Synthesis of polyfunctionally substituted benzo[5,6]chromeno[4,3,2-*de*][1,6]naphthyridines and 5*H*-benzo[5,6]chromeno[3,4-*c*]pyridines

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Abstract

Cyclocondensation of 2-(3-amino-2-cyano-1*H*-benzo[*f*]chromen-1-yl)-malononitrile (**1**) with *β*-dicarbonyles **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 5*H*-benzo[5,6]chromeno-[3,4-*c*]pyridine **14**. The structures of the products were proved by elemental analyses, IR, MS, ^{1}H and ^{13}C NMR spectroscopy.

Keywords: Heterocyclic *o*-aminonitriles, chromenes, 1,6-naphthyridines

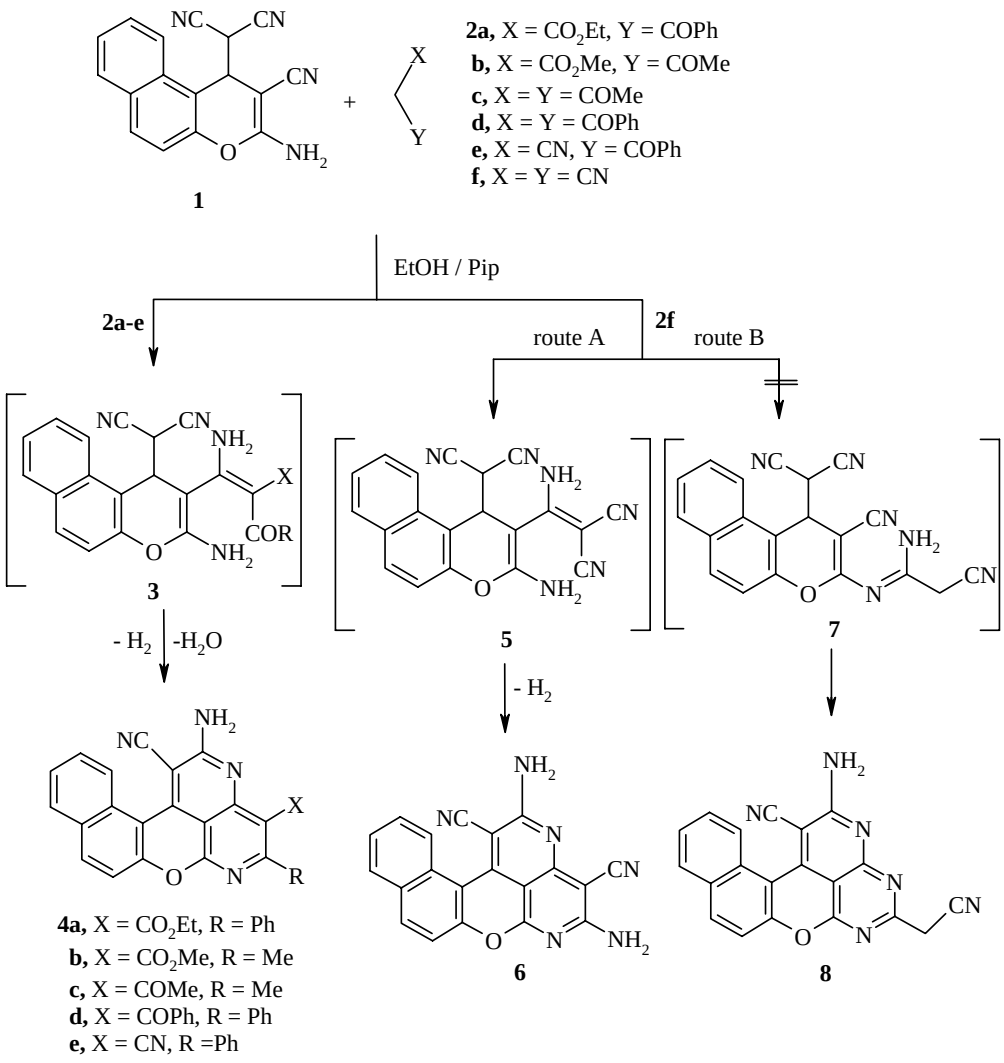
Introduction

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 *o*-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-1*H*-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

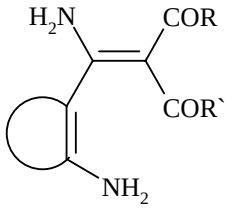
The formation of the trinitrile **1** (from the reaction of 2-hydroxynaphthaldehyde with malononitrile in 1:2 ratio) was reported in 1984.[28] Scheme 1 illustrates on the synthesis of benzo[5,6]chromeno[4,3,2-*de*][1,6]naphthyridines **4a-d** from the reaction of the trinitriles **1** with β-dicarbonyles **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 $C_{28}H_{18}N_4O_3$ (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 ^{1}H 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, ^{1}H NMR as well as the ^{13}C NMR spectra agreed with the proposed structures **4b-d.**



Scheme 1

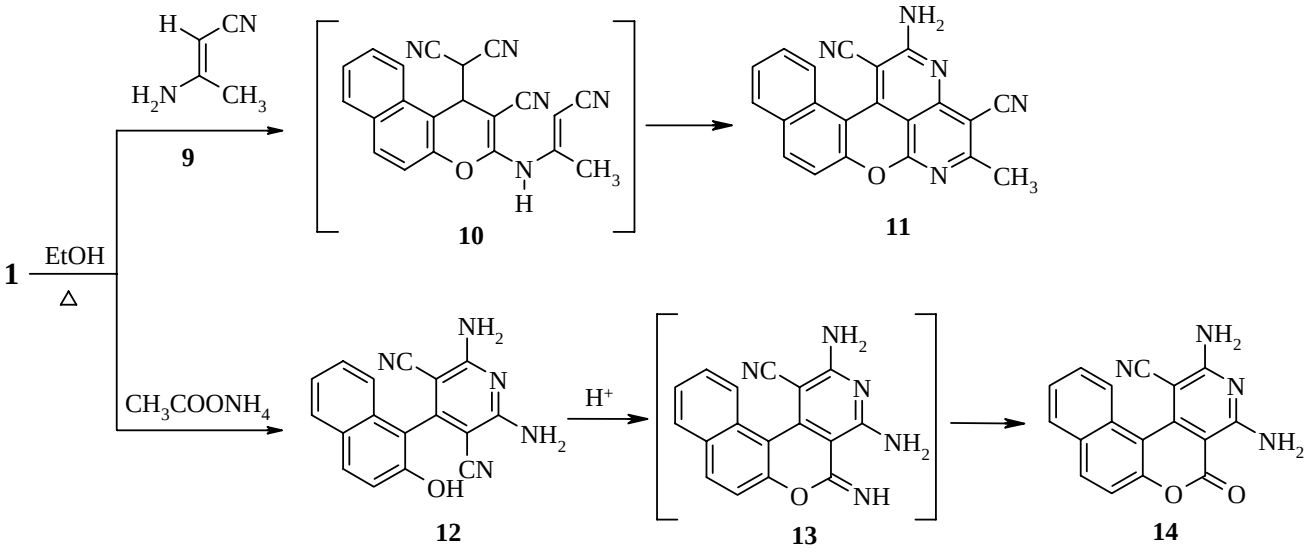
According to the literature results,[7,29-31] the heterocycles obtained in the reaction between aminonitriles and β-dicarbonyles is formed via the intermediate β-enaminodiones **A**. These intermediates have never been isolated possibly due to their fast intramolecular cyclization to heterocyclic rings. 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).



A

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 $C_{20}H_{10}N_6O$ ($M^+ = 350$) which may be formulated as naphthyridine **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,[32] 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 naphthyridine 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]naphthyridine-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-5*H*-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, ^{1}H, and ^{13}C 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 ^{1}H NMR spectra were measured in DMSO-d_6 with a JOEL Lambda 400 (400 MHz) spectrometer using TMS as an internal standard; the ^{13}C 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 (NH_2), 3053 (Ar-H), 2222 (CN), 1720 (CO). ^{1}H NMR (DMSO-d_6) δ (ppm) 1.30 (t, 3H, *J* = 8.9 Hz, CH_3), 4.29 (q, 2H, *J* = 8.9 Hz, OCH_2), 6.54 (brs, 2H, NH_2), 7.38-8.42 (m, 11H, Ar-H). ^{13}C NMR (DMSO-d_6) δ (ppm) 13.6 (CH_3), 59.2 (CH_2), 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 $C_{28}H_{18}N_4O_3$ (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 (NH_2), 3051 (Ar-H), 2220 (CN), 1718 (CO). ^{1}H NMR (DMSO-d_6) δ (ppm) 2.55 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 6.25 (brs, 2H, NH_2), 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). ^{13}C NMR (DMSO-d_6) δ (ppm) 21.4 (CH_3), 50.4 (OCH_3), 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), 126.6 (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 $C_{22}H_{14}N_4O_3$ (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 (NH_2), 3050 (Ar-H), 2200 (CN), 1720 (CO). ^{1}H NMR (DMSO-d_6) δ (ppm) 2.52 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 6.22 (brs, 2H, NH_2), 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). ^{13}C NMR (DMSO-d_6) δ (ppm) 21.6 (CH_3), 24.4 (CH_3), 90.1 (C-4), 101.4 (C-13d), 116.6 (CN), 118.5 (C-8), 119.2 (C-13b), 124.2 (C-11), 126.4 (C-12), 126.8 (C-13), 128.4 (C-10), 129.2 (C-9a), 129.7 (C-1), 130.5 (C-9), 133.4 (C-13a), 146.2 (C-3a), 147.8 (C-13c), 152.2 (C-7a), 162.5 (C-2), 162.6 (C-5), 167.2 (C-6a), 196.5 (CO). MS [m/z (% rel. int.)]: 366 [M^+, 66%]. Anal. Calcd. for $C_{22}H_{14}N_4O_2$ (366.38): C, 72.12; H, 3.85; N, 15.29%; Found: C, 72.22; H, 3.95; N, 15.18.

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 (NH_2), 3050 (Ar-H), 2220 (CN), 1725 (CO). ^{1}H NMR (DMSO-d_6) δ (ppm) 6.75 (brs, 2H, NH_2), 7.54-8.48 (m, 16H, Ar-H). ^{13}C NMR (DMSO-d_6) δ (ppm) 90.2 (C-4), 101.6 (C-13d), 118.0 (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.)]: 490 [M^+, 45%]. Anal. Calcd. for $C_{32}H_{18}N_4O_2$ (490.53): C, 78.36; H, 3.70; N, 11.42%; Found: C, 78.46; H, 3.59; N, 11.31.

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 (NH_2), 3050 (Ar-H), 2218 (CN). ^{1}H NMR (DMSO-d_6) δ (ppm) 6.34 (brs, 2H, NH_2), 7.42-8.22 (m, 11H, Ar-H). ^{13}C NMR (DMSO-d_6) 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 $C_{26}H_{13}N_5O$ (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 (NH_2), 3053 (Ar-H), 2220, 2207 (CN). ^{1}H NMR (DMSO-d_6) δ (ppm) 6.12 (brs, 4H, $2NH_2$), 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-13), 7.69 (d, 1H, *J* = 9.0 Hz, H-9), 7.73 (d, 1H, *J* = 8.5 Hz, H-10). ^{13}C NMR (DMSO-d_6) 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), 128.2 (C-10), 129.1 (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 $C_{20}H_{10}N_6O$ (350.34): C, 68.57; H, 2.88; N, 23.99%; Found: C, 68.51; H, 2.75; N, 23.84.

Synthesis of 2-amino-5-methylbenzo[5,6]chromeno[4,3,2-*de*][1,6]naphthyridine-1,4-dicarbonitrile (11). 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 (NH_2), 3050 (Ar-H), 2222, 2200 (CN). ^{1}H NMR (DMSO-d_6) δ (ppm) 2.55 (s, 3H, CH_3), 6.13 (s, 2H, NH_2), 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-13), 7.66 (d, 1H, *J* = 9.0 Hz, H-9), 7.70 (d, 1H, *J* = 8.5 Hz, H-10). ^{13}C NMR (DMSO-d_6) δ (ppm) 13.9 (CH_3), 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.)]: 349 [M^+, 100%]. Anal. Calcd. for $C_{21}H_{11}N_5O$ (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-4-(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, (NH_2), 3050 (Ar-H), 2200 (CN). ^{1}H NMR (DMSO-d_6) δ (ppm) 7.00 (d, 1H, *J* = 9.0 Hz, H-3`), 7.12 (brs, 4H,

$2NH_2$), 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). $^{13}$C NMR (DMSO-$d_6$) 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), 133.1 (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 $C_{17}H_{11}N_5O$ (301.31): C, 67.77; H, 3.68; N, 23.24%; Found: C, 67.68; H, 3.76; N, 23.33.

Synthesis of 2,4-diamino-5-oxo-5*H*-benzo[5,6]chromeno[3,4-*c*]pyridine-1-carbonitrile (14). 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 (NH_2), 3050 (Ar-H), 2200 (CN), 1690 (CO). ^{1}H NMR (DMSO-d_6) 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, $2NH_2$), 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). ^{13}C NMR (DMSO-d_6) 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 $C_{17}H_{10}N_4O_2$ (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

1. Taylor E. C.; McKillop, A. *The Chemistry of Cyclic Enaminonitriles and o-Amino-nitriles,* Interscience: New York, 1970; 415 pp.
2. Erian, A. W. *Chem. Rev.* **1993,** *93*, 1991.
3. Wamhoff, H. *Adv. Heterocycl. Chem.* **1985,** *38*, 357.
4. O'Callaghan, C. N.; McMurry, T. B. H.; O'Brien, J. E. *J. Chem. Soc., Perkin Trans 1* **1995,** 417.
5. Dave C. G.; Shah, R. D. *J. Heterocycl. Chem.* **1998,** *35*, 1295.

6. Zhao, W. G.; Li Z. M.; Yuan, D. K. *J. Chem. Res. (S)* **2002,** 454.
7. Maruoka, H.; Yamagata K.; Yamazaki, M. *Liebigs Ann. Chem.* **1993,** 1269.
8. Chan, L.; Jin, H.; Stefanac, T.; Lavallee, J. F.; Falardeau, G.; Wang, W.; Bèdard, J.; May S.; Yuen, L. *J. Med. Chem.* **1999,** *42,* 3023.
9. Falardeau, G.; Chan, L.; Stefanac, T.; May, S.; Jin H.; Lavallee, J. F. *Bioorg. Med. Chem. Lett.* **2000,** *18,* 2769.
10. Bedard, J.; May, S.; L'Heureux, L.; Stamminger, T.; Copsey, A.; Drach, J.; Huffman, J.; Chan, L.; Jin H.; Rando, R. F. *Antimicrob. Agents Chemother.* **2000,** *44,* 929.
11. Ruchelman, A. L.; Singh, S. K.; Ray, A.; Wu, X. H.; Yang, J. M.; Li, T. K.; Liu, A.; Liu L. F.; Lavoie, E. J. *Bioorg. Med. Chem.* **2003,** *11,* 2061.
12. El-Agrody, A. M.; El-Hakim, M. H.; Abd El-Latif, M. S.; Fakery, A. H.; El-Sayed E. S. M.; El-Ghareah, K. A. *Acta. Pharm.* **2000,** *50,* 111.
13. Zamocka, J.; Misikova E.; *J. Durinda, Cesk-Farm. (Ceska a Slovenska Farmacie)* **1992,** *41,* 170. *Chem. Abstr.* **1992,** *116,* 106031q.
14. Ohira T.; Yatagai, M. *J. Jpn. Wood Res. Soc.*, **1993,** 39; *Chem. Abstr.* **1993,** *119,* 19585d.
15. Mohr, S. J.; Chirigos, M. A.; Fuhrman F. S.; Pryor, J. W. *Cancer Res.* **1975,** *35,* 3750.
16. Martinez A. G.; Marco, L. J. *Bioorg. Med. Chem. Lett.* **1997,** *24,* 3165.
17. Tandon, V. K.; Vaish, M.; Jain, S.; Bhakuni, D. S.; Srimal, R. C. *Indian J. Pharm. Sci.* **1991,** *53,* 22.
18. Shaker, R. M. *Heteroatom. Chem.* **2005,** *16,* 507.
19. Shaker, R. M.; Mahmoud A. F.; Abdel-Latif, F. F. *Phosphorus, Sulfur Silicon and Relat. Elem.* **2005,** *180,* 397.
20. Hassan, A. A.; El-Shaieb, K. M.; Shaker, R. M.; D. Döpp. *Heteroatom Chem.* **2005,** *16,* 12.
21. Aly, A. A.; Hassan, A. A.; El-Shaieb K. M.; Shaker, R. M. *Z. Naturforsch.* **2005,** *60b,* 999.
22. Shaker, R. M. *Phosphorus, Sulfur Silicon and Relat. Elem.* **2003,** *178,* 1175.
23. Shaker, R. M.; Mahmoud A. F.; Abdel-Latif, F. F. *Chin. J. Chem. Soc.* **2005,** *52,* 563.
24. Shaker, R. M. *Die Pharm.* **1996,** 148.
25. Abdel-Latif, F. F.; Shaker, R. M.; Mahgoup, S. A.; Badr, M. Z. A. *J. Heterocycl. Chem.* **1989,** *26,* 769.
26. Shaker, R. M. *Phosphorus, Sulfur Silicon and Relat. Elem.* **2000,** *158,* 9.
27. Shaker, R. M.; Mahmoud A. F.; F. F. Abdel-Latif. *Phosphorus, Sulfur Silicon and Relat. Elem.* **2000,** *160,* 207.
28. Roudier, J. F.; Foucaud, A. *Synthesis* **1984,** 159.
29. Veronese, A. C.; Gandolfi, V.; Basato, M.; Corain, B. *J. Chem. Res. (S)* **1988,** 246; *J. Chem. Res. (M),* **1988,** 1843.
30. Veronese, A. C.; Callegari, R.; Salah, S. A. A. *Tetrahedron Lett.* **1990,** *31,* 3485.
31. Veronese, A. C.; Callegari R.; Morelli, C. F. *Tetrahedron* **1995,** *51,* 12277.
32. Fadda, A. A.; Zeimaty, M. T.; Gerges, M. M.; Refat, H. M.; Biehl, E. R. *Heterocycles* **1996,** *43,* 23.