and 3-amino-crotononitrile leads to the benzo[5,6]chromeno[4,3,2-de][1,6]naphthyridines. Also, compound 1 was subjected to further transformations, which produced the benzo[5,6]chromeno[3,4-c]pyridines.

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References