On the Chemistry of Cinnoline III: Condensation Reactions of (4-Amino-cinnolin-3-yl)-phenyl-methanone and 4-Amino-3-cinnoline-carbonitrile

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(4-Amino-cinnolin-3-yl)-phenyl-methanone condensed with malononitrile, ethyl cyanoacetate, acetylacetone, ethyl acetoacetate, diethyl-malonate and ethyl thioglycolate gave the pyrido[3,2-c]cinnoline derivatives 3a–f respectively. (4-Amino-cinnolin-3-yl)-phenyl-methanone could be annelated to the corresponding 1,2-dihydro-4-phenyl-2-oxopyrido[3,2-c]cinnoline via the (4-acetamido-cinnolin-3-yl)-phenyl-methanone. Treatment of 4-amino-3-cinnoline-carbonitrile 7 with formamide, formic acid, thiourea and phenyl isothiocyanate gave pyrimidino[5,4-c]cinnoline derivatives. 1H-Pyrazolo[4,3-c]cinnoline is also described. Chemical and spectroscopic evidences for the structures of the new compounds are presented.

Key words: cycloadditions, aminonitrile, cinnoline, pyridine, pyrimidine

Heterocyclic annelated pyridazines attract considerable attention, which mainly arises from the large variety of interesting pharmacological activities observed with pyridazine derivatives [1]. The recent discovery [2] of a natural antifungal antibiotic, containing this heteroarene system, (Pyridazmycin) most probably will stimulate even broader interest in 1,2-diazine chemistry. On the other hand, derivatives of cinnolines and their benzo and heterocyclic analogs exhibit biological activity in various areas, including antihypertensive, antithrombotic, antitumor, antisecretory and bactericidal activities [3–6]. 4-Amino-cinnolines became of recent importance due to their antibacterial, antihistamine and insecticde properties [7]. Moreover, in recent years, these derivatives have been extensively utilized as intermediate for the synthesis of fused cinnolines of potential biological activity [8–11]. Previously [12], we reported the synthesis of condensed tricyclic systems of potential biological activity with a cinnoline ring as the central nucleus.

In connection with our interest in the synthetic potential of fused nitrogen heterocyclic compounds [13–14], we report in this paper the utility of (4-amino-cinnolin-3-yl)-phenyl-methanone 1 and 4-amino-3-cyanocinnoline 7 as a synthon for the preparation of new pyrido[3,2-c]cinnolines and pyrimidino[5,4-c]cinnolines with respect to a projected investigation of their utility as pharmacological agents.

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RESULTS AND DISCUSSION

We describe here several new and efficient methods for the synthesis of fused cinnoline derivatives. Cyclocondensation of the (4-amino-cinnolin-3-yl)-phenyl-methanone 1 with active methylene compounds such as malononitrile, ethyl cyano-acetate, acetylacetone, ethyl acetoacetate, diethyl-malonate and ethyl thioglycolate gave the pyrido[3,2-c]cinnoline derivatives 3a–f, respectively. The structures of the obtained compounds 3a–f were confirmed by IR, $^1$H NMR and mass spectra. Treatment of 1 with acetic anhydride under reflux readily afforded (4-acetamido-cinnolin-3-yl)-phenyl-methanone 4, which underwent cyclization to the 1,2-dihydro-4-phenyl-2-oxopyrido[3,2-c]cinnoline 5 in refluxing dimethylformamide in presence of potassium carbonate (Scheme 1).

Scheme 1

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Scheme 1

682 A.M. Amer et al.
We investigated also the reactions of 4-amino-3-cyanocinnoline 7 with formamide and/or formic acid, in which the angular pyrimidocinnoline derivatives 8a,b respectively was obtained. When 8a was treated with acetic anhydride, the corresponding N-acetyl compound 8c was obtained. Compound 8b was obtained from 7 and formamide under condition described in [15]. However, cyclocondensation of 7 with thiourea under fusion condition afforded pyrimidino[5,4-c]cinnoline derivative 8d. Compound 7 reacted with phenyl isothiocyanate in dimethylformamide at room temperature to give N-(3-cyanocinnolin-4-yl)-N'-phenylthiourea, which was transformed into 8e after the treatment with triethylamine in boiling pyridine (Scheme 2). Finally, 2,3-dihydro-3-imino-1H-pyrazolo[4,3-c]cinnoline 9 was prepared by the reaction 7 with an excess of hydrazine hydrate under reflux condition. 9 resulted in conversion of the cyano group into an amidrazone function, which cyclizes intramolecularly by elimination of ammonia. This was supposed by comparing our data for 9 with the pyrazolo[4,3-c]cinnoline already described by Ames [16].

**Scheme 2**

![Chemical structure](image)

<table>
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**EXPERIMENTAL**

Melting points were measured on a Kofler hot microscope (Reichert, Vienna) and are uncorrected. ¹H and ¹³C NMR spectra were recorded on a Bruker DPX 200 spectrometer: chemical shifts are given in δ units relative to internal TMS at 295 K. IR spectra were obtained on Biorad FT–IR-45 instrument. The mass spectra were recorded on a Hewlett Packard 5989 A instrument (70 eV, direct probe inlet). All experiments were carried out with exclusion of moisture. For all newly synthesized compounds satisfactory elemental analyses were obtained.

*General synthesis of pyrido[3,2-c]cinnoline derivatives 3a-f:* A mixture of (4-amino-cinnolin-3-yl)-phenyl-methane [17] 1 (2.49 g, 10 mmol) and active methylene compound (10 mmol) [malononitrile,
ethyl cyanocarboxylate, acetylacetonate, ethyl acetoacetate, diethyl-malonate and ethyl thioglycolate] was refluxed for 3 h in 15 cm³ ethanol and sodium ethoxide (prepared from 0.18 g Na). The solvent was removed under reduced pressure and the residue recrystallized from the given solvent. The following compounds were obtained:

2-Methyl-3-(ethyl-carboxylate)-4-phenyl-pyrido[3,2-c]cinnoline (3a): Crystallization from aqueous ethanol gave orange yellow crystals; yield 1.97 g (67%); m.p.: 245–248°C. IR (KBr): 3446, 3030, 2933, 1738, 1697, 1628, 1589, 1486 cm⁻¹; 1H NMR (DMSO): 7.51–7.61 (m, 4H, H₂₄), 7.79–7.87 (m, 2H, H₂₂), 7.97 (dd, J = 7.8, J = 1.2, 1H, H₂₃), 8.21–8.25 (d, J = 8.0, 1H, H₂⁵), 8.55–8.59 (d, J = 8.0, 1H, H₂₀), 8.96 (br, 2H, NH exchangeable with D₂O). Elemental analysis for C₁₇H₁₁N₃O₃S (305.35), calcd. C, 66.87, H, 3.63, N, 13.76; found: C, 66.92, H, 3.58, N, 13.81.

2-Hydroxyl-3-(ethyl-carboxylate)-4-phenyl-pyrido[3,2-c]cinnoline (3b): Crystallization from methanol gave faint yellow crystals; yield 1.20 g (35%); m.p.: 180–185°C. IR (KBr): 3495, 3382, 2225, 1628, 1589, 1488 cm⁻¹; 1H NMR (DMSO): 7.45–7.60 (m, 4H, H₂₄), 7.78–7.84 (m, 2H, H₂₂), 7.95 (dd, J = 7.8, J = 1.2, 1H, H₂₃), 8.21–8.25 (d, J = 8.0, 1H, H₂₃), 8.55–8.59 (d, J = 8.0, 1H, H₂₀), 12.89 (br, 1H, NH exchangeable with D₂O). Elemental analysis for C₁₇H₁₁N₃O₂ (291.31), calcd. C, 70.09, H, 4.50, N, 14.42; found: C, 70.12, H, 4.60, N, 14.33.

3-Acetyl-2-methyl-4-phenyl-pyrido[3,2-c]cinnoline (3c): Crystallization from aqueous ethanol gave greenish yellow crystals; yield 1.40 g (45%); m.p.: 158–160°C. IR (KBr): 3103, 1700, 1623, 1589, 1500, 1382 cm⁻¹. Elemental analysis for C₂₀H₁₅N₃O (313.36), calcd. C, 76.71, H, 4.78, N, 13.22; found: C, 76.71, H, 4.78, N, 13.22.

2-Methyl-3-(ethyl-carboxylate)-4-phenyl-pyrido[3,2-c]cinnoline (3d): Crystallization from chloroform gave orange yellow crystals; yield 1.20 g (35%); m.p.: 180–185°C. IR (KBr): 3099, 1720, 1632, 1589, 1489, 1377 cm⁻¹; 1H NMR (DMSO): 1.52 (t, J = 7.5, 3H, CH₃(CH₂)₃), 3.10 (s, 3H, CH₃), 4.51 (q, J = 7.5, 2H, CH₂), 7.50–8.79 (m, 9H, H₂₄). Elemental analysis for C₁₇H₁₃N₃O₂ (343.39), calcd. C, 73.45, H, 4.99, N, 12.24; found: C, 73.50, H, 5.10, N, 12.06.

2-Hydroxy-3-(ethyl-carboxylate)-4-phenyl-pyrido[3,2-c]cinnoline (3e): Crystallization from aqueous acetic acid gave yellow crystals; yield 1.20 g (35%); m.p.: 237–240°C. IR (KBr): 3330, 3099, 1728, 1668, 1618, 1589, 1489 cm⁻¹; 1H NMR (DMSO): 1.21 (t, J = 7.5, 3H, CH₃), 4.41 (q, J = 7.5, 2H, CH₂), 7.45–8.75 (m, 9H, H₂₄). Elemental analysis for C₁₇H₁₃N₃O₂ (345.36), calcd. C, 73.45, H, 4.99, N, 12.24; found: C, 73.50, H, 5.10, N, 12.06.

(4-Acetamido-cinnolin-3-yl)-phenyl-methane (4): A solution of (4-amino-cinnolin-3-yl)-phenyl-methane (2.93 g, 10 mmol) in dry dimethylformamide (25 cm³) was heated to boiling, which resulted a dark yellow solution. Within 3 min, needle crystals began to form. After cooling in ice, the product was filtered off and recrystallized from aqueous acetic acid to give brownish grey crystals; yield 2.75 g (95%); m.p.: 160–162°C. IR (KBr): 3446, 3030, 2933, 1738, 1697, 1628, 1589, 1486 cm⁻¹; 1H NMR (DMSO): 2.25 (s, 3H, COCH₃), 7.46–7.62 (m, 2H, H₂₄), 7.77–7.81 (m, 3H, H₂₂), 7.61–7.65 (d, J = 8.0, 2H, H₂₀), 8.29–8.33 (d, J = 8.0, 2H, H₂₀), 1H NMR (DMSO): 26.13 (CH₃), 122.76, 124.00, 128.73, 129.84, 130.63, 133.41, 134.14, 134.26, 134.37, 135.53, 149.26, 151.81 (aryl), 171.79 (C=O), 193.10 (C=O). Elemental analysis for C₁₉H₁₄N₃O₂ (291.31), calcd. C, 70.09, H, 4.50, N, 14.42; found: C, 70.12, H, 4.60, N, 14.33.

1,2-Dihydro-2-oxopyrido[3,2-c]cinnoline (5): To a solution of amide 4 (2.93 g, 10 mmol) in dry dimethylformamide (25 cm³), potassium carbonate (1.40 g) was added and the mixture was heated to 130°C for 2 h. After concentration, the residue is treated with water (30 cm³), the pH is adjusted to 3–4 by addition of 2 N HCl, the precipitated solid is collected, washed with water, and recrystallized from ethanol giving faint yellow crystals; yield 1.97 g (72%); m.p.: 315–321°C. IR (KBr): 3402, 3131, 1654, 1600, 1558, 1492 cm⁻¹; 1H NMR (DMSO): 6.86 (s, 1H, H₂₄), 7.56 (s, 3H, H₂₂), 7.75–7.77 (d, J = 5.1, 2H, H₂₀), 7.98–8.06 (m, 2H, H₂₀), 8.48–8.52 (d, J = 8.0, 1H, H₂₀), 8.91–8.95 (d, J = 8.0, 1H, H₂₀), 11.92 (br, 1H, NH exchangeable with D₂O). 13C NMR (DMSO): 114.00, 122.14, 123.28, 128.05, 128.93, 129.08, 130.12, 131.14, 132.07, 132.69, 133.40, 135.32, 147.15, 151.62, 161.83 (aryl). Elemental analysis for C₁₅H₁₂N₂O (273.30), calcd. C, 74.71, H, 4.06, N, 15.43; found: C, 75.02, H, 3.96, N, 15.25.
Treatment of compound I with thioglycolic acid: formation of 6: A mixture of compound I (2.49 g, 10 mmol) and thioglycolic acid (1.00 g, 10 mmol) in acetic acid (20 cm³) was heated under reflux for 2 h, then allowed to cool to room temperature. The resulting precipitate was collected by filtration, washed with water and recrystallized from acetic acid giving yellowish green crystals; yield 2.65 g (82%); m.p.: 208–210°C. IR (KBr): 3498–3300 br, 1311, 2702, 1672, 1606, 1515 cm⁻¹. The mass spectra gave m/z: 323.25 (100%) [M⁺]; 305, 304, 292, 271, 248, 188, 186, 138, 107, 77, 74, 64, 55, 60. Elemental analysis for C₁₁H₁₀N₂O₂S (323.37), calcd. C, 63.14, H, 4.05, N, 12.99; found: C, 63.20, H, 4.16, N, 12.87.

4-Amino-pyrimidino[5,4-c]cinnoline (8a): A suspension of 4-amino-3-cyanocinnoline (1.7 g, 10 mmol) in formamide (30 cm³) was refluxed for 30 min. The solid product obtained was filtered and washed with water. Crystalization from aqueous acetic acid gave greyish crystals; yield 1.71 g (87%); m.p.: 342–344°C. IR (KBr): 3320 br, 1635, 1589, 1521, 1480, 1230 cm⁻¹. The mass spectra gave m/z: 330.4 (100%) [M⁺]; 293, 271, 261, 236, 214, 205, 150, 126, 84, 80, 77. Elemental analysis for C₁₀H₉N₅O (330.37), calcd. C, 63.14, H, 4.05, N, 22.94; found: C, 63.20, H, 4.16, N, 22.80.

Reaction of 4-amino-3-cyanocinnoline (7) with phenyl isothiocyanate; formation of 8b: To a solution of compound 7 (1.70 g, 10 mmol) in ethanol (20 cm³) and thiourea (0.07 g, 6 mmol) was fused under dry conditions on oil bath at 170–175°C. The solid product so formed after cooling, was dissolved in NaOH solution (10%), filtered off and reprecipitated by hydrochloric acid. The solid formed was crystallized from benzene to give yellow crystals. Yield 1.05 g (46%); m.p.: > 350°C. IR (KBr): 3380, 3280, 3130, 1635, 1550, 1474 cm⁻¹. ¹H NMR (DMSO): 8.07–8.12 (m, 2H, NH); 8.15–8.23 (q, 2H, Har), 8.70–8.74 (d, J = 7.8, 1H, Har), 8.88–8.92 (d, J = 7.9, 1H, Har), 9.25 (s, 1H, Har), 11.37 (s, 1H, NH). ¹³C NMR (DMSO): 25.63 (CH₃), 119.80, 122.48, 127.32, 130.15, 133.26, 141.21, 149.10, 157.13, 159.31 (aryl), 169.54 (C=O). Elemental analysis for C₁₀H₇N₅S (229.26), calcd. C, 52.39, H, 3.07, N, 30.55; found: C, 52.43, H, 3.12, N, 30.48.

4-Acetamido-pyrimidino[5,4-c]cinnoline (8c): A suspension of 8a (5 mmol) in acetic anhydride (10 cm³) was heated to boiling for 5 min. After cooling in ice, the product was filtered off to give 8c which was crystallized from methanol. Yield 1.48 g (62%); yellowish grey crystals; m.p.: 165–168°C. IR (KBr): 3191–3121, 3080, 1713, 1615, 1580, 1490, 1378 cm⁻¹. ¹H NMR (DMSO): 8.10–8.12 (m, 4H, Har), 11.37 (s, 1H, NH). ¹³C NMR (DMSO): 120.94, 124.48, 130.38, 141.21, 149.10, 157.13, 159.31 (aryl), 169.54 (C=O). Elemental analysis for C₁₀H₇N₅S (229.26), calcd. C, 52.39, H, 3.07, N, 30.55; found: C, 52.43, H, 3.12, N, 30.48.

On the chemistry of cinnoline III...
REFERENCES


