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# On the Chemistry of Cinnoline I. Synthesis and Reactions of (4-Amino-cinnolin-3-yl)-*p*-tolyl-methanones

**Atef M. Amer**[1,*], **Mohamed A. El-Bermaui**[2], **Ahmed F. S. Ahmed**[1], and **Somya M. Soliman**[1]

[1] Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt
[2] Organic Chemistry Department, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt

**Summary.** The synthesis of a series of (4-Amino-cinnolin-3-yl)-*p*-tolyl-methanones from arylhydrazonomalononitrile in a one step procedure is reported. The (4-amino-cinnolin-3-yl)-*p*-tolyl-methanones could be annelated to the corresponding 1,2-dihydro-4-(*p*-tolyl)-2-oxopyrido[3,2-*c*]cinnoline derivatives *via* (4-acetamido-cinnolin-3-yl)-*p*-tolyl-methanones. Treatment of 1,2-dihydro-9-methyl-4-(*p*-tolyl)-pyrido[3,2-*c*]cinnoline-2-one with $POCl_3$ and $P_2S_5$ gave 2-chloro-9-methyl-4-(*p*-tolyl)-pyrido[3,2-*c*]cinnoline and 1,2-dihydro-9-methyl-4-(*p*-tolyl)-pyrido[3,2-*c*]cinnoline-2-thione. Treatment of the ketone with malononitrile afforded 2-amino-3-cyano-9-methyl-4-(*p*-tolyl)-pyrido[3,2-*c*]cinnoline. Using these ketones, a facile and convenient route towards substituted pyrimidino[5,4-*c*]-cinnolines was developed. Chemical and spectroscopic evidences for the structures of the new compounds are presented.

**Keywords.** Cycloadditions; Hydrazones; Cinnolines; Pyridines; Pyrimidines.

### Zur Chemie der Cinnoline, 1. Mitt. Synthese und Reaktionen von (4-Amino-cinnolin-3-yl)-*p*-tolyl-methanonen

**Zusammenfassung.** Die Synthese einer Reihe von (4-Amino-cinnolin-3-yl)-*p*-tolyl-methanonen aus Arylhydrazonomalonitrilen in einem Schritt wird beschrieben. Die Edukte wurden über die (4-Acetamido-cinnolin-3-yl)-*p*-tolyl-methanone zu den entsprechenden 1,2-Dihydro-4-(*p*-tolyl)-2-oxopyprido[3,2-*c*]cinnolinderivaten anelliert. Behandlung der 1,2-Dihydro-9-methyl-4-(*p*-tolyl)-pyrido[3,2-*c*]cinnolin-2-one mit $POCl_3$ bzw. $P_2S_5$ ergab 2-Chlor-9-methyl-4-(*p*-tolyl)-pyrido[3,2-*c*]cinnolin und 1,2-Dihydro-9-methyl-4-(*p*-tolyl)-pyrido[3,2-*c*]cinnolin-2-thion. Umsetzung dieses Ketons mit Malonitril lieferte 2-Amino-3-cyano-9-methyl-4-(*p*-tolyl)-pyrido[3,2-*c*]cinnolin. Mit Hilfe dieser Edukte wurde eine einfache Route zu substituierten Pyrimidino[5,4-*c*]cinnolinen eröffnet. Chemische und spektroskopische Evidenzen für die Struktur der neuen Verbindungen werden mitgeteilt.

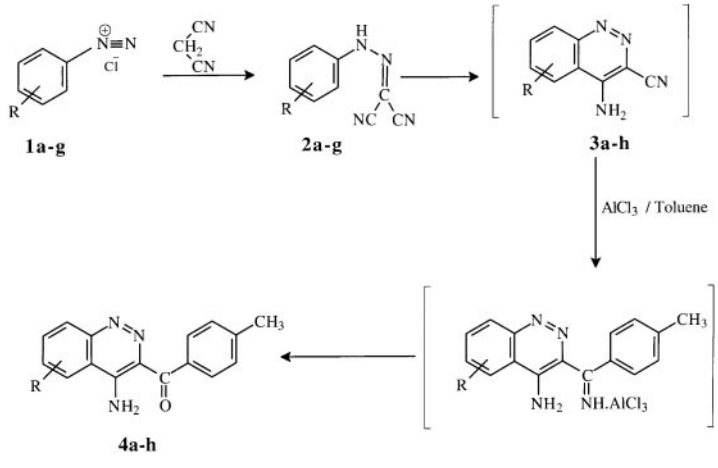
* Corresponding author

## Introduction

Cinnoline is toxic and shows antibacterial activity towards *Escherichia coli* [1]. Neither itself not its derivatives have yet been found in nature [2]. Derivatives of cinnolines and their benzo and heterocyclic analogs exhibit biological activity in various areas, including antihypertensive, autihrombotic, antitumor, antisecretory, and bactericidal activities [3–6]. 4-Aminocinnolines recently became important due to their antibacterial, antihistaminic and insecticidic properties [7]. Moreover, in recent years these derivatives have been extensively utilized as intermediates for the synthesis of fused cinnolines of potential biological activity [8–11]. *Gewald et al*. [12] have reported that the intramolecular *Friedel-Crafts* reaction of aryl hydrazone derivatives yields cinnolines. In connection with these findings and prompted by our ongoing our interest in the synthetic potential of fused nitrogen containing heterocyclic compounds [13–16] we now describe a convenient method for the synthesis of (4-amino-cinnolin-3-yl)-*p*-tolyl-methanones **4a–h** as starting materials and some substituted fused cinnoline systems like the pyrido[3,2-*c*]cinnolines **6–10** and the pyrimidino[5,4-*c*]cinnolines **11–14** with respect to a projected investigation of their utility as pharmacological agents.

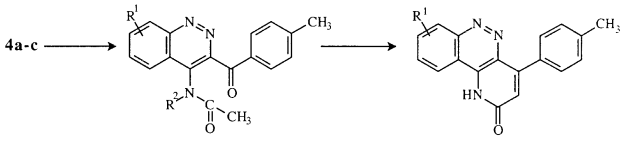
## Results and Discussion

The intention of this investigation was to explore the scope and limitations of the *Gewald* procedure as a synthetic method for the formation of (cinnolin-3-yl)-aryl-methanones **4a–h** bearing various substituents as well as to study the effect of the substituent at the aryl group during the cyclization of the aryl hydrazonomalononitriles **2a–g**. For this purpose, aryl-hydrazonomalononitriles **2a–g** were synthesized in good yield by treatment of malononitrile with diazonium salts **1a–g** obtained from the corresponding aniline derivatives (*o*-, *m*-, *p*-toluidine, 4-




**1a**, **2a**: $R = 2\text{-}CH_3$ **4a**: $R = 8\text{-}CH_3$ **1d**, **2d**: $R = 4\text{-Br}$ **4d**: $R = 6\text{-Br}$
**1b**, **2b**: $R = 3\text{-}CH_3$ **4b**: $R = 7\text{-}CH_3$ **1e**, **2e**: $R = 4\text{-}OCH_3$ **4e**: $R = 6\text{-}OCH_3$
**1c**, **2c**: $R = 4\text{-}CH_3$ **4c**: $R = 6\text{-}CH_3$ **1f**, **2f**: $R = 4\text{-}NO_3$ **4h**: $R = 6\text{-OH}$
**1g**, **2g**: $R = 4\text{-COOH}$

**Scheme 1**




| | | |
|---|---|---|
| **4a–6a** | $R^1 = 8\text{-}CH_3$ | $R^2 = H$ |
| **4b–6b** | $R^1 = 7\text{-}CH_3$ | $R^2 = COCH_3$ |
| **4c–6c** | $R^1 = 6\text{-}CH_3$ | $R^2 = COCH_3$ |

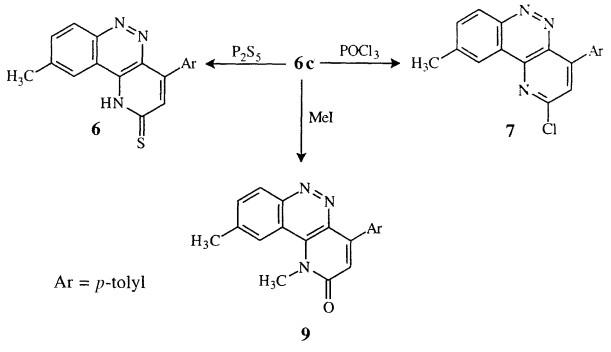
**Scheme** 14102

bromoaniline, 4-methoxyaniline, 4-nitroaniline, 4-aminobenzoic acid). It was found that the (4-amino-cinnolin-3-yl)-*p*-tolyl-methanones **4a–h** could be readily obtained *via* cyclization of **2a–g** in the presence of $AlCl_3$ and toluene under reflux (Scheme 1). As to the mechanism, we propose that an intramolecular *Friedel-Crafts* cyclization first gives **3a–h**. Then, condensation of the cyano group at position 3 of **3a–h** with toluene in the presence of the *Lewis* acid leads to the corresponding ketones **4a–h** in a reaction of the *Hoesch* type [17]. We found that only ketone **4h** could be isolated in the case of **2e** instead of **4e** due to a demethylation by $AlCl_3$. The structure of **4h** was deduced from its $^1H$ NMR spectrum where the signal corresponding to the methoxy group was absent.

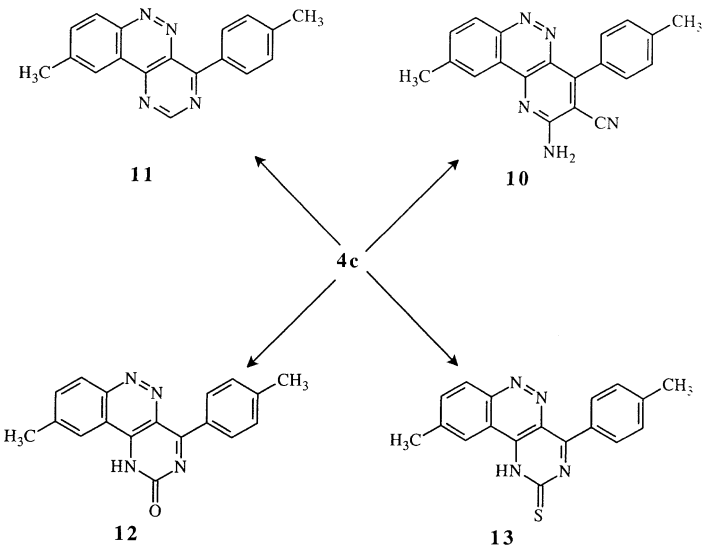
Strong electron withdrawing substituents, such as the nitro and the carboxylic group in **2**, retarded cyclization of **2** considerably, even at higher temperatures. In these cases, **2** could be partially recovered.

Having now available the ketones **4** as starting materials, we continued our efforts directed towards the synthesis of bi- and tricyclic systems containing a pyridazine subunit [18–19]. The method described provides a possible starting point for the synthesis of many new fused cinnoline derivatives. Treatment of the (4-amino-cinnolin-3-yl)-*p*-tolyl-methanones **4a–c** with acetic anhydride under reflux readily afforded the 4N-acetylated ketones **5a–c** which underwent cyclization to the pyrido[3,2-*c*]cinnoline derivatives **6a–c** in dimethylformamide solution in the presence of potassium carbonate at reflux temperature.

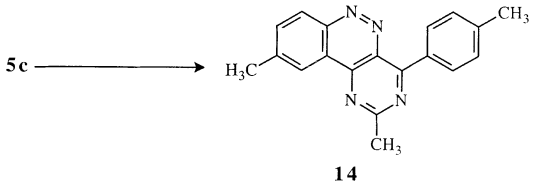
Treatment of **6c** with $POCl_3$ and $P_2S_5$ under reflux afforded the corresponding 2-chloro-pyrido[3,2-*c*]cinnoline **7** and pyrido[3,2-*c*]cinnoline-2-thione **8**. Interestingly enough, **6c** was regioselectively methylated in position 1 upon treatment with $CH_3I$/KOH to yield **9** (Scheme 3).




**Scheme 3**




**Scheme 4**




**Scheme 5**

The reaction of **4c** with malononitrile was carried out under basic conditions to give the corresponding cyclic product **10**. Finally, our study was extended to prepare the pyrimido[5,4-*c*]cinnoline derivatives **11–14** with the aim to improve the antibacterial activity relative to the same systems prepared earlier [8]. When **4c** was reacted with formamide, urea, or potassium isothiocyanate, the cinnolines **11**, **12**, and **13** were obtained (Scheme 4).

Treatment of cinnoline **5c** with ammonium acetate in presence of $NH_3$ afforded 2,9-dimethyl-4-(*p*-tolyl)-pyrimido[5,4-*c*]cinnoline **14** (Scheme 5). The structures of all novel compounds were confirmed by their elemental and spectroscopic data.

## Experimental

Melting points were measured on a Kofler hot stage microscope (Reichert, Vienna) and are uncorrected. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker DPX 200 spectrometer; chemical shifts are given in $\delta$ units relative to internal *TMS* at 295 K. IR spectra were obtained on Biorad FT-IR-45 instrument. All experiments were carried out with exclusion of moisture. For all newly synthesized compounds, satisfactory elemental analyses were obtained.

*Preparation of aryl-hydrazonomalononitriles* **2**; *general procedure*

To a well stirred solution of 6.60 g malononitrile (100 mmol) in 130 $cm^3$ ethanol and 20 $cm^3$ $H_2O$ containing 10 g $CH_3COONa$, the diazonium salt (100 mmol) prepared in the usual way from the

corresponding anilines was added gradually with stirring during 20 min at 0–5°C. The product was filtered, washed with water, dried, and recrystallized from the given solvent.

*2-Tolyl-hydrazonomalononitrile* (**2a**; $C_{10}H_8N_4$)

Prepared from *o*-toluidine; crystallization from ethanol gave fine orange crystals (95%); m.p.: 96°C; IR (KBr): 3350 br, 3199, 2920 br, 2218, 1610, 1532, 1480 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): 2.42 (s, $CH_3$), 7.18–7.32 (m, $3H_{ar}$), 7.51–7.55 (d, $1H_{ar}$), 9.65 (br, NH) ppm.

*3-Tolyl-hydrazonomalononitrile* (**2b**; $C_{10}H_8N_4$)

Prepared from *m*-toluidine; crystallization from ethanol gave fine yellow crystals (98%); m.p.: 198°C; IR (KBr): 3350 br, 3198, 2920 br, 2218, 1608, 1474 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): 2.41 (s, $CH_3$), 7.10–7.16 (m, $3H_{ar}$), 7.32 (s, $1H_{ar}$), 9.85 (br, NH) ppm; $^{13}C$ NMR ($CDCl_3$): 31.01 ($CH_3$), 95.75 (CH), 117.97, 122.23, 122.51, 126. 74, 137.28, 141.84. 154.00, 154.59 (aryl, 2CN) ppm.

*4-Tolyl-hydrazonomalononitrile* (**2c**; $C_{10}H_8N_4$)

Prepared from *p*-toluidine; crystallization from methanol gave fine yellow crystals (98%); m.p.: 158–160°C; IR (KBr): 3350 br, 3198, 2921, 2218, 1608, 1480 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): 2.37 (s, $CH_3$), 7.22 (s, $4H_{ar}$), 9.90 (br, NH) ppm; $^{13}C$ NMR ($CDCl_3$): 30.55 ($CH_3$), 95.30 (CH), 118.09, 121.97, 125.58, 140.01, 146.58, 147.10 (aryl, 2CN) ppm.

*4-Bromophenyl-hydrazonomalononitrile* (**2d**; $C_9H_5BrN_4$)

Prepared from 4-bromoaniline; crystallization from ethyl acetate gave fine crystals (80%); m.p.: 190°C; IR (KBr): 3343 br, 3195, 2218, 1610, 1480, 1450 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): 7.19–7.23 (d, $2H_{ar}$), 7.54–7.58 (d, $2H_{ar}$), 9.75 (br, NH) ppm; $^1H$ NMR ($CDCl_3$/*DMSO*-$d_6$): 7.29–7.42 (m, $4H_{ar}$), 12.76 (br, NH) ppm; $^{13}C$ NMR ($CDCl_3$/*DMSO*-$d_6$): 94.82 (CH), 119.23, 123.31, 127.95, 128.23, 141.87, 150.33 (aryl, 2CN) ppm.

*4-Methoxyphenyl-hydrazonomalononitrile* (**2e**; $C_{10}H_8N_4O$)

Prepared from 4-methoxyaniline; crystallization from petroleum ether gave greenish yellow crystals (93%); m.p.: 136–138°C; IR (KBr): 3353 br, 3194, 2950 br, 2220, 1610, 1477, 1410 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): 3.85 (s, $OCH_3$), 6.94–6.98 (d, $2H_{ar}$), 7.27–7.32 (d, $2H_{ar}$), 10.08 (br, NH) ppm; $^{13}C$ NMR ($CDCl_3$): 55.63 ($OCH_3$), 84.67 (CH), 109.00, 112.76, 115.05, 117.58, 129.32, 158.49 (aryl, 2CN) ppm.

*4-Nitrophenyl-hydrazonomalononitrile* (**2f**; $C_9H_5N_5O_2$)

Prepared from 4-nitroaniline; crystallization from ethanol gave fine yellow crystals (75%); m.p.: 180°C; IR (KBr): 3329 br, 3198, 2223, 1610, 1527, 1478 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): 7.61–7.65 (d, $2H_{ar}$), 8.29–8.33 (d, $2H_{ar}$) ppm; $^1H$ NMR (*DMSO*-$d_6$): 7.58–7.62 (d, $2H_{ar}$), 8.22–8.27 (d, $2H_{ar}$) ppm; $^{13}C$ NMR (*DMSO*-$d_6$): 98.51 (CH), 119.48, 123.84, 126.71, 135.52, 153.91, 156.84 (aryl, 2CN) ppm.

*4-Phenyl-hydrazonomalononitrile-carboxylic acid* (**2g**; $C_{10}H_6N_4O_2$)

Prepared from 4-amino-benzoic acid; crystallization from acetic acid gave fine yellow crystals (87%); m.p.: 260–262°C; IR (KBr): 3330 br, 3197, 2950 br, 2222, 1610, 1480, 1450 $cm^{-1}$; $^1H$ NMR

(*DMSO*-$d_6$): 7.49–7.53 (d, $2H_{ar}$), 7.93–7.97 (d, $2H_{ar}$), 13.00 (br, OH) ppm; $^{13}C$ NMR (*DMSO*-$d_6$): 96.63 (CH), 119.64, 124.04, 126.13, 140.96, 154.81, (aryl, 2CN), 176.65 (C=O) ppm.

*Preparation of (4-Amino-cinnolin-3-yl)-p-tolyl-methanones* **4**; *general procedure*

A mixture of 10 mmol aryl hydrazonomalononitrile **2** and 2.50 g $AlCl_3$ (0.04 mmol) in 150 $cm^3$ toluene was heated under reflux for 5 h with stirring and then allowed to cool to room temperature. The resulting product was poured on 500 $cm^3$ cold water and left for 2 h. The resulting solid product was collected by filtration, washed with petroleum ether (40–60°), and crystallized from the solvent given.

*(4-Amino-8-methyl-cinnolin-3-yl)-p-tolyl-methanone* (**4a**; $C_{17}H_{15}N_3O$)

Prepared from **2a**; crystallization from methanol gave greenish white crystals (89%); m.p.: 160°C; IR (KBr): 3340 br, 3131, 2974, 1631, 1606, 1566, 1526, 1474 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): 2.41 (s, $CH_3$), 3.00 (s, $CH_3$), 7.24–7.27 (d, $2H_{ar}$), 7.51–7.58 (t, $1H_{ar}$), 7.66–7.69 (d, $1H_{ar}$), 7.80–7.84 (d, $1H_{ar}$) 7.98–8.02 (d, $2H_{ar}$) ppm; $^{13}C$ NMR ($CDCl_3$): 27.79 ($CH_3$), 31.21 ($CH_3$), 125.40, 127.53, 137.77, 138.10, 138.54, 140.70, 142.28, 143.14, 145.67, 148.20, 151.89, 154.86 (aryl), 206.59 (C=O) ppm.

*(4-Amino-7-methyl-cinnolin-3-yl)-p-tolyl-methanone* (**4b**; $C_{17}H_{15}N_3O$)

Prepared from **2b**; crystallization from methanol gave white crystals (89%); m.p.: 270–272°C; IR (KBr): 3337 br, 3125, 2973, 2920, 1630, 1566, 1526, 1474, 1422, 1410, 1385 $cm^{-1}$; $^1H$ NMR (*DMSO*-$d_6$): 2.40 (s, $CH_3$), 2.57 (s, $CH_3$), 7.30–7.34 (d, $2H_{ar}$), 7.60–7.65 (d, $1H_{ar}$), 7.78–7.82 (d, $2H_{ar}$), 8.03 (s, $1H_{ar}$), 8.43 (d, $1H_{ar}$), 8.47 (br, $NH_2$) ppm; $^{13}C$ NMR (*DMSO*-$d_6$): 31.16 ($CH_3$), 31.36 ($CH_3$), 123.87, 132.70, 137.34, 138.22, 140.66, 140.93, 143.13, 146.46, 151.57, 153.24, 155.55, 157.33 (aryl), 205.70 (C=O) ppm.

*(4-Amino-6-methyl-cinnolin-3-yl)-p-tolyl-methanone* (**4c**; $C_{17}H_{15}N_3O$)

Prepared from **2c**; crystallization from ethanol gave faint yellowish white crystals (89%); m.p.: 288–290°C; IR (KBr): 3344, 3131, 3032, 2932, 1630, 1610, 1560, 1528, 1474 $cm^{-1}$; $^1H$ NMR (*DMSO*-$d_6$): 2.39 (s, $CH_3$), 2.54 (s, $CH_3$), 7.28–7.32 (d, $2H_{ar}$), 7.77–7.80 (d, $3H_{ar}$), 8.12–8.16 (d, $1H_{ar}$), 8.34 (s, $1H_{ar}$), 8.80 (br, $NH_2$) ppm; $^{13}C$ NMR (*DMSO*-$d_6$): 31.16 ($CH_3$), 31.52 ($CH_3$), 125.92, 131.57, 135.44, 138.22, 138.63, 140.68, 143.01, 146.53, 149.12, 151.56, 155.11, 156.12 (aryl), 205.91 (C=O) ppm.

*(4-Amino-6-bromo-cinnolin-3-yl)-p-tolyl-methanone* (**4d**; $C_{16}H_{12}BrN_3O$)

Prepared from **2d**; crystallization from ethanol gave yellow crystals (89%); m.p.: >360°C; IR (KBr): 3310, 3228, 3030, 2920, 1635, 1590, 1550, 1530 $cm^{-1}$; $^1H$ NMR ($CD_3OD$): 2.46 (s, $CH_3$), 7.37–7.41 (d, $2H_{ar}$), 7.55–7.68 (m, $5H_{ar}$) ppm; $^1H$ NMR (*DMSO*-$d_6$): 2.39 (s, $CH_3$), 7.35–7.39 (d, $2H_{ar}$), 7.56–7.74 (m, $5H_{ar}$), 8.34 (s, $1H_{ar}$), 8.80 (br, $NH_2$) ppm.

*(4-Amino-6-hydroxy-cinnolin-3-yl)-p-tolyl-methanone* (**4h**; $C_{16}H_{13}N_3O_2$)

Prepared from **2e**; crystallization from ethanol gave orange yellow crystals (89%); m.p.: 208–210°C; IR (KBr): 3563 br, 3380, 3030, 1637, 1600, 1570, 1520, 1416 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): 2.46 (s, $CH_3$), 5.18 (br, $NH_2$), 6.89–6.93 (d, $2H_{ar}$), 7.33–7.37 (d, $2H_{ar}$), 7.41 (br, OH), 7.67–7.71 (m, $3H_{ar}$) ppm.

*Acetylation of (4-amino-cinnolin-3-yl)-p-tolyl-methanones* **4**; *general procedure*

A solution of 2.77 g of **4a–c** (10 mmol) in 15 $cm^3$ acetic anhydride was heated to boiling, which resulted a dark yellow solution. Within 5 min, needles began to form. After cooling in ice, the product was filtered off to give pure **5a** or a mixture of the 4-diacetylaminocinnolines **5b**,**c**, respectively. The latter crude product was used for the next step without further purification.

*(4-Acetamido-8-methyl-cinnolin-3-yl)-p-tolyl-methanone* (**5a**: $C_{21}H_{20}N_3O_2$)

Prepared from **4a**; crystallization from acetic acid and $H_2O$ gave yellowish crystals (85%); m.p.: 160°C; IR (KBr): 3446, 3130, 2932, 1712, 1690, 1625, 1580, 1490 $cm^{-1}$; $^1$H NMR ($CDCl_3$): 2.29 (s, $COCH_3$), 2.43 (s, $CH_3$), 2.70 (s, $CH_3$), 7.29–7.82 (m, $5H_{ar}$), 8.01 (d, $2H_{ar}$) ppm.

*(4-Diacetamido-7-methyl-cinnolin-3-yl)-p-tolyl-methanone* (**5b**; $C_{23}H_{22}N_3O_3$)

Prepared from **4b**; crystallization from ethanol gave yellowish crystals (57%); m.p.: 130°C; IR (KBr): 3130, 2940, 1737, 1698, 1623, 1580, 1474 $cm^{-1}$; $^1$H NMR ($CDCl_3$): 2.32 (s, $2COCH_3$), 2.47 (s, $CH_3$), 2.73 (s, $CH_3$), 7.30 (d, $2H_{ar}$), 7.79–7.83 (m, $3H_{ar}$), 8.52 (s, $H_{ar}$), 8.80 (d, $H_{ar}$) ppm.

*(4-Diacetamido-6-methyl-cinnolin-3-yl)-p-tolyl-methanone* (**5c**; $C_{23}H_{22}N_3O_3$)

Prepared from **4c**; crystallization from ether gave faint reddish crystals (65%); m.p.: 125°C; IR (KBr): 3130, 2932, 1739, 1697, 1624, 1580, 1490 $cm^{-1}$; $^1$H NMR ($CDCl_3$): 2.32 (s, $2COCH_3$), 2.43 (s, $CH_3$), 2.66 (s, $CH_3$), 7.29 (d, $2H_{ar}$), 7.63 (s, $H_{ar}$), 7.78 (m, $3H_{ar}$), 8.61 (d, $H_{ar}$) ppm; $^{13}$C NMR ($CDCl_3$): 31.42 ($CH_3$), 32.16 ($CH_3$), 36.03 ($2COCH_3$), 129.07, 134.38, 138.56, 138.78, 140.06, 140.81, 142.73, 142.85, 144.48, 154.78, 159.57, 160.82 (aryl), 181.85 (2C=O), 201.59 (C=O) ppm.

*Preparation of 1,2-dihydro-4-(p-tolyl)-2-oxopyrido[3,2,c]cinnolines* **6**; *general procedure*

To a solution of 3.20 g of crude amide **5a–c** (10 mmol) in 25 $cm^3$ dry *DMF*, 1.4 g $K_2CO_3$ were added and the mixture was heated for 2 h. After concentration, the residue was treated with 30 $cm^3$ $H_2O$. The *pH* was adjusted to 3–4 by addition of 2 *N* HCl, and the precipitated solid was collected, washed with $H_2O$, and recrystallized from the given solvent.

*1,2-Dihydro-7-methyl-4-(p-tolyl)-2-oxopyrido[3,2-c]cinnoline* (**6a**; $C_{19}H_{15}N_3O$)

Prepared from **5a**; crystallization from ethanol gave yellowish white crystals (89%); m.p.: >350°C; IR (KBr): 3402, 3083, 2926, 1655, 1554, 1492 $cm^{-1}$; $^1$H NMR ($CDCl_3$): 2.44 (s, $CH_3$), 3.01 (s, $CH_3$), 7.07 (s, $H_{ar}$), 7.29–7.82 (m, $5H_{ar}$), 8.01 (d, $2H_{ar}$), 13.20 (br, NH) ppm.

*1,2-Dihydro-8-methyl-4-(p-tolyl)-2-oxopyrido[3,2-c]cinnoline* (**6b**; $C_{19}H_{15}N_3O$)

Prepared from **5b**; crystallization from *DMF*/$H_2O$ gave yellowish white crystals (89%); m.p.: 348–350°C; IR (KBr): 3400, 3144, 3082, 2926, 1656, 1552, 1491 $cm^{-1}$; $^1$H NMR ($CDCl_3$): 2.49 (s, $CH_3$), 2.69 (s, $CH_3$), 7.07 (s, $H_{ar}$), 7.35–7.39 (d, $2H_{ar}$), 7.77–7.81 (d, $3H_{ar}$), 8.34 (s, $1H_{ar}$), 8.85–8.89 (d, $1H_{ar}$), 13.50 (br, NH) ppm; $^{13}$C NMR ($CDCl_3$): 31.02 ($CH_3$), 31.57 ($CH_3$), 121.93, 130.74, 131.39, 138.62, 138.74, 139.92, 141.49, 141.82, 143.36, 149.32, 152.06, 158.06, 163.61 (aryl), 174.02 (C=O) ppm.

*1,2-Dihydro-9-methyl-4-(p-tolyl)-2-oxopyrido[3,2-c]cinnoline* (**6c**; $C_{19}H_{15}N_3O$)

Prepared from **5c**; crystallization from ethanol gave white crystals (89%); m.p.: >350°C; IR (KBr): 3402, 3143, 3082, 2926, 1656, 1552, 1492 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): 2.49 (s, $CH_3$), 2.75 (s, $CH_3$), 7.07 (s, $1H_{ar}$), 7.36–7.40 (d, $2H_{ar}$) 7.77–7.84 (d, $3H_{ar}$), 8.51–8.56 (d, $1H_{ar}$), 8.68 (s, $1H_{ar}$), 13.10 (br, NH) ppm.

*2-Chloro-9-methyl-4-(p-tolyl)-pyrido[3,2-c]cinnoline* (**7**; $C_{19}H_{14}ClN_3$)

A mixture of 0.30 g **6c** (1 mmol) and 10 $cm^3$ $POCl_3$ was refluxed for 3 h. Excess of $POCl_3$ was removed under reduced pressure, and the residue was poured on crushed ice and 25% $NH_3$ under vigorous stirring. The green solid thus obtained was washed with water and recrystallized from acetic acid to give green crystals.

Yield: 55%; m.p.: >360°C; IR (KBr): 3085, 2927, 1628, 1552, 1489 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): 2.49 (s, $CH_3$), 2.75 (s, $CH_3$), 7.05 (s, $1H_{ar}$), 7.33–7.40 (d, $2H_{ar}$), 7.75–7.84 (d, $3H_{ar}$), 8.51–8.56 (d, $1H_{ar}$), 8.66 (s, $1H_{ar}$) ppm.

*1,2-Dihydro-9-methyl-4-(p-tolyl)-pyrido[3,2-c]cinnoline-2-thione* (**8**; $C_{19}H_{15}N_3S$)

A mixture of 0.30 g **6c** (1 mmol), 0.15 g $P_2S_5$, and 20 $cm^3$ pyridine was refluxed for 3 h. Excess of pyridine was removed under reduced pressure, and the residue was poured on crushed ice and 15% HCl under vigorous stirring. The yellow solid thus obtained was washed with water and recrystallized from acetic acid to give yellow crystals.

Yield: 42%; m.p.: >350°C; IR (KBr): 3420, 3085, 2927, 1628, 1563, 1500, 1210 $cm^{-1}$; $^1H$ NMR (*DMSO*-$d_6$): 2.42 (s, $CH_3$), 2.57 (s, $CH_3$), 6.91 (s, $1H_{ar}$), 7.35 (d, $2H_{ar}$), 7.81–7.85 (d, $3H_{ar}$), 8.15 (d, $1H_{ar}$), 8.40 (s, $1H_{ar}$) ppm.

*1,9-Dimethyl-4-(p-tolyl)-pyrido[3,2-c]cinnoline-2-one* (**9**; $C_{20}H_{17}N_3O$)

A mixture of 0.30 g **6c** (1 mmol), 3 $cm^3$ KOH (7%), and 0.30 $cm^3$ $CH_3I$ was stirred overnight at room temperature. The resulting precipitate was washed with $H_2O$ and recrystallized from acetonitrile to give red crystals.

Yield: 32%; m.p.: >350°C; IR (KBr): 3080, 2933, 1682, 1625, 1550, 1492 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): 2.49 (s, $CH_3$), 2.75 (s, $CH_3$), 4.36 (s, $NCH_3$), 7.15 (s, $1H_{ar}$), 7.35–7.40 (d, $2H_{ar}$), 7.73–7.83 (d, $3H_{ar}$), 8.50 (d, $1H_{ar}$), 8.67 (s, $1H_{ar}$) ppm.

*2-Amino-9-methyl-4-(p-tolyl)-pyrido[3,2-c]cinnoline-3-nitrile* (**10**; $C_{20}H_{15}N_5$)

A mixture of 0.28 g **4c** (1 mmol), 0.07 g malononitrile (1 mmol), and 15 $cm^3$ pyridine was refluxed for 6 h. Excess pyridine was removed under reduced pressure, and the residue was poured on crushed ice and HCl under vigorous stirring. The solid obtained was washed with $H_2O$ and crystallized from acetic acid to give colourless crystals.

Yield: 70%; m.p.: >350°C; IR (KBr): 3380, 3300, 2932, 2218, 1625, 1553, 1489 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): 2.49 (s, $CH_3$), 2.75 (s, $CH_3$), 5.51 (br, $NH_2$), 7.35–7.40 (d, $2H_{ar}$), 7.73–7.82 (d, $3H_{ar}$), 8.50 (d, $1H_{ar}$), 8.62 (s, $1H_{ar}$) ppm.

*9-Methyl-4-(p-tolyl)-pyrimido[5,4-c]cinnoline* (**11**; $C_{18}H_{14}N_4$)

A suspension of 0.28 g **4c** (1 mmol) in 10 $cm^3$ formamide was refluxed for 2 h. The solid obtained was filtered, washed with $H_2O$, and recrystallized from acetic acid to give pale green crystals.

Yield: 43%; m.p.: 210°C; IR (KBr): 3085, 2929, 1624, 1610, 1553, 1490 $cm^{-1}$; $^1H$ NMR (*DMSO*-$d_6$): 2.42 (s, $CH_3$), 2.58 (s, $CH_3$), 7.34 (d, $2H_{ar}$), 7.83–7.98 (m, $4H_{ar}$), 8.68 (s, $1H_{ar}$), 9.62 (s, $1H_{ar}$) ppm.

*1,2-Dihydro-9-methyl-4-(p-tolyl)-pyrimido[5,4-c]cinnoline-2-one* (**12**; $C_{18}H_{14}N_4O$)

A mixture of 0.28 g **4c** (1 mmol), 0.09 g urea (1.5 mmol), and 10 $cm^3$ acetic acid was refluxed for 2 h. The solid obtained was filtered, washed with water, and recrystallized from acetic acid to give pale yellow crystals.

Yield 82%; m.p.: 178°C; IR (KBr): 3378, 3090, 1672, 1624, 1608, 1552, 1489 $cm^{-1}$; $^1H$ NMR (*DMSO*-$d_6$): 2.42 (s, $CH_3$), 2.58 (s, $CH_3$), 7.33–7.37 (d, $2H_{ar}$), 7.82–7.87 (d, $3H_{ar}$), 8.15–8.20 (d, $1H_{ar}$), 8.51 (s, $1H_{ar}$), 11.20 (br, NH, exchangable by $D_2O$) ppm.

*1,2-Dihydro-9-methyl-4-(p-tolyl)-pyrimido[5,4-c]cinnoline-2-thione* (**13**; $C_{18}H_{14}N_4S$)

0.28 g **4c** (1 mmol) was dissolved in 10 $cm^3$ glacial acetic acid and treated with a filtered solution of 0.08 g KSCN in 0.5 $cm^3$ $H_2O$ for 1 h under cooling to maintain the reaction temperature below 15°C. The mixture was stirred overnight, and the precipitate was collected by filteration and washed with $H_2O$ and then with acetone. Recrystallization from acetic acid gave pale yellow crystals.

Yield: 37%; m.p.: 170–171°C; IR (KBr): 3310, 2931, 2630, 1622, 1610, 1553, 1490 $cm^{-1}$.

*2,9-Dimethyl-4-(p-tolyl)-pyrimido[5,4-c]cinnoline* (**14**; $C_{19}H_{16}N_4$)

A suspension of 0.32 g **5c** (1 mmol) in 1.52 g molten $CH_3COONH_4$ (20 mmol) was maintained at 155–160°C for 3 h, during which time a vigorous stream of $NH_3$ was passed through the mixture. The resulting yellow solid was diluted with $H_2O$, extracted with ether, and the ethereal solution was washed with dilute aqueous NaOH and dried. Ether was removed under reduced pressure, and the residue was recrystallized from methanol to give green crystals.

Yield 35%; m.p.: 185–187°C; IR (KBr): 3087, 2933, 1627, 1608, 1582, 1489 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): 2.49 (s, $CH_3$), 2.75 (s, $CH_3$), 2.88 (s, $CH_3$), 7.41 (d, $2H_{ar}$), 7.75–7.83 (d, $3H_{ar}$), 8.50 (d, $1H_{ar}$), 8.67 (s, $1H_{ar}$) ppm.

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