PAPERS

Synthesis of 4-Amino-3-pyridinyl and 4-Amino-5-pyrimidinyl Aryl Ketones and Related Compounds *via* an *ortho*-Lithiation Reaction[1]

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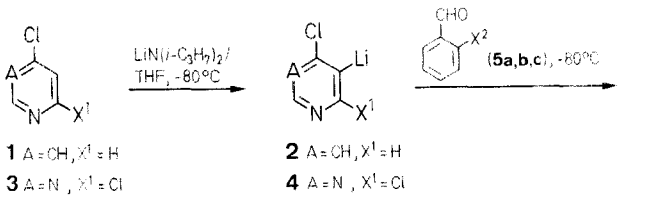
4-Chloropyridine and 4,6-dichloropyrimidine react regioselectively with lithium diisopropylamide to give 4-chloro-3-lithiopyridine and 4,6-dichloro-5-lithiopyrimidine, respectively. These intermediates react with benzaldehydes to give (4-chloro-3-pyridinyl)- and (4,6-dichloro-5-pyrimidinyl)-arylmethanols which are oxidized to the corresponding ketones by chromium(VI) oxide in acetone. These compounds can be nucleophilically substituted with ammonia or primary amines to give 4-amino-3-aroylpyridines or amino-5-aroylpyrimidines. The 3-aroyl-4-chloropyridines can also be easily converted into 3-aroyl-4(1*H*)-pyridinones.

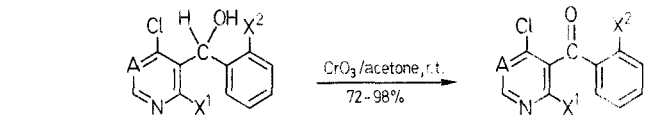
Heteroatom-facilitated lithiation has become an efficient synthetic tool[2] and has been applied to the syntheses of several heterocyclic ring systems[3]. The metallation of π-defficient heterocycles has recently acquired considerable theoretical and synthetic importance[4]. The lithio derivative of 2-fluoropyridine proved to be an appropriate intermediate for the synthesis of 2-amino-3-pyridinyl aryl ketones[5]. Substituent-directed lithiation of 4-chloropyridine **(1)** is reported to form 4-chloro-3-lithiopyridine **(2)**, trapped as 4-chloro-3-trimethylsilylpyridine[6] or as 4-chloro-3-(3-hydroxy-3-pentyl)-pyridine[2,3]. Only scarce data on the metallation of pyrimidines have been published[2].

We now confirm the *ortho*-lithiation of 4-chloropyridine **(1)** to 4-chloro-3-lithiopyridine **(2)** under the conditions described in Ref.[6] and we report that 4,6-dichloropyrimidine **(3)** is regioselectively lithiated to 4,6-dichloro-5-lithiopyrimidine **(4)** under the same conditions. We further show some synthetic applications of the reaction of both metallated heterocycles **2** and **4** with carbonyl electrophiles (Scheme **A**)

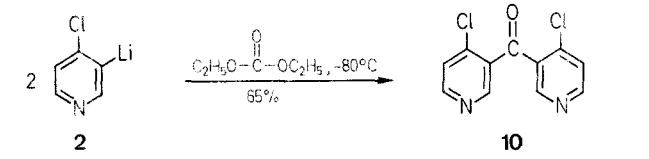
The formation of lithio derivatives **2** and **4** from 4-chloropyridine **(1)** and 4,6-dichloropyrimidine **(3)**, respectively, is proven by the subsequent reaction with benzaldehydes **(5)** at low temperature which affords 4-chloro-3-(α-hydroxybenzyl)-pyridines **(6)** or 4,6-dichloro-5-(α-hydroxybenzyl)-pyrimidine **(7a)**. Compounds **6** and **7a** are smoothly oxidized by chromium(VI) oxide in acetone at room temperature to give the aryl 4-chloro-3-pyridinyl ketones **8** and the phenyl 5-pyrimidinyl ketone **9a** (Scheme **A**). The reaction of 2 equivalents of 4-chloro-3-lithiopyridine **(2)** with diethyl carbonate at low temperature affords bis[4-chloro-3-pyridinyl] ketone **(10)** (Scheme **A**). An analogous reaction starting from 3-chloropyridine has already been reported[7].

Ammonolysis of 3-benzoyl-4-chloropyridine **(8a)** to give the known[8] 4-amino-3-benzoylpyridine **(11a)** could not be

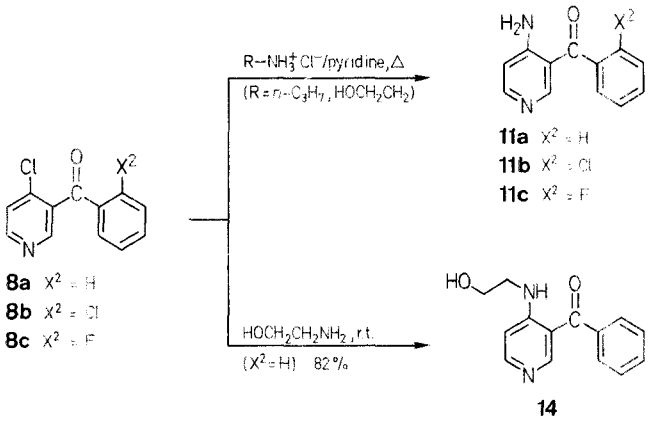


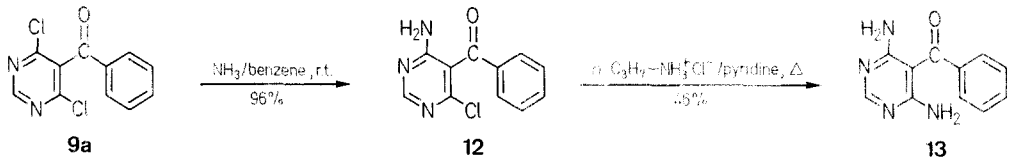


	A	X1	X2
6a, 8a	CH	H	H
6b, 8b	CH	H	Cl
6c, 8c	CH	H	F
7a, 9a	N	Cl	H

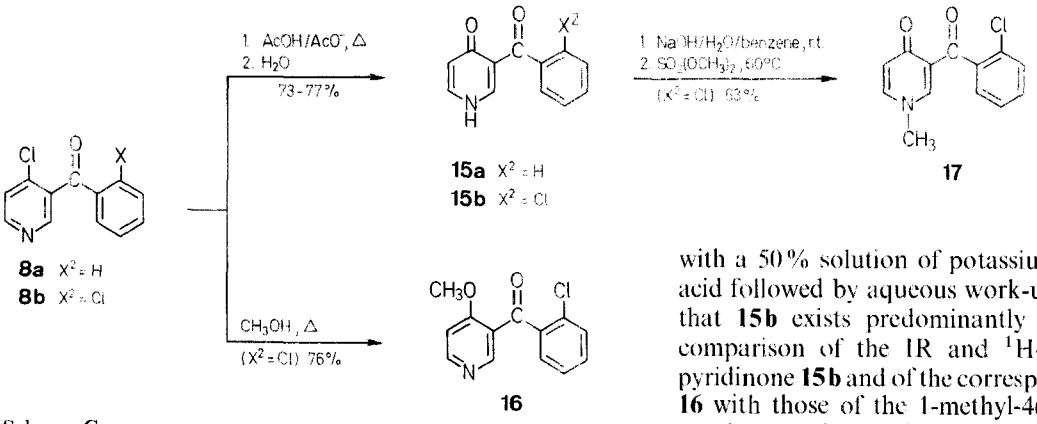


Scheme A





Scheme B



Scheme C

achieved with ammonia solutions at temperatures below 100°C; compound **11a** could be obtained in 60% yield, however, by using the standard procedure[9], i.e. by heating compound **8a** with aqueous 25% ammonia at 185–195°C in a pressure vessel. The combined electron-withdrawing effects of the two ring N-atoms facilitate the nucleophilic substitution of the 4-Cl atom in the 4,6-dichloropyrimidine **(9a)** in such a manner that treatment of compound **9a** with ammonia in dry benzene at room temperature results in the formation of 4-amino-5-benzoyl-6-chloropyrimidine **(12)** in 96% yield (Scheme **B**).

We have observed that 4-chloropyridine-3-carboxylic acid reacts with the hydrochlorides of primary amines in boiling pyridine to give 4-aminopyridine-3-carboxylic acid in good yield. We now applied this method to the 4-chloro-3-aroylpyridines **8a, b, c** and to 4-amino-5-benzoyl-6-chloropyrimidine **(12)** and obtained the 4-amino-3-aroylpyridines **11a, b, c** and 4,6-diamino-5-benzoylpyrimidine **(13)** in satisfactory yields. The analogous reaction of compound **8a** with 2-aminoethanol hydrochloride affords product **11a** along with 3-benzoyl-4-(2-hydroxyethylamino)-pyridine **(14)**. The *N*-(2-hydroxyethyl) derivative **14** can be obtained as a single product in high yield by reaction of chloro compound **8a** with 2-aminoethanol. It is assumed that the Cl/NH_2 exchange in compounds **8** and **12** is effected by ammonia which is generated under the reaction conditions; compound **14** is a side product in this reaction, not a possible intermediate, since it is recovered in 90% yield after having been refluxed in pyridine with or without the addition of 2-aminoethanol hydrochloride.

The method for the synthesis of 4-amino-3-pyridinyl aryl ketones **(11)** here described which affords these compounds in 40 to 50% overall yields from commercially available starting materials, is superior to the previously reported preparation[8] of the aminoketone **11a** from 4-aminopyridine-3-carboxylic acid (24% yield).

The 4-chloro-3-pyridinyl aryl ketones **8a, b** could not be hydrolyzed with boiling conc. hydrochloric acid. Taking into consideration Ref.[10], we converted **8a, b** into the corresponding 3-aroyl-4-(1*H*)-pyridinones **15a, b** by treatment with a 50% solution of potassium acetate in glacial acetic acid followed by aqueous work-up (Scheme **C**). We proved that **15b** exists predominantly in the oxo form by the comparison of the IR and ^{1}H-NMR spectra of 4(1H)-pyridinone **15b** and of the corresponding 4-methoxypyridine **16** with those of the 1-methyl-4(1*H*)-pyridinone **17** which was in accordance with Ref. 11.

Known synthetic methods leading to 3-aroyl-4(1*H*)-pyridinones include consecutive ring cleavage of 1,2-oxazole derivatives and recyclization[12].

The 4-chloro- and 4-amino-3-pyridinyl- and -5-pyrimidinyl aryl ketones and related compounds described here are considered to be appropriate starting materials for the synthesis of systems containing fused pyridine or pyrimidine rings, such as the pyrido- and pyrimido-1,4-diazepines[13–16] and some others[17–20].

Preparation of 4-Chloro-3-lithiopyridine (2) and 4,6-Dichloro-5-lithiopyrimidine (4) and Their Reactions with Electrophiles; General Procedure:

A solution of lithium diisopropylamide is prepared by treating diisopropylamine (28.5 ml, 0.2 mol) in anhydrous tetrahydrofuran (250 ml) with a 1.6 molar solution (125 ml, 0.2 mol) of butyllithium in hexane with stirring at −80 °C under dry argon. The solution is stirred for 1 h at −80 °C and then a solution of 4-chloropyridine (**1**; 22.7 g, 0.2 mol) in tetrahydrofuran (35 ml) or a solution of 4,6-dichloropyrimidine[21] (**3**; 29.8 g, 0.2 mol) in tetrahydrofuran (175 ml) is added dropwise. Stirring is continued for 1.5 h at −80 °C and finally a solution of the electrophilic reagent (0.22 mol) in tetrahydrofuran (110 ml) is added. The mixture is then stirred for 1 h at −80 °C and worked-up by one of the following procedures.

Work-up A: The mixture is allowed to warm to room temperature overnight under argon, then hydrolyzed with water (50 ml), and acidified with 2 normal hydrochloric acid. The organic phase is extracted with 2 normal hydrochloric acid (5 × 100 ml) and the combined acidic extracts are washed with ether (2 × 100 ml) and then basified with conc. aqueous ammonia. The aqueous mixture is extracted with chloroform (5 × 100 ml), the extract is dried with sodium sulfate, and the solvent is removed *in vacuo*. The remaining crude product is purified by recrystallization.

Work-up B: The mixture is immediately hydrolyzed by the addition of a mixture of water (50 ml) and tetrahydrofuran (50 ml), and extracted with chloroform (5 × 100 ml). The organic extract is washed with 1 normal hydrochloric acid (2 × 100 ml), then with saturated sodium chloride solution (2 × 100 ml), and dried with sodium sulfate. The solvent is removed *in vacuo* and the residual product is purified by column chromatography on alumina using hexane/chloroform (2:1 to 1:1) as eluent.

Bis[4-chloro-3-pyridinyl] Ketone (10):

4-Chloro-3-lithiopyridine (**2**) is submitted to the reaction with diethyl carbonate as described in the General Procedure. The mixture is immediately hydrolyzed with water (50 ml), extracted with chloroform (3 × 100 ml), the extract is dried with sodium sulfate, the solvent is removed *in vacuo*, and the residual product is purified over alumina using hexane/chloroform (2:1) as eluent; yield: 65%; m.p. 122–124 °C. This compound is very unstable; it polymerizes extensively even at room temperature.

$C_{11}H_6Cl_2N_2O$ (253.1)

MS: *m/e* = 253 (M^+, 100%).

^{1}H-NMR ($CDCl_3$): δ = 7.46 (d, 2H, J = 6.0 Hz, 5-H, 5′-H); 8.70 (d, 2H, J = 6.0 Hz, 6-H, 6′-H); 8.80 ppm (s, 2H, 2-H, 2′-H).

The dihydrochloride **10** · 2 HCl is highly moisture-sensitive; m.p. 130–134 °C.

IR (Nujol) of **10** · 2 HCl: ν = 1700 cm^{-1} (C=O).

Table 1. 4-Chloro-3-(α-hydroxybenzyl)-pyridines (**6**) and 4,6-Dichloro-5-(α-hydroxybenzyl)-pyrimidines (**7**) Prepared

Product	Work-up[a]	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[b]	IR($CHCl_3$) ν [cm^{-1}] (O–H)	^{1}H–NMR (solvent) δ [ppm]	^{13}C–NMR ($CDCl_3$) δ [ppm]
6a	A	91	145 (chloroform)	$C_{12}H_{10}ClNO$ (219.7)	3600	(DMSO-d_6): 5.87 (d, 1H, J = 4.5 Hz, CH–O); 6.14 (d, 1H, J = 4.5 Hz, OH, exchangeable with D_2O); 7.15–7.30 (m, 5H_{arom}); 7.27 (d, 1H, J = 6.0 Hz, 5-H); 8.21 (d, 1H, J = 6.0 Hz, 6-H); 8.60 (s, 1H, 2-H)	71.32 (d, CH–O); 124.38 (d, C_{para}); 127.18 (d, 2C_{ortho}); 127.97 (d, C-5); 128.65 (d, 2C_{meta}); 137.71 (s, C-1′); 142.32, 142.44 (2s, C-4, C-3); 149.17 (d, C-6); 150.14 (d, C-2)
6b	A	75	151 (chloroform)	$C_{12}H_9Cl_2NO$ (254.1)	3640	(DMSO-d_6): 6.14 (d, 1H, J = 4.5 Hz, CH–O); 6.28 (d, 1H, J = 4.5 Hz, OH, exchangeable with D_2O); 7.25–7.40 (m, 4H_{arom}); 7.38 (d, 1H, J = 6.0 Hz, 5-H); 8.27 (d, 1H, J = 6.0 Hz, 6-H); 8.29 (s, 1H, 2-H)	
6c	A	80	126 (chloroform/ether)	$C_{12}H_9ClFNO$ (237.7)	3640	(DMSO-d_6): 6.20 (d, 1H, J = 5.0 Hz, CH–O); 6.40 (d, 1H, J = 5.0 Hz, OH, exchangeable with D_2O); 7.05–7.30 (m, 4H_{arom}); 7.40 (d, 1H, J = 6.0 Hz, 5-H); 8.37 (d, 1H, J = 6.0 Hz, 6-H); 8.67 (s, 1H, 2-H)	
7a	B	60	127 (chloroform/pet ether)	$C_{11}H_8Cl_2N_2O$ (255.1)	3620	($CDCl_3$): 3.50 (d, 1H, J = 7.0 Hz, OH, exchangeable with D_2O); 6.60 (d, 1H, J = 7.0 Hz, CH–O; 7.3 (m, 5H_{arom}); 8.70 (s, 1H, 2-H)	70.92 (d, CH–O); 125.33 (d, 2C_{ortho}); 128.07 (d, C_{para}); 128.68 (d, 2C_{meta}); 133.24 (s, C-1′); 139.23 (s, C-5); 156.86 (d, C-2); 161.59 (s, C-4, C-6)

[a] See Experimental Part.

[b] Satisfactory microanalyses obtained: C ±0.13, H ±0.17, N ±0.13.

3-Aroyl-4-chloropyridines (8a, b, c) and 5-Benzoyl-4,6-dichloropyrimidine (9a); General Procedure:

The 4-chloro-3-(α-hydroxybenzyl)-pyridine **6a, b, c** or 4,6-dichloro-5-(α-hydroxybenzyl)-pyrimidine **(7a)** (0.02 mol) is mixed with anhydrous acetone (60 ml). Chromium(VI) oxide (6.0 g, 0.06 mol) is added portionwise with vigorous stirring at 0 °C and stirring is continued at room temperature for the period indicated in Table 2. Then, the excess of the oxidizing agent is destroyed by the addition of 2-propanol (10 ml) and stirring is continued for 15 min. The mixture is poured into saturated sodium hydrogen carbonate solution (pH 8; 300 ml), the solid is filtered off, and extracted with boiling chloroform (5 × 20 ml). The filtrate is also extracted with chloroform (3 × 100 ml) and the combined extracts are filtered through a short pad of activated alumina and the solvent is removed *in vacuo*.

4-Amino-3-aroylpyridines (11a, b, c), 4-Amino- and 4,6-Diamino-5-aroylpyrimidines (12, 13), and 4-Aminopyridine-3-carboxylic Acid; General or Individual Procedures:

Method A (for Product **11a**): 3-Benzoyl-4-chloropyridine (**8a**; 4.353 g, 0.02 mol) or its hydrochloride (**8a** · HCl; 5.082 g, 0.02 mol) is placed in a pressure vessel, conc. aqueous ammonia (80 ml) is added, and this mixture is heated at 185–195 °C. After cooling, the mixture is diluted with water and extracted with chloroform (3 × 50 ml). The organic phase is extracted with dilute (1:3) acetic acid (5 × 50 ml) and the acidic extract is basified with conc. aqueous ammonia and reextracted with chloroform (3 × 50 ml). The organic extract is dried with sodium sulfate and concentrated *in vacuo* and the aminoketone **11a** is precipitated with hexane. The crude product is purified by recrystallization or by column chromatography on alumina using hexane/chloroform (2:1) as eluent.

Method B (for Products **11a, b**): The 3-aroyl-4-chloropyridine **8a, b** or its hydrochloride (4 mmol) and 2-aminoethanol hydrochloride (1.95 g, 20 mmol) are refluxed in dry pyridine (16 ml) for the time given in Table 3. The mixture is allowed to cool to room temperature, diluted with water (50 ml), and extracted with chloroform or ether (3 × 50 ml). The extract is dried with sodium sulfate, the solvent is removed *in vacuo*, and the residue is chromatographed over an alumina column using hexane/chloroform (2:1 – 1:2) as eluent.

Method C (for Products **11a, b, c** and **13**): Analogous to Method B except that 1-aminopropane hydrochloride (1.92 g, 20 mmol) is used instead of 2-aminoethanol hydrochloride.

Method D (for Product **12**): A solution of 5-benzoyl-4,6-dichloropyrimidine (**9a**; 1.27 g, 5 mmol) in dry benzene (25 ml) is saturated with ammonia gas for 4 h and then left at room temperature overnight. The solvent is removed *in vacuo*, the residue is extracted with boiling chloroform, the extract is filtered, and the solvent is removed *in vacuo*. The crude product is purified by recrystallization.

Method E (for Preparation of 4-Aminopyridine-3-carboxylic Acid): 4-Chloropyridine-3-carboxylic acid (630 mg, 4 mmol) and 1-aminopropane hydrochloride (1.92 g, 20 mmol) are refluxed in dry pyridine (16 ml) for 4 h. After cooling, the mixture is diluted with water (20 ml) and placed in a refrigerator. The product which separates is isolated by suction, and purified by washing with cold water and with methanol.

3-Benzoyl-4-(2-hydroxyethylamino)-pyridine (14):

A homogenized mixture of 3-benzoyl-4-chloropyridine **(8a)** hydrochloride (2.54 g, 0.01 mol) and 2-aminoethanol (16 ml) is allowed to stand at room temperature overnight. The mixture is diluted with water and left in a refrigerator. The product which separates is collected by filtration, washed with water, and recrystallized from chloroform/ether (1:2); yield: 1.98 g (82%); m.p. 116–117 °C.

$C_{14}H_{14}N_2O_2$ (242.3) calc. C 69.41 H 5.82 N 11.56; found 69.06 5.90 11.36

IR ($CHCl_3$): ν = 3340 (NH); 2940, 2860 (CH_2); 1630 (C=O); 1610, 1570 cm^{-1}.

^{1}H-NMR ($CDCl_3$/HMDS): δ = 3.30 (dt, 2H, J = 5.0 Hz, 5.5 Hz, CH_2—N); 3.77 (t, 2H, J = 5.5 Hz, CH_2—O); 4.5 (br. s, 1H, OH); 6.52 (d, 1H, J = 6.2 Hz, 5-H); 7.25–7.65 (m, 5H_{arom}); 8.07 (d, 1H, J = 6.2 Hz, 6-H); 8.37 (s, 1H, 2-H); 8.98 ppm (t, 1H, J = 5.0 Hz, NH).

3-Aroyl-4-(1*H*)-pyridinones (15a, b); General Procedure:

The 3-aroyl-4-chloropyridine **8a, b** or its hydrochloride (2 mmol) is added to a 50% solution (15 ml) of potassium acetate or ammonium acetate in acetic acid. This mixture is heated to boiling for 1 h and then worked up by one of the following procedures:

Work-up A: The mixture is diluted with water (20 ml) and left in a refrigerator for 6 h. The precipitated product **15** is isolated by suction, and recrystallized.

Work-up B: The mixture is poured into saturated sodium hydrogen carbonate solution (pH 8). The resultant mixture is extracted with chloroform (2 × 10 ml) to remove the side product **11**. The pyridinone **15** is then extracted with ethyl acetate (3 × 50 ml). The organic extract is evaporated *in vacuo* and the remaining crude product **15** is purified by recrystallization.

3-(2-Chlorobenzoyl)-4-methoxypyridine (16):

The hydrochloride of 4-chloro-3-(2-chlorobenzoyl)-pyridine (**8b**; 577 mg, 2 mmol) is dissolved in boiling methanol (10 ml). The solution is then concentrated and the hydrochloride of **16** is

Table 2. 3-Aroyl-4-chloropyridines (**8**) and 5-Benzoyl-4,6-dichloropyrimidine (**9a**) Prepared

Product	Reaction time [h]	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a]	IR ν [cm^{-1}] (C=O)	^{1}H–NMR (solvent) δ [ppm]
8a[b]	3	98	125[c]	$C_{12}H_9Cl_2NO$[b,c] (254.1)	(Nujol): 1680[c]	(DMSO-d_6): 7.55–7.80 (m, 5H_{arom}); 7.93 (d, 1H, J = 5.6 Hz, 5-H); 8.83 (d, 1H, J = 5.6 Hz, 6-H); 8.85 (s, 1H, 2-H); 11.7 (br. s, 1H, NH)[c]
8b[b]	7	72[d]	106[c]	$C_{12}H_8Cl_3NO$[b,c] (288.6)	(Nujol): 1680[c]	($CDCl_3$): 7.44 (d, 1H, J = 6.0 Hz, 5-H); 7.45–7.70 (m, 4H_{arom}); 8.65 (d, 1H, J = 6.0 Hz, 6-H); 8.72 (s, 1H, 2-H)
8c[b]	1	96	100[c]	$C_{12}H_8Cl_2FNO$[b,c] (272.1)	(Nujol): 1680[c]	(DMSO-d_6): 7.35–7.85 (m, 4H_{arom}); 7.93 (d, 1H, J = 5.5 Hz, 5-H); 8.84 (d, 1H, J = 5.5 Hz, 6-H); 8.89 (s, 1H, 2-H); 9.1 (br. s, 1H, NH)[c]
9a	3	93	110 (pet.ether)	$C_{11}H_6Cl_2N_2O$ (253.1)	($CHCl_3$): 1690	(DMSO-d_6): 7.63 (dd, 2H_{meta}); 7.81 (t, 1H_{para}, J = 7.4 Hz); 8.01 (d, 2H_{ortho}, J = 7.2 Hz); 9.16 (s, 1H, 2-H)

[a] Satisfactory microanalyses obtained: C ±0.18, H ±0.18, N ±0.14.
[b] This product is moisture-sensitive.
[c] Hydrochloride.
[d] In addition, 3-(2-chlorobenzoyl)-4(1*H*)-pyridinone (**15b**) is isolated in varying amounts from the chloroform extracts by filtration (see experimental procedure). Compound **15b** was identical with an authentic specimen (m.p., mixture m.p., TLC, IR; see Table 4).

Table 3. 4-Amino-3-aroylpyridines (**11**) and 5-Benzoyl-4-aminopyrimidines (**12**, **13**) Prepared

Product	Reaction Conditions[a]		Yield [%]	m.p. [°C] (solvent)	Molecular Formula[b] or m.p. [°C] reported	IR ($CHCl_3$) ν [cm^{-1}]	^1H-NMR (solvent) δ [ppm]
	Method	Time [h]					
11a[c]	A	4	60[d]	162 (chloroform/hexane)	159–162[8]	1640 (C=C); 3390, 3540 (NH_2)	($CDCl_3$): 6.44 (d, 1H, J = 6.0 Hz, 5-H); 6.7 (br. s, 2H, NH_2, exchangeable with D_2O); 7.20–7.55 (m, $5H_{arom}$); 8.00 (d, 1H, J = 6.0 Hz, 6-H); 8.40 (s, 1H, 2-H)
	B	2.5	63[e]				
	C	4	52[f]				
11b	B	2	54	182 (chloroform)	$C_{12}H_9ClN_2O$ (232.7)	1640 (C=C); 3360, 3500 (NH_2)	($CDCl_3$): 6.61 (d, 1H, J = 6.0 Hz, 5-H); 7.1 (br. s, 2H, NH_2, exchangeable with D_2O); 7.35–7.55 (m, $4H_{arom}$); 8.22 (d, 1H, J = 6.0 Hz, 6-H); 8.33 (s, 1H, 2-H)
	C	4	72				
11c	C	4	69	170 (chloroform/pet ether)	$C_{12}H_9FN_2O$ (216.2)		(DMSO-d_6): 6.78 (d, 1H, J = 6.0 Hz, 5-H); 7.35–7.70 (m, $4H_{arom}$); 8.0 (br. s, 2H, NH_2); 8.09 (d, 1H, J = 6.0 Hz, 6-H); 8.16 (s, 1H, 2-H)
12	D	16	96	140 (chloroform/pet ether)	$C_{11}H_8ClN_3O$ (233.7)	1660 (C=C); 3440, 3540 (NH_2)	(DMSO-d_6): 7.4 (br. s, 2H, NH_2); 7.57 (dd, $2H_{meta}$); 7.72 (t, $1H_{para}$, J = 7.3 Hz); 7.83 (d, $2H_{ortho}$, J = 7.0 Hz); 8.34 (s, 1H, 2-H)
13[g]	C	4	46	227 (ethanol)	$C_{11}H_{10}N_4O$ (214.2)		(DMSO-d_6): 6.67 (s, 4H, $2NH_2$); 7.46 (dd, $2H_{meta}$); 7.56 (t, $1H_{para}$, J = 7.1 Hz); 7.63 (d, $2H_{ortho}$, J = 7.0 Hz); 7.92 (s, 1H, 2-H)
4-amino-pyridine-3-carboxylic acid[h]	E	4	50	333–4	330–340[22]	1550, 1660[i] (COOH)	

[a] See experimental procedure.
[b] Satisfactory microanalyses obtained: C ±0.11, H ±0.12, N ±0.10.
[c] This product was identical with a specimen prepared according to Ref.[8] (m.p., mixture m.p., TLC, IR).
[d] Varying (±20%) yields were obtained from parallel experiments.
[e] In addition, 3-benzoyl-4-(2-hydroxyethylamino)-pyridine (**14**) is isolated in 7% yield by chromatography on alumina using chloroform/hexane (2:1) as eluent; identical with an authentic specimen[a] (m.p., mixture m.p., TLC, IR).
[f] Yield not optimized.
[g] MSCI (*i*-C_4H_{10}): m/e = 215 ($M+1^+$).
[h] This product was identical with a specimen prepared according to Ref.[22] (m.p., mixture m.p., TLC, IR).
[i] In Nujol mull.

Table 4. 3-Aroyl-4-(1*H*)-pyridinones (**15**) Prepared

Product	Acetate used[a]	Work-up[a]	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[b]	IR (Nujol) ν [cm^{-1}] (C=O)	^1H-NMR (DMSO-d_6) δ [ppm]
15a	AcOK	A	73	218 (ethanol)	$C_{12}H_9NO_2$ (199.2)	1660 (sh) 1635	6.26 (d, 1H, J = 7.5 Hz, 5-H); 7.45–7.70 (m, $5H_{arom}$); 7.74 (d, 1H, J = 7.5 Hz, 6-H); 7.97 (s, 1H, 2-H); 11.8 (br. s, 1H, NH)
	$AcONH_4$	B	69[c]				
15b	AcOK	A	77	211 (methanol)	$C_{12}H_8ClNO_2$ (233.7)	1670 1650	6.20 (d, 1H, J = 7.5 Hz, 5-H); 7.30–7.45 (m, $4H_{arom}$); 7.70 (d, 1H, J = 7.5 Hz, 6-H); 8.19 (s, 1H, 2-H); 11.9 (br. s, 1H, NH)

[a] See experimental procedure.
[b] Satisfactory microanalyses obtained: C ±0.24, H ±0.33, N ±0.09.
[c] In addition, 4-amino-3-benzoylpyridine (**11a**) is isolated in 8% yield by chromatography on alumina eluting with hexane/chloroform (2:1). Compound **11a** was identical with an authentic specimen (m.p., mixture m.p., T.L.C., and IR; see Table 3).

precipitated with dry ether. This product is isolated by suction, and dissolved in water (20 ml). To this aqueous solution, conc. aqueous ammonia (1 ml) is added and the mixture is extracted with chloroform. The extract is dried with sodium sulfate, and concentrated *in vacuo*. Product **16** is precipitated by the addition of ether (5 ml), and isolated by suction; yield: 375 mg (76%); m.p. 98–100°C (chloroform/ether 1:2).

$C_{13}H_{10}ClNO_2$ (247.7)	calc.	C 63.04	H 4.07	N 5.66
	found	63.18	4.02	5.58

IR (Nujol): ν = 1670 (C=O); 1585, 1490, 1320, 1270 cm^{-1}.

^1H-NMR (DMSO-d_6): δ = 3.70 (s, 3H, OCH_3); 6.78 (d, 1H, J = 6.0 Hz, 5-H); 7.3 (m, $4H_{arom}$); 8.46 (d, 1H, J = 6.0 Hz, 6-H); 8.56 ppm (s, 1H, 2-H).

3-(2-Chlorobenzoyl)-1-methyl-4(1*H*)-pyridinone (17):
To a mixture of 3-(2-chlorobenzoyl)-4-(1*H*)-pyridinone (**15b**; 468 mg, 2 mmol), benzene (7 ml), and aqueous 50% sodium hydroxide solution (0.53 ml), benzyltributylammonium chloride (63 mg, 0.2 mmol) is added. The twophase mixture is stirred vigorously for 20 min at room temperature and then dimethyl sulfate

(0.38 ml, 4 mmol) is added. The mixture is stirred for 2 h at 60°C and then allowed to cool to room temperature. The product separates and is collected by filtration, washed successively with benzene, saturated aqueous sodium chloride solution, and cold water; yield: 314 mg (63%); m.p. 270–1°C (crystal conversion at 200°C).

$C_{13}H_{10}ClNO_2$	calc.	C 63.04	H 4.07	N 5.66
(247.7)	found	62.96	4.20	5.56

IR (Nujol): ν = 1670 (C=O); 1635 (C=O); 1575, 1510, 1305, 1200 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ = 3.73 (s, 3H, NCH_3); 6.22 (d, 1H, J = 7.5 Hz, 5-H); 7.32–7.42 (m, 4H_{arom}); 7.66 (dd, 1H, J = 7.5 Hz, 2.2 Hz, 6-H); 8.29 ppm (d, 1H, J = 2.2 Hz, 2-H).

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