Chemistry of Alkylheterocyclic Aromatic \( \pi \)-Deficient Compounds: A Novel Synthesis of Cinnolines

Mohamed Hilmy Elnagdi*, Fatma Abdul Maksoud Abdul-Aal, Nadia M. Taha, and Youssef Mahfouz Yassin

Department of Chemistry, Faculty of Science, Cairo University, Giza, A.R. Egypt

Z. Naturforsch. 45b, 389–392 (1990); received August 28, 1989

Cinnolines, Arylidemalononitrile Derivatives

A novel synthesis of cinnolines by reacting arylidenemalononitrile derivatives with 1-aryl-1,6-dihydro-6-oxo-pyridazin-3,5-dicarbonitriles is reported.

In previous work from our laboratories we have reported new general route to benzofused azines utilizing methylazinylcarbonitriles as starting materials [1–3]. Several polyfunctional phthalazines and quinoxalenes were obtained via this route [2, 3]. In the present paper we report results of our investigation that led to development of a novel synthesis of polyfunctionally substituted cinnolines. Several high yield synthesis of cinnolines are known [4–6]. All these syntheses utilise substituted benzene derivatives as starting materials [5]. None of these can be adopted for synthesis of polyfunctionally substituted cinnolines which are required for screening as potential biodegradable agrochemicals.

The arylhydrazones 1a, b reacted with ethyl cyanoacetate in presence of ammonium acetate to yield the pyridazin-6-one 3,5-dicarbonitriles 2a, b.

Compound 2a reacted with the arylidenemalononitrile derivatives 3a–c to yield products of condensation via hydrogen cyanide elimination. These may be formulated as the cinnolines 4 or phthalazines 5. Structure 5 was ruled out as hydrolysis of the products of reaction of 2a, b with 3a afforded acids which were assigned structure 6 as they proved different from acids 7a, b obtained via hydrolysis of the phthalazines 8a, b, prepared utilizing our recently reported procedure [1]. Moreover, the acid 6a was prepared via an independent route. Thus, condensing 1a with diethyl malonate affords the ethyl pyridazine carboxylate 9. This gave 10 on treatment with ethanolic potassium hydroxide and 10 could be converted to 6a on treatment with 3a, thus confirming the structure assigned for the latter and for compounds 4a–d.

The cinnolines 4a–d could be prepared via condensing 2a, b with aldehydes and subsequent treatment with 3a, thus confirming the structure with 3a, thus confirming the structure assigned for the latter and for compounds 4a–d.

* Reprint requests to Prof. Dr. M. H. Elnagdi.

Verlag der Zeitschrift für Naturforschung, D-7400 Tübingen

0932–0177/90/0300–0389/$ 01.00 0

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\[
\begin{align*}
\text{R} & \quad \text{Ar} = \text{R} = \text{C}_6\text{H}_5 \\
\text{a} & \quad \text{Ar} = \text{R} = \text{C}_6\text{H}_5 \\
\text{b} & \quad \text{Ar} = \text{C}_6\text{H}_4\text{CH}_3 - \text{p}; \quad \text{R} = \text{C}_6\text{H}_5 \\
\text{c} & \quad \text{Ar} = \text{C}_6\text{H}_5; \quad \text{R} = 2\text{-Furyl} \\
\text{d} & \quad \text{Ar} = \text{C}_6\text{H}_4\text{CH}_3 - \text{p}; \quad \text{R} = \text{C}_6\text{H}_5 \\
\end{align*}
\]

was collected by filtration and recrystallized from ethanol.

1,6-Dihydro-4-methyl-6-oxo-1-phenylpyridazin-3,5-dicarbonitrile (2a)

Yellow crystals; yield: 18.9 g (80%); m.p. 148 °C. IR (KBr) = 2240, 2210 (CN); 1680 (CO); 1665 (C=C); 1600 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3)/\text{TMS}_{\text{int}}\) [ppm] = 2.41 and 2.60 (CH\(_3\) and CH\(_2\)) of 2a and tautomeric 3a); 7.20–7.59 (phenyl protons) and 12.22 (OH).

C\(_{15}\)H\(_8\)N\(_4\)O (236.23; M\(^{+}\) 236)
Calcd C 66.09 H 3.41 N 23.72,
Found C 66.10 H 3.30 N 23.60.

1,6-Dihydro-4-methyl-6-oxo-1-p-tolylpyridazin-3,5-dicarbonitrile (2b)

Yellow crystals; yield 20.1 g (80%); m.p. 163 °C. IR (KBr) = 2240, 2200 (CN); 1690 (CO); 1660 (C=C); 1605 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3)/\text{TMS}_{\text{int}}\) [ppm] = 2.29 (3 H, CH\(_3\)); 2.39, 2.58 (CH\(_3\) and CH\(_2\)) for both 2b and 3b); 7.20–7.47 (4H, Arom. H) and 12.18 (OH).

Method B

A mixture of 1a, b (0.1 mole); ethyl cyanoacetate (11.3 g, 0.1 mole); ammonium acetate (1.155 g, 0.015 mole); glacial acetic acid (2.5 ml) and dry benzene (50 ml) was heated under reflux using water separator, in an oil bath at 160 °C for 20 h, and then left to cool to room temperature. The solid product, so formed, was filtered off, dried, recrystallized from ethanol and identified by (m.p. and mixed m.p.) as well as by IR as 2a, b. Yield was 80% for each of 2a, b.

8-Amino-2,6-diaryl-2,3-dihydro-3-oxocinnolin-4,7-dicarbonitrile (4a–c)

General procedure: A solution of 2a (2.36 g, 0.01 mole) (30 ml), piperidine (1 ml) and the appropriate arylidenemalononitrile derivatives 3a–c (0.01 mole) in pyridine was heated under reflux for 4 h. The reaction mixture was left to cool to room temperature and poured onto ice-cold water acidified with hydrochloric acid (1 ml, 36%). The solid product so formed on standing was filtered off and recrystallized from dioxane.

8-Amino-2,3-dihydro-2,6-diphenyl-3-oxocinnolin-4,7-dicarbonitrile (4a)

Yellow-green crystals; yield: 2.7 g (75%); m.p. >270 °C. IR (KBr) = 3460, 3320 (NH\(_2\)); 2210 (CN); 1670 (CO); 1605 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3)/
TMS$_\text{dm}$ [ppm] = 3.32 (br, 2H, NH$_2$); 6.9 (s, 1H cinnoline H-5); 7.49–7.69 (m, 10H, Arom. H).

$^1$H NMR (CDCl$_3$/TMS$_{\text{dm}}$) [ppm] = 3.32 (br, 2H, NH$_2$); 6.9 (s, 1H cinnoline H-5); 7.49–7.69 (m, 10H, Arom. H).

C$_{22}$H$_{13}$N$_4$O$_3$ (363.4; M$^+$ = 363)

8-Amino-2,3-dihydro-6-p-methoxyphenyl-3-oxo-2-phenylcinnolin-4,7-dicarbonitrile (4b)
Yellow green crystals; yield 2.9g (75%); m.p. >270 °C. IR (KBr) = 3480, 3410 (NH$_2$); 2210 (CN); 1670 (CO); 1610 cm$^{-1}$. $^1$H NMR (CDCl$_3$/TMS$_{\text{dm}}$) [ppm] = 3.2 (br, 2H, NH$_2$); 3.86 (s, 3H, OCH$_3$); 6.87 (s, 1H cinnoline H-5); 7.13–7.16 (d, 2H, anizyl ortho H) and 7.49–7.65 (m, 7H, Arom. H).

C$_{20}$H$_{15}$N$_4$O$_2$ (393.3)
Calcd C 70.22 H 3.84 N 17.80, Found C 70.10 H 3.90 N 17.60.

8-Amino-2,3-dihydro-6-(2-furyl)-3-oxo-2-phenylcinnolin-4,7-dicarbonitrile (4c)
Brown crystals; yield 2.5 g (70%); m.p. >270 °C. IR (KBr) = 3460-3200 (NH$_2$); 2210 (CN); 1690 (CO) cm$^{-1}$.

C$_{20}$H$_{15}$N$_5$O$_2$ (353.3)

8-Amino-2,3-dihydro-3-oxo-6-phenyl-2-p-tolyl-cinnolin-4,7-dicarbonitrile (4d)
The general procedure is followed using 2b (2.5 g, 0.01 mole) and phenylidenemalononitrile (1.54 g, 0.01 mole). The crude solid product is recrystallized from dioxane as yellow green crystals; yield 3.8 g (75%); m.p. >270 °C. IR (KBr) = 3460, 3310 (NH$_2$); 2210 (CN); 1670 (CO); 1610 cm$^{-1}$.

C$_{23}$H$_{15}$N$_4$O$_3$ (377.4)
Calcd C 73.19 H 4.01 N 18.56, Found C 73.10 H 4.10 N 18.60.

8-Amino-7-cyano-1,2-dihydro-2,6-diaryl-1-oxophthalazin-4-carboxylic acid (6a, b)
Orange crystals; yield 2.9 g (76%); m.p. 240 °C. IR (KBr) = 4390–2800 (NH$_2$, polymeric OH); 2210 (CN); 1670–1710 (CO); 1660 cm$^{-1}$. $^1$H NMR (DMSO/TMS$_{\text{dm}}$) [ppm] = 7.45–7.6 (m, Arom. H and phthalazin H-5) and 13.94 (br, H, OH).

C$_{22}$H$_{14}$N$_4$O$_3$ (382.36)

8-Amino-7-cyano-1,2-dihydro-1-oxo-6-phenyl-2-p-tolylphthalazin-4-carboxylic acid (7b)
Orange crystals; yield 3.0 g (70%); m.p. >270 °C. IR (KBr) = 3460–3360 (NH$_2$, OH); 2210 (CN); 1660 (CO); 1615 cm$^{-1}$.

C$_{23}$H$_{16}$N$_4$O$_3$ (396.39)

Reaction of 10a, b with 3a
Compounds 6a, b were obtained in 80% yield via refluxing equimolecular amounts of acid 10a, b and 3a in pyridine solution for 2 h then pouring the resulting solution over water, collecting formed solid and recrystallizing it from ethanol.

8-Amino-7-cyano-2,3-dihydro-2,6-diphenyl-3-oxocinnolin-4-carboxylic acid (6a)
Brown crystals; yield 3.1 g (80%); m.p. >270 °C. IR (KBr) = 3460–2800 (NH$_2$, polymeric OH); 2210 (CN); 1660 (CO); 1600 cm$^{-1}$.

C$_{22}$H$_{14}$N$_4$O$_3$ (382.32)

8-Amino-7-cyano-2,3-dihydro-2,6-diphenyl-3-oxocinnolin-4-carboxylic acid (6b)
Brown crystals; yield 2.97 g (75%); m.p. 205 °C. IR (KBr) = 3460–2600 (NH$_2$, polymeric OH); 2210 (CN); 1660 (CO) cm$^{-1}$.

C$_{23}$H$_{16}$N$_4$O$_3$ (396.39)

Ethyl-3-cyano-1-phenyl-4-methyl-1,6-dihydro-6-oxopyridazin-3-carboxylate (9)
A suspension of 1a (2.9 g, 0.01 mole) in benzene (50 ml) was heated with diethyl malonate (1.32 g, 0.01 mole), NH$_4$OAc (3.0 g), and AcOH (2 ml). The reaction flask was fitted with a water separa-
tor and the mixture refluxed till no more water was collected (ca. 26 h). The benzene was then decanted and the resulting product was triturated with water. The solid product, so formed, was collected by filtration and recrystallized from ethanol. The ester formed yellow crystals; m.p. 168°C; yield 2.3 g, 80%. IR (KBr = 1750 (CO); 1690 (ring CO); 2220 (CN) and 1630 (C=N) cm⁻¹.

C₁₃H₁₃N₃O₂ (283.28)
Caled C 63.59 H 4.62 N 14.83,
Found C 63.5 H 4.5 N 14.8.

3-Cyanoo-1,6-dihydro-4-methyl-1-phenyl-6-oxopyridazin-3-carboxylic acid (10)

A solution of 9 (2.8 g, 0.01 mole), 3 ml of water and 2 ml of HCl (36%) in ethanol (30 ml) was heated to boiling, then left to cool to room temperature and poured onto water. The solid product, so formed, was collected by filtration and recrystallized from ethanol. Yellow crystals; m.p. 204°C; yield 1.9 g (75%). IR (KBr) = 3400-3050 (br, OH); 2940 (CH₃); 2240 (CN); 1730 (CO); 1700-1620 (CO ring, C=N, C=C) cm⁻¹.

C₁₃H₉N₃O₃ (255.23)
Caled C 61.17 H 3.55 N 16.46,
Found C 61.1 H 3.5 N 16.5.

Reaction of 2a, b with aromatic aldehydes

A solution of 2a, b (0.01 mole) and the appropriate aromatic aldehydes in pyridine (30 ml) was heated under reflux for 4 h, and left to cool to room temperature. The reaction mixture was then poured onto ice-cold water, acidified with hydrochloric acid (1 ml, 36%), and the solid product, formed on standing, was collected by filtration and recrystallized from dioxane-ethanol mixture.

1-Aryl-1,6-dihydro-6-oxo-4-styrylpyridazin-5,6-dicarbonitrile (11a)

Compound 11a afforded brownish crystals; yield 2.27 g (70%); m.p. 225°C. IR (KBr) = 2240, 2220 (CN); 1690 (CO); 1630 (C=C) cm⁻¹. ¹H NMR (DMSO/TMSₙ) [ppm] = 7.27, 7.32 (d, J = 16.52 Hz, styryl H); 7.55-7.80 (Arom. H); 7.88, 7.93 (d, J = 16.52 Hz, styryl H).

C₁₃H₁₀N₄O (324.33; M⁺ = 324)
Caled C 74.06 H 3.73 N 16.48,
Found C 74.1 H 3.80 N 16.5.

Compound 11b afforded brown crystals; yield 2.48 g (70%); m.p. 200°C. IR (KBr) = 2220 (CN); 1680 (CO); 1620 (C=C) cm⁻¹.

C₁₈H₁₄N₄O (354.35)
Caled C 71.17 H 3.98 N 15.81,
Found C 71.20 H 4.10 N 15.7.

Compound 11c afforded brown crystals; yield 2.2 g (70%); m.p. 250°C. IR (KBr) = 2240, 2220 (CN); 1700-1650 (CO); 1630-1600 (C=C) cm⁻¹.

C₁₈H₁₀N₄O (314.29)
Caled C 74.54 H 4.17 N 16.56,
Found C 74.6 H 4.10 N 16.7.

Compound 11d afforded brown crystals; yield 2.4 g (70%); m.p. 223°C. IR (KBr) = 2240, 2220 (CN); 1680 (CO); 1630 (C=C) cm⁻¹.

C₁₆H₁₄N₄O (338.35)
Caled C 74.54 H 4.17 N 16.56,
Found C 74.6 H 4.10 N 16.7.

Reaction of 11a–d with malononitrile

A solution of malononitrile (0.66 g, 0.01 mole) and piperidine (1 ml) in pyridine (10 ml) was added to a solution of 11a–d (0.01 mole each) in pyridine (30 ml). The reaction mixture was heated under reflux for 4 h, then left to cool to room temperature, poured on ice-cold water acidified with hydrochloric acid (1 ml, 36%) and the solid product, so formed on standing were collected by filtration and recrystallized from dioxane-ethanol mixture to yield products 4a–d in 70, 75, 72 and 70% yields, respectively.

The authors are grateful to Prof. Dr. K. Hafner at the Technische Hochschule Darmstadt, for measurement of ¹H NMR and MS spectra.