# SYNTHESIS OF PLURIAMINATED PYRIDINES

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Abstract - The key reagent 3,5-dichloro-4-pyridinecarbonitrile (**1**) was used to synthesize 4-aminomethylpyridine derivatives 3,5-disubstituted with various amino groups, very active as inhibitors of diamine oxidase. The study of the reaction allowed to discover conditions for the gradual substitution in good yields of the two chlorine atoms to give symmetrically and unsymmetrically disubstituted derivatives (**3**), or the substitution of the cyano group, or the formation of amidines. The reduction of the cyano to aminomethyl group in compounds (**3**) afforded the target bioactive products.

## INTRODUCTION

In the field of copper containing amine oxidases, a class of enzymes simultaneously present in the same living organism including man and characterized by strict similarities in their catalytic effects, there is a persistent need of selective inhibitors as useful tool for investigating enzyme action. In this connection, we were successful in synthesizing very selective and powerful inhibitors of benzylamine oxidase corresponding to derivatives of benzylamine[1] or 4-aminomethylpyridine[2] substituted with alkoxy or hydroxyalkoxy groups. The inhibitors with pyridine structure, which show high selectivity and low toxicity and are preferred for *in vitro* and *in vivo* experiments, were synthesized by the effective utilization of the key reagent 3,5-dichloro-4-pyridinecarbonitrile (**1**). The reagent (**1**), which contains a cyano group as a suitable precursor of an aminomethyl group and is easily prepared from commercial 3,5-dichloropyridine by regioselective lithiation and functionalization at the 4 position, allowed very satisfactory nucleophilic substitution of one or two of the chlorine atoms with alkoxides[2,3] or thiolates.[4] Since pharmacological tests showed that 4-aminomethylpyridine derivatives with either oxygen or sulphur containing substituents differing in coordinative ability afforded a remarkably different inhibitory bioactivity and selectivity a prominent interest developed in 4-aminomethylpyridine derivatives with nitrogen containing substituents.

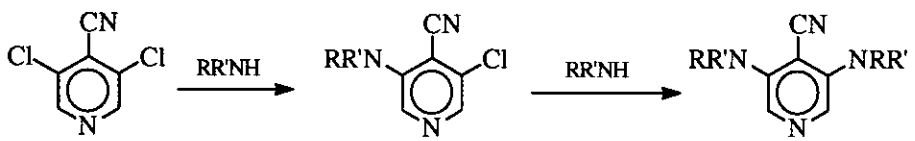
The present work describes a new series of 4-aminomethylpyridine derivatives containing various amino substituents at the 3 and 5 positions prepared on the basis of an extensive study of the reactions between **1** and lithium amides or amines.

## RESULTS AND DISCUSSION

Treatment of **1** with lithium amides in the corresponding amine or in a different solvent gave dark mixtures of various products in a composition strongly dependent on the reaction conditions. The use of milder nitrogen nucleophiles like amines or ammonia in place of lithium amides caused a sharp simplification of the process which afforded only chlorine substitution products without darkening of the reaction mixture.

*Reaction of* **1** *with amines*

The reaction of **1** with excess amines or ammonia was found to follow a two step process of nucleophilic substitution of one or two of the chlorine atoms (Scheme 1) with a remarkable difference in the reaction rate of the two steps. This allowed the preparation of either monosubstituted or disubstituted products in good yields working between room temperature and 55 °C for the former and between 65 and 150 °C for the latter.




**1** **2a-h** **3a-g**

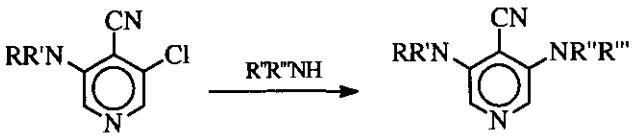
RR'N = $CH_3NH$ (a), $CH_3CH_2NH$ (b), $(CH_3)_2CHNH$ (c), $CH_3(CH_2)_3NH$ (d), $C_6H_5CH_2NH$ (e), $(CH_3)_2N$ (f), $(CH_3CH_2)_2N$ (g), $NH_2$ (h)

**Scheme 1**

Generally, the reactivity was higher for primary than secondary amines. The reactivity of diethylamine was considerably lower than that of dimethylamine, and the substitution of the second chlorine atom with diethylamine group remained incomplete after four weeks. Ammonia shows a peculiar low reactivity giving no substitution product of the second chlorine atom; attempts of forcing the reaction by increasing pressure and temperature only afforded pyridine ring disruption.

When monosubstitution products were submitted to the action of a different amine the lower reactivity of the second chlorine atom was confirmed, nevertheless unsymmetrically substituted compounds were produced (Scheme 2).

Mixed unsymmetrical substitution products could be obtained with nucleophiles of different nature. Thus 3-ethoxy-5-chloro-4-pyridinecarbonitrile[2] (**4**) was allowed to react with excess methylamine. Monitoring the reaction by GCMS, the slow substitution of the chlorine atom and the slightly more rapid substitution of the ethoxy group with the formation of a mixture of **2a** and **5** followed by the conversion

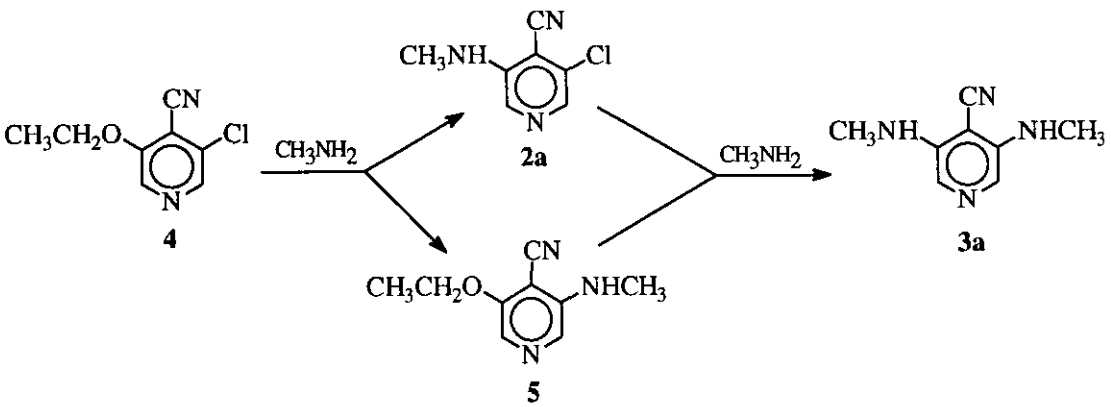



**2a, b, d, e, f, h** **3ab, af,ad, ae, bf, ah**

RR'N = $CH_3NH$ (a), $CH_3CH_2NH$ (b), $CH_3(CH_2)_3NH$ (d), $C_6H_5CH_2NH$ (e), $(CH_3)_2N$ (f), $NH_2$ (h)
R"R'"N = $CH_3NH$ (a), $CH_3CH_2NH$ (b), $(CH_3)_2N$ (f)

**Scheme 2**

of both the products to **3a** were observed (Scheme 3). The sluggishness of the process allowed the isolation of the intermediates (**2a**) and (**5**).




**Scheme 3**

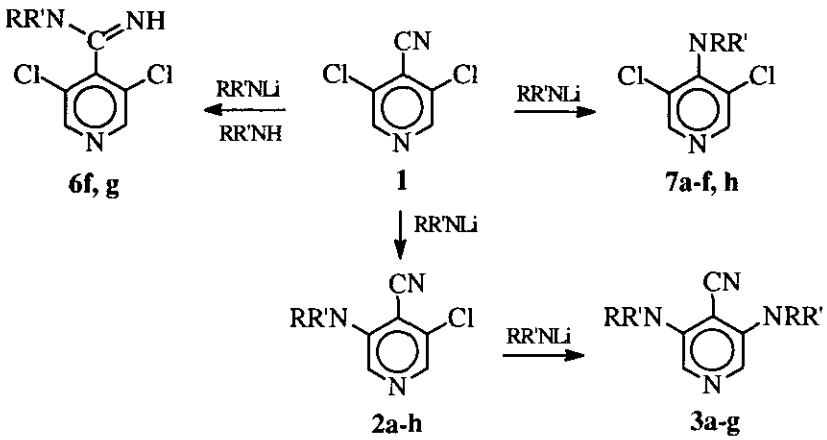
For a better understanding of the observed faster substitution of the ethoxy group compared with the chlorine atom in the compound (**4**), where the reciprocal influence of such leaving groups is possible, pure **2a** and **5** were allowed to react with methylamine giving in both cases the same product (**3a**), with **2a** reacting faster than **5**.

*Reaction of* **1** *with lithium amides*

The reaction of **1** with lithium amides using different reagent ratios and concentrations in various conditions of temperature and solvent revealed four different transformations: addition to the cyano group with formation of amidines, substitution of the cyano group, substitution of one chlorine atom and substitution of two chlorine atoms (Scheme 4).

The formation of amidines from **1** was observed only with lithium amides of secondary amines in molar ratio nitrile/amide equal to or higher than 1:4 and only when the solvent was the amine corresponding to the employed amide. This is analogous to the formation of imino ethers and imino thioethers by the reaction of **1** with lithium alkoxides and alkanethiolates in the presence of the corresponding conjugated acids,[4] but lithium amides do not give rise to a chemical equilibrium differently from the formation of imino ethers and imino thioethers. The absence of chemical equilibrium was confirmed by treating pure

amidine samples, prepared according to the Garigipati[5] and Moss[6] method, with lithium amides under conditions in which **1** afforded compounds (**2**) or (**7**). The amidine samples remained unaltered for long reaction time without browning or yielding traces of other products.




RR'N = $CH_3NH$ (a), $CH_3CH_2NH$ (b), $(CH_3)_2CHNH$ (c), $CH_3(CH_2)_3NH$ (d), $C_6H_5CH_2NH$ (e), $(CH_3)_2N$ (f), $(CH_3CH_2)_2N$ (g), $NH_2$ (h)

**Scheme 4**

The substitution of the chlorine atoms in the compound (**1**) was observed in the amine corresponding to the used lithium amide, or DMF with $LiNMe_2$, or *N,N*-diethylformamide with $LiNEt_2$, or THF where the reaction was remarkably slower. The reaction rates increased with the dielectric constant of the solvent in agreement with the reaction of **1** with lithium alkoxides and alkanethiolates.[4] The substitution of the first chlorine atom of **1** was observed with lithium amides of all the amines examined and ammonia. The substitution of the second chlorine atom of **1** proceeded generally with difficulty, and failed with $LiNH_2$ in spite of various attempts.

The substitution of the cyano group of **1** with production of compounds (**7**) was observed with all the examined lithium amides except for $LiNEt_2$, using as solvent the corresponding amines, or DMF for $LiNMe_2$. Such substitution was always accompanied by a sudden appearance of a dark red colour and needed an amide concentration equal to or higher than 0.5 M and a molar ratio nitrile/amide equal to or higher than 1:4.

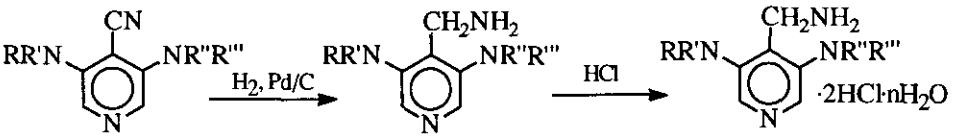
*Reduction of pyridinecarbonitriles*

The reduction of cyano to aminomethyl group in compounds (**3**) for the preparation of molecules devoted to the enzyme study was found to be noticeably influenced by the substituents placed ortho to the cyano group. Among several catalytic procedures attempted, satisfactory results were obtained with hydrogen and palladium on activated charcoal under the same conditions already set up for 3,5-dialkoxy-4-pyridinecarbonitriles.[2]

Several experiments with metal hydrides excluded the utility of fairly anionic reagents. Acceptable reductions were obtained with Lewis acid reductive agents as aluminum hydride, while gaseous diborane failed because it forms with our substrates a too stable unfruitful complex.

Scheme 5 reports the performed reductions of some cyano compounds (**3**) to aminomethyl derivatives which are most promising for essays with enzymes.

As the free bases (**8**) were moderately unstable, they were transformed into the more stable hydrochlorides (**9**) and fully characterized as such. It is remarkable that all the hydrochlorides, part of which in form of hydrated crystals, contain only two molecules of HCl as 4-aminomethylpyridines containing less basic alkoxy or alkylthio[2-4] in place of amino groups.




**3a, b, d, ah** **8a, b, d, ah** **9a, b, d, ah**

RR'N = R"R'"N = $CH_3NH$ (a), $CH_3CH_2NH$ (b), $CH_3(CH_2)_3NH$ (d); RR'N = $CH_3NH$, R"R'"N = $NH_2$ (ah)

**Scheme 5**

In preliminary tests compounds (**9**) showed extraordinary activities as diamine oxidase inhibitors confirming the great versatility of **1** as key reagent for the preparation of 3,4,5-trisubstituted pyridines bioactive towards extramitochondrial amine oxidase enzymes.

## EXPERIMENTAL

Melting points were determined on a Reichert-Thermovar hot stage apparatus and are uncorrected. $^1$H-NMR spectra were obtained on Bruker WM-300 or AcP-300 spectrometer. Chemical shifts are reported on the δ scale and are referred to TMS (Table 1). MS spectra were recorded on a Hewlett-Packard GC-MSD 5972 instrument. IR spectra were recorded on Perkin Elmer 1330 or FT-IR Paragon 1000 PC spectrophotometers. 3,5-Dichloro-4-pyridinecarbonitrile[2] (**1**) and 3-chloro-5-ethoxy-4-pyridinecarbonitrile[2] (**4**) were prepared according to known procedures. Elemental analysis of all the prepared new compounds are collected in Table 2.

**Determination of the reaction pattern of chloro derivatives of 4-pyridinecarbonitrile with nitrogen nucleophiles.** The chloro derivatives of 4-pyridinecarbonitrile together with ammonia or amines or solution of lithium amides in the corresponding amine or in a different solvent were introduced at -70 °C under nitrogen into a 25 mL pressure resistant glass vial with *rotaflo* stopcock and allowed to react in thermostatic bath at different temperatures in the range from -70 to 145 °C. At different reaction times samples were drawn from the vial and submitted to GCMS analysis after a rapid treatment of removal of all the volatiles at reduced pressure, addition of water, extraction with chloroform and drying over anhydrous $Na_2SO_4$.

**Syntheses from 3,5-dichloro-4-pyridinecarbonitrile (1) and ammonia or amines.** Compound (1) and excess of the proper amine or ammonia were introduced at -50 °C under nitrogen into a 50-100 mL pressure resistant glass vial with *rotaflo* stopcock and allowed to react in thermostatic bath for times and

**Table 1.** $^1$H-NMR spectra of the prepared pyridines.

| Compound | $^1$H-NMR ($CDCl_3$, δ ppm) |
|---|---|
| **2a** | 3.05 (d, J=5.2 Hz, 3H); 4.80 (br s, 1H); 8.01 (s, 1H); 8.09 (s, 1H) |
| **2b** | 1.33 (t, J=7.4 Hz, 3H); 3.34 (m, 2H); 4.61 (br s, 1H); 7.9 (s, 1H); 8.05 (s, 1H) |
| **2c** | 1.23 (d, J=8.1 Hz, 6H); 3.78 (m, 1H); 4.39 (br s, 1H); 7.90 (s, 1H); 8.02 (s, 1H) |
| **2d** | 0.99 (t, J=7.3 Hz, 3H); 1.46 (m, 2H); 1.68 (m, 2H); 3.30 (m, 2H); 4.61 (br s, 1H); 7.97(s, 1H); 8.08 (s, 1H) |
| **2e** | 4.48 (d, J=6.4 Hz, 2H); 5.10 (br s, 1H); 7.34 (m, 5H); 8.00 (s, 1H); 8.06 (s, 1H) |
| **2f** | 3.21 (s, 6H); 8.07 (s, 1H); 8.20 (s, 1H) |
| **2g** | 1.28 (t, J=7.1 Hz, 6H); 3.56 (q, J=7.1 Hz, 4H); 8.02 (s, 1H); 8.19 (s, 1H) |
| **2h** | * 7.82 (s, 1H); 8.11 (s, 1H) |
| **3a** | 2.97 (d, J=5.0 Hz, 6H); 4.34 (br s, 2H); 7.50 (s, 2H) |
| **3b** | 1.31 (t, J=7.2 Hz, 6H); 3.30 (m, 4H); 4.19 (br s, 2H); 7.48 (s, 2H) |
| **3c** | 1.27 (d, J=6.4 Hz, 12H); 3.81 (m, 2H); 4.06 (d, J=7.4 Hz, 2H); 7.46 (s, 2H) |
| **3d** | 0.97 (t, J=7.3 Hz, 6H); 1.44 ( m, 4H); 1.63 (m, 4H); 3.24 (m, 4H); 4.24 (br s, 2H); 7.47 (s, 2H) |
| **3e** | 4.35 (d, J=7.2 Hz, 4H); 4.62 (br s, 2H); 7.20 (m, 10H); 7.43 (s, 2H) |
| **3f** | 3.07(s, 12H); 7.76 (s, 2H) |
| **3g** | 1.20 (t, J=7.0 Hz, 12H); 3.40 (q, J=7.0 Hz, 8H); 7.80 (s, 2H) |
| **3ab** | 1.31(t, J=7.2 Hz, 3H); 2.97(d, J=5.2 Hz, 3H); 3.27(m, 2H);4.19(br s, 1H);4.36(br s,1H);7.48(s, 1H);7.51(s, 1H) |
| **3af** | 2.97 (d, J=5.5 Hz, 3H); 3.09 (s, 6H); 4.57 (br s, 1H); 7.58 (s, 1H); 7.62 (s, 1H) |
| **3ad** | 0.97 (t, J=7.3 Hz, 3H); 1.45 (m, 2H); 1.65 (m, 2H); 2.96(d, J=5.3 Hz, 3H); 3.24 (m, 2H); 4.24 (br s, 1H); 4.36 (br s, 1H); 7.47 (s, 1H); 7.51 (s, 1H) |
| **3ae** | 2.96 (d, J=5.2 Hz, 3H); 4.40 (br s, 1H); 4.44 (d, J=5.6 Hz, 2H); 4.76 (br s, 1H); 7.32 (m, 5H); 7.50 (s, 2H) |
| **3bf** | 1.32 (t, J=7.2 Hz, 3H); 3.09 (s, 6H); 3.27 (m, 2H); 4.39 (br s, 1H); 7.58 (s, 1H); 7.59 (s, 1H) |
| **3ah** | * 2.87 (s, 3H); 7.23 (s, 1H); 7.40 (s, 1H) |
| **5** | 1.47 (t, J=7.0 Hz, 3H); 3.01 (d, J=5.2 Hz, 3H); 4.21(q, J=7.0 Hz, 2H); 4.59(br s, 1H); 7.71 (s, 1H); 7.81(s,1H) |
| **6a** | 2.98 (s, 3H); 8.52 (s, 2H) |
| **6b** | 1.27 (t, J=7.2 Hz, 3H); 3.38 (m, 2H); 8.52 (s, 2H) |
| **6f** | 2.76 (br s, 3H); 3.14 (br s, 3H); 8.53 (s, 2H) |
| **6g** | 1.08 (t, J=7.1 Hz, 3H); 1.29 (t, J=7.1 Hz, 3H); 2.98 (q, J=7.1 Hz, 2H); 3.62 (q, J=7.1 Hz, 2H); 8.53 (s, 2H) |
| **7a** | 3.32 (d, J=5.7 Hz, 3H); 4.80 (br s, 1H); 8.16 (s, 2H) |
| **7b** | 1.28 (t, J=7.2 Hz, 3H); 3.74 (m, 2H); 4.68 (br s, 1H); 8.16 (s, 2H) |
| **7c** | 1.25 (d, J=5.9 Hz, 6H); 4.54 (m, 2H); 8.18 (s, 2H) |
| **7d** | 0.89 (t, J=7.6 Hz, 3H); 1.44 (m, 2H); 1.63 (m, 2H); 3.70 (m, 2H); 4.74 (br s, 1H); 8.17 (s, 2H) |
| **7e** | 4.87 (d, J=6.0 Hz, 2H); 5.02 (br s, 1H); 7.33(m, 5H); 8.19 (s, 2H) |
| **7f** | 3.02 (s, 6H); 8.31 (s, 2H) |
| **7h** | 5.02 (br s, 2H); 8.20 (s, 2H) |
| **9a** | * 2.91 (s, 6H); 4.23 (s, 2H); 7.50 (s, 2H) |
| **9b** | * 1.34 (t, J=7.2 Hz, 6H); 3.27 (q, J=7.2 Hz, 4H); 4.27 (s, 2H); 7.52 (s, 2H) |
| **9d** | * 1.00 (t, J=7.3 Hz, 6H); 1.49 (m, 4H); 1.70 (m, 4H); 3.22 (t, J=7.3 Hz, 4H); 4.25 (s, 2H); 7.50 (s, 2H) |
| **9ah** | * 2.90 (s, 3H); 4.21 (s, 2H); 7.39 (s, 1H); 7.52 (s, 1H) |

*Solvent $CD_3OD$

temperatures optimized by checking the reaction course with GCMS analysis. For the substitution of one chlorine atom (products **2**) temperatures and times were in the range of rt - 70 °C and 2.5-192 h respectively. For the substitution of both chlorine atoms (products **3**) temperatures and times were in the range of 65-140 °C and 48-522 h respectively with the exception of the reaction with diethylamine in which after 720 h at 150 °C the monosubstituted product (**2g**) was still present in a molar ratio 1.33:1 with **3g**. The colourless reaction mixture, after evaporation at reduced pressure to remove all the volatiles, treatment with water, extraction with chloroform, anhydrification over anhydrous $Na_2SO_4$ and evaporation to dryness, was

purified by column chromatography on Merck neutral alumina grade I using a mixture hexane/chloroform 1:1 as eluent. Further purification was carried out by sublimation at reduced pressure. The separation of **2g** and **3g** was carried out on Merck silica gel plate using chloroform as eluent (Table 3).

**Table 2.** Elemental analysis of all the prepared new compounds.

| Compound | Formula | Calcd/Found C(%)/C(%) | H(%)/H(%) | N(%)/(%) | Cl(%)/Cl(%) |
|---|---|---|---|---|---|
| **2a** | $C_7H_6N_3Cl$ | 50.17 / 49.98 | 3.61 / 3.70 | 25.07 / 25.26 | 21.15 / 21.23 |
| **2b** | $C_8H_8N_3Cl$ | 52.90 / 52.90 | 4.44 / 4.25 | 23.14 / 23.20 | 19.52 / 19.48 |
| **2c** | $C_9H_{10}N_3Cl$ | 55.25 / 54.99 | 5.15 / 5.26 | 21.49 / 21.34 | 18.12 / 18.19 |
| **2d** | $C_{10}H_{12}N_3Cl$ | 57.28 / 57.39 | 5.77 / 5.80 | 20.04 / 20.15 | 16.91 / 16.82 |
| **2e** | $C_{13}H_{10}N_3Cl$ | 64.07 / 63.98 | 4.14 / 4.20 | 17.24 / 16.99 | 14.55 / 14.69 |
| **2f** | $C_8H_8N_3Cl$ | 52.90 / 52.75 | 4.44 / 4.36 | 23.14 / 22.99 | 19.52 / 19.70 |
| **2g** | $C_{10}H_{12}N_3Cl$ | 57.28 / 57.10 | 5.77 / 5.91 | 20.04 / 19.98 | 16.91 / 17.02 |
| **2h** | $C_6H_4N_3Cl$ | 46.93 / 46.94 | 2.63 / 2.60 | 27.36 / 27.48 | 23.09 / 23.00 |
| **3a** | $C_8H_{10}N_4$ | 59.24 / 59.13 | 6.21 / 6.09 | 34.54 / 34.49 | |
| **3b** | $C_{10}H_{14}N_4$ | 63.13 / 63.00 | 7.42 / 7.30 | 29.45 / 29.29 | |
| **3c** | $C_{12}H_{18}N_4$ | 66.02 / 66.14 | 8.31 / 8.20 | 25.67 / 25.59 | |
| **3d** | $C_{14}H_{22}N_4$ | 68.26 / 68.34 | 9.00 / 9.10 | 22.74 / 22.59 | |
| **3e** | $C_{20}H_{18}N_4$ | 76.41 / 76.62 | 5.77 / 5.86 | 17.82 / 17.66 | |
| **3f** | $C_{10}H_{14}N_4$ | 63.13 / 63.27 | 7.42 / 7.38 | 29.45 / 29.45 | |
| **3g** | $C_{14}H_{22}N_4$ | 68.26 / 68.00 | 9.00 / 9.12 | 22.74 / 22.55 | |
| **3ab** | $C_9H_{12}N_4$ | 61.34 / 61.53 | 6.86 / 6.94 | 31.79 / 31.58 | |
| **3af** | $C_9H_{12}N_4$ | 61.34 / 61.51 | 6.86 / 6.93 | 31.79 / 31.59 | |
| **3ad** | $C_{11}H_{16}N_4$ | 64.68 / 64.59 | 7.90 / 7.83 | 27.43 / 27.25 | |
| **3ae** | $C_{14}H_{14}N_4$ | 70.57 / 70.33 | 5.92 /6.02 | 23.51 / 23.58 | |
| **3bf** | $C_{10}H_{14}N_4$ | 63.13 / 63.01 | 7.42 / 7.23 | 29.45 / 29.26 | |
| **3ah** | $C_7H_8N_4$ | 56.74 / 56.59 | 5.44 /5.26 | 37.81 / 37.71 | |
| **5** | $C_9H_{11}N_3O$ | 61.00 / 61.12 | 6.26 / 6.18 | 23.71 / 23.56 | |
| **6a** | $C_7H_7N_3Cl_2$ | 41.20 / 41.55 | 3.46 / 3.49 | 20.59 / 20.71 | 34.75 / 34.61 |
| **6b** | $C_8H_9N_3Cl_2$ | 44.06 / 44.21 | 4.16 / 4.30 | 19.27 / 19.44 | 32.51 / 32.60 |
| **6f** | $C_8H_9N_3Cl_2$ | 44.06 / 44.12 | 4.16 / 4.07 | 19.27 / 19.48 | 32.51 / 32.45 |
| **6g** | $C_{10}H_{13}N_3Cl_2$ | 48.80 / 49.01 | 5.32 / 5.40 | 17.07 / 16.99 | 28.81 / 28.66 |
| **7a** | $C_6H_6N_2Cl_2$ | 40.71 / 40.82 | 3.42 / 3.50 | 15.82 / 15.63 | 40.05 / 39.92 |
| **7b** | $C_7H_8N_2Cl_2$ | 44.01 / 44.14 | 4.22 / 4.33 | 14.66 / 14.59 | 37.11 / 37.18 |
| **7c** | $C_8H_{10}N_2Cl_2$ | 46.85 / 46.94 | 4.91 / 4.98 | 13.66 / 13.57 | 34.57 / 34.39 |
| **7d** | $C_9H_{12}N_2Cl_2$ | 49.33 / 49.18 | 5.52 / 5.60 | 12.79 / 12.67 | 32.36 / 32.48 |
| **7e** | $C_{12}H_{10}N_2Cl_2$ | 56.94 / 57.02 | 3.98 / 3.90 | 11.07 / 11.20 | 28.01 / 28.10 |
| **7f** | $C_7H_8N_2Cl_2$ | 44.01 / 44.12 | 4.22 / 4.30 | 14.66 / 14.73 | 37.11 / 37.01 |
| **7h** | $C_5H_4N_2Cl_2$ | 36.84 / 37.03 | 2.47 / 2.47 | 17.19 / 17.28 | 43.50 / 43.36 |
| **9a·H$_2$O** | $C_8H_{18}N_4OCl_2$ | 37.36 / 37.15 | 7.06 / 6.96 | 21.79 / 21.78 | 27.57 / 27.78 |
| **9b** | $C_{10}H_{20}N_4Cl_2$ | 44.95 / 44.70 | 7.54 / 7.54 | 20.97 / 21.05 | 26.54 / 26.36 |
| **9d·2H$_2$O** | $C_{14}H_{32}N_4O_2Cl_2$ | 46.79 / 46.97 | 8.98 / 8.99 | 15.59 / 15.53 | 19.73 / 19.50 |
| **9ah·2H$_2$O** | $C_7H_{18}N_4O_2Cl_2$ | 32.19 / 32.38 | 6.94 / 6.81 | 21.45 / 21.26 | 27.15 / 26.87 |

**Syntheses of unsymmetrically 3,5-disubstituted 4-pyridinecarbonitriles.** Specimens of compounds (**2**) or (**4**) were treated with an excess of the proper amine and the products were separated and purified as described above for the syntheses from **1**. Reaction temperatures and times were respectively in the range

of 70-80 °C and 72-264 h. The reaction between **4** and methylamine at 70 °C for 22 h allowed to separate a mixture of **2a** and **5** in the molar ratio 2.47:1 which was separated by further column chromatography (adsorbent 70-230 mesh Merck 60 silica gel, eluent chloroform/ethyl acetate 9:1) (Table 3).

**Table 3.** Synthesis data, melting points, MS and IR (KBr pellet or film) data of compounds (**2**, **3**, **5** and **7**).

| Product | Reagents | Yield % | mp °C | MS (m/z) $M^+$ | (%) | 100% peak | IR ν $cm^{-1}$ |
|---|---|---|---|---|---|---|---|
| **2a** | **1** + $CH_3NH_2$ | 84 | 134-135 | 167 | (100) | | 3374, 2210, 1562, 844, 588 |
| **2b** | **1** + $C_2H_5NH_2$ | 67 | 105-107 | 181 | (34) | 166 | 3228, 2224, 1558, 841, 586 |
| **2c** | **1** + $(CH_3)_2CHNH_2$ | 85 | 80-82 | 195 | (18) | 180 | 3307, 2226, 1552, 847, 587 |
| **2d** | **1** + $C_4H_9NH_2$ | 73 | 86-89 | 209 | (14) | 166 | 3363, 2228, 1560, 842, 586 |
| **2e** | **1** + $C_6H_5CH_2NH_2$ | 65 | 145-146 | 243 | (21) | 91 | 3357, 2229, 1561, 855, 583 |
| **2f** | **1** + $(CH_3)_2NH$ | 75 | 98-100 | 181 | (83) | 180 | 2220, 1565, 850, 583 |
| **2g** | **1** + $(C_2H_5)_2NH$ | 90 | 52-53 | 209 | (20) | 194 | 2214, 1568, 857, 579 |
| **2h** | **1** + $NH_3$ | 77 | 169-170 | 153 | (100) | | 3172, 2226, 1545, 844, 596 |
| **3a** | **1** + $CH_3NH_2$ | 60 | 119-121 | 162 | (100) | | 3379, 2202, 1561, 586 |
| **3b** | **1** + $C_2H_5NH_2$ | 94 | 117-118 | 190 | (100) | | 3350, 2211, 1561, 588 |
| **3c** | **1** + $(CH_3)_2CHNH_2$ | 45 | oil | 218 | (86) | 203 | 3354, 2207, 1557, 587 |
| **3d** | **1** + $C_4H_9NH_2$ | 65 | 145-147 | 246 | (59) | 203 | 3377, 2210, 1561, 582 |
| **3e** | **1** + $C_6H_5CH_2NH_2$ | 65 | oil | 314 | (33) | 91 | 3376, 2205, 1567, 586 |
| **3f** | **1** + $(CH_3)_2NH$ | 63 | 64-65 | 190 | (100) | | 2210, 1549, 583 |
| **3g** | **1** + $(C_2H_5)_2NH$ | 30 | waxy solid | 246 | (40) | 231 | 2206, 1602, 581 |
| **3ab** | **2a** + $C_2H_5NH_2$ | 57 | 126-128 | 176 | (97) | 161 | 3352, 2206, 1560, 592 |
| | **2b** + $CH_3NH_2$ | 65 | | | | | |
| **3af** | **2a** + $(CH_3)_2NH$ | 62 | 145-147 | 176 | (100) | | 3366, 2200, 1560, 584 |
| **3ad** | **2d** + $CH_3NH_2$ | 71 | 99-101 | 204 | (53) | 161 | 3378, 2204, 1566, 587 |
| **3ae** | **2e** + $CH_3NH_2$ | 90 | 138-140 | 238 | (61) | 91 | 3384, 2202, 1561, 588 |
| **3bf** | **2f** + $C_2H_5NH_2$ | 65 | 54-55 | 190 | (100) | | 3347, 2209, 1559, 584 |
| **3ah** | **2h** + $CH_3NH_2$ | 65 | 169-171 | 148 | (100) | | 3383, 2211, 1561, 588 |
| **5** | **4** + $CH_3NH_2$ | 19 | 110-112 | 177 | (100) | | 3233, 2222, 1561,1043, 586 |
| **7a** | **1** + $CH_3NHLi$ | 64 | 92-94 | 177 | (69) | 175 | 3238, 1577, 799, 575 |
| **7b** | **1** + $C_2H_5NHLi$ | 58 | 53-55 | 191 | (6) | 175 | 3268, 1570, 794, 576 |
| **7c** | **1** + $(CH_3)_2CHNHLi$ | 42 | oil | 205 | (3) | 175 | 3383, 1567, 785, 573 |
| **7d** | **1** + $C_4H_9NHLi$ | 58 | oil | 219 | (1) | 175 | 3401, 3301, 1571, 795, 579 |
| **7e** | **1** + $C_6H_5CH_2NHLi$ | 37 | oil | 253 | (2) | 91 | 3396, 3288, 1568, 799, 579 |
| **7f** | **1** + $(CH_3)_2NLi$ | 45 | oil | 191 | (69) | 189 | 1555, 810, 593 |
| **7h** | **1** + $LiNH_2$ | 54 | oil | 163 | (7) | 162 | 3448, 3278, 1635, 797, 615 |

**Syntheses from 3,5-dichloro-4-pyridinecarbonitrile (1) and lithium amides.** Commercial hexane solution of butyllithium and an excess of the proper amine were introduced at -50 °C under nitrogen into a 50-100 mL pressure resistant glass vial with *rotaflo* stopcock and allowed to react. The obtained lithium amide was in turn brought to dryness to remove hexane, taken with the same amine or with a different solvent, then treated with **1** operating between -70 °C and rt. The vial was placed in a thermostatic or cryostatic bath, for the time necessary to the consumption of **1** as checked by GCMS, then the products were recovered as for the reaction of **1** with amines using hexane/chloroform 9:1 as chromatographic eluent. As each reaction affords mixture of products whose distribution for preparative purpose is susceptible to be optimized acting on various parameters, the best operating conditions concerning molar ratio (**1** : amide), solvent and temperature for the products (**2**, **3**, **6** and **7**) are respectively: **2** (1:1.1), DMF, rt; **3** (1:2),

DMF, 50 °C; **6** (1:4), corresponding amine, 0 °C - rt; **7** (1:5), corresponding amine, 0 °C - rt. Specific reaction data are reported only for compounds (**7**) (Table 3).

**Reduction of 4-pyridinecarbonitriles (3) to 4-aminomethylpyridines (8) and their transformation into hydrochlorides (9).** A 0.3 M solution of **3** in glacial acetic acid and 10% palladium on activated charcoal (3.5 g per mmol of **3**) was hydrogenated with $H_2$ at 0.5 atm, then the mixture was in turn filtered, evaporated at reduced pressure, taken with 1 N aqueous NaOH, extracted with chloroform, dried over anhydrous $Na_2SO_4$, evaporated at reduced pressure, taken with anhydrous THF, saturated with gaseous HCl, filtered and crystallized from ethanol 95% to give **9**. (Table 4).

**Table 4**. Synthesis data, melting points and IR (KBr pellet) bands of compounds (**9**).

| Product | Reagent | Yield % | mp °C | IR ν $cm^{-1}$ |
|---|---|---|---|---|
| **9a**·$H_2O$ | **3a** | 75 | 264-265 (decomp) | 3337, 3291, 1607, 1553, 532 |
| **9b** | **3b** | 71 | 286-289 (decomp) | 3330, 1609, 1549, 542 |
| **9d**·$2H_2O$ | **3d** | 65 | 211-214 (decomp) | 3307, 1610, 1554, 557 |
| **9ah**·$2H_2O$ | **3ah** | 36 | 170-172 (decomp) | 3316, 3228, 1606, 1556, 540 |

**Preparations of amidine samples (6).** Compound (**1**) was allowed to react with the proper methylchloroaluminum amide according to the Garigipati[5] and Moss[6] procedure. The reaction mixture, hydrolyzed with 0.1*N* NaOH was in turn extracted with chloroform, dried over anhydrous $Na_2SO_4$, evaporated at reduced pressure and chromatographed on Merck neutral alumina gel grade I with hexane/chloroform 1:1 as eluent. The obtained amidines were further purified by sublimation at reduced pressure (Table 5).

**Table 5**. Yields, melting points, MS and IR (KBr pellet) data of compounds (**6**).

| Product | Yield % | mp °C | MS (m/z) $M^+$ (%) | MS (m/z) 100% peak | IR ν $cm^{-1}$ |
|---|---|---|---|---|---|
| **6a** | 59 | 164-165 | 203 (27) | 168 | 3324, 1608, 820, 594 |
| **6b** | 34 | 149-150 | 217 (14) | 182 | 3264, 1611, 820, 599 |
| ***6f*** | 64 | 112-113 | 217 (8) | 182 | 3282, 1605, 815, 598 |
| **6g** | 31 | 58-59 | 245 (5) | 210 | 3292, 1595, 820, 591 |

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