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3,5-DICHLORO-4-PYRIDINECARBONITRILE: A MULTISITE SUBSTRATE FOR CARBON NUCLEOPHILES

Nevio Picci, Marco Pocci,[‡]* Annarosa Gugliuzza, Francesco Puoci, Angela De Munno,[§] Francesca Iemma, and Vincenzo Bertini[‡]

Dipartimento di Chimica, Università della Calabria, Arcavacata di Rende, I-87030 Italy; [‡]Dipartimento di Chimica e Tecnologie Farmaceutiche ed Alimentari, Universita' di Genova, Via Brigata Salerno, I-16147 Genova, Italy; [§]Dipartimento di Chimica e Chimica Industriale, Universita' di Pisa, Via Risorgimento, 35, I-56126 Pisa, Italy
E-mail: pocci@dictfa.unige.it

Abstract – The reactivity of 3,5-dichloro-4-pyridinecarbonitrile (**1**) towards lithium or magnesium organometallic reagent is described. Conditions for substitution of cyano with alkyl or phenyl group, alkylation at the position 2 with removal of the 5-positioned chlorine, and formation of methyl or phenyl dichloro-pyridyl imines are reported. The obtained 4-alkyl-3,5-dichloropyridines can undergo a further alkylation at the position 2. The 3,5-dichloro-4-pyridyl residue is shown to be a good leaving group in form of anion yielding 3,5-dichloropyridine either from **1** or 3,5-dichloro-4-pyridinecarboxaldehyde.

INTRODUCTION

3,5-Dichloro-4-pyridinecarbonitrile (**1**) is an attractive molecule for its flexible chemical behavior deriving from the presence of different sites sensitive to a nucleophilic attack. Starting from **1**, through the controlled nucleophilic substitution of chlorine atoms and the successive reduction of the cyano group, we successfully prepared numerous 4-aminomethylpyridine derivatives carrying in the positions 3 and 5 alkoxy,[1] mercapto[2] and alkylamino[3] residues, endowed with a remarkably high inhibitory activity and selectivity towards benzylamine oxidase and diamine oxidase, different members of the copper containing amine oxidase class.[4]

In this work we report about the reactivity of **1** with carbon nucleophiles such as organolithium or magnesium reagent which allow new synthetic applications of **1**, affording mono- and dialkylated dichloropyridines or giving rise to an unexpected evolution of the nucleophilic attack at the position 2 of the pyridine ring.

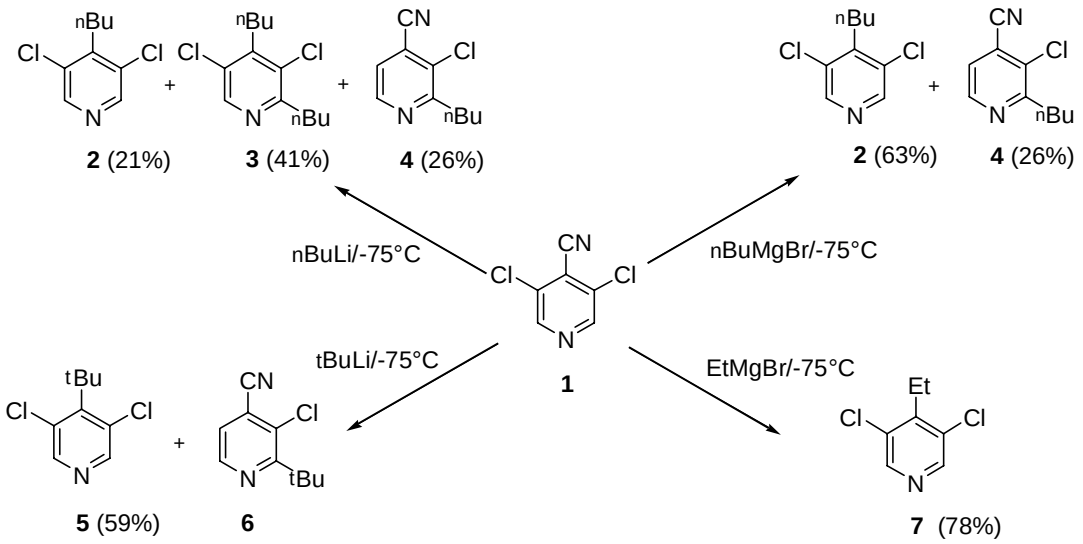
RESULTS AND DISCUSSION

As it is well documented by review works,[5] and recently alerted by papers on pyridylmagnesium reagents,[6] the pyridine ring containing halogens may undergo with organometallics a variety of reactions such as metal-halogen exchange, addition to the ring itself, proton abstraction, halogen substitution or migration, and even ring opening. It is also known that 3-chloro-4-pyridinecarbonitrile[7] reacts at room temperature with methylmagnesium bromide undergoing cyano group attack to afford 4-acetyl-3-chloro-pyridine after hydrolysis. Finally, the cyano function of **1** can undergo substitution as we found in reactions with lithium amides.[3]

We started our study by making react substrate (**1**) with a molar excess (usually 1:2) of organometallic reagents such as MeLi, MeMgI, EtMgBr, *n*-BuLi, *t*-BuLi, *n*-BuMgBr, PhLi, and PhMgBr endowed with different nucleophilic character, steric hindrance and polarity of the carbon-metal bond. For fast explorations on small scale (less than one mmol) the progress of the reactions was followed by GC-MS. Successively, the reactions were repeated on a larger scale and the main stable products were isolated by column chromatography or PLC and fully characterized by IR, ^{1}H NMR, MS spectra and elemental analysis. Compound (**11**) was identified by comparison with an authentic commercial sample. The structure of **6** prepared in small quantity and of difficult purification was deduced from GC-MS data ensuring the molecular weight of the product and the presence of only one chlorine atom through its peculiar isotopic pattern.

Scheme 1, which collects the reactivity pattern of **1** with *n*-BuLi, *t*-BuLi, *n*-BuMgBr, and EtMgBr, shows that with these reagents the predominant effect is the attack at the position 4 of the pyridine ring with substitution of the cyano group and complementarily the alkylation of the position 2, while no addition to the nitrile function or substitution of the chlorine were recorded. For what concerns products (**2**) and (**3**), the reaction between **1** and *n*-BuLi repeated with reagent molar ratio 1:1 showed an increase of **2** with disappearance of **3** in agreement with a two step process made of nucleophilic substitution of the cyano group followed by alkylation at the position 2 of the pyridine ring.

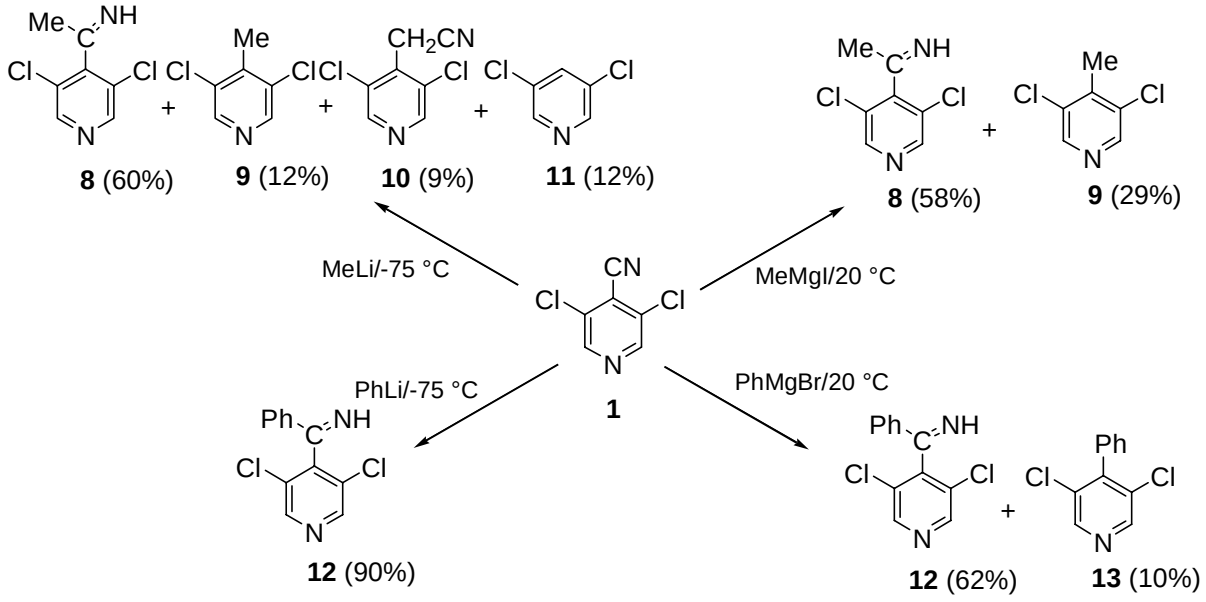
The Grignard reagents, less reactive with respect to the alkyllithiums, showed a major selectivity towards the position 4 thus proving more useful for the production of 4-alkyl-3,5-dichloropyridines.



Scheme 1

The formation of the unexpected products (**4**) and (**6**), formally corresponding to alkylation at the position 2 of the pyridine ring and removal of the 5-positioned chlorine, is not satisfactorily explainable, because an alkylation which gives a delocalized non aromatic anionic intermediate able to eliminate a chloride ion and leave an uncharged carbon with six electrons which forms a bond with the proton released from the position 2 through conjugation is unprecedented.

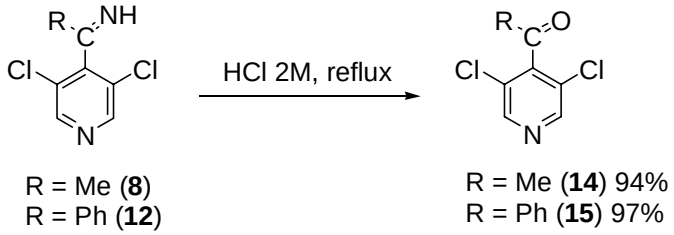
When MeLi, MeMgI, or aryl C-nucleophiles such as PhLi or PhMgBr were made to react with **1,** the prevalent attack at the cyano function with respect to its substitution was observed, the Grignard reagents requiring room temperature to be effective (Scheme 2).



Scheme 2

The above results can derive from the poor nucleophilic character of the reagents in a solvent of moderate polarity. It is known for example that in reactions of 2-chlorobenzonitriles with stabilized carbanion[8] solvents of low polarity such as chlorobenzene induce addition to nitrile, whereas markedly polar solvents such as DMF or 1,2-dimethoxyethane promote the halogen substitution.

The imines (**8**) and (**12**), stable at room temperature, were isolated and characterized by ^{1}H NMR, IR, MS spectra and also through their quantitative conversion into the corresponding ketones (**14)** and (**15)** (Scheme 3).

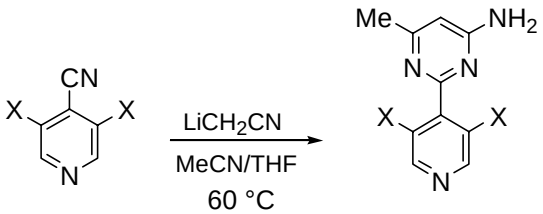


R = Me (**8**)
R = Ph (**12**)

R = Me (**14**) 94%
R = Ph (**15**) 97%

Scheme 3

In order to clarify the origin of **10**, **1** was allowed to react with the lithium salt of acetonitrile in THF obtaining the expected product (**10**) (90%) and a new compound (**16**) (10%) corresponding to an addition to **1** of two molecules of acetonitrile according to a known scheme.[9] The synthesis of **16** from **1** and also of **18** from **17** as a further example could be forced to give high yields by using a mixture MeCN/THF as solvent, thus attaining a process with a certain synthetic interest for the production of functionalized pyridylpyrimidines (Scheme 4).

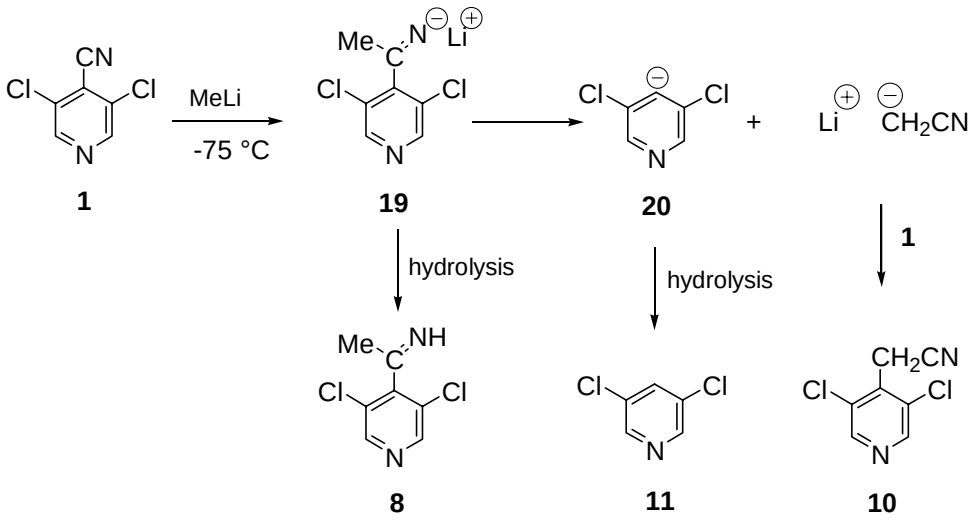


X=Cl (**1**)
X=H (**17**)

X = Cl (**16**) 90%
X = H (**18**) 85%

Scheme 4

The high yield production of **10** from **1** and acetonitrile lithium salt allows to rationalize the formation of **8**, **10**, and **11** (Scheme 2) as follows: the nucleophilic attack at the cyano group forms the intermediate (**19**) which partially decomposes into the 3,5-dichloropyridyl anion (**20**) and acetonitrile, successively the reaction of acetonitrile with **1** in the presence of nucleophile produces **10**. The final hydrolysis gives **8** and **11** from **19** and **20** respectively (Scheme 5).



Scheme 5

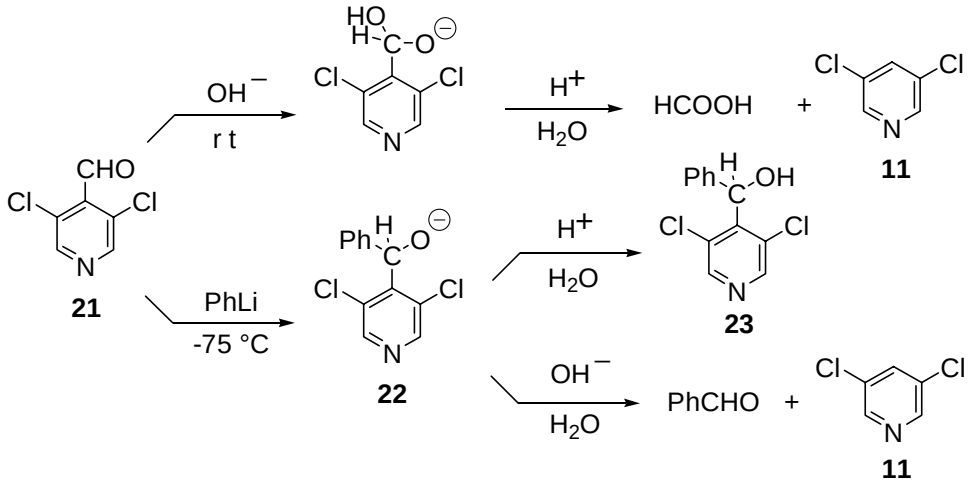
Scheme 5 was further confirmed either by performing the reaction with MeLi at 20 °C where the decreased stability of **19** made the system evolve towards higher yields of **10** (39%) and **11** (45%) (Table 1, sixth row) or by applying high dilution conditions that favored the production of **11** in good yield preventing the formation of **10**.

Table 1. Typical reactions between **1** and organometallic reagent

Reagent	Temperature (°C)	ReactionTime (min)	Yield (%)
n-BuLi	–75	20	**2** (21); **3** (41); **4** (26)
t-BuLi	–75	40	**5** (59)
n-BuMgBr	–75	20	**2** (63); **4** (26)
EtMgBr	–75	20	**7** (78)
MeLi	–75	20	**8** (60) ; **9** (12); **10** (9); **11** (12)
MeLi	20	20	**9** (3); **10** (39); **11** (45)
MeMgI	20	20	**8** (58); **9** (29)
$LiCH_2CN$	20	5	**10** (73) ; **20** (8)
PhLi	-75	20	**12** (90)
PhMgBr	20	120	**12** (62); **13** (10)

The release of **20** collected as **11** after hydrolysis that qualifies the 3,5-dichloro-4-pyridyl anion as a good leaving group was already encountered in our laboratory when 3,5-dichloro-4-pyridinecarboxaldehyde (**21**) was treated at room temperature with 10% NaOH to produce **11**, or when **21** was added with

phenyllithium to afford the intermediate (**22**) which by treatment with 1 N NaOH produced **11** and benzaldehyde, while by acidic hydrolysis the expected alcohol (**23**) was yielded (Scheme 6).



Scheme 6

EXPERIMENTAL

MaterialsandMethods. 3,5-Dichloropyridine (**11**), 4-pyridinecarbonitrile (**17**), MeLi (1.4NinEt$_2$O), *n*-BuLi (1.7 N in hexane), *n*-BuMgBr (1.6 N in THF), *t*-BuLi (1.5 N in pentane), PhLi (1.8 N in cyclohexane/Et$_2$O70/30) were purchased from Sigma-Aldrich. 3,5-Dichloro-4-pyridinecarbonitrile,[1]3,5-dichloro-4-pyridinecarboxaldehyde,[1] MeMgI[11] (1.0 N in THF), EtMgBr[11] (2.7 N in Et$_2$O), and PhMgBr[11] (1.6 N in THF) were prepared according to known procedures.

Melting points were determined on a Reichert Thermovar hot stage apparatus and are uncorrected. ^{1}H NMR spectra were acquired on Bruker WM 300 spectrometer using TMS as internal reference. Chemical shifts are given in ppm on the δ scale. IR spectra were recorded on FTIR Paragon 1000 PC spectrophotometer as film or KBr pellets. GC-MS analyses were acquired on a Hewlett-Packard GC-MSD 5972 instrument. PLCs were performed on Merck silica gel 60 F_{254} glass plates (20x20 cm, thickness 2 mm). Column chromatographies were performed on Merck silica gel (230-400 mesh), eluents are given below for each compound.

General Procedure for the Reaction of 1 with Organometallic Reagent. The organometallic reagent was added dropwise under nitrogen and magnetic stirring to a 0.2 M solution of **1** (molar ratio 2:1) in dry THF at the desired temperature, stirred up to the disappearance of 1, hydrolyzed and extracted with

$CHCl_3$ or EtOAc. The organic extracts were dried over Na_2SO_4, vacuum evaporated and purified by column chromatography or PLC. Table 1 collects temperatures, reaction times and yields of representative reactions of 1 with the examined organometallic reagents.

4-*n*-Butyl-3,5-dichloropyridine (2). Yield 63%. Oil. Column. Hexane/EtOAc 90/10. ^{1}H NMR ($CDCl_3$) 0.93 (t, *J* = 6.0 Hz, 3H), 1.51 (m, 4H), 2.91 (t, *J* = 7.0 Hz, 2H), 8.40 (s, 2H). MS (EI) *m/z* 207 (M^+ [Cl^{37}/Cl^{37}], 10%), 205 (M^+ [Cl^{37}/Cl^{35}], 29%), 203 (M^+ [Cl^{35}/Cl^{35}], 49%), 161 (100%). Anal. Calcd for $C_9H_{11}NCl_2$: C, 52.96; H, 5.43; N, 6.86. Found C, 53.01; H, 5.40; N, 6.79.

2,4-Di-*n*-butyl-3,5-dichloropyridine (3). Yield 34%. Oil. Column. Hexane. ^{1}H NMR ($CDCl_3$) 0.96 (t, *J* = 7.0 Hz, 3H), 0.97 (t, *J* = 7.0 Hz, 3H), 1.36-1.74 (m, 8H), 2.90 (t, *J* = 7.8 Hz, 2H), 2.91 (t, *J* = 7.8 Hz, 2H), 8.34 (s, 1H). MS (EI) *m/z* 259 (M^+, 1%), 217 (100%). Anal. Calcd for $C_{13}H_{19}NCl_2$: C, 60.01; H, 7.36; N, 5.38. Found C, 59.98; H, 7.41; N, 5.30.

2-*n*-Butyl-3-chloro-4-pyridinecarbonitrile (4). Yield 26%. Oil. Column. Hexane/EtOAc 95/5. IR (film) ν 2241 (CN) cm^{-1}. ^{1}H NMR ($CDCl_3$) 0.97 (t, *J* = 7.3 Hz, 3H), 1.43 (m, 2H), 1.73 (m, 2H), 3.02 (t, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 4.7 Hz, 1H), 8.59 (d, *J* = 4.7 Hz, 1H). MS (EI) *m/z* 194 (M^+, 1%), 152 (100%). Anal. Calcd for $C_{10}H_{11}N_2Cl$: C, 61.70; H, 5.70; N, 14.39. Found C, 61.58; H, 5.73; N, 14.48.

4-*tert*-Butyl-3,5-dichloropyridine (5). Yield 43%. Oil. Column. Hexane/EtOAc 90/10. ^{1}H NMR ($CDCl_3$) 1.25 (s, 9H), 8.70 (s, 2H). MS (EI) *m/z* 207 (M^+ [Cl^{37}/Cl^{37}], 5%), 205 (M^+ [Cl^{37}/Cl^{35}], 31%), 203 (M^+ [Cl^{35}/Cl^{35}], 47%), 160 (100%). Anal. Calcd for $C_9H_{11}NCl_2$: C, 52.95; H, 5.43; N, 6.86. Found C, 52.80; H, 5.38; N, 6.90.

4-Ethyl-3,5-dichloropyridine (7). Yield 52%. Oil. Column. Hexane. ^{1}H NMR ($CDCl_3$) 1.18 (t, *J* = 7.7 Hz, 3H), 2.93 (q, *J* = 7.7 Hz, 2H), 8.40 (s, 2H). MS (EI) *m/z* 179 (M^+ [Cl^{37}/Cl^{37}], 11%), 177 (M^+ [Cl^{37}/Cl^{35}], 61%), 175 (M^+ [Cl^{35}/Cl^{35}], 100%). Anal. Calcd for $C_7H_7NCl_2$: C, 47.76; H, 4.01; N, 7.96. Found C, 47.69; H, 4.00; N, 8.01.

Methyl 3,5-dichloro-4-pyridyl imine (8). Yield 57%. mp 72-74 °C. Column. Hexane/EtOAc 60/40. IR (KBr) ν 3147 (NH), 1647 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$) 2.37 (s, 3H), 8.53 (s, 2H). MS (EI) *m/z* 192 (M^+ [Cl^{37}/Cl^{37}], 3%), 190 (M^+ [Cl^{37}/Cl^{35}], 18%), 188 (M^+ [Cl^{35}/Cl^{35}], 30%), 173 (100%). Anal. Calcd for $C_7H_6N_2Cl_2$: C, 44.47; H, 3.20; N, 14.82. Found C, 44.52; H, 3.12; N, 14.91.

4-Methyl-3,5-dichloropyridine (9). Yield 19%. Oil. Column. Hexane/EtOAc 60/40. ^{1}H NMR ($CDCl_3$) 2.46 (s, 3H), 8.41 (s, 2H). MS (EI) *m/z* 165 (M^+ [Cl^{37}/Cl^{37}], 12%), 163 (M^+ [Cl^{37}/Cl^{35}], 60%), 161 (M^+ [Cl^{35}/Cl^{35}], 100%). Anal. Calcd for $C_6H_5NCl_2$: C, 44.48; H, 3.11; N, 8.65. Found C, 44.49; H, 3.20; N, 8.68.

3,5-Dichloro-4-pyridylacetonitrile (10). Yield 32%. mp 115-116 °C. Column. Hexane/EtOAc 60/40. IR (KBr) ν 2252 (CN) cm^{-1}. ^{1}H NMR ($CDCl_3$) 4.01 (s, 2H), 8.58 (s, 2H). MS (EI) *m/z* 190 (M^+ [Cl^{37}/Cl^{37}], 11%), 188 (M^+ [Cl^{37}/Cl^{35}], 67%), 186 (M^+ [Cl^{35}/Cl^{35}], 100%). Anal. Calcd for $C_7H_4N_2Cl_2$: C, 44.95; H, 2.16; N, 14.98. Found C, 45.00; H, 2.20; N, 14.02.

Phenyl 3,5-dichloro-4-pyridyl imine (12). Yield 80%. mp 157-158 °C. Column. Hexane/EtOAc 70/30. IR (KBr) ν 3218 (NH), 1608 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$) 7.53 (m, 5H), 8.60 (s, 2H), 10.00 (very broad s, 1H). MS (EI) *m/z* 252 (M^+ [Cl^{37}/Cl^{35}], 7%), 250 (M^+ [Cl^{37}/Cl^{35}], 11%), 215 (100%). Anal. Calcd for $C_{12}H_8N_2Cl_2$: C, 57.40; H, 3.21; N, 11.16. Found C, 57.38; H, 3.23; N, 11.21.

4-Phenyl-3,5-dichloropyridine (13). Yield 5%. Oil. PLC. Hexane/EtOAc 70/30. ^{1}H NMR(hexadeutero-acetone) 7.13 (m, 1H), 7.37 (m, 2H), 7.56 (m, 2H), 8.66 (s, 2H). MS (EI) *m/z* 227 (M^+ [Cl^{37}/Cl^{37}], 9%), 225 (M^+ [Cl^{37}/Cl^{35}], 64%), 223 (M^+ [Cl^{35}/Cl^{35}], 100%). Anal. Calcd for $C_{11}H_7NCl_2$: C, 58.96; H, 3.15; N, 6.25. Found C, 59.00; H, 3.16; N, 6.19.

Methyl 3,5-dichloro-4-pyridyl ketone (14). Yield 94%. Oil. Column. Hexane/EtOAc 70/30. IR (film) ν 1721 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$) 2.59 (s, 3H), 8.54 (s, 2H). MS (EI) *m/z* 190 (M^+, 3%), 174 (100%). Anal. Calcd for $C_7H_5NOCl_2$: C, 44.24; H, 2.65; N, 7.37. Found C, 44.04; H, 2.60; N, 7.21.

Phenyl 3,5-dichloro-4-pyridyl ketone (15). Yield 97%. mp 66-68 °C. IR (KBr) ν 1681 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$) 7.66 (m, 5H), 8.61 (s, 2H). MS (EI) *m/z* 252 (M^+, 3%), 105 (100%). Anal. Calcd for $C_{12}H_7NOCl_2$: C, 57.17; H, 2.80; N, 5.56. Found C, 57.04; H, 2.68; N, 5.31.

Pyridylpyrimidines (16) and (18). To a stirred solution of freshly prepared LDA (24 mmol) in THF (10 mL), dry acetonitrile (4.5 mL) was added at rt. The heterogeneous mixture was then treated with the proper cyanopyridine (5.7 mmol) and refluxed for 5 h up to the disappearance of the reagent checked by GC-MS, hydrolyzed with water (20 mL), and extracted with EtOAc (4x20 mL). The organic layers were dried over anhydrous Na_2SO_4 and removed of the solvent at reduced pressure to afford the crude pyridylpyrimidine which was purified through column chromatography.

4-Amino-6-methyl-2-(3,5-dichloro-4-pyridyl)pyrimidine (16). Yield 90% mp 228-230 °C. Column. $CHCl_3$/MeOH 99/1. IR (KBr) ν 3325 (NH_2) cm^{-1}. ^1H NMR (CD_3OD) 2.35 (s, 3H), 6.45 (s, 1H), 8.64 (s, 2H). MS (EI) *m/z* 258 (M^+ [Cl^{37}/Cl^{37}], 5%), 256 (M^+ [Cl^{37}/Cl^{35}], 35%), 254 (M^+ [Cl^{35}/Cl^{35}], 53%), 219 (100%). Anal. Calcd for $C_{10}H_8N_4Cl_2$: C, 47.08; H, 3.16; N, 21.96. Found C, 47.21; H, 3.11; N, 22.01. Hydrochloride: mp 240-243 °C (acetonitrile).

4-Amino-6-methyl-2-(4-pyridyl)pyrimidine (18). Yield 85%. mp 191-193 °C. [lit.,[12] 192-194 °C]. MS (EI) *m/z* 186 (M^+, 100%). Hydrochloride: mp 243-245 °C (ethanol).

Phenyl(3,5-dichloro-4-pyridyl)methanol (23). A solution of **21** (0.50 g, 2.85 mmol) in dry Et_2O (15 mL) was cooled to –75 °C and added with a 1.8 M solution (3.42 mmol) of phenyllithium in hexane (1.9 mL). The yellow mixture was stirred for 2 h up to disappearance of **21** as checked by GC-MS, hydrolyzed with 1 N HCl (20 mL), and extracted with $CHCl_3$. The organic layers were combined, dried over Na_2SO_4 and removed of the solvent to afford crude **23** which was purified by column chromatography using a mixture hexane/$CHCl_3$ 50/50 as eluent: oil, 0.40 g (55%). IR (film) ν 3382 (OH) cm^{-1}. ^1H NMR ($CDCl_3$) 3.77 (s broad, 1H), 6.58 (s, 1H), 7.31 (m, 5H), 8.47 (s, 2H). MS (EI) *m/z*. 257 (M^+ [Cl^{37}/Cl^{37}], 6%), 255 (M^+ [Cl^{37}/Cl^{35}], 40%), 253 (M^+ [Cl^{35}/Cl^{35}], 64%), 79 (100%). Anal. Calcd for $C_{12}H_9NOCl_2$: C, 56.72; H, 3.57; N, 5.51. Found C, 56.65; H, 3.51; N, 5.40.

When the hydrolysis of the reaction mixture was performed with 1 N NaOH solution, the organic phase was composed of 3,5-dichloropyridine (48%) and benzaldehyde (28%) as revealed by GC-MS.

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