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Synthesis of new 3*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-diones *via* the tandem intramolecular Pinner/Dimroth rearrangement

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Abstract: The reaction of 2-amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles with excess aliphatic carboxylic acids in the presence of phosphoryl chloride ($POCl_3$) afforded new 2-alkyl-5-aryl-8,8-dimethyl-8,9-dihydro-3*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-diones in high yields. The suggested mechanism involves a tandem intramolecular Pinner/Dimroth rearrangement. The synthesized compounds were characterized by infrared (IR), proton nuclear magnetic resonance (^{1}H NMR), carbon-13 nuclear magnetic resonance (^{13}C NMR) and elemental analysis.

Keywords: carboxylic acids; chromeno[2,3-*d*]pyrimidines; Pinner/Dimroth rearrangement; $POCl_3$.

Introduction

Certain chromenes possess important biological properties such as anticancer [1, 2], antimicrobial [3, 4], antiproliferative [5], anticonvulsant [6], antimalarial [7], antibacterial [8], anti-influenza [9] and anti-rhinovirus [10, 11] activities. Other compounds with a chromene moiety are potential inhibitors of aldose reductase [12], tumor necrosis fact (TNF)-α [13], PTP1B [14], DPP-IV [14], α-glucosidase [14, 15], h-MAO-B [16], PI3Kβ [17], PI3Kδ [17] and Src kinase [18]. On the other hand, the pyrimidine moiety is found in a range of compounds exhibiting a broad spectrum of biological activities such as antitumor [19], antiproliferative [20], antileishmanial [21], antibacterial [22], antifungal [23] and antioxidant [24] properties.

Chromeno[2,3-*d*]pyrimidines have received much attention because of their interesting biological properties such as anticancer [25], antimicrobial [26, 27], antitubercular [27], antibacterial [28], antiproliferative [29] and antioxidant [30] activities. In conjunction with our interest in the synthesis of heterocyclic compounds [31–40], in this paper we report the synthesis of new chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-diones **3a–h** by the reaction of substituted 5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles **1a–d** with excess aliphatic carboxylic acids **2a**, **b** in the presence of phosphoryl chloride ($POCl_3$) (Scheme 1).

Results and discussion

The starting materials **1a–d** were prepared according to methods cited in the literature [41–46]. In a model reaction, 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**1a**) was allowed to react with excess acetic acid (**2a**) under reflux without any solvent and catalyst. After a prolonged reaction time, only a low yield of the product was observed and a large amount of the starting material was recovered. Next, the reaction was investigated in excess acetic acid (**2a**) in the presence of $POCl_3$ as the chlorinating agent. After stirring at room temperature for 300 min the mixture showed only little conversion. However, after reflux for 150 min, no starting material was observed on monitoring of the reaction by thin-layer chromatography (TLC), and a single spot for the formation of a product was seen. The product was identified as 2,8,8-trimethyl-5-phenyl-8,9-dihydro-3*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (**3a**). Decreasing the reaction temperature to 100°C decreased the yield of the product from 90% to 78% under otherwise identical conditions. For comparison, synthesis of the model compound **3a** was also carried out using thionyl chloride ($SOCl_2$) under reflux conditions. Under these conditions, the product **3a** was obtained in 82% yield after 180 min. Consequently, all subsequent reactions for the synthesis of compounds **3b–h** were carried out in the presence of $POCl_3$ at reflux temperature.

The structures of the newly synthesized compounds **3a–h** were confirmed by analysis of spectral data and elemental analysis. For example, the proton nuclear magnetic resonance (^{1}H NMR) spectrum of compound **3a** in

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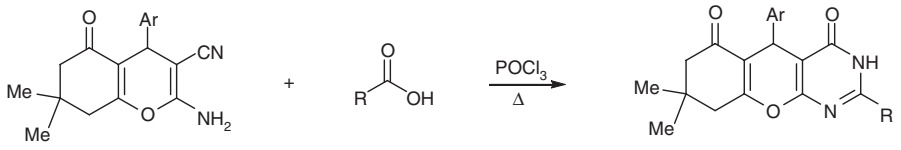


1a: Ar = Ph
1b: Ar = 3-$O_2NC_6H_4$
1c: Ar = 4-ClC_6H_4
1d: Ar = 4-MeC_6H_4

2a: R = Me
2b: R = Et

3a: Ar = Ph; R = Me
3b: Ar = Ph; R = Et
3c: Ar = 3-$O_2NC_6H_4$; R = Me
3d: Ar = 3-$O_2NC_6H_4$; R = Et
3e: Ar = 4-ClC_6H_4; R = Me
3f: Ar = 4-ClC_6H_4; R = Et
3g: Ar = 4-MeC_6H_4; R = Me
3h: Ar = 4-MeC_6H_4; R = Et

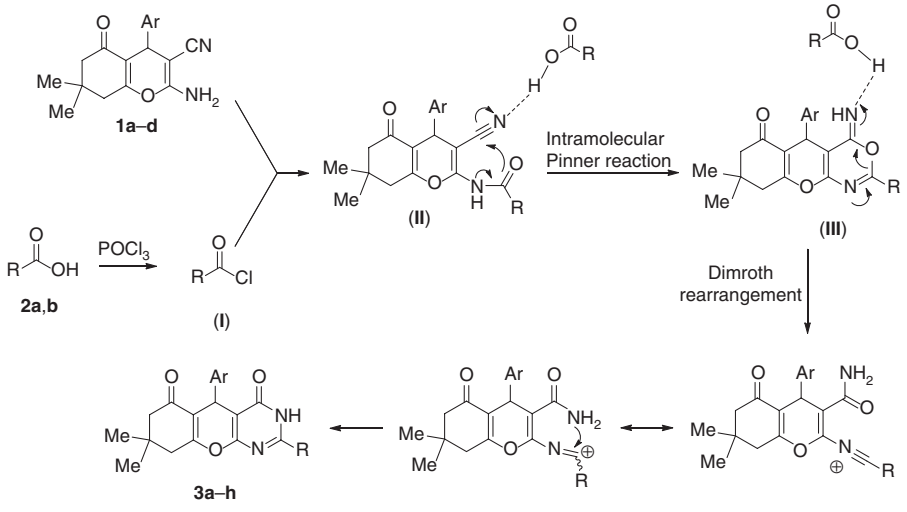
Scheme 1

dimethyl sulfoxide-d_6 (DMSO-d_6) contains a broad singlet at δ 12.55 for the NH group and a singlet at δ 2.27 for new methyl group. These new signals along with other signals including two singlets at δ 0.97 and 1.07 for diastereotopic methyl groups and a singlet at δ 4.70 for aliphatic methine group are fully consistent with the formation of compound **3a**. The infrared (IR) spectrum is devoid of the CN absorption band at 2199 cm^{-1} of the precursor but instead shows the NH absorption band at 3434 cm^{-1}, which indicates the involvement of the nitrile group in the cyclization process.

On the basis of a related transformation [40, 41], a plausible mechanism for the formation of compounds **3a–h** *via* the tandem intramolecular Pinner/Dimroth rearrangement is presented in Scheme 2. First, chlorination of carboxylic acid **2a** or **2b** with $POCl_3$ affords acyl chloride **I** which undergoes a reaction with the starting material **1a–d** to give the intermediate product **II**. This compound undergoes an intramolecular Pinner reaction followed by the Dimroth rearrangement to give the final product **3a–h** *via* the oxazine intermediate **III**. Unfortunately, attempts to isolate the proposed intermediate products failed even with careful monitoring of the reaction.

Conclusion

Synthesis of new 2-alkyl-5-aryl-8,8-dimethyl-8,9-dihydro-3*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione derivatives **3a–h** by the reaction of 2-amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles **1a–d** with excess aliphatic carboxylic acid **2a** or **2b** in the presence of $POCl_3$ is reported. An intramolecular Pinner/Dimroth rearrangement was suggested for the formation of the products.



Scheme 2

Experimental

All chemicals were purchased from Merck and Aldrich and used without additional purification. IR spectra were obtained as KBr pellets using a Tensor 27 Bruker spectrophotometer. The ^{1}H NMR (300 MHz) and carbon-13 nuclear magnetic resonance (^{13}C NMR) (75 MHz) spectra were recorded on a Bruker 300 FT spectrometer in DMSO-d_6 using tetramethylsilane (TMS) as the internal standard. Elemental analyses were performed on a Thermo Finnigan Flash EA microanalyzer. Melting points were recorded on a Stuart SMP3 melting point apparatus and are not corrected. The starting materials **1a–d** were prepared according to the methods cited in the literature [41–46].

General procedure for synthesis of compounds 3a–h

A mixture of 2-amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile **1a–d** (1 mmol) and excess acetic acid (**2a**, 2 mL) or propionic acid (**2b**, 2 mL) in $POCl_3$ (1 mL) was heated under reflux for 60–150 min. Upon completion, as monitored using TLC plates, the mixture was poured into cold water (40 mL). The crude product **3a–h** was collected, washed with water and crystallized from ethyl acetate.

2,8,8-Trimethyl-5-phenyl-8,9-dihydro-3*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3a) White powder; yield 90%; mp 318–320°C; IR: ν 3434 (NH), 1676 cm^{-1} (C=O); ^{1}H NMR: δ 0.97 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.13 (d, 1H, J = 16.1 Hz, one proton of diastereotopic protons in CH_2), 2.22–2.35 (m, 4H, a doublet for one proton of diastereotopic protons in CH_2 overlapped with a singlet for CH_3), 2.62 (s, 2H, CH_2), 4.70 (s, 1H, CH), 7.10–7.30 (m, 5H, H_{Ar}), 12.55 (s br., 1H, NH); ^{13}C NMR: δ 21.4, 27.2, 29.0, 32.4, 32.9, 50.5, 102.2, 114.2, 126.8, 128.4, 128.5, 144.3, 159.1, 160.5, 162.5, 164.2, 196.3. Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.16; H, 6.17; N, 8.54.

2-Ethyl-8,8-dimethyl-5-phenyl-8,9-dihydro-3*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3b) Creamy powder; yield 85%; mp 315–317°C; IR: ν 3432 (NH), 1674 cm^{-1} (C=O); ^{1}H NMR: δ 0.98 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.17 (t, 3H, J = 7.5 Hz, CH_3), 2.22 (AB_q, 2H, $\Delta\nu$ = 49.4 Hz, J_{AB} = 16.1 Hz, CH_2), 2.45–2.60 (m, 2H, CH_2 overlapped with solvent), 2.63 (s, 2H, CH_2), 4.70 (s, 1H, CH), 7.10–7.30 (m, 5H, H_{Ar}), 12.51 (s br., 1H, NH); ^{13}C NMR: δ 11.3, 27.2, 27.6, 29.0, 32.4, 33.0, 50.5, 102.4, 114.1, 126.8, 128.4, 128.6, 144.3, 160.6, 162.6, 163.0, 164.3, 196.4. Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 72.27; H, 6.14; N, 8.23.

2,8,8-Trimethyl-5-(3-nitrophenyl)-8,9-dihydro-3*H*-chromeno-[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3c) Creamy powder; yield 82%; mp 320–322°C; IR: ν 3437 (NH), 1669 cm^{-1} (C=O); ^{1}H NMR: δ 0.98 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 2.15 (d, 1H, J = 16.1 Hz, one proton of diastereotopic protons in CH_2), 2.28 (s, 3H, CH_3), 2.32 (d, 1H, J = 16.1 Hz, one proton of diastereotopic protons in CH_2), 2.66 (s, 2H, CH_2), 4.82 (s, 1H, CH), 7.54–7.61 (m, 1H, H_{Ar}), 7.69–7.73 (m, 1H, H_{Ar}), 8.02–8.07 (m, 2H, H_{Ar}), 12.58 (br s, 1H, NH); ^{13}C NMR: δ 21.5, 27.1, 28.9, 32.4, 33.4, 50.4, 101.1, 113.1, 122.1, 123.1, 130.0, 135.4, 146.3, 147.9, 159.8, 160.5, 162.5, 164.9, 196.5. Anal. Calcd for $C_{20}H_{19}N_3O_5$: C, 62.99; H, 5.02; N, 11.02. Found: C, 63.30; H, 5.24; N, 10.78.

2-Ethyl-8,8-dimethyl-5-(3-nitrophenyl)-8,9-dihydro-3*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3d) Creamy powder; yield 80%; mp 301–303°C; IR: ν 3426 (NH), 1673 cm^{-1} (C=O); ^{1}H NMR: δ 0.99 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.17 (t, 3H, J = 7.4 Hz, CH_3), 2.24 (AB_q, 2H, $\Delta\nu$ = 49.4 Hz, J_{AB} = 16.0 Hz, CH_2), 2.45–2.62 (m, 2H, CH_2 overlapped with solvent), 2.67 (s, 2H, CH_2), 4.82 (s, 1H, CH), 7.57 (t, 1H, J = 7.7 Hz, H_{Ar}), 7.71 (t, 1H, J = 7.6 Hz, H_{Ar}), 8.01–8.10 (m, 2H, H_{Ar}), 12.49 (br., 1H, NH); ^{13}C NMR: δ 11.2, 19.0, 27.2, 27.8, 28.9, 32.4, 33.5, 50.4, 101.2, 113.1, 122.0, 123.2, 130.0, 135.4, 146.4, 147.9, 160.6, 162.8, 163.8, 165.0, 196.5. Anal. Calcd for $C_{21}H_{21}N_3O_5$: C, 63.79; H, 5.35; N, 10.63. Found: C, 63.50; H, 5.54; N, 10.85.

5-(4-Chlorophenyl)-2,8,8-trimethyl-8,9-dihydro-3*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3e) White powder; yield 87%; mp 316–318°C; IR: ν 3423 (NH), 1663 cm^{-1} (C=O); ^{1}H NMR: δ 0.97 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.90–2.40 (m, 5H, CH_2 overlapped with CH_3), 2.61 (s, 2H, CH_2), 4.68 (s, 1H, CH), 7.15–7.45 (m, 4H, H_{Ar}), 12.60 (s br., 1H, NH); ^{13}C NMR: δ 21.4, 27.2, 28.9, 31.2, 32.4, 32.7, 50.4, 101.7, 113.7, 128.4, 130.4, 131.4, 143.2, 159.3, 160.4, 162.5, 164.4, 196.4. Anal. Calcd for $C_{20}H_{19}ClN_2O_3$: C, 64.78; H, 5.16; N, 7.55. Found: C, 64.59; H, 5.01; N, 7.73.

5-(4-Chlorophenyl)-2-ethyl-8,8-dimethyl-8,9-dihydro-3*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3f) Yellow powder; yield 86%; mp 260–262°C; IR: ν 3441 (NH), 1673 cm^{-1} (C=O); ^{1}H NMR: δ 0.98 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.17 (t, 3H, J = 7.5 Hz, CH_3), 2.22 (AB_q, 2H, $\Delta\nu$ = 47.5 Hz, J_{AB} = 16.1 Hz, CH_2), 2.50–2.60 (m, 2H, CH_2 overlapped with solvent), 2.63 (s, 2H, CH_2), 4.68 (s, 1H, CH), 7.24 (d, 2H, J = 8.6 Hz, H_{Ar}), 7.31 (d, 2H, J = 8.6 Hz, H_{Ar}), 12.57 (br., 1H, NH); ^{13}C NMR: δ 11.2, 27.3, 27.7, 28.9, 32.4, 32.8, 50.5, 101.9, 113.7, 128.4, 130.5, 131.4, 143.2, 160.6, 162.5, 163.3, 164.4, 196.4. Anal. Calcd for $C_{21}H_{21}ClN_2O_3$: C, 65.54; H, 5.50; N, 7.28. Found: C, 65.77; H, 5.31; N, 7.49.

2,8,8-Trimethyl-5-(4-methylphenyl)-8,9-dihydro-3*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3g) Yellow powder; yield 88%; mp 262–265°C; IR: ν 3446 (NH), 1672 cm^{-1} (C=O); ^{1}H NMR: δ 0.97 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 2.12 (d, 1H, J = 16.1 Hz, one proton of diastereotopic protons in CH_2), 2.22 (s, 3H, CH_3), 2.24–2.34 (m, 4H, a doublet for one proton of diastereotopic protons in CH_2 overlapped with a singlet for CH_3), 2.60 (s, 2H, CH_2), 4.65 (s, 1H, CH), 7.03 (d, 2H, J = 8.0 Hz, H_{Ar}), 7.10 (d, 2H, J = 8.0 Hz, H_{Ar}), 12.54 (s br., 1H, NH); ^{13}C NMR: δ 14.6, 21.0, 21.4, 27.1, 29.0, 32.4, 32.5, 50.5, 102.3, 114.3, 128.4, 129.0, 135.9, 141.4, 158.9, 160.4, 162.5, 164.0, 196.3. Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.70; H, 6.17; N, 8.19.

2-Ethyl-8,8-dimethyl-5-(4-methylphenyl)-8,9-dihydro-3*H*-chromeno[2,3-*d*]pyrimidine-4,6(5*H*,7*H*)-dione (3h) White powder; yield 87%; mp 318–320°C; IR: ν 3433 (NH), 1672 cm^{-1} (C=O); ^{1}H NMR: δ 0.97 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.16 (t, 3H, J = 7.5 Hz, CH_3), 2.12 (d, 1H, J = 16.1 Hz, one proton of diastereotopic protons in CH_2), 2.22 (s, 3H, CH_3), 2.29 (d, 1H, J = 16.1 Hz, one proton of diastereotopic protons in CH_2), 2.50–2.60 (m, 2H, CH_2 overlapped with solvent), 2.62 (s, 2H, CH_2), 4.66 (s, 1H, CH), 7.03 (d, 2H, J = 7.9 Hz, H_{Ar}), 7.10 (d, 2H, J = 7.9 Hz, H_{Ar}), 12.51 (s br., 1H, NH); ^{13}C NMR: δ 11.3, 21.0, 27.2, 27.6, 29.0, 32.4, 32.6, 50.5, 102.5, 114.2, 128.4, 129.0, 135.9, 141.4, 160.5, 162.5, 162.9, 164.1, 196.3. Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.50; H, 6.64; N, 7.69. Found: C, 72.73; H, 6.46; N, 7.88.

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