Directed Lithiation of 4-Halopyridines: Chemoselectivity, Regioselectivity and Application to Synthesis

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4-Chloro and 4-fluoropyridines were *ortho*-lithiated by *n*-butyllithium-TMEDA chelate or lithium diisopropylamide at low temperature. The resulting 3-lithio 4-halopyridines were reacted with electrophiles which led to various 3,4-disubstituted pyridines. The versatility of this functionalization is enhanced by the 4-halogen reactivity towards nucleophiles such as water, methylate and amines. Some of the 3,4-disubstituted synthons were annelated to naphthyridine, xanthone and coumarin or condensed to Hantsch-ester or to "chlotrimazol" analogues. Lithiation of 4-fluoropyridine led in one step to 3,4-pyridyne, which was trapped by cycloaddition with furans.

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Metalation [1] of pi-deficient heterocycles (pyridine, quinoline ...) has been masked for a while by numerous competitive reactions [2], which generally result from nucleophilic attacks on these low LUMO-level aromatics. Nevertheless this reaction has developed and grown in interest during the last fifteen years. It has quickly appeared as a powerful functionalization strategy, inasmuch as electrophilic substitutions are often difficult to achieve in these series.

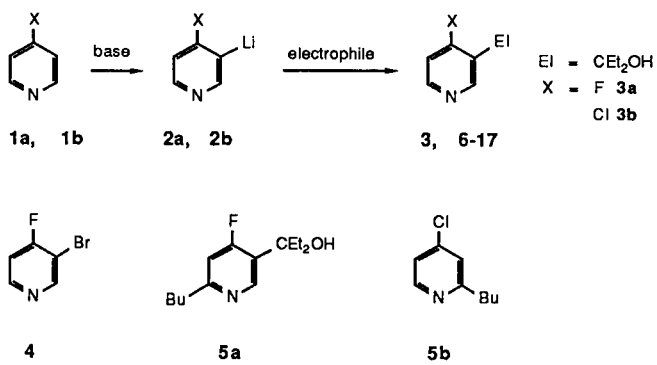
Today, many groups are available for directing *ortho*-lithiation of pyridines [2]. This provides a valuable route to polyfunctional heteroaromatic synthons, which could not be previously obtained by classical methods. Our laboratory has significantly contributed to this work, and as soon as 1972, we found that halogens could induce *ortho*-lithiation of pyridine [3].

We wish to report here that 4-halopyridines (chloro and fluoro) were selectively lithiated either by butyllithium or lithium diisopropylamide. This allows convenient synthesis of 3,4-disubstituted pyridines, and some applications are also described.

Metalation Conditions.

4-Fluoropyridine (**1a**) and 4-chloropyridine (**1b**) were *ortho*-lithiated by the *n*-Buli/TMEDA chelate in THF, and the resulting 4-halo-3-lithiopyridines **2a** and **2b** were characterized by reaction with 3-pentanone (Scheme 1).

Scheme I



Univocal synthesis of **3a** was carried out by bromine-lithium exchange between 3-bromo-4-fluoropyridine and *n*-butyllithium in diethyl ether at −60°, followed by reaction with 3-pentanone.

Lithiation of 4-halopyridines **1a** and **1b** by butyllithium, is not completely chemoselective, and competitive additions could not be avoided. This led to the side formation of small amounts (less than 10%) of 3-(2-butyl-4-fluoro-5-pyridyl)-3-pentanol (**5a**) and 2-butyl-4-chloropyridine (**5b**) together with metalation products of 4-fluoro and 4-chloropyridines respectively.

Table I

X	Base	Electrophile	El	Compound	Yield
F	*n*-Buli	$ClSiMe_3$	$SiMe_3$	**6a**	75%
F	*n*-Buli	$IAsMe_2$	$AsMe_2$	**7**	55%
Cl	LDA	$ClSiMe_3$	$SiMe_3$	**6b**	70%
Cl	LDA	PhS-SPh	SPh	**8**	30%
Cl	LDA	I-CH_3	CH_3	**9**	70%
Cl	LDA	CH_2-CH_2 (O)	CH_2-CH_2OH	**10**	30%
F	LDA	Ph-CHO	CHOH-Ph	**11a**	65%
Cl	LDA	Ph-CHO	CHOH-PH	**11b**	90%
F	*n*-Buli	EtCOEt	CEt_2OH	**3a**	65%
Cl	*n*-Buli	EtCOEt	CEt_2OH	**3b**	60%
F	*n*-Buli	MeCOMe	CMe_2OH	**12a**	65%
Cl	LDA	MeCOMe	CMe_2OH	**12b**	60%
Cl	LDA	Ph_2CO	CPh_2OH	**13**	55%
Cl	LDA	MeCHO	CHOHMe	**14**	40%
NMe_2	*n*-Buli	Me_2NCHO	CHO	**15**	45%
Cl	LDA	HCO_2Et	CHO	**16**	40%
F	LDA	2-MeOPh-CHO	CHOH-2-MeOPh	**17**	80%

Ortho-lithiation of **1a** and **1b** was carried out with complete chemoselectivity by LDA (metalation of **1b** by LDA has also been studied by other groups [4,5]). The intermediate 4-chloro-3-lithiopyridine (**2b**) precipitated in diethyl ether, which allowed higher metalation yields than in THF (this was not observed with 4-fluoropyridine). 4-Halo-3-lithiopyridines **2a** and **2b** are quite stable between $-70°$ and $-40°$.

Application to Synthesis.

Reaction of **2a** and **2b** with electrophiles afforded 3-substituted 4-halopyridines in moderate to good yields (Scheme 1) (Table 1). A wide variety of functions could be introduced at the 3-position, such as Me_3Si, Me_2As, C_6H_5-S, CR_2OH, CHROH, CH_2-CH_2-OH, CH_3 and CHO. Most of these new 3,4-disubstituted pyridines are stable, especially the secondary and tertiary 4-halo-3-pyridylmethanols **3,11-14**.

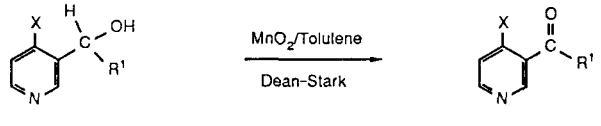
Reaction of 4-chloro-3-lithiopyridine (**2b**) with ethyl formate or dimethylformamide, led to the expected 4-chloropyridine-3-carboxaldehyde (**16**), together with small amounts of the corresponding hydrate. Formylation of 4-fluoro-3-lithiopyridine (**2a**) by dimethylformamide gave 4-dimethylaminopyridine-3-carboxaldehyde (**15**), due to nucleophilic substitution of fluorine by lithium dimethylamide [6].

Synthesis of 3,4-Disubstituted Pyridines.

Some of these 3-functionalized derivatives could be further transformed into new synthons, either by halogen-substitution or by modification of the 3-substituent. 4-Halo, 4-hydroxy, 4-methoxy and 4-aminopyridines bearing a 3-carboxy substituent have been thus prepared.

Secondary 4-halo-3-pyridylalcohols **11a,b**, **14-17** were oxidized to the corresponding ketones **18a,b**, and **19-20** using activated manganese dioxide in refluxing toluene [7] (Scheme 2). Attempts to prepare chloroketone **18b** in one step by reaction of 4-chloro-3-lithiopyridine (**2b**) with methyl benzoate failed and bis(4-chloro-3-pyridyl)phenylmethanol (**21**) was obtained.

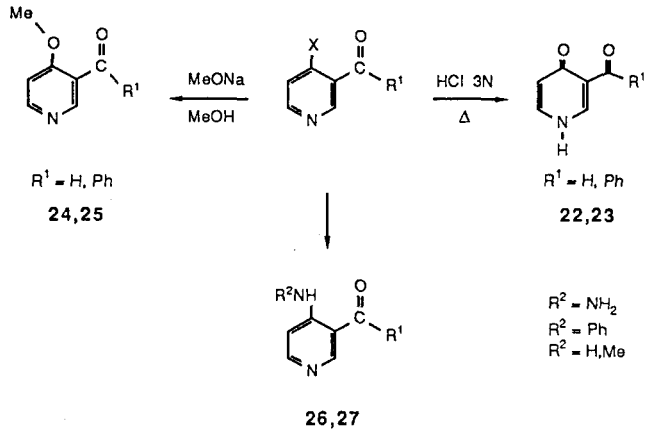
Scheme II



11a,11b,14,17 (R^1 = Ph, Me, 2-MeOPh) **18a,18b,19,20**

4-Halopyridines activated by a 3-carbonyl moiety underwent nucleophilic substitutions by reaction with hydrochloric acid, sodium methylate, ammonia or methylamine (Scheme 3).

Scheme III



R^1 = H, Ph **24,25** **22,23** R^1 = H, Ph

R^2 = NH_2, Ph, H,Me

26,27

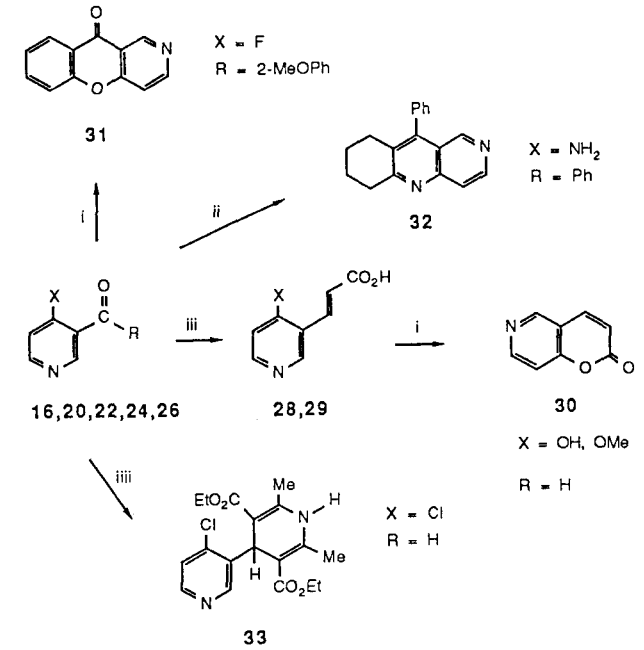
Reaction of (4-fluoro-3-pyridyl)phenylmethanone (**18a**) with ethanolic ammonia or methylamine was carried out at room temperature, whereas ammonolysis of 4-chloroketone (**18b**) required more drastic conditions (48 hours in a sealed tube at 160°).

Synthesis of Polyheteroaromatics.

Some of the latter difunctional pyridine synthons were cyclized into condensed polyheterocycles, such as azacoumarin, azaxanthone, naphthyridine or isoquinolines. Substituted polyheteroaromatics, which are aza-analogues of biologically active structures, were also synthesized.

4-Hydroxy and 4-methoxypyridine-3-carboxaldehydes **22** and **24** were condensed with malonic acid in basic

Scheme IV



31 **32** **16,20,22,24,26** **28,29** **30** **33**

i: boiling pyridinium chloride. ii: cyclohexanone/H_2SO_4/boiling AcOH. iii: $CH_2(CO_2H)_2$/boiling pyridine + piperidine. iiii: ethyl acetoactate/boiling NH_4OH + EtOH.

medium, to yield (*E*)-3-(3-pyridyl)acrylic acids **28** and **29**. Boiling pyridinium chloride induced isomerization to the *Z*-configuration and cyclization to 6-azacoumarin (**30**) (Scheme 4).

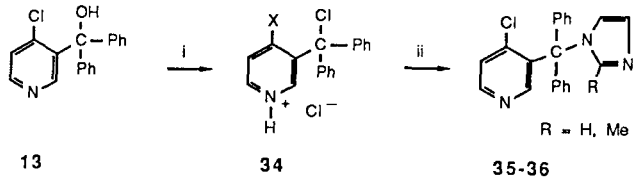
Friedlander's annelation of (4-amino-3-pyridyl)phenylmethanone (**26**) with cyclohexanone under Fehnel's conditions [8], gave a high yield of the 1,6-naphthyridine **32** (Scheme 4).

Cyclization of (4-fluoro-3-pyridyl)-2-methoxyphenylmethanone (**20**) in boiling pyridinium chloride afforded quantitatively 2-azaxanthone (**31**) (Scheme 4).

Condensation of 4-chloropyridine-3-carboxaldehyde (**16**) with ethyl acetoacetate in ethanolic ammonia gave the 4-chloro-3-pyridyl Hantsch-ester **33** (Scheme 4).

Aza-analogues **35** and **36** of the antimycotic agent "chlotrimazol" [9] were prepared in two steps from (4-chloro-3-pyridyl)diphenylmethanol (**13**) (Scheme 5).

Scheme V

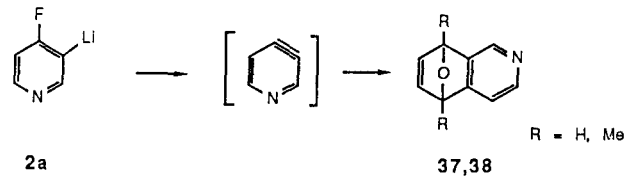


13 34 35-36

i: $SOCl_2/C_6H_6$, ii: imidazol/CH_3CN

Finally 3,4-pyridyne could be generated through lithium halide elimination on the *ortho*-lithiated 4-fluoropyridine. This was achieved by warming the lithiation mixture after addition of simple furandienes, which allowed the trapping of the highly reactive hetaryne intermediate by cycloaddition (Scheme 6).

Scheme VI



2a 37,38

Discussion.

Metalation of 4-halopyridines (F, Cl) by *n*-Buli or LDA is *ortho*-directed by the halogen-attractive effect. Chemoselectivity is very good with LDA and good with *n*-Buli. Very surprisingly, 4-halopyridines are much less sensitive to nucleophilic addition of *n*-Buli than the 2-isomers [10]. This can be related to the higher LUMO level of the 4-halo derivatives, as is shown by CNDO/2 quantum calculations performed on 2-fluoro and 4-fluoropyridines using standard geometry [11].

Ortho-lithiation of 4-halopyridines is a powerful and versatile strategy for elaboration of 3,4-disubstituted pyridine synthons, due to the peculiar reactivities of the 3 and 4 positions of 4-halo-3-lithiopyridines. This allows very fast synthesis of such useful synthons as *ortho*-amino or *ortho*-hydroxypyridyl ketones or aldehydes [12].

Directed *ortho*-lithiation of 4-fluoropyridines affords a one-step access to 3,4-pyridyne, which often needed the previous and tedious synthesis of 3,4-disubstituted derivatives [13].

EXPERIMENTAL

The ^{1}H-nmr spectra were obtained using a Varian T-60 spectrometer and were recorded in ppm downfield from the internal standard of tetramethylsilane in deuteriochloroform or hexamethyldisiloxane in deuterated dimethylsulfoxide. The ^{1}H-^{1}H and ^{1}H-^{19}F coupling constants are in good agreement (unless otherwise noted) with the common values: [14] $J_{2-3} = 4.5$ Hz, $J_{2-5} = 1.5$ Hz, J_{2-F} and $J_{3-F} = 8$-10 Hz. The ir spectra were obtained either as thin films or potassium bromide pellets with a Perkin-Elmer R-12 spectrophotometer. Elemental analysis were performed on a Carlo Erba instrument.

Diethyl ether and tetrahydrofuran were distilled from benzophenone-sodium and stored over molecular sieves (3A). Water content of the solvents was estimated by the modified Karl-Fischer method [15] (tetrahydrofuran and diethyl ether respectively less than 45 and 10 ppm). Diisopropylamine, tetramethylethylene diamine and trimethylchlorosilane were distilled from calcium hydride and stored over calcium hydride. Metalations were performed under a dry deoxygenated argon atmosphere (pyrogallol + soda + water; sulfuric acid; potassium hydroxide).

Solvents and reagents were handled under argon with syringues through *septums*.

The butyllithium content of the commercial hexane solution was estimated by the Gilman double titration method. 4-Halopyridines were prepared on a one molar scale by diazotation of 4-aminopyridine in aqueous 34% fluoroboric acid [16] or concentrated hydrochloric acid [17]. The two products were extracted with diethyl ether, dried over magnesium sulfate and concentrated in good yields: 70% for 4-fluoropyridine (**1a**) and 85% for 4-chloropyridine (**1b**). The two crude products were pure enough to be stored and used in cold etheral solution (reduced pressure distillation could be also achieved, but polymerization often occured with formation of greenish solids as by-products [16].

4-Fluoropyridine (**1a**).

This compound was a colorless liquid, bp = 65° (180 mm Hg); ^{1}H-nmr (deuteriochloroform): 7.00 (2H, ddd, $H_3 + H_5$), 8.50 (2H, ddd, $H_2 + H_6$), $J_{2-3} = 6$ Hz, $J_{2-5} = 1.5$ Hz, $J_{2-F} = 8.5$ Hz, $J_{3-F} = 9$ Hz.

4-Chloropyridine (**1b**).

This colorless liquid, bp = 84° (100 mm Hg); ^{1}H-nmr (deuteriochloroform): 7.40 (2H, dd, $H_3 + H_5$), 8.50 (2H, dd, $H_2 + H_6$).

4-Amino-3-bromopyridine.

A mixture of 3-bromo-4-nitropyridine N-oxide (180 g) [18], ferrous sulfate (1500 g) and water (3 l) was boiled under efficient stirring. Concentrated aqueous ammonia was slowly added until complete disappearance of the initial yellow color. Black iron salts were filtered off and the resulting aqueous solution was continuously extracted by diethyl ether during 48 hours. Drying and vacuum evaporation of the solvent afforded 100 g (70%) of 4-amino-3-bromopyridine, mp = 70° [19]; ^{1}H-nmr (deuteriochloroform): 5.25 (2H, s, NH_2), 6.60 (1H, d, H_5), 8.05 (1H, d, H_6), 8.40 (1H, s, H_2): ir (potassium bromide): 3430, 3370, 3140, 3020, 1625, 1580, 1500, 1420 cm^{-1}.

Anal. Calcd. for $C_5H_5BrN_2$: C, 34.71; N, 16.19; H, 2.91. Found: C, 34.5; N, 16.1; H, 2.90.

3-Bromo-4-fluoropyridine (**4**).

4-Amino-3-bromopyridine was diazotized in aqueous 34% fluoroboric

acid between 0° andd 5° and the resulting diazonium salt was decomposed above 30°. Fast alkalinization by sodium hydroxide and extraction with diethyl ether under 0°, drying and concentration gave a crude yellow oil. Reduced pressure distillation yielded 10% of 3-bromo-4-fluoropyridine (**4**), bp = 70° (20 mm Hg), together with a great amount of polymerization products; ^{1}H-nmr (deuteriochloroform): 7.20 (1H, dd, H_5), 8.55 (1H, dd, H_6), 8.80 (1H, d, H_2); ir (neat): 3060, 1580, 1570, 1460, 1410 cm^{-1}.

Anal. Calcd. for C_5H_3BrFN: C, 34.12; N, 7.96; H, 1.72. Found: C, 33.8; N, 7.90; H, 1.80.

General Procedure for Metalation by the Butyllithium Tetramethylethylenediamine Chelate.

Dry tetrahydrofuran or diethyl ether (125 ml), *n*-butyllithium (1.6 *M* in hexane, 31.5 ml, 0.05 mole) and dry tetramethylethylenediamine (5.8 g, 0.05 mole) were introduced into a 500 ml flask under a dry deoxygenated argon stream at −60° and stirred for 1 hour at −20°. The mixture was cooled to −70° and a tetrahydrofuran or ethyl ether (25 ml) solution of 4-halopyridine (0.05 mole) was added dropwise. Stirring was continued for half an hour at −40°, before slow addition of the required electrophile (0.05 mole) in tetrahydrofuran (25 ml) solution at −70° and further reaction for 3 hours at this temperature. Water (150 ml) was introduced at −10°, the aqueous layer was extracted with diethyl ether (3 x 150 ml) and the combined extract was dried over anhydrous magnesium sulfate. Solvent removal afforded a crude product, which was purified either by crystallization, vacuum distillation or flash-chromatography on silica.

General Procedure for Metalation by Lithium Diisopropylamide.

Into a cold solution (−20°) of tetrahydrofuran of diethyl ether (125 ml) and *n*-butyllithium (1.6 *M* in hexane, 31.5 ml, 0.05 mole) under dry deoxygenated argon, contained in a 500 ml flask, was added dropwise a tetrahydrofuran or diethyl ether (25 ml) solution of diisopropylamine (5.05 g, 0.05 mole) and the mixture was allowed to stand for 1 hour at 0°. Addition of 4-halopyridine (0.05 mole) in tetrahydrofuran or diethyl ether (25 ml) was achieved at −70° and stirring was continued for 4 hours at −70°. The resulting lithiation mixture was then treated as in the foregoing procedure I.

3-(4-Fluoro-3-pyridyl)-3-pentanol (**3a**).

Metalation of **1a** according to procedure I) followed by reaction of 3-pentanone afforded, after vacuum distillation, 60% of tertiary alcohol **3a**, bp = 100° (4 mm Hg); ^{1}H nmr (deuteriochloroform): 0.80 (6H, t, CH_3), 1.95 (4H, m, CH_2), 4.00 (1H, s, OH), 6.95 (1H, dd, H_5), 8.45 (1H, dd, H_6), 8.85 (1H, d, H_2), $J_{CH_3-CH_2}$ = 7.5 Hz, J_{5-6} = 5.5 Hz, J_{2-F} = 11 Hz, J_{5-F} = 11.5 Hz, J_{6-F} = 7.5 Hz; ir (neat): 3250, 3060, 2980, 2950, 2890, 2870, 1610, 1580, 1490, 1470, 1410 cm^{-1}.

Anal. Calcd. for $C_{10}H_{14}FNO$: C, 65.55; N, 7.64; H, 7.70. Found: C, 65.5; N, 7.50; H, 7.90.

A small amount (less than 10%) of 3-(2-butyl-4-fluoro-5-pyridyl)-3-pentanol (**5a**) was isolated, bp = 130° (4 mm Hg); ^{1}H nmr (deuteriochloroform): 0.80 (6H, t, CH_3-pentanol), 0.95 (3H, t, CH_3-butyl), 1.20 to 2.20 (8H, m, CH_2-pentanol + CH_2-butyl), 2.30 (1H, s, OH), 2.80 (2H, t, CH_2-butyl), 6.80 (1H, d, H_3), 8.70 (1H, d, H_6), J_{3-F} = 12.5 Hz, J_{6-F} = 11 Hz; ir (neat): 3270, 3080, 2980, 2950, 2890, 2880, 1620, 1570, 1490, 1470, 1381 cm^{-1}.

Anal. Calcd. for $C_{14}H_{22}FNO$: C, 70.26; N, 5.85; H, 9.27. Found: C, 70.0; N, 5.90; H, 9.20.

Reaction of 3-bromo 4-fluoropyridine (**4**) with butyllithium in diethyl ether according to procedure I, followed by addition of 3-pentanone afforded the tertiary alcohol **3a** in 85% yield, bp = 110° (5 mm Hg).

3-(4-Chloro-3-pyridyl)-3-pentanol (**3b**).

Metalation of **1b** by butyllithium in ethyl ether according to procedure I, reaction with 3-pentanone and vacuum distillation afforded a mixture of 2-butyl-4-chloropyridine (**6**) and the tertiary alcohol **3b**. The two products were purified by preparative gc using a 1.5 m long column filled with 10% SE 30 over chromosorb W 80/100.

Compound **3b**.

This compound was obtained in a yield of 60%; ^{1}H nmr (deuteriochloroform): 0.75 (6H, t, CH_3), 2.10 (4H, m, CH_2), 3.70 (1H, s, OH), 7.30 (1H, d, H_5), 8.40 (1H, d, H_6), 9.05 (1H, s, H_2); ir (neat): 3280, 3040, 2960, 2930, 2870, 2850, 1570, 1555, 1450, 1430 cm^{-1}.

Anal. Calcd. for $C_{10}H_{14}ClNO$: C, 60.15; N, 7.01; H, 7.07. Found: C, 60.1; N, 7.00; H, 7.20.

Compound **5b**.

This compound was obtained in a yield of less than 10%; ^{1}H nmr (deuteriochloroform): 0.90 (3H, t, CH_3), 1.50 (4H, m, CH_2), 2.70 (2H, t, CH_2), 7.10 (1H, d, H_5), 7.15 (1H, s, H_3), 8.40 (1H, d, H_6); ir (neat): 3040, 2960, 2920, 2860, 1550, 1440 cm^{-1}.

Anal. Calcd. for $C_9H_{12}ClN$: C, 63.72; N, 8.26; H, 7.13. Found: C, 63.6; N, 8.30; H, 7.30.

4-Fluoro-3-trimethylsilylpyridine (**6a**).

Metalation of **1a** according to procedures I or II and reaction of chlorotrimethylsilane yielded 75% of **6a**, bp = 72° (15 mm Hg); ^{1}H nmr (deuteriochloroform): 0.35 (9H, m, CH_3), 6.95 (1H, dd, H_5), 8.80 (2H, dd + d, H_6+H_2), J_{5-F} = 8 Hz, J_{6-F} = 9 Hz, J_{2-F} = 9 Hz; ir (neat): 3030, 2960, 2900, 1590, 1550, 1490, 1395 cm^{-1}.

Anal. Calcd. for $C_8H_{12}FNSi$: C, 56.76; N, 8.27; H, 7.15. Found: C, 56.6; N, 8.35; H, 6.99.

4-Chloro-3-trimethylsilylpyridine (**6b**).

Metalation of **1b** according to procedure II and reaction of chlorotrimethylsilane yielded 70% of **6b**, bp = 105° (20 mm Hg); ^{1}H nmr (deuteriochloroform): 0.40 (9H, s, CH_3), 7.10 (1H, d, H_5), 8.35 (1H, d, H_6), 8.45 (1H, s, H_2); ir (neat): 3020, 2960, 2880, 1550, 1530, 1440 cm^{-1}.

Anal. Calcd. for $C_8H_{12}ClNSi$: C, 51.74; N, 7.54; H, 6.51. Found: C, 51.9; N, 7.49; H, 6.62.

3-Dimethylarsino-4-fluoropyridine (**7**).

Metalation of **1a** according to procedure I and reaction of $IAsMe_2$ [20] afforded 55% of **7**, bp = 95° (13 mm Hg); ^{1}H nmr (deuteriochloroform): 1.30 (6H, s, CH_3), 6.95 (1H, dd, H_5), 8.50 (1H, dd, H_6), 8.55 (1H, d, H_2), J_{5-F} = 8.5 Hz, J_{6-F} = 8.5 Hz, J_{2-F} = 9 Hz; ir (neat): 3040, 2980, 2920, 1585, 1560, 1550, 1480, 1420 cm^{-1}.

Anal. Calcd. for C_7H_9AsFN: C, 41.81; N, 6.96; H, 4.51. Found: C, 41.7; N, 6.95; H, 4.32.

(4-Chloro-3-pyridyl)phenylsulfide (**8**).

Metalation of **1b**according to procedure II and reaction of diphenyl disulfide gave 30% of **8**, which was precipitated by a 1:1 mixture of diethyl ether and ligroin, mp <50°; ^{1}H nmr (deuteriochloroform): 7.20 (1H, d, H_5), 7.33 (5H, m, phenyl), 8.16 (1H, s, H_2), 8.26 (1H, d, H_6); ir (potassium bromide): 3040, 1580, 1550, 1475, 1440, 1390 cm^{-1}.

Anal. Calcd. for $C_{11}H_8ClNS$: C, 59.55; N, 6.32; H, 3.64. Found: C, 59.5; N, 6.25; H, 3.65.

4-Chloro-3-methylpyridine (**9**).

Metalation of **1b** according to procedure II and reaction of methyl iodide gave 70% of **9**, bp = 66° (22 mm Hg); ^{1}H nmr (deuteriochloroform): 2.35 (3H, s, CH_3), 7.20 (1H, d, H_5), 8.30 (1H, d, H_6), 8.40 (1H, s, H_2); ir (neat): 3030, 2960, 2930, 2860, 1580, 1560, 1480, 1440, 1400 cm^{-1}.

2-(4-Chloro-3-pyridyl)ethanol (**10**).

Metalation of **1b** according to procedure II, reaction with a cold etheral solution of ethylene oxide, and liquid chromatography on silica (methanol) yielded 30% of **10**; ^{1}H nmr (deuteriochloroform): 2.35 (2H, t, CH_2), 3.85 (2H, t, CH_2-O), 4.60 (1H, m, OH), 7.35 (1H, d, H_5), 8.25 (1H, d, H_6), 8.45 (1H, s, H_2); ir (neat): 3300, 2960, 2880, 1620 cm^{-1}.

Anal. Calcd. for C_7H_8ClNO: C, 53.30; N, 8.89; H, 5.11. Found: C, 53.3; N, 8.75; H, 5.05.

(4-Fluoro-3-pyridyl)phenylmethanol (**11a**) [5].

Metalation of **1a** according to procedure II, reaction with freshly

distilled benzaldehyde and vacuum evaporation of the solvent afforded a crude oily product. Addition of anhydrous ethyl ether yielded 65% of **11a**, as a white solid, mp = 110°; ^{1}H nmr (deuteriochloroform): 5.55 (1H, s, OH), 6.00 (1H, s, CH), 6.75 (1H, dd, H_5), 7.25 (5H, m, phenyl), 8.10 (1H, dd, H_6), 8.55 (1H, d, H_2), $J_{2\text{-}F} = J_{5\text{-}F} = 10$ Hz, $J_{6\text{-}F} = 7$ Hz); ir (potassium bromide): 3080, 3020, 2880, 2830, 2710, 2680, 1610, 1500, 1490, 1480, 1450, 1410 cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}FNO$: C, 70.93; N, 6.89; H, 4.96. Found: C, 70.6; N, 6.74; H, 4.91.

(4-Chloro-3-pyridyl)phenylmethanol (**11b**).

Metalation of **1b** according to procedure II, reaction with freshly distilled benzaldehyde and hydrolysis afforded 90% of a white solid **11b**, mp = 152°; ^{1}H nmr (deuteriochloroform): 3.25 (1H, m, OH), 6.20 (1H, s, CH), 7.25 (1H, d, H_5), 7.35 (5H, m, phenyl), 8.35 (1H, d, H_6), 8.85 (1H, s, H_2); ir (potassium bromide): 3120, 2820, 1570, 1540, 1460, 1400 cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}ClNO$: C, 65.61; N, 6.37; H, 4.55. Found: C, 65.4; N, 6.25; H, 4.60.

2-(4-Fluoro-3-pyridyl)-2-propanol (**12a**).

Metalation of **1a** according to procedure I and reaction with 2-propanone yielded 65% of alcohol **12a**, bp = 124° (15 mm Hg); ^{1}H nmr (deuteriochloroform): 1.65 (6H, d, CH_3), 4.80 (1H, s, OH), 6.95 (1H, dd, H_5), 8.40 (1H, dd, H_6), 8.85 (1H, d, H_2), $J_{CH\text{-}F} = 1.5$ Hz, $J_{5\text{-}F} = J_{2\text{-}F} = 11$ Hz, $J_{6\text{-}F} = 6$ Hz; ir (neat): 3180, 3060, 2970, 2930, 1605, 1570, 1480, 1460, 1400 cm^{-1}.

Anal. Calcd. for $C_8H_{10}FNO$: C, 61.92; N, 9.03; H, 6.50. Found: C, 61.8; N, 8.70; H, 6.54.

2-(4-Chloro-3-pyridyl)-2-propanol (**12b**).

Metalation of **1b** according to procedure II and reaction with 2-propanone gave a crude oil, which was purified by liquid chromatography on silica (methanol) to yield 60% of a viscous oil **12b**; ^{1}H nmr (deuteriochloroform): 1.90 (6H, s, CH_3), 7.20 (1H, d, H_5), 8.25 (1H, d, H_6), 8.50 (1H, s, H_2); ir (neat): 3300, 2980, 2940, 2880, 1580, 1550, 1400 cm^{-1}.

Anal. Calcd. for $C_8H_{10}ClNO$: C, 55.95; N, 8.16; H, 5.87. Found: C, 55.8; N, 8.05; H, 5.75.

(4-Chloro-3-pyridyl)diphenylmethanol (**13**).

Metalation of **1b** according to procedure II, reaction with benzophenone and hydrolysis led to 55% of a white solide **13**, mp = 118°; ^{1}H nmr (deuteriochloroform): 4.80 (1H, s, OH), 7.25 (1H, d, H_5), 7.30 (10H, m, phenyl), 8.05 (1H, s, H_2), 8.33 (1H, d, H_6); ir (potassium bromide): 3100, 1580, 1560, 1540, 1480, 1450, 1440, 1400 cm^{-1}.

Anal. Calcd. for $C_{18}H_4ClNO$: C, 73.06; N, 4.73; H, 4.73. Found: C, 73.0; N, 4.90; H, 5.08.

1-(4-Chloro-3-pyridyl)ethanol (**14**).

Metalation of **1b** according to procedure II, reaction with acetaldehyde and precipitation by a 10:1 mixture of hexane-diethyl ether afforded 40% of a yellow solid **14**, mp = 70°; ^{1}H nmr (deuteriochloroform): 1.55 (3H, d, CH_3), 4.00 (1H, s, OH), 5.30 (1H, q, CH), 7.25 (1H, d, H_5), 8.30 (1H, d, H_6), 8.75 (1H, s, H_2), $J_{CH\text{-}CH} = 7$ Hz; ir (potassium bromide): 3300, 2960, 1580, 1560, 1480, 1460, 1410 cm^{-1}.

Anal. Calcd. for C_7H_8ClNO: C, 53.30; N, 8.89; H, 5.11. Found: C, 53.1; N, 8.80; H, 5.00.

4-Dimethylaminopyridine-3-carboxaldehyde (**15**).

Metalation of **1a** according to procedure I and reaction with dimethylformamide yielded after vacuum distillation 45% of **15**, bp = 120° (4 mm Hg), mp = 69°; ^{1}H nmr (deuteriochloroform): 3.05 (6H, s, CH_3), 6.70 (1H, d, H_5), 8.30 (1H, d, H_6), 8.65 (1H, s, H_2), 9.95 (1H, s, CHO); ir (potassium bromide): 3000, 2970, 2930, 2875, 1670, 1600, 1525, 1460, 1450, 1410 cm^{-1}.

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.98; N, 18.65; H, 6.71. Found: C, 64.5; N, 18.3; H, 6.61.

4-Chloropyridine-3-carboxaldehyde (**16**).

Metalation of **1b** according to procedure II and reaction with ethyl formate afforded 40% of aldehyde **16**, which was crystallized from diethyl ether-hexane. Aldehyde **16** was separated from traces of its hydrate by precipitation of the latter in chloroform. Compound **16** had mp < 50°; ^{1}H nmr (deuteriochloroform): 7.45 (1H, d, H_5), 8.65 (1H, d, H_6), 9.00 (1H, s, H_2), 10.45 (1H, s, CHO); ir (potassium bromide): 3085, 2890, 1695, 1570, 1470, 1450 cm^{-1}.

Anal. Calcd. for C_6H_4ClNO: C, 50.91; N, 9.89; H, 2.85. Found: C, 50.6; N, 9.78; H, 2.92.

Hydrate of **16**.

This compound had mp = 188° dec; ^{1}H nmr (dimethylsulfoxide): 6.05 (1H, s, CH), 7.45 (1H, d, H_5), 8.45 (1H, d, H_6), 8.80 (1H, d, H_2); ir (potassium bromide): broad band between 3400 and 2400, 1585 cm^{-1}.

Anal. Calcd. for $C_6H_6ClNO_2$: C, 45.16; N, 8.78, H, 3.79. Found: C, 45.3; N, 8.76; H, 3.95.

(4-Fluoro-3-pyridyl)-2-methoxyphenylmethanol (**17**).

Metalation of **1a** according to procedure II and reaction with freshly distilled *ortho*-anisaldehyde gave a crude oil. Addition of diethyl ether yielded 80% of **17**, mp = 157°; ^{1}H nmr (dimethylsulfoxide): 3.60 (3H, s, OCH_3), 5.90 (1H, d, OH), 6.15 (1H, d, CH), 6.70-7.50 (5H, m, phenyl + H_5), 8.35 (2H, m, H_2 + H_6); ir (potassium bromide): 3170, 3070, 3020, 2970, 2940, 2920, 2840, 1600, 1585, 1490, 1470, 1440, 1415 cm^{-1}.

Anal. Calcd. for $C_{13}H_{12}FNO_2$: C, 66.95; N, 6.00; H, 5.19. Found: C, 66.7; N, 5.90; H, 5.26.

(4-Fluoro-3-pyridyl)phenylmethanone (**18a**).

Secondary alcohol **11a** was oxidized in toluene by 4 equivalents of active manganese dioxide [17] at ebullition temperature using a Dean-Stark apparatus (reaction was monitored by ir-spectroscopy). Filtration of manganese dioxide over asbestos, washing of the filtered cake by chloroform, drying of the organic filtrate and vacuum evaporation of the solvents yielded 65% of crude **18a**. It was not further purified and must be stored at −5°; ^{1}H nmr (deuteriochloroform): 7.15 (1H, dd, H_5), 7.50 and 7.75 (5H, m, phenyl), 8.70 (2H, dd + d, H_6 + H_2), $J_{5\text{-}6} = 6$ Hz, $J_{5\text{-}F} = J_{6\text{-}F} = 10$ Hz, $J_{2\text{-}F} = 8$ Hz; ir (neat): 3070, 3050, 1670, 1600, 1580, 1490, 1450, 1410 cm^{-1}.

(4-Chloro-3-pyridyl)phenylmethanone (**18b**) [5].

The same foregoing procedure was applied to the secondary alcohol **11b** and led to 90% of ketone **18b**, which was crystallized by an heterogenous mixture of water and ligroin, mp < 50°; ^{1}H nmr (deuteriochloroform): 7.45 (1H, d, H_5), 7.50 and 7.90 (5H, m, phenyl), 8.65 (1H, s, H_2); 8.70 (1H, d, H_6); ir (potassium bromide): 3320, 3080, 3050, 1670, 1600 cm^{-1}.

Anal. Calcd. for $C_{12}H_8ClNO$: C, 66.20; N, 6.43; H, 3.67. Found: C, 66.0; N, 6.39; H, 3.61.

1-(4-Chloro-3-pyridyl)ethanone (**19**).

Oxidation of **14** with manganese dioxide as previously described gave 70% of crude **19**, which is an unstable liquid. ^{1}H nmr (deuteriochloroform): 2.70 (3H, s, CH_3), 7.45 (1H, d, H_5), 8.60 (1H, d, H_6), 8.85 (1H, s, H_2).

(4-Fluoro-3-pyridyl)-2-methoxyphenylmethanone (**20**).

Oxidation of **17** with manganese dioxide as previously described gave 77% of **20**, mp = 70°; ^{1}H nmr (deuteriochloroform): 3.60 (3H, s, OCH_3), 7.00 (3H, m, $H_{3,4,5\text{-phenyl}}$), 7.50 (2H, m, $H_{6\text{-phenyl}}$ + $H_{5\text{-pyr}}$), 8.60 (2H, m, H_2 + $H_{6\text{-pyr}}$); ir (potassium bromide): 3080, 3040, 3010, 2980, 2940, 2840, 1645, 1600, 1565, 1485, 1465, 1435, 1410 cm^{-1}.

Anal. Calcd. for $C_{13}H_{10}FNO_2$: C, 67.53; N, 6.06; H, 4.36. Found: C, 67.7; N, 5.92; H, 4.58.

Di(4-chloro-3-pyridyl)phenylmethanol (**21**).

Metalation of **1b** according to procedure II and reaction with methyl benzoate yielded 25% of tertiary alcohol **21**, which was precipitated by ligroin, mp = 76°; ^{1}H nmr (deuteriochloroform): 4.50 (7H, s, OH), 7.35

(1H, d + m, H_5 + phenyl), 8.25 (2H, s, H_2), 8.40 (2H, d, H_6); ir (potassium bromide): 3060, 1560, 1540, 1460, 1400 cm^{-1}.

Anal. Calcd. for $C_{17}H_{12}Cl_2N_2O$: C, 61.65; N, 8.46; H, 3.65. Found: C, 62.0; N, 8.45; H, 3.70.

4-Hydroxypyridine-3-carboxaldehyde (**22**) [21].

A mixture of chloroaldehyde **16** (2 g, 0.014 mole), hydrochloric acid (3*N*, 20 ml) and hydrogen peroxide (3%, 4 drops) was refluxed for 6 hours. Neutralization with sodium carbonate, evaporation to dryness, extraction with ethanol, evaporation of the solvent and sublimation (150° under 16 mm Hg gave 90% of **22** as a white solid, mp >250°; ^1H nmr (dimethylsulfoxide): 6.35 (1H, d, H_5), 7.70 (1H, dd, H_6), 8.15 (1H, d, H_2), 10.10 (1H, s, CHO), J_{2-6} = 2 Hz; ir (potassium bromide): 3290, 3055, 2850, 2755, 1685, 1670, 1610, 1515, 1495 cm^{-1}.

Anal. Calcd. for $C_6H_5NO_2 \cdot 1/2\ H_2O$: C, 54.55; N, 10.6; H, 4.58. Found: C, 54.3; N, 10.4; H, 4.09.

(4-Hydroxy-3-pyridyl)phenylmethanone (**23**) [5].

Chloroketone **18b** was hydrolysed as for **22**. Neutralization by sodium carbonate yielded a crude solid, which was washed with chloroform and crystallized from ethanol to give 75% of **23**, mp = 222°; ^1H nmr (dimethylsulfoxide): 3.20 (1H, m, N-H), 6.25 (1H, d, H_5), 7.50 (5H, m, phenyl), 7.75 (1H, dd, H_6), 7.95 (1H, d, H_2), J_{2-6} = 1.5 Hz; ir (potassium bromide): broad band between 3150 and 2800, 1660, 1630, 1585, 1530, 1510 cm^{-1}.

Anal. Calcd. for $C_{12}H_9NO_2$: C, 72.35; N, 7.03; H, 4.55. Found: C, 72.0; N, 7.17; H, 4.88.

4-Methoxypyridine-3-carboxaldehyde (**24**).

Chloroaldehyde **16** was refluxed with a five fold excess of sodium methoxide in methanol for 1/2 hour. Evaporation to dryness and hydrolysis afforded a crude solid, which was crystallized from diethyl ether/hexane (1/1), 90%; mp <50°; ^1H nmr (deuteriochloroform): 4.00 (3H, s, OCH_3), 7.00 (1H, d, H_5), 8.70 (1H, d, H_6), 8.90 (1H, s, H_2), 10.50 (1H, s, CHO); ir (potassium bromide): 3100, 2880, 2850, 2770, 1685, 1585, 1505, 1490, 1440, 1400 cm^{-1}.

Anal. Calcd. for 85% of **24** and 15% of its hydrate: C, 60.12; N, 10.0; H, 5.26. Found: C, 60.3; N, 9.80; H, 5.20.

(4-Methoxy-3-pyridyl)phenylmethanone (**25**).

Chloroketone **18b** was reacted as for **24**. Crystallization from chloroform/diethyl ether (1/1) gave 85% of **25**, mp = 67°; ^1H nmr (deuteriochloroform): 3.75 (3H, s, OCH_3), 6.90 (1H, d, H_5), 7.50 and 7.80 (3H + 2H, m, phenyl), 8.50 (2H, m, H_2 + H_6); ir (potassium bromide): 3030, 2960, 2920, 1660, 1580, 1480, 1440, 1400 cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}NO_2$: C, 73.23; N, 6.57; H, 5.20. Found: C, 73.2; N, 6.60; H, 5.29.

(4-Amino-3-pyridyl)phenylmethanone (**26**) [12].

Crude **18a** (2.75 g, 0.014 mole) was added to ammonia saturated ethanol (100 ml) at 0°. The mixture was then stirred at room temperature during 48 hours. Evaporation to dryness and hydrolysis afforded 80% of amine **26**, as a pale yellow solid, mp = 162°; ^1H nmr (deuteriochloroform): 6.55 (1H, d, H_5), 6.80 (2H, s, NH_2), 7.50 (5H, m, phenyl), 8.10 (1H, d, H_6), 8.50 (1H, s, H_2), J_{5-6} = 6 Hz; ir (potassium bromide): 3460, 3280, 3050, 1650, 1595, 1575, 1540, 1480, 1440, 1430 cm^{-1}.

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 72.71; N, 14.13; H, 5.08. Found: C, 72.5; N, 14.0; H, 5.20.

Dissolution of amine **26** in dilute hydrochloric acid, evaporation to dryness and addition of ligroin yielded quantitatively the corresponding hydrochloride; ^1H nmr (Deuteriumoxide + tetramethylsilane): 7.45 (1H, d, H_5), 8.00 (5H, m, phenyl), 8.40 (1H, dd, H_6), 8.80 (1H, d, H_2), J_{2-6} = 0.5 Hz, J_{5-6} = 4 Hz; ir (potassium bromide): 3360, 3320, 3020, 1645, 1635, 1600, 1430 cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}ClN_2O$: C, 61.41; N, 11.94; H, 4.72. Found: C, 61.2; N, 11.5; H, 4.60.

(4-Methylamino-3-pyridyl)phenylmethanone (**27**).

A mixture of fluoroketone **18a** (2 g, 0.01 mole) and methylamine (40% aqueous solution, 50 ml) in ethanol (100 ml) was stirred during 4 hours at room temperature. Evaporation to dryness, hydrolysis afforded 85% of amine **27**, which was washed by diethyl ether, mp = 108°; ^1H nmr (deuteriochloroform): 2.95 (3H, d, CH_3), 6.55 (1H, d, H_5), 7.50 (5H, m, phenyl), 8.25 (1H, d, H_6), 8.50 (1H, s, H_2), 8.75 (1H, m, NH), J_{NH-CH} = 5 Hz, J_{5-6} = 6 Hz; ir (potassium bromide): 3340, 3060, 3030, 2930, 2910, 2880, 2860, 1625, 1595, 1560, 1515, 1440, 1415, 1400 cm^{-1}.

Anal. Calcd. for $C_{13}H_{12}N_2O$: C, 73.57; N, 13.20; H, 5.70. Found: C, 73.2; N, 12.6; H, 5.25.

(*E*)-3-(4-Hydroxy-3-pyridyl)acrylic Acid (**28**).

A mixture of hydroxy aldehyde **22** (1.25 g, 0.01 mole), malonic acid (1.15 g, 0.011 mole), piperidine (0.8 ml) and pyridine (20 ml) was refluxed for 3 hours. Evaporation of the amines gave a crude oil which was crystallized from methanol (10 ml), to give 74% of **28**, mp >250°; ^1H nmr (dimethylsulfoxide): 6.20 (1H, d, H_5-pyr), 6.90 (1H, d, H_2), 7.30 (1H, d, H_3), 7.55 (1H, dd, H_6-pyr), 8.00 (1H, d, H_2-pyr), J_{2-3} = 16 Hz, J_{2-6}pyr = 1.5 Hz; ir (potassium bromide): broad band between 3500 and 2500, 1640, 1570, 1540, 1390 cm^{-1}.

Anal. Calcd. for $C_8H_7NO_3$: C, 58.18; N, 8.48; H, 4.27. Found: C, 57.9; N, 8.29; H, 4.43.

(*E*)-3-(4-Methoxy-3-pyridyl)acrylic Acid (**29**).

Methoxyaldehyde **24** was reacted as for **28** to give 53% of **29**, mp >250°; ^1H nmr (dimethylsulfoxide): 4.00 (3H, s, OCH_3), 6.70 (1H, d, H_2), 7.15 (1H, d, H_5-pyr), 7.75 (1H, d, H_3), 8.50 (1H, d, H_6-pyr), 8.75 (1H, s, H_2-pyr), J_{2-3} = 16 Hz; ir (potassium bromide): 3080, 3020, 2980, 2960, 2400, 1680, 1590, 1570, 1500, 1450, 1410 cm^{-1}.

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; N, 7.82; H, 5.06. Found: C, 60.1; N, 7.79; H, 5.42.

2-Oxo-2*H*-pyranno[3,2-*c*]pyridine (**30**).

Acrylic acid **28** or **29** (0.005 mole) was reacted for 20 minutes at 220° with pyridinium chloride (20 g) and the warm reaction mixture was added to ice. Extraction with chloroform drying over magnesium sulfate evaporation and vacuum sublimation gave 60% of a very hygroscopic solid **30**; ^1H nmr (dimethylsulfoxide): 6.85 (1H, d, H_3), 7.90 (1H, d, H_8), 8.35 (1H, d, H_4), 9.00 (1H, d, H_7), 9.40 (1H, s, H_5), J_{3-4} = 9.5 Hz, J_{7-8} = 6 Hz; ir (potassium bromide): 3120, 3080, 3050, 3020, 2550, 1760, 1645, 1630, 1590, 1480, 1410 cm^{-1}.

10-Oxo-10*H*-benzopyranno[3,2-*c*]pyridine (**31**) [22].

Fluoroketone **20** was reacted as described for **30** to give 80% of **31**, mp = 184°; ^1H nmr (deuteriochloroform): 7.30 (1H, d, H_5), 7.50 (3H, m, H_5 + H_6 + H_7), 8.25 (1H, m, H_8), 8.75 (1H, d, H_3), 9.45 (1H, s, H_1); ir (potassium bromide): 3050, 3020, 3000, 2920, 1655, 1620, 1600, 1560, 1485, 1460, 1430 cm^{-1}.

Anal. Calcd. for $C_{12}H_7NO_2$: C, 73.09; N, 7.10; H, 3.58. Found: C, 72.88; N, 6.79; H, 3.56.

10-Phenyl-6,7,8,9-tetrahydrobenzo[*b*][1,6]naphtyridine (**32**).

Amine **26** (2 g, 0.01 mole) was dissolved in a mixture of cyclohexanone (2 g, 0.02 mole) and acetic acid (10 ml), before addition of sulfuric acid (0.1 ml) and warming at reflux temperature during 4 hours. The cold solution was poured on a mixture of concentrated aqueous ammonia (40 ml) and ice (20 g), which gave a brown tarry product. Extraction with chloroform, drying, solvent evaporation and flash-chromatography on silica (diethyl ether) afford 80% of **32**, as a white solid, mp = 160°; ^1H nmr (deuteriochloroform): 1.95 (4H, m, H_7 + H_8), 2.65 (2H, t, H_9), 3.20 (2H, t, H_6), 7.10 to 7.60 (5H, m, phenyl), 7.75 (1H, d, H_4), 8.60 (1H, d, H_3), 8.75 (1H, s, H_1), J_{8-9} = 6 Hz, J_{6-7} = 6.5 Hz, J_{3-4} = 3 Hz; ir (potassium bromide): 3050, 3030, 2950, 2940, 2890, 2860, 1600, 1565, 1500, 1485, 1460, 1450, 1430, 1420, 1400 cm^{-1}.

Anal. Calcd. for $C_{18}H_{16}N_2$: C, 83.05; N, 10.76; H, 6.19. Found: C, 83.0; N, 10.5; H, 6.39.

Ethyl (4-Chloro-3-pyridyl)-3,5-dimethyl-1,4-dihydropyridine-2,6-dicarboxylate (**33**).

A mixture of chloroaldehyde **16** (1.42 g, 0.01 mole), ethylacetoacetate (2.90 g, 0.02 mole), concentrated aqueous ammonia (1.5 ml) and ethanol (20 ml) was refluxed for 7 hours. After a night at room temperature, addition of water (80 ml) gave 88% of **33**, mp = 171°; ^{1}H nmr (deuteriochloroform): 1.20 (6H, t, CH_3), 2.30 (6H, s, CH_3), 4.10 (4H, q, CH_2), 5.40 (1H, s, H_4), 7.00 (1H, s, NH), 7.30 (1H, d, H_5-pyr), 8.30 (1H, d, H_6-pyr), 8.70 (1H, s, H_2-pyr); ir (potassium bromide): 3180, 3020, 2980, 2940, 2900, 1690, 1670, 1640. 1570, 1510 cm^{-1}.

Anal. Calcd. for $C_{18}H_{21}ClN_2O_4$: C, 59.26; N, 7.68; H, 5.80. Found: C, 58.9; N, 7.59; H, 5.62.

Chloro(4-chloro-3-pyridyl)diphenylmethane (**34**).

A mixture of (4-chloro-3-pyridyl)diphenylmethanol **13** (4.5 g, 0.015 mole) and thionyl chloride (50 ml) in benzene (150 ml) was refluxed during 5 hours. Evaporation to dryness and addition of diethyl ether afforded the hydrochloride of **34** in 85% yield; ^{1}H nmr (dimethylsulfoxide): 7.35 (10H, m, phenyl), 8.10 (1H, d, H_5), 8.45 (1H, s, H_2), 8.85 (1H, d, H_6); ir (potassium bromide): 3060, 3040, 2450, 1620, 1590, 1500, 1445 cm^{-1}.

Anal. Calcd. for $C_{18}H_{14}Cl_3N$: C, 61.63; N, 3.99; H, 4.03. Found: C, 62.0; N, 4.10; H, 4.20.

1-[(4-Chloro-3-pyridyl)diphenylmethyl]-1*H*-imidazole (**35**).

A solution of imidazole (0.68 g, 0.01 mole) and the hydrochloride of **34** (1 g, 0.003 mole) in acetonitrile (5 ml) was refluxed during 1 hour. Water (10 ml) was added and the resulting mixture was extracted by chloroform after alkalinization by sodium carbonate. Drying, evaporation to dryness and addition of diethyl ether yielded 65% of **35**, mp = 162°; ^{1}H nmr (deuteriochloroform): 6.75 (1H, s, H_2-imidazole), 7.10 (1H, d, H_5-imidazole), 7.20 (1H, d, H_4-imidazole), 7.30 (10H, m, phenyl), 7.45 (1H, d, H_5), 8.15 (1H, s, H_2), 8.50 (1H, d, H_6), J_{4-5}-imidazole = 4 Hz; ir (potassium bromide): 3060, 1570, 1550, 1490, 1450, 1400 cm^{-1}.

Anal. Calcd. for $C_{21}H_{16}ClN_3$: C, 72.93; N, 12.15; H, 4.66. Found: C, 72.8; N, 12.2; H, 4.47.

1-[(4-Chloro-3-pyridyl)diphenylmethyl]-2-methyl-1*H*-imidazole (**36**).

The foregoing procedure using the hydrochloride of **34** and 2-methylimidazole afforded **36** in 70% yield, mp = 130°; ^{1}H nmr (deuteriochloroform): 1.60 (3H, s, CH_3), 7.00 to 7.40 (12H, m, phenyl + imidazole), 8.10 (1H, d, H_5), 8.35 (1H, s, H_2), 8.50 (1H, d, H_6); ir (potassium bromide): 3060, 1590, 1450, 1400 cm^{-1}.

Anal. Calcd. for $C_{22}H_{18}ClN_3$: C, 73.49; N, 11.68; H, 5.04. Found: C, 72.8; N, 11.5; H, 5.25.

5,8-Endoxo-5,8-dihydroisoquinoline (**37**).

After metalation of **1a** according to procedure I and addition of furan (100 ml), the resulting mixture was quickly warmed to room temperature and further stirred for 4 hours. Hydrolysis, extraction, drying and solvent removal gave a crude oil, which was distilled under reduced pressure to yield 15% of **37**, bp = 105° (4 mm Hg); ^{1}H nmr (deuteriochloroform): 5.75 (2H, m, H_5 + H_8, 7.00 (2H, m, H_6 + H_7), 7.20 (1H, d, H_4), 8.25 (1H, d, H_3), 8.45 (1H, s, H_1), J_{3-4} = 4.5 Hz; ir (neat): 3030, 2960, 1620, 1600, 1590, 1455, 1420 cm^{-1}.

Anal. Calcd. for C_9H_7NO: C, 74.47; N, 9.65; H, 4.86. Found: C, 74.1; N, 9.75; H, 4.95.

5,8-Dimethyl-5,8-endoxo-5,8-dihydroisoquinoline (**38**).

After metalation of **1a** according to procedure I and addition of 2,5-dimethylfuran, the resulting mixture was quickly warmed to room temperature and further stirred for 4 hours. Hydrolysis, extraction, drying and solvent removal gave a crude oil, which was distilled under reduced pressure to yield 15% of **38**, bp = 115° (4 mm Hg) mp = 92°; ^{1}H nmr (deuteriochloroform): 1.80 and 1.85 (6H, 2s, CH_3), 6.75 (2H, m, H_6 + H_7), 7.05 (1H, m, H_4), 8.25 (1H, d, H_3), 8.30 (1H, s, H_1); ir (potassium bromide): 3080, 3040, 2990, 2940, 1610, 1595, 1460, 1450, 1425, 1395 cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.28; N, 8.09; H, 6.40. Found: C, 75.9; N, 8.00; H, 6.20.

5,8-Dimethylisoquinoline (**39**).

Adduct **38** (0.5 g, 0.003 mole) was reacted with tin (2 g) in acetic acid (50 ml) at the boiling temperature during 24 hours, before hydrolysis (100 ml). After removal of acetic acid under vacuum, the mixture was extracted by chloroform. Drying of the organic layer and solvent removal afford a crude oil which was distilled under reduced pressure, bp = 90-95° (4 mm Hg); ^{1}H nmr (deuteriochloroform): 2.60 (3H, s, CH_3), 2.75 (3H, s, CH_3), 7.10 (2H, m, H_6 + H_7), 7.70 (1H, d, H_4), 8.55 (1H, d, H_3), 9.40 (1H, s, H_1).

CNDO/2 quantum calculations: first LUMO energies of 2-fluoro and 4-fluoropyridines were respectively found at 0.111 and 0.120 atomic units.

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