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Metallation of diazines XIV. First *O*-Directed Metallation of Cinnolines. Metallation of 3-, 4-Chloro and 3-, 4-Methoxycinnolines.

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Abstract: The lithiation of 3-, 4-chloro and 3-, 4-methoxycinnolines was studied and good yields were obtained. When iodine was used as electrophile, 4,8-diiodo or 4,8-iodochloro compounds were prepared. A xanthone and diazepines were synthetized.

INTRODUCTION

During the last years the *ortho* directed metallation of diazines has been developped[1] but, in the field of benzodiazines, there are only two papers[2,3] dealing with the metallation of quinoxalines. The *ortho* directed metallation of cinnolines opens a new route to *ortho* disubstituted compounds. Cinnoline derivatives have been patented in the last years as agrochemical and pharmaceutical drugs. In agrochemistry they act as microbicides,[4] pollen suppressant,[5-7] fungicides[8] and herbicides.[9,10] In the pharmaceutical field they are mainly patented as bactericides.[11-14]

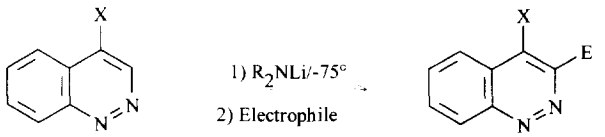
We present here the *ortho* directed metallation of 3-, 4-chloro and 3-, 4-methoxycinnolines and the attempts with 4-pivaloylaminocinnoline. Two examples of syntheses via metallation affording a xanthone and diazepines are described.

RESULTS AND DISCUSSION

Synthesis and metallation of 4-chloro and 4-methoxycinnoline **1** *and* **2.**

4-Hydroxycinnoline was prepared by the Richter method[15] modified by Schofield,[16] and reacted with phosphorous oxychloride and pyridine in chlorobenzene. This chlorination method gave a much cleaner reaction than the use of phosphorous oxychloride alone[17] or a mixture of phosphorous oxychloride and pentachloride.[17,18] 4-Methoxycinnoline was prepared by reaction of **1** with sodium methoxide with an almost quantitative yield. Compounds **1** and **2** were metallated using various experimental conditions and reacted with electrophiles; the results are summarized in tables 1 and 2 (Scheme 1).

Scheme 1



X = Cl **1**

X = OCH_3 **2**

X = Cl **3 - 8**

X = OCH_3 **9 - 14**

Table 1. Metallation of 4-chlorocinnoline **1** and reaction with electrophiles.

Entry	Metallation conditions	Electrophile	Product number	Reaction conditions	Yield	Starting material recovered
1	1.1 LTMP/15 min.	CH_3CHO/20eq	**3**	2h/-75°	65 %	-
2	1.1 LDA/15 min.	"	**3**	" "	78 %	19 %
3	1.1 LDA/30 min.	"	**3**	" "	89 %	-
4	" "	CH_3I/3.6eq	**4**	" "	86 %	-
5	" "	I_2/1.1eq	**5**	" "	70 %	10 %
6	" "	CO_2/20eq	**6**	" "	57 %	-
7	" "	Ph-CHO/1.1eq	**7**	" "	35 %	57 %
8	" "	"	**7**	2h/-60°	51 %	29 %
9	" "	PhCHO/5 eq.	**7**	2h/-75°	54 %	35 %
10	" "	"	**7**	4h/-75°	88 %	3 %
11	" "	*p*OCH_3Ph CHO /1.1eq	**8**	2h/-75°	47 %	39 %
12	" "	"	**8**	2h/-50°	70 %	8 %

LTMP: lithium 2,2,6,6-tetramethylpiperidide
LDA: lithium diisopropylamide

After optimization of the experimental conditions, good results were obtained with LDA as metallating agent (Table1: entries 3-6, 10, 12). It can be noticed that when aromatic electrophiles were reacted (entries 7 to 12) the reactions with the lithio derivatives were slower and it was necessary to increase the temperature or the reaction time to get good yields.

Table 2. Metallation of 4-methoxycinnoline **2** and reaction with electrophiles.

Entry	Metallation conditions	Electrophile	Product number	Yield	Starting material recovered
1	1.1 LDA/30 min.	CH_3CHO/20eq	**9**	33 %	62 %
2	2.2 LDA/30 min.	"	**9**	81 %	-
3	1.1 LDA/30 min.	Ph CHO/1.1eq	**10**	39 %	58 %
4	2.2 LDA/30 min.	" /2.2eq	**10**	81 %	-
5*	" "	" /2.2eq	**10**	85 %	-
6	" "	HCOOEt/2.2eq	**11**	57 %	29 %
7	" "	I_2/2.2eq	**12**	77 %	9 %
8*	" "	ICH_3/2.2eq	**13**	34 %	18 %
			14	24 %	18 %

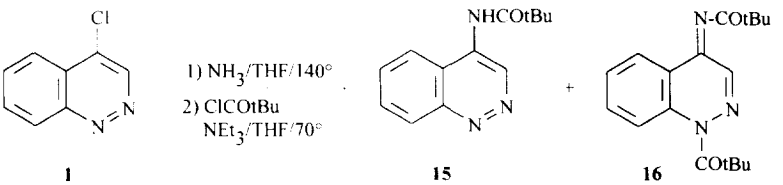
* entry 5: the reaction with electrophile was performed at -50°.
* entry 8: **14**: 3-methyl-4-methoxycinnoline.

As frequently observed with methoxy derivative of diazines[19] a 2,2 equivalents amount of metallating agent was necessary to obtain good yields (Table 2: entries 2, 4). The reaction with methyl iodide as electrophile (entry 8) afforded two products **13** and **14**; product **14** was the result of a further metallation of the 3-methyl group. Some experimental variations were tested but this side reaction could not be avoided.

Metallation attempts with 4-pivaloylaminocinnoline **15**.

This compound was prepared from **1** following scheme 2:

Scheme 2



1 **15** 32 % **16** 16 %

Besides compound **15** a disubstituted compound **16** resulting from the reaction of **15** with pivaloyl chloride was isolated.

All the attempts to metallate compound **15** failed and the starting material was recovered in medium to good yields besides untractable tars. These experiments are listed in the experimental part.

After the metallation of 4-substituted cinnolines the metallation of the 3-substituted ones is now described.

3-Chlorocinnoline **17** was prepared by Alford and Schofield[20a,b] from 3-hydroxycinnoline in 9 % yield. An increase of the chlorination time from 5 h to 6 days allowed us to obtain the 3-chloro derivative with a

72 % yield. The substitution of the chlorine atom by a methoxy group afforded the 3-methoxycinnoline **21** in 93 % yield.

Metallation of 3-chlorocinnoline **17**.

Scheme 3

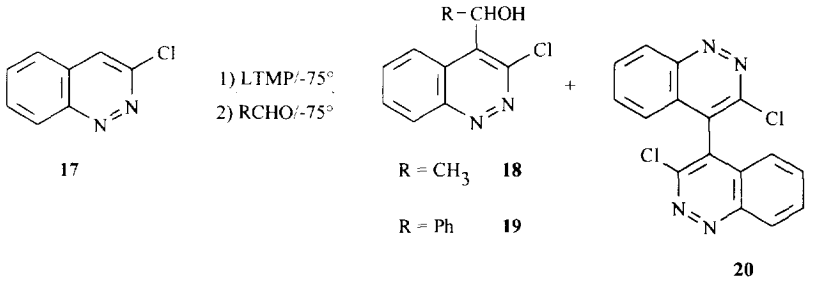


Table 3. Metallation of 3-chlorocinnoline **17** and reaction with electrophiles.

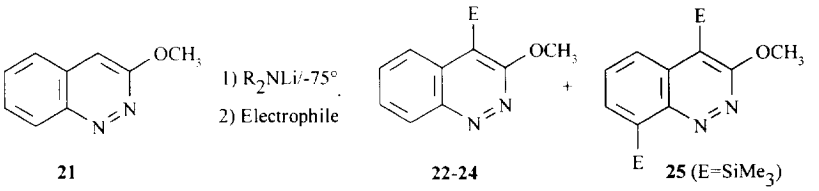
Entry	Metallation conditions	Electrophile	Product number	Yield	Yield of dimer **20**	Starting material recovered
1	1.1 LTMP/30 min.	EtOD	-	-	-	100 %
2	"	CH_3CHO/20eq	-	-	10 %	76 %
3	2.2 LTMP/30 min.	"	**18**	60 %	6 %	14 %
4	2.2 LTMP/1 h	"	**18**	81 %	-	9 %
5	2.2 LTMP/2 h	"	**18**	83 %	-	6 %
6	" "	PhCHO/2.2eq	**19**	88 %	-	-

The formation of a dimer like **20** had also been noticed in the metallation of 2-chloroquinoxaline[3] and was caused by the addition of the lithio derivative on the starting material followed by air oxidation during the workup of the reaction.

The need for an excess of metallating agent in the case of a chloro derivative was unusual, in most case the metallation of chlorodiazines needed only the stochiometric amount of alkylamide. This could be explained by the slow rate of the metallation reaction which needed 2 h to afford good yields and to recover only small quantities of the starting material (Table 3).

Metallation of 3-methoxycinnoline **21**.

Scheme 4



21 **22-24** **25** (E=$SiMe_3$)

Table 4. Metallation of 3-methoxycinnoline **21** and reaction with electrophiles.

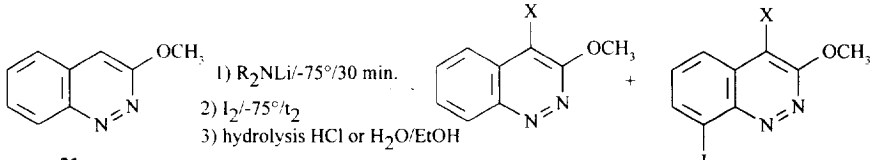
Entry	Metallation conditions	Electrophile	Product number	Yield
1	2.2 LTMP/30 min.	CH_3CHO/20eq	**22**	86 %
2*	2.2 LDA/30 min.	"	**22**	45 %
3	2.2 LDA/1 h	"	**22**	83 %
4	2.2 LTMP/30 min.	Ph CHO/2.2eq	**23**	91 %
5	" "	$ClSiMe_3$/2.2eq	**24**	74 %
			25	14 %
6*	" "	$ClSiMe_3$/2.2eq	**24**	63 %
			25	18 %

* entry 2: 52 % of starting material was recovered. None in the other experiments.
* entry 6: metallation by "in situ trapping technique"[21]

The yields with acetaldehyde and benzaldehyde were good and no dimer was present (Table 4: entries 1, 3, 4). The use of trimethylchlorosilane as electrophile (entry 5) afforded besides the *ortho* disubstituted product **24** a trisubstituted compound **15** bearing a trimethylsilyl moiety on the benzene ring. The result was the same with the "in situ trapping technique" (entry 6). As this electrophile did not react with the metallating agent, compound **24** could be metallated again in the reaction medium.

The metallation of **21** followed by reaction with iodine as electrophile gave some unexpected results (scheme 5).

Scheme 5



21 X = I **26** X = I **28**

X = Cl **27** X = Cl **29**

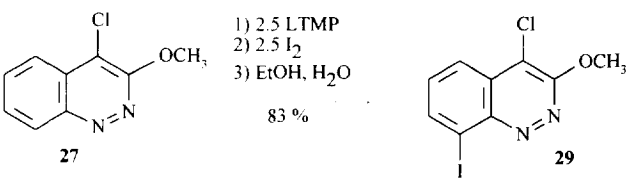
Table 5. Metallation of **21** followed by action of iodine.

Entry	1	2	3	4	5
Amount of LTMP	1.2	2.2	2.2	3	4
Amount of I_2	1.2	1.2	2.2	4	4
Hydrolysis medium	HCl/H_2O	HCl/H_2O	$EtOH/H_2O$	$EtOH/H_2O$	$EtOH/H_2O$
Starting material	23 %	-	-	-	-
27	48 %	88 %	-	-	-
26	-	-	73 %	39 %	25 %
28	-	-	22 %	51 %	69 %
29	-	5 %	-	-	-

The occurrence of a chlorine atom on the pyridazine nucleus could only be explained by a very easy nucleophilic substitution of the iodine atom which was present before the hydrolysis by a solution of aqueous hydrochloric acid, ethanol and THF. When ethanol and water was used for the hydrolysis, the iodo compound was found unchanged (Table 5: entries 3-5). To ascertain this hypothesis, compound **26** was reacted with hydrochloric acid in the same conditions as for the hydrolysis of the metallation reaction. A quantitative yield of compound **27** was obtained.

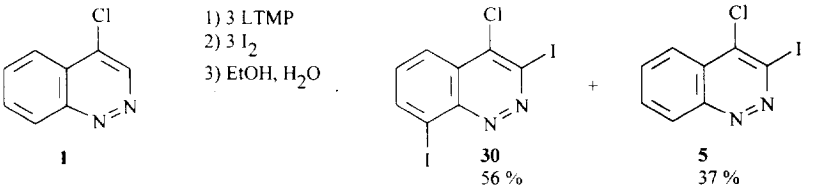
Disubstituted compounds **28**, **29** bearing a substituent on the benzene moiety were obtained. This disubstitution was also observed with chlorotrimethylsilane as electrophile (compound **25**). To verify the occurrence of a metallation on the benzene ring when the pyridazine ring was completely substituted, product **27** was metallated with an excess of metallating agent and product **29** was obtained with a good yield (Scheme 6).

Scheme 6



When considering the metallation of compound **27** on the benzene ring it was possible to suppose that the metallation of 4-chlorocinnoline **1** would afford similar results and that was tested successfully (Scheme 7).

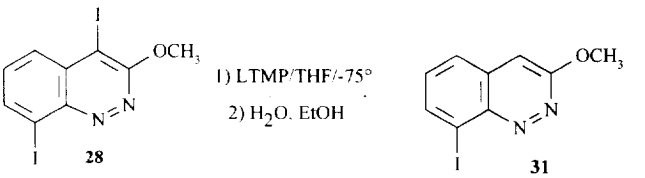
Scheme 7



The site of the iodine atom on the benzene ring remains to be identified unambiguouly.

In order to obtain the compound **31** which is unsubstituted in the 4 position we have performed a halogen lithium exchange reaction with LTMP and compound **28** followed by reaction with water (Scheme 8). A similar reaction has been recently described in the pyrimidine series.[22]

Scheme 8



The structure of compound **31** which bears a hydrogen at C_4 has been established by NMR. The spectra of this product have been compared with those of 3-methoxycinnoline **21** which presents a long range coupling between H_4 and H_8 (J= 0.8Hz). The more simple spectrum of the monoiodo compound **31** presented two doublets of doublet at 7.62 and 8.20 ppmn, a multiplet at 7.25 ppm and a singlet at 7.12 ppm which was attributed to H_4. This indicated that the iodine atom could be on C_5 or C_8; the absence of cross peak between H_4 and any signal in long range cosy spectrum and the absence of the $^5J_{4,8}$ coupling indicated that the iodine atom was on C_8. To check this result a N.O.E. difference experiment was performed; the N.O.E. difference spectrum resulting from continuous irradiation of H_4 highlighted a 6 % N.O.E. for the signal at 7.62 ppm which was so assigned to H_5.

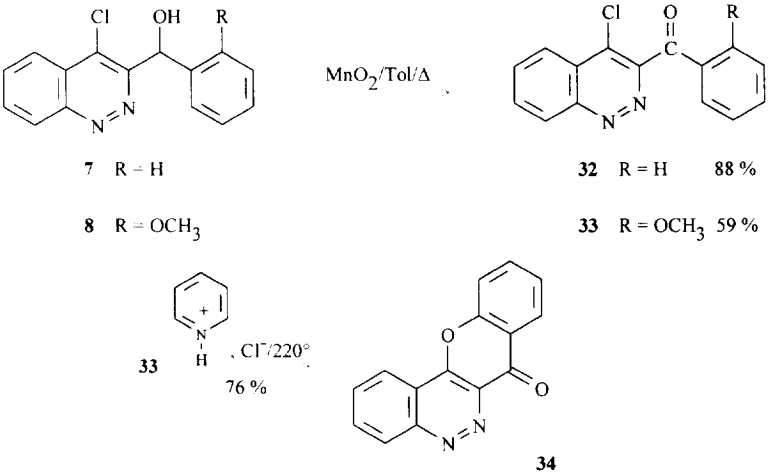
An MNDO calculation of the net charges of the hydrogen atoms of 3-methoxycinnoline **21** indicated that the second more charged hydrogen was H_8. So this is in good agreement with the fact that the second metallation site was on C_8 in peri of the N_1 nitrogen.

After having studied the metallation of cinnolines we present now the syntheses of a xanthone and diazepines using this reaction in a key step.

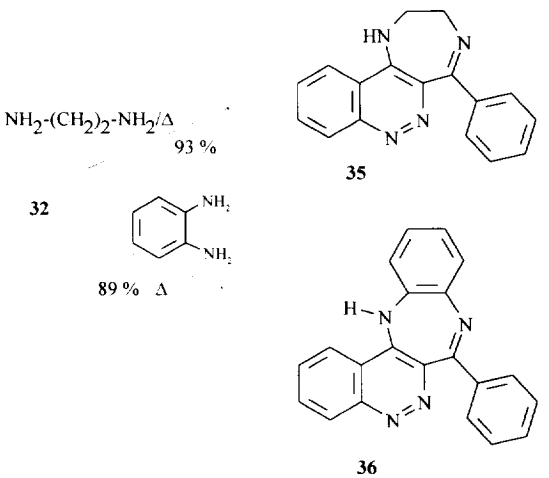
Synthesis of a xanthone and diazepines via metallation reaction

Compounds **7** and **8** were oxidized with manganese IV oxide to afford ketones **32** and **33**. Ketone **33** was cyclised with pyridinium hydrochloride following the method of Royer[23] and afforded xanthone **34** (Scheme 9).

Scheme 9



Two diazepines **35** and **36** were prepared from ketone **32**.



CONCLUSION

The great synthetic interest of the *o*-directed metallation reaction in the benzodiazine series was tested by the preparation of 3,4 *ortho* disubstituted compounds with yields in excess of 80 % from 3- and 4-chloro or 3- and 4-methoxycinnolines. The occurrence of a metallation on the benzene ring has also been highlighted and this could conduct also to synthetic applications which are currently under study in our laboratory.

EXPERIMENTAL

Melting points were determined on a Kofler Hot Stage and are uncorrected. The ^1H nmr spectra were recorded in deuteriochloroform or in deuterated dimethylsulfoxide on a Bruker AC 200 instrument. Microanalyses were performed on a Carlo Erba CHNOS 1106 apparatus. The IR spectra were obtained as potassium bromide pellets with a Perkin Elmer R12 spectrophotometer.

Tetrahydrofuran was distilled from benzophenone sodium and used immediately. Water content of the solvent was estimated by the modified Karl Fischer method (THF less than 50 ppm water). Metallations were performed under an argon atmosphere.

The compounds to react were handled with syringues through septa. All reagents were of commercial quality and were purchased from Aldrich Chemical Co or Janssen Pharmaceutica.

4-Chlorocinnoline 1

A mixture of 4-hydroxycinnoline (2 g, 13.7 mmoles), phosphorus oxychloride (1.94 ml, 20.5 mmoles) and pyridine (0.33 ml, 4.1 mmoles) in chlorobenzene (50 ml) was refluxed for 1 hour. After cooling and concentration of the solution, hydrolysis was carried out using water (50 ml) and made neutral with a saturated sodium carbonate solution. The mixture was extracted with dichloromethane (3 x 100 ml). The organic extract was dried (magnesium sulphate) and evaporated. The crude product was purified by column chromatography on silica gel [eluent dichloromethane/ethylacetate (8:2)], yield: 87 % of **1**, mp 78°; ^1H NMR ($CDCl_3$): δ 7.93 (m, 2H, H_6, H_7), 8.20 (d, 1H, J_{56}= 7.8 Hz, H_5), 8.56 (d, 1H, J_{78}= 8.3 Hz, H_8), 9.36 (s, 1H, H_3). Anal. Calcd for $C_8H_5N_2Cl$: C, 58.32; H, 3.04; N, 17.01. Found: C, 58.6; H, 3.0; N, 16.7.

4-Pivaloylaminocinnoline 15 and 1-pivaloyl-4-pivaloylimino-1,4-dihydrocinnoline 16

The reaction was performed in a pressure vessel. 4-Chlorocinnoline (2 g, 12.1 mmoles) was added to a saturated solution of ammonia in THF (40 ml) and the pressure vessel was heated at 140° for 12 h. After cooling to room temperature, the solvent was removed and the product was recrystallized in water, 1.47 g of 4-aminocinnoline was obtained, yield: 84 %, mp 211°.

A suspension of 4-aminocinnoline (1.4 g, 9.65 mmole) and triethylamine (1.49 ml, 10.6 mmoles) in tetrahydrofuran (30 ml) was cooled to 0° and pivaloylchloride (1.3 ml, 10.6 mmoles) was slowly introduced. The solution was stirred for 24 hours at room temperature. The mixture was then hydrolysed with water (50 ml) and extracted with dichloromethane (3 x 100 ml). The organic layer was dried (magnesium sulphate) and evaporated. The crude product was purified by column chromatography on silica gel (eluent dichloromethane) for a first fraction then dichloromethane/ethylacetate (4:6) for a second fraction).

The first fraction afforded compound **16** as a pale yellow powder, yield: 16 %, mp 100°; ^1H NMR ($CDCl_3$): δ 1.25 (s, 9H, COtBu), 1.42 (s, 9H, COtBu), 7.33 (t, 1H, J= 7.2 Hz, H_6), 7.56 (t, 1H, J= 8 Hz, H_7), 7.66 (s, 1H, H_3), 8.16 (d, 1H, J_{56}= 8 Hz, H_5), 8.32 (d, 1H, J_{78}= 8.7 Hz, H_8); ir: ν 3000-2870, 1717, 1670, 1618, 1459, 1166, 1068, 906, 765 cm^{-1}. Anal. Calcd for $C_{18}H_{23}N_3O_2$: C, 68,92; H, 7.34; N, 13.40. Found: C, 68.8; H, 7.4; N, 13.6.

The second fraction gave white crystals of **15**, yield: 32 %, mp 150°. ^1H NMR ($CDCl_3$): δ 1.40 (s, 9H, COtBu), 7.68 (m, 3H), 8.28 (d, 1H), 8.6 (s, 1H, NH), 9.96 (s, 1H, H_3). [The chemical shifts are very influenced by concentration due to π-stacking]; ir: ν 3381-2872, 1700, 1621, 1547, 1512, 1480, 1314, 1117, 765 cm^{-1}. Anal. Calcd for $C_{13}H_{15}N_3O$: C, 68,03; H, 6.54; N, 18.32. Found: C, 68.3; H, 6.5; N, 18.3.

3-Chlorocinnoline 17

A mixture of 3-hydroxycinnoline (2 g, 13.7 mmoles) and phosphorus oxychloride (60 ml) was refluxed for 6 days. After cooling and evaporation of the phosphorus oxychloride, hydrolysis was carried out using water (100 ml) and the reaction mixture was made neutral with a saturated sodium carbonate solution. The mixture was extracted with dichloromethane (3 x 100 ml). The organic extract was dried over magnesium sulphate and evaporated. The crude product was purified by column chromatography on silica gel [eluent dichloromethane/ethylacetate (97:3)], yield: 72 % of **17**, mp 90°; ^1H NMR ($CDCl_3$): δ 7.74 (m, 3H), 7.85 (s, 1H, H_4), 8.39 (d, 1H). Anal. Calcd for $C_8H_5N_2Cl$: C, 58,32; H, 3.04; N, 17.01. Found: C, 58.2; H, 3.0; N, 16.9.

3-Methoxycinnoline 21

In a 125 ml pressure vessel, 3-chlorocinnoline (2 g, 12.2 mmoles) was dissolved in methanol (20 ml). A solution of sodium methylate prepared with sodium (0.84 g, 36.5 mmoles) and methanol (20 ml) was added. Then the pressure vessel was heated in an oven at 120° for 4 hours. After cooling to room temperature the mixture was poured on a mixture of ice and water (100 ml) and stirred for 30 minutes. The solid was extracted with dichloromethane (3 x 100 ml). The organic layers were dried over magnesium sulphate and evaporated. The crude product was purified by sublimation, yield 93 %, mp 41°; ^{1}H NMR ($CDCl_3$): δ 4.30 (s, 3H, OCH_3), 7.26 (s, 1H, H_4), 7.66 (m, 3H), 8.38 (m, 1H, H_8). Anal. Calcd for $C_9H_8N_2O$: C, 67.50; H, 5.0; N, 17.50. Found: C, 67.4; H, 5.0; N, 17.6.

General procedure for metallation

A solution of n-butyllithium (1.6 M or 2.5 M in hexane) was added to cold (-30°), stirred, anhydrous tetrahydrofuran (25 ml) under an atmosphere of argon. Then diisopropylamine or 2,2,6,6-tetramethylpiperidine was added and the mixture was allowed to stand at 0° for 15 minutes after which it was cooled to -75°. The 3 or 4 substituted cinnoline dissolved in tetrahydrofuran (10 ml) was then added at -75° and the solution was stirred at -75° for a time t_1. The electrophile was introduced and stirring was continued for a time t_2 at -75°. Hydrolysis was then carried out at -75° using a mixture of 35 % aqueous hydrochloric acid (2 ml), ethanol (3 ml) and tetrahydrofuran (5 ml). The solution was then gently warmed to room temperature, made slightly basic with a saturated sodium hydrogenocarbonate solution. When the electrophile was iodine, the solution was discoloured with sodium thiosulphate and evaporated nearly to dryness. The residue was extracted with dichloromethane (3 x 50 ml). The organic extract was dried over magnesium sulphate then evaporated. The crude product was purified by column chromatography on silica gel.

(4-Chloro-3-cinnolinyl)ethanol 3

Metallation of **1** (165.8 mg, 1 mmole) according to the general procedure with n-butyllithium 2.5 M (450 µl, 1.1. mmole) and diisopropylamine (160 µl, 1.1. mmole) (t_1= 0.5 h) and reaction with 1 ml of acetaldehyde (t_2= 1 h), gave after chromatography [eluent dichloromethane/ethylacetate (65:35)] a yellow powder, yield: 89 % of **3**, mp 90°; ^{1}H NMR ($CDCl_3$): δ 1.69 (d, 3H, CH_3), 4.47 (s, 1H, OH), 5.58 (q, 1H, CH), 7.91 (m, 2H), 8.21 (t, 1H), 8.57 (t, 1H). ir: ν 3344, 3100-2929, 1541, 1475, 1363, 1264, 1095, 1011, 758 cm^{-1}. Anal. Calcd for $C_{10}H_9N_2OCl$: C, 57.53; H, 4.31; N, 13.42. Found: C, 57.6; H, 4.4; N, 13.2.

4-Chloro-3-methylcinnoline 4

Metallation of **1** (134.6 gm, 0.818 mmoles) according to the general procedure with n-butyllithium 2.5 M (360 µl, 0.90 mmole) and diisopropylamine (130 µl, 0.90 mmoles) (t_1= 0.5 h). Then reaction with 200 µl of iodomethane (t_2= 2 h), and chromatography [eluent dichloromethane/ethylacetate (8.2)] gave **4** as a green powder, yield 86 %, mp 88°; ^{1}H NMR ($CDCl_3$): δ 3.05 (s, 3H, CH_3), 7.83 (m, 2H), 8.16 (m, 1H), 8.53 (m, 1H); ir: ν 3100-2919, 1551, 1477, 1375, 775 cm^{-1}. Anal. Calcd for $C_9H_7N_2Cl$: C, 60.46; H, 3.92; N, 15.68. Found: C, 60.8; H, 3.8; N, 15.5.

4-Chloro-3-iodocinnoline 5

Metallation of **1** (200 mg, 1.22 mmoles) with 1.1. equivalent of LDA according to the general procedure (t_1= 0.5 h) then reaction with a solution of 370 mg (1.45 mmoles) of iodine in 5 ml of tetrahydrofuran (t_2= 2 h), gave after purification by column chromatography [eluent dichloromethane/ethylacetate (9:1)] 245.7 mg of a yellow powder, yield 70 % of **5**, mp 166°; ^{1}H NMR ($CDCl_3$): δ 7.87 (t, 1H), 7.95 (t, 1H), 8.14 (d, 1H, J_{56}= 7.7 Hz, H_5), 8.50 (d, 1H, J_{78}= 8.3 Hz, H_8); ir: ν 3100, 1606, 1542, 1501, 1460, 1411, 1328, 1242, 1154, 1053, 908, 768 cm^{-1}. Anal. Calcd for $C_8H_4N_2ICl$: C, 33.05; H, 1.38; N, 9.64. Found: C, 33.2; H, 1.2; N, 9.6. Another fraction gave 10 % of starting material.

4-Chlorocinnoline 3-carboxylic acid 6

Metallation of **1** (178.3 mg, 1.08 mmole) with 1.1 equivalent of LDA according to the general procedure (t_1= 0.5 h) then reaction with solid carbon dioxyde in excess (t_2= 2 h) afforded after filtration and drying in an oven 127 mg of **6** as a white powder, yield 57 %, mp > 260 °; ^{1}H NMR (DMSO-d_6): δ 7.68 (t, 1H), 7.84 (d, 1H), 7.99 (t, 1H), 8.23 (d, 1H); ir: ν 3200-2913, 1701, 1626, 1569, 1467, 1294, 1169, 774 cm^{-1}. Anal. Calcd for $C_9H_5N_2O_2Cl$: C, 51.80; H, 2.40; N, 13.43. Found: C, 51.6; H, 2.7; N, 13.4.

(4-Chloro-3-cinnolinyl)phenylmethanol 7

Metallation of **1** (254.4 mg, 1.54 mmoles) according to the general procedure with n-butyllithium and diisopropylamine (1.1 equivalent) (t_1= 0.5 h) and reaction with benzaldehyde (190 µl, 1.85 mmoles) (t_2= 4 h), gave after chromatography [eluent dichloromethane/ethylacetate (8:2)] 368 mg of a pale yellow solide, yield 88 % of **7**, mp 168°; ^{1}H NMR ($CDCl_3$): δ 5.40 (s, 1H, OH), 6.45 (s, 1H, CH), 7.33 (m, 3H), 7.46 (d, 1H), 7.52 (d, 1H), 7.91 (m, 2H), 8.19 (d, 1H), 8.59 (d, 1H); ir: ν 3400, 3050-3000, 2875, 1554, 1470, 1456, 1365, 1251, 1190, 1088, 1066, 1010, 770, 753, 702 cm^{-1}. Anal. Calcd for $C_{15}H_{11}N_2OCl$: C, 66.49; H, 4.06; N, 10.34. Found: C, 66.7; H, 3.9; N, 10.3. 3 % of starting material was recovered in another fraction.

(4-Chloro-3-cinnolinyl)-2-methoxyphenylmethanol 8

Metallation of **1** (177 mg, 1.07 mmoles) according to the general procedure with 1.1 equivalent of LDA according to the general procedure (t_1= 0.5 h) and reaction with orthoanisaldehyde (161 mg, 1.18 mmoles) in tetrahydrofuran (5 ml) (t_2= 2 h) gave after chromatography [eluent dichloromethane/ethylacetate (8:2)] 227 mg of **8** as a beige solid, yield 70 %, mp 148°; ^{1}H NMR ($CDCl_3$): δ 3.85 (s, 3H, OCH_3), 5.25 (s, 1H, OH), 6.79 (s, 1H, CH), 6.88 (2d, 2H), 7.25 (d+t, 2H), 7.86 (m, 2H), 8.17 (d, 1H), 8.57 (d, 1H); ir: ν 3400, 3068-2839, 1599, 1494, 1467, 1251, 1110, 768 cm^{-1}. Anal. Calcd for $C_{16}H_{13}N_2O_2Cl$: C, 63.84; H, 4.32; N, 9.31. Found: C, 63.9; H, 4.3; N, 9.2. 8 % of starting materiel was recovered in another fraction.

(4-Methoxy-3-cinnolinyl)methanol 9

Metallation of **2** (112 mg, 0.7 mmoles) according to the general procedure with n-butyllithium 1.6 M (1 ml, 1.54 mmoles) and diisopropylamine (220µl, 1.54 mmoles) (t_1= 0.5 h) and reaction with acetaldehyde (1 ml) (t_2= 1 h), gave after chromatography (eluent ethylacetate) a white solid, yield 81 % of **9**, mp 96°; ^{1}H NMR ($CDCl_3$): δ 1.68 (d, 3H, J= 6.5 Hz, CH_3), 4.14 (s, 3H, OCH_3), 4.40 (s, 1H, OH), 5.50 (s, 1H, J= 6.5 Hz), 7.79 (m, 2H), 8.09 (d, 1H), 8.50 (d, 1H); ir: ν 3395-2974, 1560, 1491, 1402, 1379, 1284, 1094, 987, 794 cm^{-1}. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.63; H, 5.88; N, 13.71. Found: C, 64.6; H, 5.9; N, 13.7.

(4-Methoxy-3-cinnolinyl)phenylmethanol 10

Metallation of **2** (111.1 mg, 0.7 mmoles) according to the general procedure with 2.2 equivalents of LDA (t_1= 0.5 h) and reaction with benzaldehyde (155 µl, 1.52 mmoles) (t_2= 2 h at T= -50°) gave after chromatography (eluent ethylacetate) a white powder, yield 81 % of **10**, mp 143°; ^{1}H NMR ($CDCl_3$): δ 3.87 (s, 3H, OCH_3), 5.59 (d, 1H, J= 6.9 Hz, OH), 6.37 (d, 1H, J= 6.9 Hz, CH) 7.24 (m, 3H), 7.46 (d, 2H), 7.67 (t, 1H), 7.75 (t, 1H), 8.00 (d, 1H), 8.49 (d, 1H); ir: ν 3372, 3084, 2943, 1561, 1491, 1400, 1381, 1326, 1187, 1100, 1063, 986, 934, 787, 764 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72,18; H, 5.26; N, 10.53. Found: C, 72.5; H, 5.3; N, 10.5.

5-Formyl 4-methoxycinnoline 11

Metallation of **2** (101.5 mg, 0.63 mmoles) with 2.2 equivalents of LDA according to the general procedure (t_1= 0.5 h) and reaction with ethylformiate (113 µl, 1.4 mmoles) (t_2= 2 h) gave after purification by chromatography [eluent ethylacetate/cyclohexane (6:4)] a white solid, yield 57 %, mp 198°; ^{1}H NMR ($CDCl_3$): δ ; 4.26 (s, 3H, OCH_3), 7.78 (t, 1H), 7.94 (t, 1H), 8.31 (d, 1H), 8.50 (d, 1H), 10.64 (s, 1H, CHO). ir: ν 3500, 2956, 2856, 1696, 1613, 1533, 1489, 1365, 940, 768 cm^{-1}. Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.26; N, 14.89. Found: C, 63.6; H, 4.2; N, 14.8.

3-Iodo-4-methoxycinnoline 12

Metallation of **2** (81 mg, 0.506 mmoles) with 2.2 equivalents of LDA according to the general procedure (t_1= 0.5 h) then reaction with a solution of 283 mg (1.11 mmoles) of iodine in 5 ml of tetrahydrofuran (t_2= 2 h) gave after column chromatography [eluent dichloromethane/ethylacetate (4:6)] a beige solid, yield 77 % of **12**, mp 124°; ^{1}H NMR ($CDCl_3$): δ 4.15 (s, 3H, OCH_3), 7.78 (t, 1H), 7.88 (t, 1H), 8.08 (d, 1H), 8.51 (d, 1H); ir: ν 3060, 2960, 1600, 1560, 1480, 1440, 1370, 1270, 1200, 1150, 1100, 1060, 960, 900, 840, 780 cm^{-1}. Anal. Calcd for $C_9H_7N_2OI$: C, 37.78; H, 2.45; N, 9.79. Found: C, 38.0; H, 2.2; N, 9.9. Another fraction gave 9 % of starting material.

4-Methoxy-3-methylcinnoline 13 and 3-ethyl-4-methoxycinnoline 14

Metallation of **2** (233.9 mg, 1.46 mmoles) with 2.2 equivalents of LDA according to the general procedure (t_1= 0.5 h) then reaction with 300 µl of iodomethane (t_2= 2 h) and chromatography [eluent dichloromethane/ethylacetate (5:5)] gave in a first fraction **14**, yield 24 %, mp 228°; ^{1}H NMR ($CDCl_3$): δ 1.47 (t, 3H, J= 7.5 Hz, CH_3), 3.25 (q, 2H, J= 7.5 Hz, CH_2), 4.05 (s, 3H, OCH_3), 7.73 (m, 2H), 8.05 (d, 1H), 8.47 (d, 1H). ir: ν 3100-2875, 1546, 1476, 1375, 1261, 1193, 1096, 751 cm^{-1}. Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.21; H, 6.38; N, 14.89. Found: C, 70.1; H, 6.2; N, 15.0.

Another fraction gave **13** as white crystals, yield 34 %, mp 77°; H NMR ($CDCl_3$): δ 2.93 (s, 3H, Ch_3), 4.07 (s, 3H, OCH_3), 7.74 (m, 2H), 8.10 (d, 1H), 8.49 (d, 1H). ir: ν 3100-2925, 1615, 1566, 1487, 1399, 1368, 1264, 1092, 978, 774 cm^{-1}. Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.97; H, 5.75; N, 16.09. Found: C, 68.9; H, 5.7; N, 16.1.

Attempts of metallation with 4-pivaloylaminocinnoline 15

Metallation of **15** (203 mg, 0.89 mmoles) according to the general procedure with 4 equivalents of LDA (t_1= 0.5 h) then reaction with iodomethane (t_2= 2 h) returned 92 % of **15**. Metallation of **15** with 4 equivalents of LDA (t_1= 1 h) then reaction with acetaldehyde (t_2= 2 h) gave 97 % of starting material. The same attempt with 4 equivalents of LTMP gave quantitatively the starting material. The attempt with 4 equivalents of LDA performed at -40° and at 0° gave respectively 98 % and 76 % of starting material. Metallation of **15** with 4 equivalents of LDA (t_1= 0.5 h) at room temperature then deuteriolysis with a mixture of DCl (0.5 ml), EtOD (0.3 ml) and THF (5 ml) returned 73 % of **15**. Metallation of **15** with 2.8 equivalents of phenyllithium at -75° (t_1= 1 h) then deuteriolysis gave 86 % of starting material. Metallation of **15** with 2.2 equivalents of methyllithium (t_1= 1 h) at -75° then deuteriolysis returned 97 % of **15**. Metallation of **15** with 2.2 equivalents of n-butyllithium at -75° (t_1= 1 h) then deuteriolysis gave 90 % of starting material. The same attempt (t_1 = 3h) gave 76 % of **15**. The same attempt (t_1= 1 h) performed at -40° returned 56 % of starting material **15**. The same attempt at -75° (t_1= 1 h) with 2.2 equivalents of tetramethylethylenediamine in addition returned 76 % of starting material.

(3-Chloro-4-cinnolinyl)methanol 18

Metallation of **17** (196 mg, 1.19 mmoles) with n-butyllithium 1.6 M (1.64 ml, 2.62 mmoles) and 2,2,6,6-tetramethylpiperidine (442 µl, 2.62 mmoles) according to the general procedure (t_1= 2 h) then reaction with 1 ml of acetaldehyde (t_2= 1 h) gave after chromatography [eluent petroleum ether/ethylacetate (5:5)] a white solid, yield 83 % of **18**, mp 144°; ^{1}H NMR ($CDCl_3$): δ 1.67 (d, 3H, J= 6.8 Hz, CH_3), 4.75 s, 1H, OH), 5.72 (q, 1H, J= 6.8 Hz, CH), 7.70 (m, 2H), 8.22 (d, 1H), 8.84 (d, 1H); ir: ν 3386, 2978, 1613, 1554, 1511, 1404, 1276, 1170, 1124, 1059, 764 cm^{-1}. Anal. Calcd for $C_{10}H_9N_2OCl$: C, 57.53; H, 4.31; N, 13.42. Found: C, 57.7; H, 4.2; N, 13.3. Another fraction afforded 6 % of starting material.

(3-Chloro-4-cinnolinyl)phenylmethanol 19

Metallation of **17** (191.5 mg, 1.16 mmoles) with 2.2 equivalents of LTMP according to the general procedure (t_1= 2h) and reaction with benzaldehyde (260 µl, 2.56 mmoles) gave after chromatography [eluent petroleum ether/ethylacetate (7:3)] the compound **19** as a beige solid, yield 88 %, mp 215°; H NMR (DMSO-d_6): δ 6.60 (d, 1H, J= 4.3 Hz, CH), 6.97 (d, 1H, J= 4.3 Hz, OH), 7.29 (m, 5H), 7.87 (2t, 2H), 8.46 (2d, 2H);

ir: ν 3194, 1552, 1517, 1491, 1426, 1275, 1171, 1096, 1049, 934, 768, 700 cm^{-1}. Anal. Calcd for $C_{15}H_{11}N_2OCl$: C, 66.49; H, 4.06; N, 10.34. Found: C, 66.5; H, 4.0; N, 10.4.

3,3'-Dichloro-4,4'-bicinnolinyl 20

Metallation of **17** (195 mg, 1.19 mmoles) with 1.1 equivalent of LTMP according to the general procedure (t_1= 0.5 h) and reaction with 1 ml of acetaldehyde (t_2= 1 h) gave after chromatography [eluent cyclohexane/ethylacetate (6:4)] a pale yellow powder, yield 10 % of **20**, mp > 265°; ^1H NMR ($CDCl_3$): δ 7.12 (d, 1H), 7.73 (t, 2H), 7.96 (t, 2H), 8.75 (d, 2H) ; ir: ν 3066, 1559, 1508, 1436, 1271, 1248, 1190, 1167, 1062, 759 cm^{-1}. Anal. Calcd for $C_{16}H_8N_4Cl_2$: C, 58.72; H, 2.45; N, 17.13. Found: C, 59.1; H, 2.5; N, 17.1. In a first fraction 76 % of starting material were recovered.

(3-Methoxy-4-cinnolinyl)methanol 22

Metallation of **21** (109.8 mg, 0.686 mmoles) with n-butyllithium 2.3 M (656 µl, 1.5 mmoles) and 2,2,6,6-tetramethylpiperidine (255 µl, 1.5 mmoles) according to the general procedure (t_1= 0.5 h) and reaction with 1 ml of acetaldehyde (t_2= 1 h) then purification by column chromatography [eluent dichloromethane/ethylacetate (8:2)] gave the alcohol **22**, yield 86 %, mp 125°; ^1H NMR ($CDCl_3$): δ 1.56 (d, 3H, J= 6.7 Hz, CH_3), 4.13 (s, 3H, OCH_3), 4.43 (s, 1H, OH), 5.58 (q, 1H, J= 6.7 Hz, CH), 7.44 (m, 2H), 8.12 (m, 1H), 8.31 (m, 1H); ir: ν 3275, 2974, 1561, 1458, 1322, 1082, 760 cm^{-1}. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.66; H, 5.88; N, 13.72. Found: C, 64.9; H, 5.9; N, 13.6.

(3-Methoxy-4-cinnolinyl)phenylmethanol 23

Metallation of **21** (201.7 mg, 1.26 mmoles) with 2.2 equivalents of LTMP according to the general procedure (t_1= 0.5 h) then reaction with benzaldehyde (280 µl, 2.77 mmoles) (t_2= 2 h) and purification by column chromatography [eluent cyclohexane/ethylacetate (6:4)] gave a beige solid **23**, yield 91 %, mp 145°; ^1H NMR ($CDCl_3$): δ 4.28 (s, 4H, OCH_3 + OH), 6.67 (s, 1H, CH), 7.31 (m, 5H), 7.57 (m, 2H), 8.20 (m, 1H), 8.34 (m, 1H); ir: ν 3168, 2942, 1558, 1532, 1458, 1410, 1319, 1240, 1128, 1054, 758 cm^{-1}. Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.10; H, 5.26; N, 10.51. Found: C, 72.1; H, 5.6; N, 10.7.

3-Methoxy-4-trimethylsilylcinnoline 24 and 3-methoxy-4,8-ditrimethylsilylcinnoline 25

21 was metallated by "in situ trapping technique". LTMP was prepared according to the general procedure with n-butyllithium 1.6 M (1.22 ml, 3.05 mmoles), 2,2,6,6-tetramethylpiperidine (515 µm, 3.05 mmoles). **21** (222 mg, 1.39 mmoles) and trimethylsilylchloride (390 µl, 3.05 mmoles) were introduced simultaneously and stirring was continued at -75° for 0.5 h. Then hydrolysis, neutralisation and extraction were performed as in the general procedure. The purification of the crude product by column chromatography [eluent cyclohexane/ethylacetate (9:1)] afforded in a first fraction compound **25** as a solid, yield 18 %, mp 70°; ^1H NMR ($CDCl_3$): δ 0.50 (s, 9H, $SiMe_3$), 0.52 (s, 9H, $SiMe_3$), 4.31 (s, 3H, OCH_3), 7.51 (t, 1H, J_{67}= 8.7 Hz, J_{56}= 6.5 Hz, H_6), 7.73 (d, 1H, J_{56}= 6.5 Hz, H_5), 8.04 (d, 1H, J_{67}= 8.7 Hz, H_7); ir: ν 3000, 2951, 2998, 1506, 1380, 1298, 1246, 1112, 928, 843, 767 cm^{-1}. Anal. Calcd for $C_{15}H_{24}N_2OSi_2$: C, 59.13; H, 7.88; N, 9.20. Found: C, 59.0; H, 8.1; N, 9.1.

A second fraction gave a yellow solid, yield 63 % of **24**, mp 52°; ^1H NMR ($CDCl_3$): δ 0.45 (s, 9H, $SiMe_3$), 4.24 (s, 3H, OCH_3), 7.45 (m, 2H), 7.95 (m, 1H), 8.29 (m, 1H); ir: ν 3000, 2943, 2897, 1546, 1511, 1456, 1315, 1240, 1112, 998, 849, 773 cm^{-1}. Anal. Calcd for $C_{12}H_{16}N_2OSi$: C, 61.97; H, 6.89; N, 12.05. Found: C, 62.2; H, 7.1; N, 12.1.

4-Chloro-3-methoxycinnoline 27 and 4-chloro-8-iodo-3-methoxycinnoline 29

Metallation of **21** (210 mg, 1.31 mmoles) with n-butyllithium 2.5 M (1.15 ml, 2.58 mmoles) and 2,2,6,6-tetramethylpiperidine (487 µl, 2.58 mmoles) according to the general procedure (t_1= 0.5 h) and reaction with a solution of 400 mg (1.58 mmoles) of iodine in 5 ml of tetrahydrofuran (t_2= 0.5 h) gave after chromatography [eluent cyclohexane/ethylacetate (8:2)] a yellow powder, yield 88 % of **27**, mp 110°; ^1H NMR ($CDCl_3$): δ 4.27 (s, 3H, OCH_3), 7.49 (m, 2H), 7.80 (d, 1H), 8.18 (d, 1H); ir: ν 3000, 2948, 1582, 1461,

1421, 1326, 1237, 1114, 1072, 774 cm^{-1}. Anal. Calcd for $C_9H_7N_2OCl$: C, 55.53; H, 3.60; N, 14.40. Found: C, 55.7; H, 3.5; N, 14.3.

In a first fraction compound **29** was obtained as a beige powder, yield 5 %, mp 182°; ^1H NMR ($CDCl_3$): δ 4.43 (s, 3H, OCH_3), 7.39 (t, 1H, J_{6-7}= 7.1 Hz, J_{5-6}= 8.6 Hz, H_6), 8.06 (d, 1H, J_{5-6}= 8.6 Hz, H_5), 8.29 (d, 1H, J_{6-7}= 7.1 Hz, H_7); ir: ν 3000, 1600, 1565, 1391, 1311, 1125, 1077, 764 cm^{-1}. Anal. Calcd for $C_9H_6N_2ClOI$: C, 33.70; H, 1.87; N, 8.74. Found: C, 34.0; H, 1.9; N, 8.7.

Compound **26** (90 mg, 0.314 mmoles) after dissolution in 15 ml of tetrahydrofuran was reacted with a mixture of hydrochloric acid (2 ml), ethanol (3ml) and tetrahydrofuran (5 ml) for 15 minutes at 0° then 15 minutes at room temperature, after neutralization, extraction and evaporation of solvents, a quantitative yield of **27** was obtained.

Compound **29** was also obtained by metallation of **27** (120 mg, 0.617 mmoles) according to the general procedure with 2.5 equivalents of LTMP (t_1= 0.5 h) and reaction with a solution of iodine (383 mg, 1.51 mmoles) in 10 ml of tetrahydrofuran (t_2= 2 h). Hydrolysis was performed with a mixture ethanol/water (8:2) at -75°. After purification as above, **29** was obtained, yield 83 %.

4-Iodo-3-methoxycinnoline 26 and 4,8-diodo-3-methoxycinnoline 28

21 (228 mg, 1.43 mmoles) was metallated according to the general procedure with 2.2 equivalents of LTMP (t_1= 0.5 h) and reacted with a solution of iodine (798 mg, 3.14 mmoles) in 10 ml of tetrahydrofuran (t_2= 2 h). Hydrolysis was performed with a mixture ethanol/water (8:2) at -75°. After purification by column chromatography, in a first fraction a yellow powder was obtained, yield 23 % of **28**, mp 162°; ^1H NMR ($CDCl_3$): δ 4.39 (s, 3H, OCH_3), 7.36 (t, 1H, J_{67}= 7.1 Hz and J_{56}= 8.6 Hz, H_6), 7.84 (d, 1H, J_{56}= 8.6 Hz, H_5), 8.27 (d, 1H, J_{67}= 7.1 Hz, H_7)$_7$$_H$; ir: ν 2944, 1552, 1391, 1302, 1166, 1124, 1070, 677 cm^{-1}. Anal. Calcd for $C_9H_6N_2OI_2$: C, 26.23; H, 1.46; N, 6.80. Found: C, 26.4; H, 1.5; N, 6.8.

A second fraction gave yellow crystals, yield 73 % of **26**, mp 155°; ^1H NMR ($CDCl_3$): δ 4.37 (s, 3H, OCH_3), 7.64 (m, 2H), 7.81 (d, 1H), 8.30 (d, 1H); ir: ν 2945, 1548, 1521, 1455, 1318, 1238, 1113, 1060, 758 cm^{-1}. Anal. Calcd for $C_9H_7N_2OI$: C, 37.75; H, 2.45; N, 9.79. Found: C, 37.7; H, 2.6; N, 9.7.

4-Chloro-3,8-diodocinnoline 30

Metallation of **1** (198.6 mg, 1.21 mmoles) with 3 equivalents of n-butyllithium and 2,2,6,6-tetramethylpiperidine according to the general procedure (t_1= 0.5 h) and reaction with a solution of iodine (918 mg, 3.62 mmoles) in tetrahydrofuran (10 ml) (t_2= 2 h) gave after chromatography [eluent dichloromethane) 37 % of **5** and compound **30**, yield 56 % , mp 242°; ^1H NMR ($CDCl_3$): δ 7.55 (t, 1H, H_6), 8.20 (d, 1H, J_{56}= 8.5 Hz, H_5),$_5$ 8.55 (d, 1H, J_{67}= 7.3 Hz, H_7); ir: ν 3000, 1654, 1592, 1438, 1381, 1328, 1079, 996, 812, 772 cm^{-1}. Anal. Calcd for $C_8H_3N_2I_2Cl$: C, 23.05; H, 0.72; N, 6.72. Found: C, 23.2; H, 0.7; N, 6.7.

8-Iodo-3-methoxycinnoline 31

Metallation of **29** (121.2 mg, 0.294 mmoles) with 3 equivalents of LTMP according to the general procedure for 3.5 hours, with temperature from -70° to -20°, and hydrolysis with a mixture ethanol/water (8:2) at -20°, gave after column chromatography (eluent dichloromethane) 88 % of starting material and a yellow powder, yield 12 % of **31**, mp 124°; ^1H NMR ($CDCl_3$): δ 4.23 (s, 3H, OCH_3), 7.04 (s, 1H, H_4), 7.15 (t, 1H, H_6), 7.55 (d, 1H, J_{56}= 8.6 Hz, H_5),8.1 (d, 1H, J_{67}=7.1 Hz, H_7); ir: ν 3050, 2981, 1607, 1582, 1446, 1394, 1321, 1251, 1147, 1021, 777 cm^{-1}. Anal. Calcd for $C_9H_7N_2OI$: C, 37.75; H, 2.45; N, 9.79. Found: C, 37.8; H, 2.5; N, 9.8.

General procedure for oxidation of alcohols 7 and 8

A suspension of alcohol, 50 ml of dry toluene and manganese IV oxide (10 equivalents) was heated at reflux with a Dean Stark apparatus for 15 h. The mixture was filtered, manganese oxide was washed with dichloromethane (20 ml) and solvents evaporated under vacuum. The crude product was purified by column chromatography on silica gel.

7-Oxo-7H-benzopyrano[2,3-c]cinnoline 34

Oxidation of **8** (230.0 mg, 0.76 mmoles) according to the general procedure then purification by chromatography [eluent dichloromethane/ethylacetate (9:1)], yield 59 % of ketone **33**, mp 130°; ^{1}H NMR (DMSO-d_6): δ 3.42 (s, 3H, OCH_3), 6.92 (d, 1H), 7.14 (t, 1H), 7.58 (t, 1H), 7.98 (m, 3H), 8.35 (d, 1H), 8.61 (d, 1H); ir: ν 3253-2927, 1662, 1598, 1470, 1245, 753 cm^{-1}. Anal. Calcd for $C_{16}H_{11}N_2O_2Cl$: C, 64.32; H, 3.69; N, 9.38. Found: C, 64.5; H, 3.8; N, 9.1.

A solution of this ketone (90 mg, 0.301 mmoles) in hot anhydrous pyridinium hydrochloride (10 ml) was heated at 210° for 20 minutes. The hot solution was poured on to ice (50 g) and this mixture was extracted with dichloromethane (3 x 50 ml). This extract was dried (magnesium sulphate) and evaporated to dryness. The crude product was purified by column chromatography on silica gel [eluent ethylacetate/dichloromethane (8:2)], yield 76 % of **34**, mp > 260°; ^{1}H NMR ($CDCl_3$): δ 7.53 (t, 1H), 7.70 (d, 1H), 7.86 (t, 1H), 8.0 (t, 1H), 8.09 (t, 1H), 8.53 (d, 1H), 8.60 (d, 1H), 8.78 (d, 1H); ir: ν 3058, 1661, 1609, 1467, 1424, 1283, 787, 758 cm^{-1}. Anal. Calcd for $C_{15}H_8N_2O_2$: C, 72.58; H, 3.22; N, 11.29. Found: C, 72.8; H, 3.1; N, 11.1.

2,3-Dihydro-1H-5-phenylcinnolino[3,4-b][1,4]diazepine 35

Oxidation of 7 (289.6 mg, 1.07 mmoles) according to the general procedure followed by purification by chromatography (eluent dichloromethane) yielded 88 % of ketone **32**, mp 194°; ^{1}H NMR (DMSO-d_6): δ 7.52 (m, 3H), 7.68 (m, 2H), 7.87 (m, 3H), 8.10 (d, 1H); ir: ν 3191-2966, 1676, 1570, 1473, 1238, 1163, 759 cm^{-1}. Anal. Calcd for $C_{15}H_9N_2OCl$: C, 66.98; H, 3.35; N, 10.42. Found: C, 67.0; H, 3.6; N, 10.2.

A solution of this ketone (100.8 mg, 0.38 mmoles) in 1 ml of ethylenediamine was heated at 95° under an atmosphere of argon for 3 hours. After cooling, the mixture was poured onto a saturated sodium hydrogenocarbonate solution and extracted with chloroform (3 x 50 ml). Organic layers were washed with 10 ml of saturated sodium carbonate solution, 10 ml of water and dried (magnesium sulphate) and evaporated to dryness. The crude product was purified by column chromatography on alumine [eluent ethylacetate/dichloromethane (9:1)]. A white powder was obtained, yield 93 % of **35**, mp 225° (decomposition); ^{1}H NMR (DMSO-d_6): δ 3.73 (m, 2H, CH_2N), 4.13 (m, 2H, CH_2N), 7.36 (m, 5H, Ph), 7.71 (t, 1H), 7.83 (t, 1H), 8.16 (d, 1H), 8.21 (s, 1H, NH), 8.34 (d, 1H); ir: ν 3500-3299, 2927, 1609, 1561, 1348, 1232, 1136, 768, 697 cm^{-1}. Anal. Calcd for $C_{17}H_{14}N_4$: C, 74.37; H, 5.10; N, 20.41. Found: C, 74.3; H, 5.3; N, 20.1.

7-Phenyl-13H-benzo[f]cinnolino[3,4-b][1,4]diazepine 36

A solution of ketone **32** (120.9 mg, 0.45 mmoles) obtained from **7** according to the general procedure, in 7 ml of dimethylformamide was heated with o-phenylenediamine (54 mg, 0.49 mmoles) at 155° under a dry atmosphere of argon for 24 hours. The mixture was then evaporated to dryness. The crude product was purified by column chromatography on silica gel [eluent dichloromethane/ethylacetate (9:1)]. Golden yellow needles were obtained, yield 89 % of **36**, mp 188° (decomposition); ^{1}H NMR ($CDCl_3$): δ 6.08 (s, 1H, NH), 6.81 (d, 1H), 7.07 (t, 1H), 7.16 (t, 1H), 7.43 (m, 4H), 7.67 (2d, 2H), 7.79 (t, 1H), 7.90 (t, 1H), 8.04 (d, 1H), 8.49 (d, 1H); ir: ν 3273, 1617, 1473, 1421, 1232, 1169, 1108, 767, 694 cm^{-1}. Anal. Calcd for $C_{21}H_{14}N_4$: C, 78.15; H, 4.34; N, 17.37. Found: C, 78.3; H, 4.3; N, 17.2.

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