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On the Chemistry of Cinnoline V [1]. Reactions of 4-Aminocinnolines with Amines

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Summary. We describe the effect of the solvent during the intra-cyclization of the arylhydrazonomalononitrile to obtain new and useful substituted cinnolines, namely 4-amino-3-cyanocinnolines and (4-amino-cinnolin-3-yl)arylmethanones. 4-Amino-3-cyano-5,7-dimethyl-cinnoline was treated with *n*-hexylamine, cyclohexylamine, and isopropylamine to yield the corresponding cinnoline-3-carboxamidine derivatives. Furthermore, 4-amino-3-cyano-5,7-dimethylcinnoline was reacted with diaminoethane to give 4-amino-5,7-dimethyl-3-(4,5-dihydroimidazol-2-yl)cinnoline. Treatment of 4-amino-3-cyano-5,7-dimethylcinnoline with hydrazine hydrate provided 3-amino-7,9-dimethyl-1*H*-pyrazolo[4,3-*c*]cinnoline. Moreover, (4-aminocinnolin-3-yl)phenylmethanones were treated with hydrazine hydrate to give 3-phenyl-1*H*-pyrazolo[4,3-*c*]cinnolines. Finally, reactions of (4-aminocinnolin-3-yl)phenylmethanone with 3,5-dimethylaniline, phenyl hydrazine, hydroxylamine, and phenyl isothiocyanate are discussed. Chemical and spectroscopic evidence for the structures of the new compounds is presented.

Keywords. Cycloadditions; Hydrazones; Cinnolines; Pyrazoles; Amines.

Introduction

Recent studies have shown that cinnolines and their derivatives exhibit various biological activities [2–5] such as antihypertensive, antihromobotic, antitumor, antisecretory, and bactericidal activities. 4-Aminocinnolines have recently become of importance due to their antibacterial, antihistaminic, antidepressive, and sedative properties [6–9]. Our group has recently been interested in the synthesis of derivatives containing the cinnoline system, in order to evaluate their antitumor activity [10–12]. We have continued our investigations by expanding the structure activity relationship studies of new series of cinnoline derivatives. Now we synthesized a series of new substituted 4-aminocinnoline derivatives, 4-aminocinnoline-3-carboxamidines, 3-(4,5-dihydroimidazol-2-yl)cinnoline, and pyrazolo[4,3-*c*]cinno-

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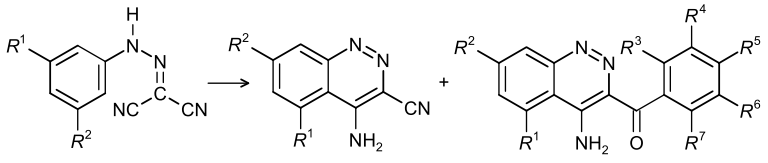
lines with respect to a projected investigation of their utility as pharmacological agents.

Results and Discussion

We previously have described the synthesis of (4-aminocinnolin-3-yl)-*p*-tolylmethanones from arylhydrazone derivatives [11]. We now report the results of experiments designed to explore the scope and the limitations of this procedure as a synthetic method for the formation of (4-aminocinnolin-3-yl)arylmethanones bearing various substitutents. In addition, we studied the effect of the solvent on the cyclization of the arylhydrazonomalononitriles **1a** and **1b** to obtain new and useful substituted cinnolines at position three **3a**–**3h**. For this purpose, arylhydrazonomalononitriles **2a** and **2b** were synthesized in good yield by treatment of malononitrile with diazonium salts obtained from the corresponding aniline or 3,5-dimethylaniline as shown in Scheme 1.

It was found that 4-amino-3-cyanocinnoline **2a** and **2b** and (4-amino-cinnolin-3-yl)phenylmethanone **3a** and **3b** were readily obtained *via* intracyclization of **1a** and **1b** in the presence of $AlCl_3$ and benzene under reflux. Only compound **2a** was obtained under similar conditions by *Gewald* [13]. The structure of **3a** was elucidated on the basis of its spectral data. The IR spectrum of **3a** showed no absorption band due to a cyano group, the ^{13}C NMR spectrum gave a signal at $\delta = 196.43$ for the carbonyl group, and the mass spectra of **3a** gave $m/z = 249.3$ (100%) $[M]^+$ and 172.2 $[M\text{-}Ph]^+$. Compound **3a** was only obtained when the reaction time was increased to 5 h. From the mechanistic standpoint, intramolecular *Friedel-Craft* cyclization first gives **2a** and **2b**. Then, condensation of the cyano group at position 3 of **2a** and **2b** with benzene in the presence of the *Lewis* acid leads to the



1a, 1b **2a, 2b** **3a-3h**

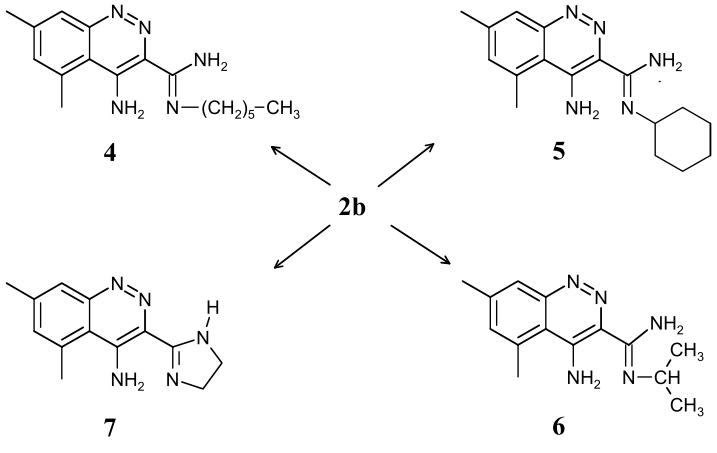
1-3	R^1	R^2	R^3	R^4	R^5	R^6	R^7
a	H	H	H	H	H	H	H
b	CH_3	CH_3	H	H	H	H	H
c	H	H	H	H	CH_3	H	H
d	H	H	H	H	CH_2CH_3	H	H
e	H	H	H	CH_3	CH_3	H	H
f	H	H	CH_3	H	CH_3	H	H
g	H	H	CH_3	H	H	CH_3	H
h	H	H	CH_3	H	CH_3	H	CH_3

Scheme 1

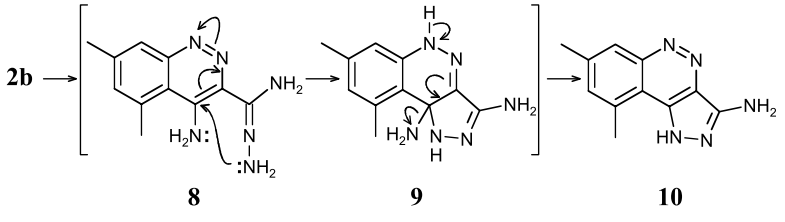
corresponding ketones **3a** and **3b** by a *Hoesch* type [14] reaction. Other solvents instead of benzene, such as toluene, ethylbenzene, *o*-xylene, *m*-xylene, *p*-xylene and 1,3,5-trimethylbenzene under the same conditions *via* intracyclization of **1a** gave **3c**–**3h** in excellent yields, but **2a** was not detected (Scheme 1). Furthermore, we found that in certain solvents such as carbon disulfide, dichloromethane, carbon tetrachloride, pyridine, or without solvent the cyclization of **1a** at lower or higher temperature did not occur. In most of all these cases compound **1a** could be partially recovered.

It seemed to be of interest to study the reactivity of the cyano group in **2b** towards amines. The cyano group at position 3 in the cinnoline derivatives exhibits the normal characteristic of this group [15]. Thus **2b** condensed with *n*-hexylamine, cyclohexylamine, and isopropylamine afforded 4-aminocinnoline-3-carboxamidines **4**–**6**. When **2b** was treated with diaminoethane the sole product was **7**. The formation of the product is accounted for by a stepwise nucleophilic attack of the cyanide followed by cyclization and elimination of ammonia to give **7** as shown in Scheme 2.

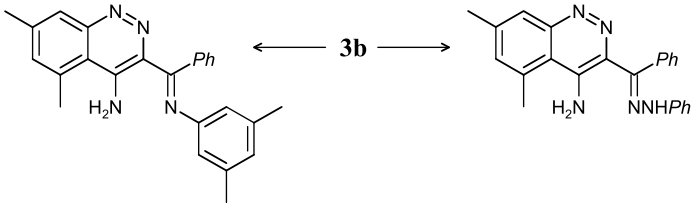
Treatment of **2b** with hydrazine hydrate gave 3-amino-7,9-dimethyl-1*H*-pyrazolo[4,3-*c*]cinnoline **10**. The mass spectrum of **10** exhibits a strong molecular ion peak M^+ at $m/e = 213.2$ which represents also the base peak. The mechanism illustrated in Scheme 3 is proposed: hydrazine adds to the cyano group, then the amino group of the hydrazone unit initiates an addition-elimination of the ring amino-group.



Scheme 2

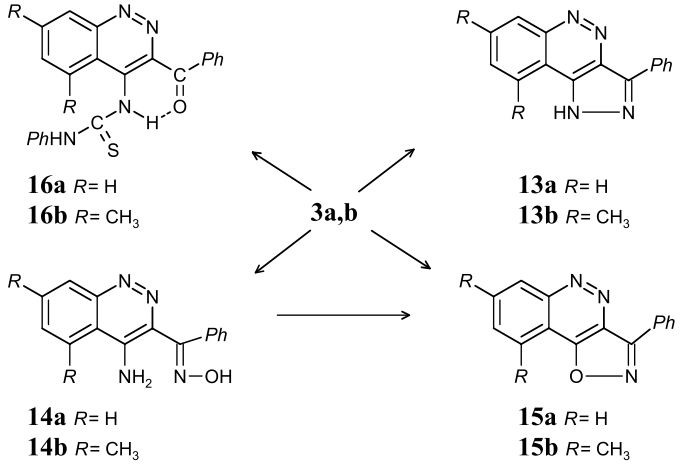


Scheme 3



11 **12**

Scheme 4



16a *R*= H
16b *R*= CH_3

13a *R*= H
13b *R*= CH_3

14a *R*= H
14b *R*= CH_3

15a *R*= H
15b *R*= CH_3

Scheme 5

Furthermore, the carbonyl group at position 3 in the cinnoline derivatives **3a** and **3b** exhibits the normal characteristics of this group. Thus, the reaction of **3b** with 3,5-dimethylaniline or phenylhydrazine gave **11** and **12**.

Finally, the reaction of **3a** and **3b** with hydrazine hydrate in ethanol and few drops of concentrated hydrochloric acid under reflux condition afforded **13a** and **13b**. The first step is the nucleophilic attack at the carbonyl group rather than substitution of the amino group [16] followed by cyclization to give the pyrazolo[4,3-*c*]cinnoline (Scheme 5). Similarly, the reaction of **3a** and **3b** with hydroxylamine hydrochloride afforded isoxazolo[4,3-*c*]cinnoline derivatives **15a** and **15b** in 20% yield *via* the oximes **14a** and **14b**. Treatment of **3a** and **3b** with phenyl isothiocyanate at reflux temperature gave the corresponding *N*,*N*′-disubstituted thioureas **16a** and **16b**.

Most of the compounds were tested in *vitro* at the national cancer institute using their panel of 60 human tumor cell lines [17]. (4-Aminocinnoline-3-yl)arylmethanones **3** demonstrated considerable cytotoxicity against a number of human cancer cell lines.

Experimental

Melting points were measured on a *Kofler* hot stage microscope (Reichert, Vienna) and are uncorrected. ^{1}H (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Bruker DPX 200 spectro-

meter; chemical shifts are given in ppm relative to internal *TMS* at 295 K. IR spectra were obtained on a Biorad FT-IR-45 instrument. The mass spectra were measured on a Hewlett Packard 5989 AMS instrument (79 eV, direct probe inlet). For all novel compounds satisfactory elemental analyses were obtained.

Preparation of Arylhydrazonomalononitriles **1**

To a well stirred solution of 6.66 g of malononitrile (100 mmol) in 130 cm^3 of *Et*OH and 20 cm^3 of H_2O containing 10 g of CH_3COONa, the diazonium salt (100 mmol) prepared in the usual way from the corresponding aniline was added gradually with stirring during 20 min at 0–5°C. The product was filtered, washed with H_2O, dried, and recrystallized from the given solvent.

Phenylhydrazonomalononitrile (**1a**, $C_9H_6N_4$)

Prepared from aniline; crystallization from benzene gave fine yellow crystals (87%); mp 143°C [18]; ^{1}H NMR ($CDCl_3$): $\delta = 7.30$–7.42 (m, Ph), 10.24 (br, NH) ppm; ^{1}H NMR (*DMSO*-d_6): $\delta = 7.15$–7.48 (m, Ph), 12.9 (br, NH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 86.42$ (CH), 108.34, 112.21, 116.03, 126.82, 129.91, 139.70 (phenyl, 2CN) ppm.

3,5-Dimethylphenylhydrazonomalononitrile (**1b**, $C_{11}H_{10}N_4$)

Prepared from 3,5-dimethylaniline; crystallization from *Et*OH gave fine yellow crystals (92%); mp 158–160°C; IR (KBr): $\bar{\nu} = 3212$, 3162, 3082, 2916, 2228, 1622, 1595, 1562, 1487 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.67$ (s, $2CH_3$), 7.21 (s, $1H_{ar}$), 7.26 (s, $2H_{ar}$), 10.25 (br, NH) ppm.

General Procedure for the Preparation of 4-Aminocinnolin-3-carbonitrile and (4-Aminocinnolin-3-yl)arylmethanone Derivatives

A mixture of 10 mmol of **1** and 2.50 g of $AlCl_3$ (0.04 mmol) in 150 cm^3 of a nonpolar aromatic solvent (benzene, toluene, ethylbenzene, *o*-xylene, *m*-xylene, *p*-xylene, 1,3,5-trimethylbenzene) was heated under reflux for 3 h with stirring and then allowed to cool to room temperature. The resulting product was poured on 500 cm^3 of cold H_2O and left for 2 h. The resulting solid product was collected by filtration, washed with petroleum ether (40–60°C), and crystallized from the solvent given.

4-Aminocinnolin-3-carbonitrile (**2a**, $C_9H_6N_4$)

Prepared from **1a**; crystallization from CH_3COOH gave greenish yellow crystals (36%); mp 312–318°C; IR (KBr): $\bar{\nu} = 3371$, 3341, 3102, 3081, 2227, 1681, 1616, 1571, 1516 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 7.74$ (t, $J = 7.5$ Hz, $1H_{ar}$), 8.17 (br, NH_2), 8.21 (d, $J = 8.4$ Hz, $1H_{ar}$), 8.41 (d, $J = 8.4$ Hz, $1H_{ar}$) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 114.26$, 115.52, 116.90, 122.27, 128.75, 129.75, 132.96, 146.08, 147.61 (aryl, CN) ppm.

4-Amino-5,7-dimethylcinnolin-3-carbonitrile (**2b**, $C_{11}H_{10}N_4$)

Prepared from **1b**; crystallization from $CHCl_3$ gave fine yellow crystals (52%); mp 270–275°C; IR (KBr): $\bar{\nu} = 3498$, 3308, 3214, 2895, 2217, 1612, 1561, 1495 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.40$ (s, CH_3), 2.78 (s, CH_3), 7.20 (br, NH_2), 7.28 (s, $1H_{ar}$), 7.77 (s, $1H_{ar}$) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 20.98$ (CH_3), 23.00 (CH_3), 111.99, 116.83, 116.94, 125.99, 133.96, 134.49, 142.78, 146.81, 149.77 (aryl, CN) ppm.

(4-Aminocinnolin-3-yl)phenylmethanone (**3a**, $C_{15}H_{11}N_3O$)

Prepared from **1a** and benzene; crystallization from *Et*OH gave yellow crystals (34%); mp 150–153°C; IR (KBr): $\bar{\nu} = 3563$ br, 3381, 3033, 1617, 1600, 1570, 1416 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 7.50$–7.64 (m, $3H_{ar}$), 7.77–7.98 (m, $4H_{ar}$), 8.26 (d, $J = 8.0$ Hz, $1H_{ar}$), 8.58 (d, $J = 8.3$ Hz, $1H_{ar}$), 8.94 (br, NH_2) ppm; ^{13}C NMR (*DMSO*-d_6); $\delta = 115.95$, 122.94, 127.59, 128.72, 128.97, 130.30, 131.26, 132.66, 132.99, 139.32, 145.62, 147.24 (aryl), 196.43 (C=O) ppm; MS: $m/z = 249.3$ (100%) [M^+], 172.2 [M^+-Ph], 171.2, 122.2, 105.05, 91.15, 63.13, 57.20, 55.20.

(4-Amino-5,7-dimethylcinnolin-3-yl)phenylmethanone (**3b**, $C_{17}H_{15}N_3O$)

Prepared from **1b** and benzene; crystallization from ethyl acetate gave yellow crystals (18%); mp 168°C; IR (KBr): $\bar{\nu} = 3445$, 3251, 3190, 2900, 1620, 1587, 1515, 1431 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.48$ (s, CH_3), 2.91 (s, CH_3), 7.36 (s, $1H_{ar}$), 7.46 (m, $3H_{ar}$), 7.78 (d, $J = 7.7$ Hz, $2H_{ar}$), 7.87 (s, $1H_{ar}$), 8.53 (br, NH_2) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 20.97$ (CH_3), 23.24 (CH_3), 113.20, 126.26, 127.49, 130.17, 131.05, 133.20, 133.48, 135.43, 139.68, 142.69, 147.39, 149.21 (aryl), 196.95 (C=O) ppm.

(4-Aminocinnolin-3-yl)-p-tolylmethanone (**3c**, $C_{16}H_{13}N_3O$)

Prepared from **1a** and toluene; crystallization from ethyl acetate gave white crystals (53%); mp 208–218°C [13]; IR (KBr): $\bar{\nu} = 3310$, 3228, 3030, 2920, 1635, 1590, 1550, 1530 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.40$ (s, CH_3), 7.30 (d, $J = 8.0$ Hz, $2H_{ar}$), 7.79 (m, $3H_{ar}$), 7.90 (t, $J = 7.6$ Hz, $1H_{ar}$), 8.22 (d, $J = 8.5$ Hz, $1H_{ar}$), 8.53 (d, $J = 8.0$ Hz, $1H_{ar}$), 9.19 (br, NH_2) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 21.10$ (CH_3), 115.93, 122.78, 128.17, 128.70, 128.87, 130.65, 132.53, 133.20, 136.41, 141.56, 145.38, 147.28 (aryl), 195.76 (C=O) ppm.

(4-Aminocinnolin-3-yl)(4-ethylphenyl)methanone (**3d**, $C_{17}H_{15}N_3O$)

Prepared from **1a** and ethylbenzene; crystallization from *Me*OH gave fine yellow crystals (77%); mp 220–221°C; IR (KBr): $\bar{\nu} = 3344$, 3284, 3131, 3032, 2932, 1630, 1616, 1560, 1528 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.25$ (t, $J = 7.5$ Hz, CH_3), 2.70 (q, $J = 7.5$ Hz, CH_2), 7.35 (d, $J = 7.8$ Hz, $2H_{ar}$), 7.86 (m, $3H_{ar}$), 7.97 (t, $J = 7.8$ Hz, $1H_{ar}$), 8.25 (d, $J = 8.2$, $1H_{ar}$), 8.55 (d, $J = 8.2$ Hz, $1H_{ar}$), 8.87 (br, NH_2) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 15.40$ (CH_3), 26.20 (CH_2), 115.95, 122.82, 127.04, 128.74, 128.94, 130.73, 132.61, 133.20, 136.71, 145.41, 147.29, 147.71 (aryl), 196.00 (C=O) ppm.

(4-Aminocinnolin-3-yl)(3,4-dimethylphenyl)methanone (**3e**, $C_{17}H_{15}N_3O$)

Prepared from **1a** and *o*-xylene; crystallization from *Et*OH gave yellowish white crystals (78%); mp 265°C (dec); IR (KBr): $\bar{\nu} = 3320$, 3180, 3030, 2917, 1636, 1610, 1516, 1430 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.27$ (s, CH_3), 2.29 (s, CH_3), 7.10 (m, $1H_{ar}$), 7.25 (d, $J = 7.8$ Hz, $1H_{ar}$), 7.65 (s, $1H_{ar}$), 7.80–8.00 (m, $1H_{ar}$), 8.20 (d, $J = 7.8$ Hz, $1H_{ar}$), 8.60 (d, $J = 8.4$ Hz, $1H_{ar}$), 9.15 (br, NH_2) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 19.40$ (CH_3), 19.57 (CH_3), 116.23, 123.20, 126.55, 128.31, 128.85, 129.06, 131.43, 133.31, 133.40, 135.65, 136.29, 140.94, 145.51, 146.36 (aryl), 195.12 (C=O) ppm.

(4-Aminocinnolin-3-yl)(2,4-dimethylphenyl)methanone (**3f**, $C_{17}H_{15}N_3O$)

Prepared from **1a** and *m*-xylene; crystallization from CH_3COOH and H_2O gave pale yellow crystals (66%); mp 268–269°C; IR (KBr): $\bar{\nu} = 3310$, 3200, 2920, 1641, 1612, 1425 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.26$ (s, CH_3), 2.37 (s, CH_3), 7.13 (m, $2H_{ar}$), 7.33 (d, $J = 7.6$ Hz, $1H_{ar}$), 7.87 (t, $J = 7.8$ Hz, $1H_{ar}$), 8.10–8.18 (m, $2H_{ar}$), 8.71 (d, $J = 8.2$ Hz, $1H_{ar}$), 9.70 (s, NH_2) ppm; ^{13}C NMR (*DMSO*-d_6):

$\delta = 19.64$ (CH_3), 20.92 (CH_3), 116.69, 123.68, 124.24, 125.38, 129.26, 130.95, 133.00, 134.28, 135.84, 136.34, 139.63, 143.41, 147.69 (aryl), 198.42 (C=O) ppm.

(4-Aminocinnolin-3-yl)(2,5-dimethylphenyl)methanone (**3g**, $C_{17}H_{15}N_3O$)

Prepared from **1a** and *p*-xylene; crystallization from ethyl acetate gave pale yellow crystals (49%); mp 260°C (dec); IR (KBr): $\bar{\nu} = 3274$, 3155, 3029, 2910, 1637, 1602, 1514, 1416 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.07$ (s, CH_3), 2.28 (s, CH_3), 7.05 (m, $2H_{ar}$), 7.16 (s, $1H_{ar}$), 7.81 (t, $J = 7.6$ Hz, $1H_{ar}$), 7.98 (t, $J = 7.6$ Hz, $1H_{ar}$), 8.08 (d, $J = 8.4$ Hz, $1H_{ar}$), 8.65 (d, $J = 8.4$ Hz, $1H_{ar}$), 9.75 (br, NH), 11.30 (br, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 18.90$ (CH_3), 20.47 (CH_3), 116.73, 120.45, 124.06, 127.82, 129.06, 129.77, 130.95, 132.64, 134.37, 135.20, 139.50, 149.79 (aryl), 187.63 (C=O) ppm.

(4-Aminocinnolin-3-yl)(2,4,6-trimethylphenyl)methanone (**3h**, $C_{18}H_{17}N_3O$)

Prepared from **1a** and 1,3,5-trimethylbenzene; crystallization from *DMF* and *Et*OH gave orange crystals (82%); mp 250–255°C; IR (KBr): $\bar{\nu} = 3384$ br, 3179, 2919, 1616, 1510, 1430 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.05$ (s, $2CH_3$), 2.31 (s, CH_3), 6.96 (s, $2H_{ar}$), 7.90 (t, $J = 8.0$ Hz, $1H_{ar}$), 8.01 (m, $2H_{ar}$), 8.65 (d, $J = 8.4$ Hz, $1H_{ar}$), 9.77 (br, NH), 11.29 (br, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 19.82$ ($2CH_3$), 21.15 (CH_3), 117.08, 120.6, 124.18, 128.33, 129.97, 133.10, 134.24, 136.16, 138.00, 138.09, 140.42, 150.34 (aryl), 188.36 (C=O) ppm.

*Reaction of 4-Amino-5,7-dimethylcinnoline-3-carbonitrile (**2b**) with Aliphatic Amines*

A mixture of 1.00 g of **2b** (5 mmol) and 6 mmol of an aliphatic amine in 10 cm^3 of CH_3OH was heated at reflux temperature for 5 h. Then the solvent was removed under reduced pressure to give a yellow orange solid which was recrystallised from the given solvent.

4-Amino-5,7-dimethyl-N-hexylcinnoline-3-carboxamidine (**4**, $C_{17}H_{25}N_5$)

Prepared from *n*-hexylamine; crystallization from ethyl acetate gave buff crystals (85%); mp 102–105°C; IR (KBr): $\bar{\nu} = 3533$, 3443, 3348, 2922, 2800, 1628, 1496 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 0.85$ (t, $J = 12$ Hz, CH_3), 1.30 (m, $3CH_2$), 1.64 (m, CH_2), 2.42 (s, CH_3), 2.85 (s, CH_3), 3.15–3.32 (m, CH_2 and NH_2), 6.77 (br, NH_2), 7.16 (s, $1H_{ar}$), 7.71 (s, $1H_{ar}$) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 13.97$ (CH_3), 20.83 (CH_3), 23.49 (CH_3), 22.16, 26.98, 30.82, 31.22, 47.19 ($5CH_2$), 113.65, 125.55, 129.24, 132.06, 134.60, 142.77, 145.01, 150.29, 156.87 (aryl and C=N) ppm; MS: $m/z = 299$ [M^+], 228, 199, 169, 144, 115, 91, 77, 43 (100%).

4-Amino-5,7-dimethyl-N-cyclohexylcinnoline-3-carboxamidine (**5**, $C_{17}H_{23}N_5$)

Prepared from cyclohexylamine; crystallization from *Et*OH gave yellow crystals (77%); mp 180–182°C; IR (KBr): $\bar{\nu} = 3522$, 3431, 3277, 3150, 1620, 1530 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.28$–1.81 (m, $5CH_2$), 2.42 (s, CH_3), 2.85 (s, CH_3), 3.32 (s, CH), 6.82 (br, NH_2), 7.16 (s, $1H_{ar}$), 7.71 (s, $1H_{ar}$), 12.15 (br, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 20.88$ (CH_3), 23.54 (CH_3), 24.28, 25.69, 33.34, 53.19 (cyclohexane), 113.68, 125.58, 129.33, 132.10, 134.66, 140.11, 145.19, 150.30, 155.16 (aryl and C=N) ppm.

4-Amino-5,7-dimethyl-N-isopropylcinnoline-3-carboxamidine (**6**, $C_{14}H_{19}N_5$)

Prepared from isopropylamine; crystallization from ethyl acetate gave orange yellow crystals (46%); mp 170–173°C; IR (KBr): $\bar{\nu} = 3530$, 3440, 3320, 1628, 1510 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 1.46$ (d, $J = 7.0$ Hz, CH_3), 2.44 (s, CH_3), 2.86 (s, CH_3), 3.25 (m, CH), 7.17 (s, $1H_{ar}$), 7.73 (s, $1H_{ar}$) ppm;

^{13}C NMR (*DMSO*-d_6): $\delta = 13.96$ ($2CH_3$), 20.89 (CH_3), 23.55 (CH_3), 40.32 (CH), 113.60, 125.57, 129.25, 132.12, 134.65, 140.16, 145.07, 150.33, 157.43 (aryl and C=N) ppm.

4-Amino-5,7-dimethyl-3-(4,5-dihydroimidazol-2-yl)cinnoline (**7**, $C_{13}H_{15}N_5$)

Prepared from 1,2-diaminoethane; crystallization from *Me*OH gave white crystals (54%); mp 228–230°C; IR (KBr): $\bar{\nu} = 3417$, 3395, 3107, 1621, 1494 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.46$ (s, CH_3), 2.88 (s, CH_3), 3.18 (s, CH_2), 3.94 (t, $J = 9.4$ Hz, CH_2), 7.24 (s, NH_2), 7.41 (s, $1H_{ar}$), 7.79 (s, $1H_{ar}$), 10.48 (br, NH); signals at 7.24 and 10.48 disappear by addition of D_2O; ^{13}C NMR (*DMSO*-d_6): $\delta = 20.94$ (CH_3), 23.48 (CH_3), 43.01 (CH_2), 55.05 (CH_2), 113.07, 125.81, 128.19, 132.49, 134.70, 140.72, 143.98, 150.10, 165.52 (aryl and C=N) ppm.

3-Amino-7,9-dimethylpyrazolo[4,3-c]cinnoline (**10**, $C_{11}H_{11}N_5$)

A solution of 1.94 g of **2b** (10 mmol) in 5 cm^3 of hydrazine hydrate (99%) was kept at room temperature for one day. The solid product obtained was filtered off and crystallized from ethyl acetate to give yellow crystals (82%); mp 306–308°C; IR (KBr): $\bar{\nu} = 3460$, 3380, 3138, 2932, 1630, 1580, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.43$ (s, CH_3), 2.87 (s, CH_3), 5.34 (br, NH), 7.17 (s, $1H_{ar}$), 7.71 (s, $1H_{ar}$) ppm; MS: $m/z = 213.2$ (100%) [M^+], 196.05 [M^+-NH_3], 170.15 [M^+-($CH_3 + CN^-$)], 157.15, 142.15, 128.15, 115.2, 77.05, 51.15.

*Reaction of **3b** with Dimethylaniline or Phenylhydrazine*

A solution of 2.78 g of **3b** (10 mmol) and 1.21 g of 3,5-dimethylaniline (10 mmol) or 1.05 g of phenylhydrazine (10 mmol) was refluxed for 8 h by using a *Dean Stark* apparatus and allowed to cool. The solid product was filtered off and crystallized from *DMF*/H_2O to give **11** and **12**.

4-Amino-5,7-dimethyl-N-(3,5-dimethylphenyl)cinnoline-3-carboxamidine (**11**, $C_{25}H_{24}N_4$)

Prepared from 3,5-dimethylaniline; crystallization from *DMF*/H_2O gave a yellow powder (75%); mp 171°C; IR (KBr): $\bar{\nu} = 3438$, 3239, 3185, 2977, 1590, 1549, 1519, 1428 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.60$ (s, $2CH_3$), 2.93 (s, CH_3), 2.98 (s, CH_3), 7.38 (s, $1H_{ar}$), 7.50 (m, $5H_{ar}$ and NH), 7.88 (s, $1H_{ar}$), 8.34 (s, $1H_{ar}$), 8.45 (br, NH), 8.62 (d, $J = 7.5$ Hz, $2H_{ar}$) ppm.

(4-Amino-5,7-dimethylcinnolin-3-yl)phenylmethanphenylhydrazone (**12**, $C_{23}H_{21}N_5$)

Prepared from phenylhydrazine; crystallization from *DMF*/H_2O gave buff crystals (60%); mp >300°C; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.62$ (s, CH_3), 2.97 (s, CH_3), 6.70 (br, NH), 7.50–8.00 (m, $12H_{ar}$), 8.42 (s, NH_2) ppm.

*Reaction of **3a** or **3b** with Hydrazine Hydrate*

A solution of **3a** or **3b** (10 mmol), hydrazine hydrate (99%, 40 mmol) and 3 cm^3 of HCl in 30 cm^3 of *Et*OH was refluxed for 30 h. After diluting with 20 cm^3 of H_2O it was cooled. The precipitate was filtered off to give **13a** and **13b**.

3-Phenyl-1H-pyrazolo[4,3-c]cinnoline (**13a**, $C_{15}H_{10}N_4$)

Prepared from **3a**; crystallization from *Et*OH gave a yellow powder (64%); mp 295°C; IR (KBr): $\bar{\nu} = 3375$, 3096, 1619, 1599, 1482 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 7.47$ (m, $3H_{ar}$), 7.99 (m, $2H_{ar}$), 8.44 (d, $J = 8.5$ Hz, $1H_{ar}$), 8.61 (m, $3H_{ar}$), 13.65 (br, NH) ppm.

7,9-Dimethyl-3-phenyl-1H-pyrazolo[4,3-c]cinnoline (**13b**, $C_{17}H_{14}N_4$)

Prepared from **3b**; crystallization from *Et*OH gave a yellow powder (72%); mp $>300°C$; ^1H NMR (*DMSO*-d_6): $\delta = 2.60$ (s, CH_3), 2.95 (s, CH_3), 7.58 (m, $5H_{ar}$), 8.32 (s, $1H_{ar}$), 8.66 (s, $1H_{ar}$), 14.12 (br, NH) ppm; ^1H NMR ($CDCl_3$): $\delta = 2.55$ (s, CH_3), 2.99 (s, CH_3), 7.26 (s, $1H_{ar}$), 7.46 (m, $3H_{ar}$), 7.96 (m, $3H_{ar}$) ppm.

*Reaction of **3a** or **3b** with Hydroxylamine Hydrochloride*

A solution of **3a** or **3b** (10 mmol) and $NH_2OH \cdot HCl$ (60 mmol) in 20 cm^3 of *Et*OH was refluxed for 20 h, left to cool, 20 cm^3 of H_2O were added, and the mixture was cooled. The precipitate formed was filtered off and dried to give **15a** and **15b**. The mother liquor was concentrated under reduced pressure to a volume of 20 cm^3, neutralized with solid $NaHCO_3$, extracted with $CHCl_3$, and dried (Na_2SO_4). After evaporation of the solvent under vacuum the solid was recrystallized from dioxan to give the oximes **14a** and **14b**. Thermal conversion of **14a** to **15a** occured by heating 15 mg of the crude oxime at 150°C for 3 h under vacuum. Pure **15a** (50%) was obtained by sublimation.

(4-Aminocinnolin-3-yl)phenylmethanoxime (**14a**, $C_{15}H_{12}N_4O$)

Prepared from **3a**; crystallization from dioxan gave yellow crystals (61%); mp 210°C; IR (KBr): $\bar{\nu} = 3310$, 2786, 1622, 1565, 1000 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 7.50$ (m, $5H_{ar}$), 8.21 (m, $2H_{ar}$), 8.35 (d, $J = 8.6$ Hz, $1H_{ar}$), 8.75 (d, $J = 8.6$ Hz, $1H_{ar}$), 9.00 (br, NH_2), 12.10 (br, OH) ppm; MS: $m/z = 264$ [M^+], 77 (100%).

3-Phenylisoxazolo[4,3-d]cinnoline (**15a**, $C_{15}H_9N_3O$)

Prepared from **3a**; crystallization from ethyl acetate gave faint brown crystals (20%); mp 192°C; IR (KBr): $\bar{\nu} = 3098$, 1612, 1595, 1552, 1489 cm^{-1}; MS: $m/z = 247$ [M^+], 220, 205, 159, 143, 118, 77 (100%), 65.

4,6-Dimethyl-3-phenylisoxazolo[4,3-d]cinnoline (**15b**, $C_{17}H_{13}N_3O$)

Prepared from **3b**; crystallization from ethyl acetate gave buff crystals (22%); mp 196°C; ^1H NMR (*DMSO*-d_6): $\delta = 2.62$ (s, CH_3), 3.19 (s, CH_3), 7.50 (m, $5H_{ar}$), 8.32 (s, $1H_{ar}$), 8.66 (s, $1H_{ar}$) ppm.

*Reaction of **3a** or **3b** with Phenylisothiocyanate*

A solution of **3a** or **3b** (10 mmol) and phenyl isothiocyanate (12 mmol) in 25 cm^3 of *Et*OH, and a few drops of triethylamine was refluxed for 20 h. Then the solvent was removed under reduced pressure and the residue was recrystallized from ethyl acetate to give *N,N′*-disubstituted thioureas **16a** and **16b**.

N-(3-Benzoylcinnolin-1-yl)-N′-phenylthiourea (**16a**, $C_{22}H_{16}N_4OS$)

Prepared from **3a**; crystallization from ethyl acetate gave yellowish crystals (66%); mp 141°C; IR (KBr): $\bar{\nu} = 3443$, 3387, 3177, 2887, 1635, 1612, 1596, 1520, 1206 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 5.89$ (br, NH), 7.49–7.52 (m, $5H_{ar}$), 7.74 (d, $J = 7.2$ Hz, $2H_{ar}$), 7.91 (m, $5H_{ar}$), 8.41 (d, $J = 8.6$ Hz, $2H_{ar}$) ppm.

N-(5,7-Dimethyl-3-benzoylcinnolin-1-yl)-N′-phenylthiourea (**16b**, $C_{24}H_{20}N_4OS$)

Prepared from **3b**; crystallization from ethylacetate gave yellow crystals (72%); mp 147°C; ^1H NMR ($CDCl_3$): $\delta = 2.53$ (s, CH_3), 2.95 (s, CH_3), 4.20 (br, NH), 7.23 (m, $6H_{ar}$), 7.45 (d, $J = 7.4$ Hz, $3H_{ar}$),

7.96 (d, $J = 7.4$ Hz, $3H_{ar}$) ppm; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.50$ (s, CH_3), 2.92 (s, CH_3), 3.99 (br, NH), 7.36 (m, $9H_{ar}$), 7.79 (d, $J = 7.0$ Hz, $2H_{ar}$), 7.88 (s, $1H_{ar}$), 8.55 (br, NH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 20.98$ (CH_3), 23.30 (CH_3), 113.14, 125.81, 126.20, 127.45, 127.84, 129.79, 129.99, 130.25, 130.99, 133.23, 133.36, 135.29, 139.69, 142.56, 147.42, 149.06 (aryl, C=S), 188.33 (C=O) ppm.

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