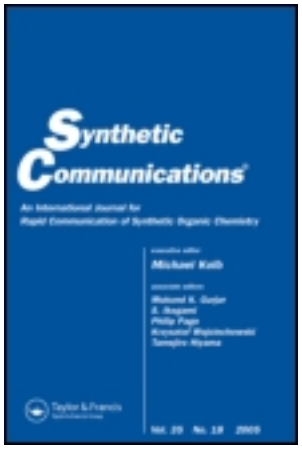

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MICROWAVE IRRADIATION–ASSISTED AMINATION OF 2-CHLOROPYRIDINE DERIVATIVES WITH AMIDE SOLVENTS

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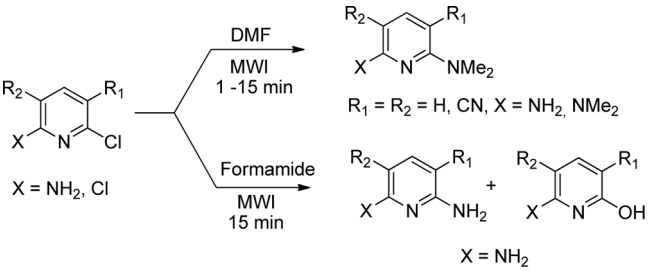
GRAPHICAL ABSTRACT



Abstract *A simple, quick, and high-yielding microwave-assisted synthesis of 2-(*N,N*-dimethyl)amine- and 2-aminopyridine derivatives is reported here for the first time in the reaction of 2-chloro substituted pyridines with amide solvents such as dimethylformamide or formamide, without transition-metal catalysts.*

Keywords Amides; amination; 2-aminopyridines; 2-chloropyridines; 2-(*N,N*-dimethyl)-aminopyridines; microwave irradiation

INTRODUCTION

The 2-aminopyiridine functional motif is present in a number of important biologically active compounds, such as the nitric oxide synthase (NOS) inhibitors bearing the 2-amino-4-methylpyridine nucleus,[1] the antiproliferative 2,6-dibenzylamino-3,5-dicyanopyridines,[2a] and the antitumoral 2-amimo-4-aryl-6-dialkylamino-3,5-dicyanopyridines.[2b] 2-Aminopyridines have been also investigated as starting precursors in organic synthesis and as useful chelating ligands for catalytic and organometallic applications.[3] The synthesis of 2-aminopyridine

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derivatives has been extensively reviewed.[4] The usual methods for the synthesis of 2-aminopyridines start either by *N*-akylation of *N*-alkyl pyridinium salts[5,6] or by substitution of 2-halopyridines,[7] a method that usually requires the presence of organometallic complexes as catalysts,[8] high temperatures, and pressure.[9]

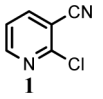
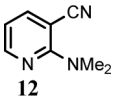
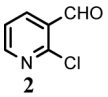
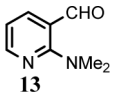
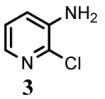
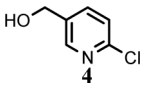
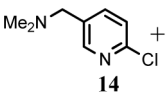
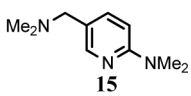
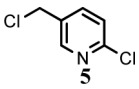
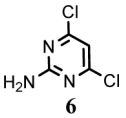
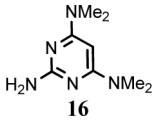
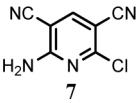
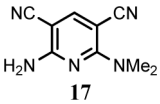
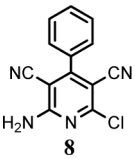
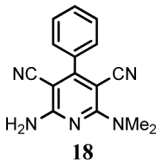
Very interestingly, the amination of other ring systems such as 4-chloro-2-arylquinolines has been reported in yields ranging from 11% to 91%, using common amide solvents, such as dimethylformamide (DMF) or formamide, as source of the amines by heating at reflux overnight.[10] The dimethylamino group has been also installed in [1,8]-naphtyridines by palladium-catalyzed reaction of halonaphthyridines with DMF in aqueous medium.[11] *N,N*-Dimethylamination of chloropyridazines with DMF under reflux either in the presence or absence of copper powder as catalyst has been reported.[12] 2-Chloropyrazine and 2-bromopyridine react easily with *N*-methylformamide or *N,N*-dimethylformamide in the presence of potassium hydroxide.[13] A recent article by Muzart [14] reviews the use of DMF as a source of carbon monoxide, dimethylamine, and other species involved in the reaction. DMF is considered an excellent polar solvent for various classes of compounds.

With these precedents in mind, and because of the well-known advantages and uses of microwave irradiation in organic synthesis (dramatic increases in yields, rates, and purities of products),[15] we now report here the first microwave irradiation–assisted reaction of differently substituted 2-chloropyridines with DMF and formamide to give the corresponding 2-amino substituted pyridines in short reaction times, mild reaction conditions, and excellent yields.[16]

RESULTS AND DISCUSSION

In our study, DMF gave more satisfactory results when used as a reaction medium. Nevertheless, through optimization runs, some results revealed that microwave-assisted rapid decomposition of DMF under specific reaction conditions can be a source of dimethylamine, which in the presence of chloropyridin generates the corresponding products. Table 1 lists the 2-dimethylaminopyridine derivatives formed by reaction of 2-chloropyridine derivatives and dimethylformamide under microwave irradiation. As precursors, we selected commercial 2-chloropyridines **1**–**6,** readily available 2-amino-6-chloropyridine-3,5-dicarbonitrile **7**,[17] and 2-amino-6-chloro-4-phenylpyridine-3,5-dicarbonitrile **8**.[18] Under the standard experimental conditions, the reaction of 2-chloronicotinonitrile **1** cleanly gave the expected 2-(*N,N*-dimethylamino)nicotinonitrile **12**[16,19] in good yield. 2-Chloronicotinaldehyde (**2**) afforded 2-(*N,N*-dimethylamino)nicotinaldehyde **13**.[20] With 3-amino-2-cholorpyridine **3,** no reaction was found after 5 h of irradiation in the same experimental conditions. Similarly, the reaction of 2-chloro-5-methanolpyridine **4** with DMF gave the unexpected 2-chloro-5-(*N,N*-dimethylmethylamine)pyridine **14** in 5% yield and 2-dimethylamino-5-[(*N,N*-dimethylamino)methyl]pyridin **15** in 75% yield. To confirm this result, we reacted the compound 2-chloro-5-(chloromethyl)-pyridine (**5**) with DMF to give the same products **14** and **15** in 50% and 33% yields, respectively. Compound **6**, after reaction with DMF, gave the product **16**.[21] Siu et al.[22] have described the dimethylamine amination product of 2-chloro-3-cyanopyridine derivative in DMF under microwave irradiation. Similarly, in

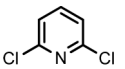
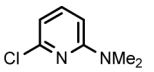
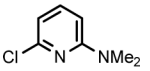
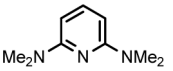
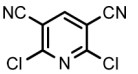
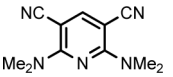
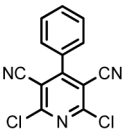
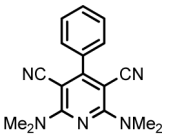
Table 1. Amination of 2-chloropyridine derivatives **1–8** with dimethylformamide under microwave irradiation

Entry	Precursors	Product	Temp. (°C)	Time	Yield (%)
a	 **1**	 **12**	180	25 min	96
b	 **2**	 **13**	180	15 min	87
c	 **3**	no reaction	180	5 h	—
d	 **4**	 **14** +  **15**	180	175 min	5 + 73
e	 **5**	**14** + **15**	180	5 min	10 + 65
f	 **6**	 **16**	160	2 min	86
g	 **7**	 **17**	150	15 min	61
h	 **8**	 **18**	180	3 min	74

our cases, the reaction of precursors **7** and **8** with DMF gave 2-amino-6-(*N,N*-dimethylamino)pyridine-3,5-dicarbonitrile **17**[23] and 2-amino-6-(*N,N*-dimethylamino)-4-phenylpyridine-3,5-dicarbonitrile **18**, respectively. Consequently, it is clear that the ability of displacement of chloro atom in a pyridine ring by the dimethylamine is highly influenced by the substitution on the pyridine ring.

Compounds containing two chloro atoms such as the 2,6-dicholopyridine derivatives also have been used as precursors (Table 2). Commercially available pyridine **9**, 2,6-dichloropyridine-3,5-dicarbonitrile **10**,[24] and 2,6-dichloro-4-phenylpyridine-3,5-dicarbonitrile **11**[25] were irradiated in the presence of DMF. Compound **9** gave

Table 2. Amination of 2,6-dichloropyridine derivatives **9–11** with DMF under microwave irradiation

Entry	Precursors	Product	Temp. (°C)	Time	Yield (%)
a	 **9**	 **19**	180	120	98
b	 **19**	 **20**	180	14 h	100
c	 **10**	 **21**	150	1	92
d	 **11**	 **22**	150	3	54

only the monosubtituted 6-chloro-2-*N,N*-dimethylaminopyridine **19** in quantitative yield after irradiating it for 2 h. Its conversion to 2,6-bis(*N,N*-dimethylamino)pyridine **20**[26] was achieved after 14 h by irradiating it at 180 °C. However, compounds **10** and **11** afforded only disubstituted derivatives **21** and **22**, respectively, in very short reaction times. The differences in reactivity between compounds **9** and **10** or **11** could be attributed probably to the positive activating effect resulting from the nitrile groups present at the C3 and C5 positions in the pyridine regarding the substitution of both chloro atoms.

The efficiency of this amination process, using DMF as the dimethylamine source, depends on the experimental conditions, and the reaction of chloropyridine derivatives with DMF was found to be temperature dependent. For compound **8**, the reaction takes place in 15 min at 150 °C, but at 180 °C the reaction was over in 3 min.

Standard heating reaction conditions also have been carried out to compare results with those obtained by microwave irradiation. Thus, compounds **7** and **8** were refluxed with DMF in the same experimental conditions. As shown in Table 3, the amination was rapid and complete within 15 and 3 min, whereas it required 12 h at 180 °C under conventional thermal conditions.

Attempts to conduct the reaction with formamide in some cases cause an uncontrollable high pressure in the reaction vessel. The cause of the high pressure may be attributed to the liberation of carbon monoxide and ammonia gases. In the case of DMF, the pressure in the reaction vessel during the reaction was relatively low. The reaction was carried out using compounds **1**, **5**, and **7–9** (Table 4). Irradiation of compound **1** in the presence of formamide afforded 2-hydroxynicotinonitrile **23**.[27] Irradiation of compound **5** gave exclusively the commercially

Table 3. Reaction of compounds **7** and **8** with DMF under thermal heating and microwave irradiation

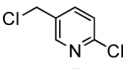
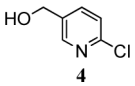
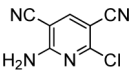
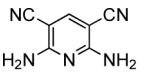
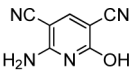
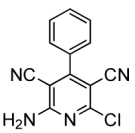
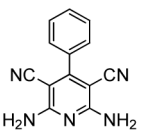
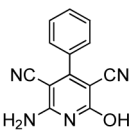
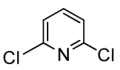
			Thermal heating		MWI	
Entry	Precursor	Product	Time	Yield (%)	Time	Yield (%)
a	**7**	**17**	12 h	20	15 min	61
b	**8**	**18**	12 h	50	3 min	74

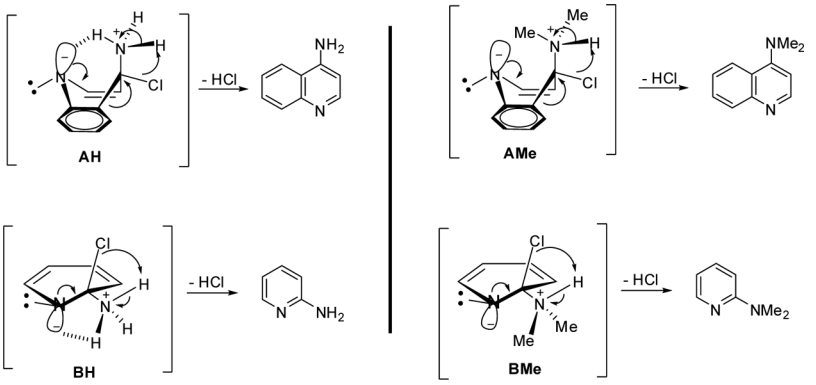
available product **4**. Irradiation of compound **7** afforded 2,6-diaminopyridine-3,5-dicarbonitrile **24**[28] and 2-hydroxy-6-aminopyridine-3,5-dicarbonitrile **25**.[29] Similarly, for compound **8**, after irradiation afforded compounds 2,6-diamino-4-phenylpyridine-3,5-dicarbonitrile **26**[15] and 2-hydroxy-6-amino-4-phenylpyridine-3,5-dicarbonitrile **27**.[30] No reaction was found after irradiating compound **9** 30 min at 180 °C.

The structure of the new reaction products has been established by their analytical and spectroscopic data, and when known, by comparison of these values with those reported in literature.

Concerning the mechanism of the amination reaction, some researchers [16,22,31] pointed that DMF easily decompose to form dimethylamine and carbon monoxide under microwave irradiation. Due to its nucleophilic character, the formed dimethylamine should react with 2-chloropyridine to give the formation of 2-dimethylaminopyridine derivatives. It was observed that the yield of the reaction is strongly

Table 4. Amination of chloropyridine derivatives **1, 5, 7–9** with formamide under microwave irradiation

Entry	Precursors	Product	Temp. (°C)	Time	Yield (%)
a	 **1**	 **23**	180	20	30
b	 **5**	 **4**	180	1	57
c	 **7**	 **24** +  **25**	180	15	30 + 43
d	 **8**	 **26** +  **27**	180	3	44 + 47
e	 **9**	No reaction	180	30	–



Scheme 1. Possible intermediates in the amination reaction of 2-chloroquinoliones and 2-chloropyridines with DMF and formamide, under microwave irradiation.

influenced by the substituent present on the aromatic ring.[32] In our work, compound **9** gave the disubstituted derivative **20** in 14 h, whereas compound **10** provided the disubstituted compound **21** in a short reaction time. Theses differences in reactivity were attributed to the presence of the two nitrile groups in molecule **10**. A similar result was obtained when we used formamide. The amination of 2-chloropyridine in the presence of formamide also depends on the subsistent on the aromatic ring. However, it remains to be explained the diverse reactivity observed depended on the amide used. For the amination of 4-chloro-2-phenylquinolines[10] and 2-chlopyridines, we think that the critical intermediates could be species AH(Me) or BH(Me) (Scheme 1), which under the reaction conditions should evolve to the final product in a concerted fragmentation process, liberating HCl, which should be neutralized in the reaction medium.

In conclusion, we have reported for the first time microwave-assisted amination of substituted 2-chloropyridine using amides as solvent and as the amine source to give 2-amino- and 2-*N,N*-dimethylamino substituted pyridines in a very efficient process under mild reaction conditions. As expected, the reaction times and chemical yields were superior to the results obtained for a similar reaction under conventional conditions.[10]

EXPERIMENTAL

Melting points were determined on a Kofler-type microscope and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature (rt) in $CDCl_3$ or dimethylsulfoxide (DMSO-d_6) at 300, 400, or 500 MHz and at 75.4, 100.6, or 125.6 MHz, respectively, using solvent peaks [$CDCl_3$: 7.27 (*D*), 77.2 (*C*) ppm and DMSO-d_6 2.50 (D) and 39.7 (C) ppm] as internal reference. The assignment of chemical shifts is based on standard NMR experiments [^{1}H, ^{13}C, ^{1}H-^{1}H correlation spectroscopy (COSY), ^{1}H-^{13}C heteronuclear multiple quantum correlation (HMQC), heteronuclear multiple bond correlation (HMBC), dimensionless enhancement by polarization transfer (DEPT)]. Mass spectra were recorded on a gas chromatography/mass spectrometry (GC/MS) instrument with an atmospheric

pressure ionization-electrospray (API-ES) ionization source. Elemental analyses were performed at the Instituto de Química Orgánica General (CSIC, Spain). Thin-layer chromatography (TLC) was performed on silica F254 and detection by ultraviolet light at 254 nm or by spraying with phosphomolybdic-H_2SO_4 dying reagent. Where anhydrous solvents were needed, they were purified following the usual procedures. Column chromatography was performed on silica gel 60 (230 mesh). Reactions under microwave irradiation were performed in a Biotage system equipped with electromagnetic sample stirrer and with temperature and power control. The reaction was performed in a 10-mL or 30-mL glass tube equipped with septa.

General Methods for the Synthesis of 2-(Dimethylamino)pyridine Derivatives

Method A-1 general method with MWI. A solution of compounds **1–11** (1.5 mmol) in DMF (5 mL) was placed in a 10-mL glass tube equipped with septa. The reaction mixture was stirred for 30 s, and then exposed to microwave irradiation at 250 W at temperatures and times shown in Table 1. After completion showed by TLC (hexane/AcOEt, 3/2, *v*/*v* or CH_2Cl_2/MeOH, 10/1, *v*/*v*), the reaction mixture was concentrated and the residue was purified by column chromatography to yield the corresponding product.

Method A-2 general method for classical heating. A solution of compounds **7** or **8** (0.393 mmol) in dry DMF (2 mL) was heated to reflux for 12 h. After complete reaction (TLC analysis), the solvent was removed under vacuum, and the residue was purified by column chromatography (hexane/EtOAc, 3/2, *v*/*v*) to yield compounds **17** (14.7 mg, 20%) and **18** (50.6 mg, 50%).

Method B General Method for the Synthesis of 2-Aminopyridine Derivatives

A solution of compounds **1**, **5**, and **7–9** (1.5 mmol) in formamide (10 mL) was placed in a 30 mL glass tube equipped with septa. The reaction mixture was stirred for 30 s and then irradiated for the times and temperatures showed in Table 4. After complete reaction (TLC analysis) (hexane/AcOEt, 3/2), the reaction mixture was diluted with water, and the precipitate was filtered and washed with water. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 25/1 to 10/1, *v*/*v*) to yield the corresponding compounds shown in Table 4.

Selected Data

2-Chloro-5-[(*N,N*-dimethylamino)methyl]pyridine (14). Following the general procedure and starting from precursor **5** (243 mg, 1.5 mmol), compound **14** was obtained as a yellow oil (25.5 mg, 10%): $R_f = 0.32$ (CH_2Cl_2/MeOH, 10/1, *v*/*v*); IR (KBr) ν 3391, 2960, 2924, 2852, 2664, 1660, 1614, 1462, 1261, 1104, 1021, 810. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, $J = 2.4$ Hz, 1 H), 7.63 (dd, $J = 8.1$ and 2.4 Hz, 1 H), 7.27 (d, $J = 8.1$ Hz, 1 H), 3.38 (s, 2H, CH_2), 2.21 (s, 6H, NMe_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.4 (C2), 150.2 (C6), 139.7 (C4), 133.6 (C5),

124.2 (C3), 60.7 (CH_2), 45.5 ($2 \times CH_3$); MS (EI) m/z (%): 170 (34) $[M]^+$, 135 (43) $[M - Cl]^+$, 126 (55) $[M - NMe_2]^+$.

2-*N,N*-Dimethylamino-5-[(*N,N*-dimethylamino)methyl]pyridine (15). Following the general procedure and starting from precursor **4** (215.5 mg, 1.5 mmol), compound **15** (196 mg, 73%) was obtained as a light yellow solid: $R_f = 0.07$ (CH_2Cl_2/MeOH, 10/1, v/v); mp 187–189 °C; IR (KBr) ν 3412, 2930, 2662, 1611, 1520, 1403 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, $J = 2.4$ Hz, H6, 1H), 7.91 (dd, $J = 8.9$ and 2.5 Hz, H4, 1H), 6.56 (d, $J = 8.9$ Hz, H3, 1H), 3.99 (s, 2H, CH_2), 3.09 (s, 6H, NMe_2), 2.69 (s, 6H, NMe_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.6 (C2), 149.8 (C6), 139.6 (C4), 111.2 (C5), 106.2 (C3), 58.7 (CH_2), 41.6 ($2 \times CH_3$), 37.9 ($2 \times CH_3$); MS (EI) m/z (%): 179 (19) $[M]^+$, 135 (100) $[M - NMe_2]^+$. Anal. calcd. for $C_{10}H_{17}N_3$: C, 67.00; H, 9.56; N, 23.44. Found: C, 66.91; H, 9.44; N, 23.32.

2-Amino-6-(*N,N*-dimethylamino)-4-phenylpyridine-3,5-dicarbonitrile (18). Following the general procedure and starting from precursor **8** (190 mg, 1.5 mmol) compound **18** was obtained as a white solid (0.145 g, 74%): $R_f = 0.63$ (CH_2C_2/AcOEt, 10/1, v/v); mp 251–253 °C; IR (KBr) ν 3473, 3320, 3221, 2210, 1624, 1586, 1570, 1550, 1515, 1491, 1420, 1400, 1228 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.54 (m, $5 \times$ CH-ar), 735 (s, NH_2, 2H), 3.21 (s, 6H, $2 \times CH_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.4 (C), 160.6 (C), 159.8 (C), 135.9 (C), 130.3 (CH), 129.1 ($2 \times$ CH), 129.0 ($2 \times$ CH), 118.5 (CN), 116.8 (CN), 81.0 (C-CN), 80.6 (*C*-CN), 40.46 ($2 \times CH_3$); MS (EI) m/z (%): 262 (110) $[M - H]^+$, 263 (50) $[M]^+$. Anal. calcd. for $C_{15}H_{13}N_5$ (263.117): C, 68.42; H, 4.98; N, 26.60. Found: C, 68.19; H, 4.90; N, 26.31.

2-(*N,N*-Dimethylamino)-6-chloropyridine (19). Following the general procedure and starting from precursor **9** (220 mg, 1.5 mol), compound **19** (228 mg, 98%) was obtained as a yellow oil: $R_f = 0.2$ (hexane/CH_2C_2, 3/2, v/v); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (dd, $J = 8.4$ and 7.5 Hz, H4, 1H), 6.51 (d, $J = 7.4$ Hz, H3, 1H), 6.34 (d, $J = 8.4$ Hz, H5, 1H), 3.06 (s, 6H, NMe_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.4 (C2), 149.5 (C6), 139.5 (C4), 110.5 (C5), 103.8 (C3), 38.2 ($2 \times CH_3$); MS (EI) m/z (%): 156 (65) $[M]^+$, 141 (87) $[M - Me]^+$; 127 (100) $[M - 2CH_3]^+$.

2,6-Bis-(*N,N*-dimethylamino)pyridine-3,5-dicarbonitrile (21). Following the general procedure and starting from precursor **10** (48.2 mg, 0.24 mmol), compound **21** was obtained after 1 min of microwave irradiation as a light yellow solid (32.4 mg, 92%): $R_f = 0.23$ (hexane/ethyl acetate 3:1, v/v); mp 170–172 °C; IR (KBr) ν 2935, 2202, 1603, 1526 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 1H, H-4py, 1H), 3.20 (12 H, s, 4 N-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.9 (C-2, C-6 py), 153.0 (C-4 py), 118.8 (2 CN), 78.90 (C-3, C-5 py), 39.6 (4 CH_3); MS (EI) m/z (%): 215 (100) $[M]^+$, 200 (39) $[M - CH_3]^+$, 186 (99) $[M - 2CH_3 + H]^+$. Anal. calcd. for $C_{11}H_{13}N_5$: C, 61.38; H, 6.09; N, 32.54. Found: C, 61.22; H, 5.91; N, 32.36.

2,6-Bis-(*N,N*-dimethylamino)-4-phenylpyridine-3,5-dicarbonitrile (22). Following the general procedure and starting from precursor **11**, compound **22** was obtained after 1 min of microwave irradiation as a white solid (90.7 mg, 54%):

$R_f = 0.20$ (hexane/ethyl acetate 3:1, *v*/*v*); mp 227–229 °C; IR (KBr) ν 2939, 2204, 1582, 1526 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.49 (brs, 5 H, C_6H_5), 3.31 (s, 6 H, 2 N-CH_3), 3.32 (s, 6 H, 2 N-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.9 (C-4 py), 158.9 (C-2, C-6 py), 135.5 (C′-1 Ph), 130.2 (C′-4 Ph), 129.0 (C′-2, C′-6 Ph), 128.6 (C′-3, C′-5 Ph), 118.2 (2 × CN), 81.1 (C-3, C-5 py), 40.5 (4 × CH_3); MS (EI) *m*/*z* (%): 291 (80) $[M]^+$, 290 (100) $[M - H]^+$, 276 (25) $[M - CH_3]^+$. Anal. calcd. for $C_{17}H_{17}N_5$: C, 70.08; H, 5.88; N, 24.04. Found: C, 69.82; H, 5.59; N, 23.96.

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