COMPLEX BASE-INDUCED GENERATION OF 3,4-DIDEHYDROPYRIDINE DERIVATIVES : NEW ACCESS TO AMINOPYRIDINES OR PYRIDONES

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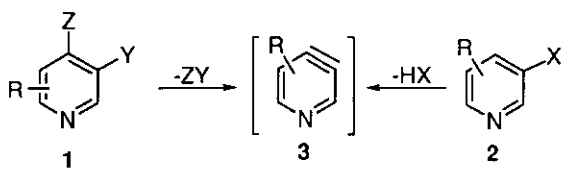
Abstract - The complex base, $NaNH_2$-*tert*-BuONa, in THF easily transforms 3-bromopyridine and 2-pyridone derivatives into the corresponding hetarynes. The reaction of representative amines (dialkylamines, morpholine, piperidine) with these reactive intermediates leads to the preparation of aminopyridines in good yields and illustrates the synthetic usefulness of such reactions.

Free radicals have been recognized to be essential mediators in the appearance and development of numerous human pathologies.[1] As a consequence antioxidants as well as radical inhibitors continue to be the targets of active investigations in medicinal chemistry. As part of a program dealing with the continuation of our own investigations in this area[2] we were confronted with the functionalisation of the C_3 and/or C_4 positions of pyridine ring. The experience of our laboratory in arynic chemistry[3] led us to consider the use of didehydropyridines as possible intermediates. Examination of the literature showed that two main pathways have been used to generate 3,4-didehydropyridines (Scheme 1).

Scheme 1



1 3 2

$Z = CO_2^-$; $Y = N_2^+$; Z, Y = Halogene
$Z = SiEt_3$; Y = OTf

A number of compounds (**1**) have been described as very efficient in the generation of **3** .[4] The drawback to the use on a large scale of such elaborate precursors is their tedious preparation as well as their expensiveness. On the contrary 3-halopyridines (**2**) appeared as very attractive since numerous such derivatives are commercialy available or easily prepared. However these attractive precursors have found only limited applications in hetarynic chemistry due to the generation mode of the reactive intermediates. Thus the oldest hetarynic elimination-additions were performed with the not easily available on a large scale, KNH_2 in liquid ammonia[5] a not very easily handled protic solvent. Moreover such a procedure was limited to the synthesis of *N*-unsubstituted aminopyridines since the reactions of nucleophiles other than NH_2^-/NH_3 are strongly limited in liquid ammonia.

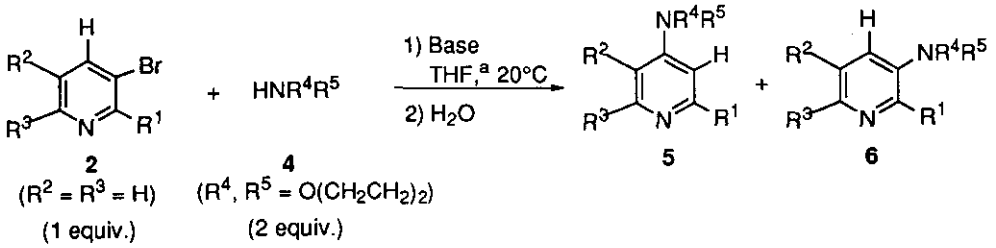
On the other hand, a few *N*-substituted aminopyridines were obtained in ethereal solvents from **2** and the appropriate amine using the corresponding lithium salts as a base and nucleophile.[6] The use of lithium dialkylamides such as lithium diisopropylamide (LDA) and lithium tetramethylpiperidine (LTMP) was further extended to the generation of didehydropyridines.[7] Although lithium dialkylamides continue to be used in arynic reactions, they are not without drawbacks. Indeed lithium amides as well as the corresponding amines generated during the elimination step may compete with any nucleophile to be reacted with the dehydro intermediate. Moreover lithium amides are rather expensive, not easily prepared on a large scale and inefficient in the generation of a number of arynic species.[8]

On the contrary, $NaNH_2$ can be industrially prepared, and is inexpensive. A low solubility as well as a rather weak reactivity of $NaNH_2$ in ethereal solvents are the main drawbacks of this otherwise very attractive reagent. Many years ago[9] we introduced the concept of base activation which applied to $NaNH_2$ eliminated the above mentioned disadvantages. Thus we established that $NaNH_2$ might be activated with a number of sodium alkoxides or enolates (activating agents) to lead to Unimetal Super Bases (USB)[3b] called Complex Bases (CB). CB's are easily prepared by simple addition of the activating agent precursors to $NaNH_2$ and have already found industrial applications.[10] Moreover their properties may be easily modulated by just changing the nature of the activating agent.[3]

Among the numerous applications of CB's we demonstrated that such reagents are very useful in performing elimination-additions and more particularly arynic reactions for which $NaNH_2$ containing CB's were found much more efficient than lithiumamides.[11] Taking account of these data, we thought that CB's could be of use in the generation and nucleophilic condensation of dehydropyridines. Exploratory experiments reported in a short previous note[12] supported our expectation. In the present publication we report extension of our first results as well as more details on the CB generation of didehydropyridines and their reaction with amines.

Reaction of morpholine with 3-bromo- and 3-bromo-2-ethoxypyridines[13] was chosen for exploratory experiments. The most significant results obtained are gathered in Table 1.

Table 1



2 ($R^2 = R^3 = H$) (1 equiv.) **4** ($R^4, R^5 = O(CH_2CH_2)_2$) (2 equiv.) **5** **6**

run	R^1	base (equiv.)	time (h)	**5/6**	yield (%)
1	H	$NaNH_2$ (4)	15	58/42	80
2	H	$NaNH_2$ (6)	4	59/41	81
3	H	$NaNH_2$-*tert*-BuONa (2/1)	6	57/43	83
4	H	$NaNH_2$-*tert*-BuONa (3/1.5)	0.5	56/44	83
5	H	$NaNH_2$-*tert*-BuONa (4/2)	0.33	55/45	84
6	H	$NaNH_2$-$Et(OCH_2CH_2)_2ONa$ (4/2)	0.1	58/42	80.5
7	H	$NaNH_2$-*tert*-BuONa (4/2)	0.1[b]	56/44	79.5
8	H	$NaNH_2$-*tert*-BuONa (4/2)	0.1[c]	57/43	83
9	H	$NaNH_2$-*tert*-BuONa (4/2)	1.5[d]	57/43	83.5
10	EtO	$NaNH_2$ (4)	16	86/14	83
11	EtO	$NaNH_2$ (6)	4	86/14	93
12	EtO	$NaNH_2$-*tert*-BuONa (2/1)	3.5	86/14	95
13	EtO	$NaNH_2$-*tert*-BuONa (3/1.5)	0.75	86/14	96
14	EtO	$NaNH_2$-*tert*-BuONa (4/2)	0.25	85/15	99
15	EtO	$NaNH_2$-$Et(OCH_2CH_2)_2ONa$ (4/2)	0.75	83/17	93.5
16	EtO	$NaNH_2$-*tert*-BuONa (4/2)	0.2[b]	84/16	96.5
17	EtO	$NaNH_2$-*tert*-BuONa (4/2)	0.2[c]	84/16	95.5
18	EtO	$NaNH_2$-*tert*-BuONa (4/2)	1.5[d]	84/16	95

[a] Unless otherwise specified; [b] Reaction performed in DME; [c] Reaction performed in a mixture THF/HMPA (9/1); [d] Reaction performed in a mixture THF/benzene (1/1)

From these data the following interesting points emerged. The simultaneous formation of 3- and 4-aminopyridines agreed with the generation of transient 3,4-didehydropyridines. The slight excess of **5** observed with the 3-bromopyridine is due to the weak electron withdrawing effect of the pyridinic nitrogen. As expected from the appreciable meta directing effect of alkoxy groups in arynic reactions, the presence of 2-ethoxy substituents considerably increased the formation of **5** . Unexpectedly $NaNH_2$ under such mild conditions was able to generate the didehydropyridines in very good yields. However $NaNH_2$ activated by *tert*-BuONa in the corresponding CB was much more efficient (compare runs 1 with 5 and 10 with 14).

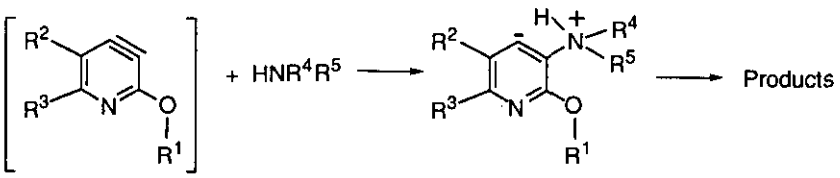
From our experience with arynic reactions we knew that a large excess of $NaNH_2$ favored the formation of benzynes. So it was of interest, from a simple practical aspect, to examine reactions performed with the total amount of $NaNH_2$ necessary for the preparation of the CB. Even under such conditions (runs 2 and 11) $NaNH_2$ was much less efficient than CB (runs 5 and 14). Although the CB containing 3 equivalents of $NaNH_2$ appeared as convenient (runs 4 and 13) we retained, for the present work, the CB containing 4 equivalents of $NaNH_2$ which allowed the shorter reaction times (runs 5 and 14). On the other hand the following information was also obtained : i) other activating agents, such as $Et(OCH_2CH_2)_2ONa$ (runs 6 and 15), may be used instead of *tert*-BuONa. However the latter is very convenient and thus was retained ; ii) THF may be replaced by solvents such as dimethoxyethane (runs 7 and 16) or a mixture of THF-HMPA runs 8 and 17). Finally in an nonpolar solvent such as C_6H_6 the reaction took place although the rate was quite low. However it is of interest to note that in THF-C_6H_6 (1/1) morpholine reacted with (**2**) (R^1 = H, EtO) to lead to the corresponding aminopyridines in 84% and 95% yields respectively after 1.5 h. In other words it is possible to partially replace the THF by a less expensive nonpolar solvent, a point of interest on large scale syntheses.

With these data in hand we studied (Table 2) the condensation of several amines with representative bromopyridines. Whatever the amine condensed with 3-bromopyridine, the yields varied from good to excellent and the ratio of the two products formed remained unchanged. Unexpectedly *N,N*-diisopropylamine (run 5) led to by-products and the reaction had to be performed at low temperature to obtain acceptable yields.

With 2-ethoxy-3-bromopyridine very good yields were obtained even with *N,N*-diisopropylamine (run 11). However, although the spectroscopic data (Experimental part) completely supported the structure of **6** for the less abundant isomer, this product appeared as not very stable and we were unable to obtain a good centesimal analysis.

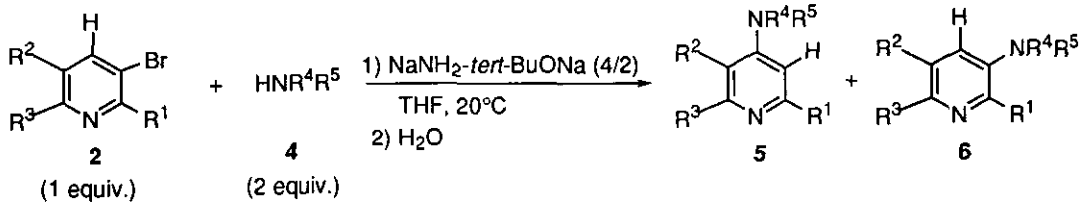
Finally it appeared (runs 7 to 14) that the increase in the steric interactions between the entering amine and the 2-alkoxy substituents favor, as expected, the formation of the corresponding 4-dialkylaminopyridines. However according to the mechanism given in Scheme 2 it may be assumed that the steric repulsions arise essentially from the entering amine since the bent structure of the alkoxy group may maintain the oxygen substituent far from the reaction site.

Scheme 2



This hypothesis was verified by study of the reaction of morpholine with a few alkoxy-didehydropyridines (runs 7, 13 and 14) for which the ratios (**5**)/(**6**) remained identical. Indirect evidence of this behavior was also obtained during the condensation of amines with the more steric demanding 2-*N,N*-disubstituted amino-didehydropyridines which led to only the formation of **5** in very good yields (runs 15, 16).

Table 2



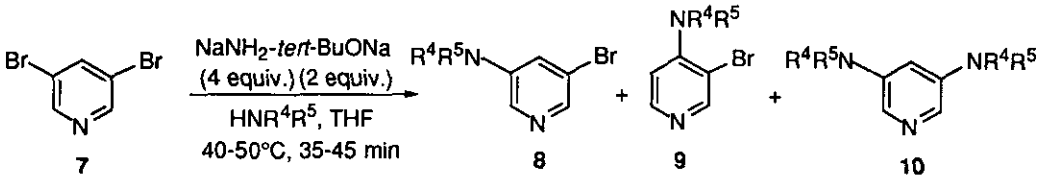
run	R^1	R^2	R^3	R^4	R^5	time (min)	5/6	yield (%)
1	H	H	H	$O(CH_2CH_2)_2$		20	55/45	84
2	H	H	H	$(CH_2)_5$		45	58/42	85
3	H	H	H	Et	Et	10	56/44	75.5
4	H	H	H	Pr	Pr	10	57/43	83
5	H	H	H	*i*-Pr	*i*-Pr	270[a]	57/43	49
6	H	H	H	Et	$(CH_2)_2NEt_2$	60	54/46	70
7	EtO	H	H	$O(CH_2CH_2)_2$		15	85/15	99
8	EtO	H	H	$(CH_2)_5$		40	85/15	95
9	EtO	H	H	Et	Et	20	88/12	91
10	EtO	H	H	Pr	Pr	40	89/11	97
11	EtO	H	H	*i*-Pr	*i*-Pr	25	92/8	80
12	EtO	H	H	Et	$(CH_2)_2NEt_2$	120	100/0	70
13	MeO	H	H	$O(CH_2CH_2)_2$		20	85/15	92
14	Me_3CCH_2O	H	H	$O(CH_2CH_2)_2$		90	85/15	91
15	$O(CH_2CH_2)_2N$	H	H	$O(CH_2CH_2)_2$		25	100/0	97
16	Pr_2N	H	H	Pr	Pr	10	100/0	91
17	H	H	EtO	$O(CH_2CH_2)_2$		20	62/38	87[a]
18	H	H	$O(CH_2CH_2)_2N$	$O(CH_2CH_2)_2$		120	67/33	91
19	H	H	Pr_2N	Pr	Pr	150	69/31	97
20	H	EtO	H	$O(CH_2CH_2)_2$		120	0/100	65
21	H	$O(CH_2CH_2)_2N$	H	$O(CH_2CH_2)_2$		45	0/100	86
22	H	Pr_2N	H	Pr	Pr	150	0/100	71

[a] Reaction performed at -10°C.

Continuing our exploration, the reactions were easily extended to 2- and 3-substituted 5-bromopyridines. Thus 2-ethoxy- and 2-*N*,*N*-disubstituted amino-5-bromopyridines (runs 17 to 19) led to **5** and **6** with a *ratio close to that* found with 3-bromopyridine. This result is due to the removing of the substituent from the pseudo triple bond of the hetaryne. On the contrary with the corresponding 3-substituted 5-bromopyridines (runs 20-22) only C_3 substitutions took place. This result is rather surprising with the ethoxy derivative which, according to results obtained with 2-ethoxy-3-bromopyridine should have led to the formation of some **5** .

To end the discussion we will give a brief comment on the synthesis of the starting materials used in Table 2. They were all obtained from the corresponding dibromopyridines according to the literature (see experimental part). However the 3-amino-5-bromopyridines have been prepared[14] by the reaction of an amine with 3,5-dibromopyridines in sealed glass under harsh conditions not easily performed on a large scale. So we devised the new synthesis reported in Scheme 3.

Scheme 3

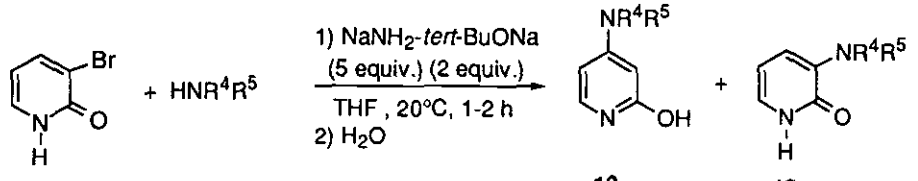


	8	9	10
R^4, R^5 = $O(CH_2CH_2)_2$	40%	22%	17%
R^4 = R^5 = Pr	30%	10%	10%

The 3,4-didehydro-5-bromopyridine was the first intermediate. In spite of the fair yields obtained, the reaction was of interest since it could be performed on a large scale and the products easily separated.

Finally since we had previously shown that CB generated *o*-hydroxy-dehydrobenzene from *o*-bromophenol[15] we expected that the same kind of reaction ought to take place from 2-hydroxy-3-bromopyridine (actually 3-bromopyridone). Two reactions (Scheme 4) were performed under our conditions.

Scheme 4



	12	13
R^4, R^5 = $O(CH_2CH_2)_2$ (82%)	60	40
R^4, R^5 = Pr (78%)	80	20

The formation of two isomers is in agreement with the formation of didehydropyridone as reactive intermediate. The increase in the formation of 4-substituted derivative paralleled the increase in steric demand of the entering amine. Compared to the results obtained with 2-alkoxy-3,4-didehydropyridine, it seems that didehydropyridone was more sensitive to steric variations.

CONCLUSION

The present work confirms that the inexpensive and easily prepared superbase $NaNH_2$-*tert*-BuONa is particularly well suited to perform elimination-additions. We have shown here that didehydropyridines may

be very easily generated in an ethereal solvent and in the presence of amines to lead to aminopyridines in good conditions.

EXPERIMENTAL SECTION

Melting points were determined on a Tottoli melting point apparatus and are uncorrected. ^{13}C NMR spectra were recorded with a Bruker AM 400 or a Bruker 300 MHz spectrometer (Attached Proton Test Method, APT). ^{1}H NMR spectra were recorded on a Jeol PMX 60 at 60 MHz, or a Bruker AM 400 instrument at 400 MHz. Me_4Si was the internal standard. IR spectra of thin liquid films between NaCl plates or KBr pellets were recorded with a Perkin Elmer 841 instrument. Elemental analyses were performed by CNRS laboratory (Vernaison) and by E.N.S.C.M. Microanalysis Department of Montpellier. MS spectra were recorded on Hewlett Packard 5971A instrument. The plates were developed with petroleum ether/EtOAc. The silica gels used for column chromatography and flash chromatography were Kieselgels of 0.063-0.2 mm and 0.04-0.063 mm particle size, respectively.

Preparation of compounds: General procedure.

Preparation of complex base: To a suspension of 6 equiv. or 7 equiv. (in the special case of condensation of 3-bromopyrid-2-one) of $NaNH_2$ in the reaction solvent (5 ml for 20 mmol of $NaNH_2$) was added dropwise 2 equiv. of *tert*-BuOH at rt. After the addition the mixture was warmed at 45-50°C for 2 h.

Addition of amine: To the complex base or 4 equiv. of $NaNH_2$, were added at 40°C, 2 equiv. of amine in the reaction solvent (5 mL for 10 mmol). The mixture was stirred for 2 h.

Condensation procedure: After this time, the condensation was performed for the temperature and the time indicated respectively in the Table 1, Table 2, Scheme 3, and Scheme 4 by adding a solution of bromopyridines (1 equiv.) in the reaction solvent (5 mL for 5 mmol). The reaction monitored by GPC was stopped after the total disappearance of the bromo compound. The mixture was poured on ice, extracted with ether. The organic layer was washed with water, and dried on $MgSO_4$ and evaporated under reduced pressure. The different components of the reactions were separated by liquid chromatography or by flash chromatography.

Table 1

4-(4-Morpholyl)pyridine (5 R^1 = R^2 = R^3 = H; R^4, R^5 = $O(CH_2CH_2)_2$): Eluent: 50% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 3.1 (m, 4 H, 2 x NCH_2), 3.7 (m, 4 H, 2 x OCH_2), 6.5 (d, J = 5 Hz, 2 H, H_{arom}), 8.2 (d, 2 H, J = 5 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 46.1 (NCH_2), 66.3 (OCH_2), 108.1 (C_{arom}), 149.7 (C_{arom}), 115.3 (C_{arom}); (spectroscopic data identical to those previously described).[12]

3-(4-Morpholyl)pyridine (6 R^1 = R^2 = R^3 = H; R^4, R^5 = $O(CH_2CH_2)_2$): Eluent: 50% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 3.1 (m, 4 H, 2 x NCH_2), 3.8 (m, 4 H, 2 x OCH_2), 6.9-7.1 (m, 2 H, H_{arom}), 8.1 (m, 2 H, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 48.4 (NCH_2), 66.4 (OCH_2), 121.9-123.3 (C_{arom}), 137.9-140.8 (C_{arom}), 146.7 (C_{arom}); (spectroscopic data identical to those previously described).[12]

2-Ethoxy-4-(4-morpholyl)pyridine (5 R^1 = EtO; R^2 = R^3 = H; R^4, R^5 = $O(CH_2CH_2)_2$): Eluent: 10% AcOEt/PE; Liquid; ^{1}H-NMR ($CDCl_3$) δ: 1.1-1.4 (t, 3 H, J = 7 Hz, CH_3), 2.9-3.3 (m, 4 H, 2 x NCH_2), 3.4-3.8 (m, 4 H, 2 x OCH_2), 4.0-4.5 (q, 2 H, J = 7 Hz, OCH_2CH_3), 5.9 (d, 1 H, J_1 =2 Hz, H_{arom}), 6.1-6.3 (dd, 1 H, J_1 = 2 Hz, J_2 = 5 Hz, H_{arom}), 7.6-7.9 (d, 1 H, J_2 = 5 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 14 (CH_3), 45.7 (NCH_2), 60.4 (CH_2CH_3), 65.4 (OCH_2), 92.4 (C_{arom}), 103.1 (C_{arom}), 146.3 (C_{arom}), 157.1 (C_{arom}), 164,8 (C_{arom}). *Anal.* Calcd for $C_{11}H_{16}N_2O_2$: C, 63.43; H, 7.74; N, 13.45. Found: C, 63.19; H, 7.83; N, 13.28.

2-Ethoxy-3-(4-morpholyl)pyridine (6 R^1 = EtO; R^2 = R^3 = H; R^4, R^5 = $O(CH_2CH_2)_2$): Eluent: 10% AcOEt/PE; Liquid; ^{1}H-NMR ($CDCl_3$) δ: 1.1-1.6 (t, 3 H, J = 7 Hz, CH_3), 2.7-3.2 (m, 4 H, 2 x NCH_2), 3.5-3.9 (m, 4 H, 2 x OCH_2), 4.1-4.5 (q, 2 H, J = 7 Hz, OCH_2CH_3), 6.4-7.0 (m, 2 H, H_{arom}), 7.4-7.7 (dd, 1 H, J_1 = 2 Hz, J_2 = 4 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 14.4 (CH_3), 50.1 (NCH_2), 61.3 (CH_2CH_3), 66.6 (OCH_2), 116.5 (C_{arom}), 124 (C_{arom}), 135.5 (C_{arom}), 138.8 (C_{arom}), 156.2 (C_{arom}). MS 208. *Anal.* Calcd for $C_{11}H_{16}N_2O_2$: C, 63.43; H, 7.74; N, 13.45. Found: C, 63.18; H, 7.93; N, 13.36.

Table 2

4-Piperidinopyridine (5 R^1 = R^2 = R^3 = H; R^4, R^5 = $(CH_2)_5$): Eluent: 50% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 1.3-1.8 (m, 6 H, 3 x CH_2), 3.1-3.4 (m, 4 H, 2 x NCH_2), 6.5 (d, 2 H, J = 5 Hz, H_{arom}), 8.1 (d, 2 H, J = 5 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 123.8 (CH_2), 24.6 (CH_2), 46.6 (NCH_2), 107.7 (C_{arom}), 149.3 (C_{arom}), 154.4 (C_{arom}); (spectroscopic data identical to those previously obtained).[12]

3-Piperidinopyridine (6 R^1 = R^2 = R^3 = H; R^4, R^5 = $(CH_2)_5$): Eluent: 50% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 1.3-1.8 (m, 6 H, 3 x CH_2), 2.9-3.4 (m, 4 H, 2 x NCH_2), 6.9-7.1 (m, 2 H, H_{arom}), 7.8-8.2 (m, 2 H, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 23.8 (CH_2), 25.2 (CH_2). 49.5 (NCH_2), 122.4 (C_{arom}), 123.2 (C_{arom}), 138.2 (C_{arom}), 139.4 (C_{arom}), 147.4 (C_{arom}); (identical to the product previously obtained).[12]

4-Diethylaminopyridine (5 R^1 = R^2 = R^3 = H; R^4 = R^5 = Et): Eluent: 50% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 1.1 (t, 6 H, J = 7 Hz, 2 x CH_3), 3.2 (q, 4 H, J = 7 Hz, 2 x NCH_2), 6.3 (d, 2 H, J = 5 Hz, H_{arom}), 7.9 (d, 2 H, J^1 = 5 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 12 (CH_3), 43.5 (CH_2), 105.9 (C_{arom}), 149.5 (C_{arom}), 151.7 (C_{arom}); (spectroscopic data identical to those previously obtained).[12]

3-Diethylaminopyridine (6 R^1 = R^2 = R^3 = H; R^4 = R^5 = Et): Eluent: 50% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 1.1 (t, 6 H, J = 7 Hz, 2 x CH_3), 3.2 (q, 4 H, J = 7 Hz, 2 x NCH_2), 6.6-7.1 (m, 2 H,

H_{arom}), 7.6-8.1 (m, 2 H, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 12.1 (CH_3), 43.8 (CH_2), 117.5 (C_{arom}), 123.3 (C_{arom}), 134.3 (C_{arom}), 136.4 (C_{arom}), 143.3 (C_{arom}); (spectroscopic data identical to those previously obtained).[12]

4-Dipropylaminopyridine (5 $R^1 = R^2 = R^3 = H$; $R^4 = R^5 = Pr$): Eluent: 50% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 0.6-1,1 (t, 6 H, J = 7 Hz, 2 x CH_3), 1.2-1.8 (m, 4 H, 2 x CH_2), 2.8-3.5 (m, 4 H, 2 x NCH_2), 6.2-6.5 (d, 2 H, J = 5 Hz, H_{arom}), 7.7-8.3 (d, 2 H, J = 5 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ 10.6 (CH_3), 19.5 (CH_2), 51.2 (NCH_2), 105.7 (C_{arom}), 148.2 (C_{arom}), 152.1 (C_{arom}); MS 178. *Anal.* Calcd for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.71. Found: C, 74.14; H, 9.95; N, 15.98.

3-Dipropylaminopyridine (6 $R^1 = R^2 = R^3 = H$; $R^4 = R^5 = Pr$): Eluent: 50% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 0.6-1.1 (t, 6 H, 2 x CH_3), 1.2-1.8 (m, 4 H, 2 x CH_2), 2.9-3.4 (m, 4 H, 2 x NCH_2), 6.6-6.9 (m, 2 H, H_{arom}), 7.7-8.1 (m, 2 H, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 11.5 (CH_3), 20.4 (CH_2), 52.6 (NCH_2), 117.9 (C_{arom}), 123.7 (C_{arom}), 134.6 (C_{arom}), 136.6 (C_{arom}), 144.1 (C_{arom}); MS 178. *Anal.* Calcd for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.71. Found: C, 74.04; H, 9.92; N, 16.04.

4-Diisopropylaminopyridine (5 $R^1 = R^2 = R^3 = H$; $R^4 = R^5 = i$-Pr): Eluent: 50% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 1.2-1.4 (s, 12 H, 4 x CH_3), 3.6-4.2 (m, 2 H, 2 x NCH), 6.4-6.7 (d, 2 H, J = 5 Hz, H_{arom}), 7.8-8.2 (d, 2 H, J = 5 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 20.1 (CH_3), 46.7 (CH), 108.9 (C_{arom}), 148.1 (C_{arom}), 152,3 (C_{arom}); MS 178. *Anal.* Calcd for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.71. Found: C, 74.35; H, 10.14; N, 15.51.

3-Diisopropylaminoyridine (6 $R^1 = R^2 = R^3 = H$; $R^4 = R^5 = i$-Pr): Eluent: 50% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 1.1-1.2 (s, 12 H, 4 x CH_3), 3.2-3.9 (m, 2 H, 2 x NCH), 6.7-7.1 (m, 2 H, H_{arom}), 7.7-8.2 (m, 2 H, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 21.1 (CH_3), 43.3 (CH), 122.9-124.4 (C_{arom}), 138.6 (C_{arom}), 114.1 (C_{arom}); MS 178. *Anal.* Calcd for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18; N, 15.71. Found: C, 73.78; H, 10.14; N, 16.08.

***N,N,N'*-Triethyl-*N'*-(4-pyridyl)-1,2-ethanediamine (5 $R^1 = R^2 = R^3 = H$; $R^4 = Et$; $R^5 = (CH_2)_2NEt_2$):** Eluent: 50% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 0.7-1.3 (m, 9 H, 3 x CH_3), 2.2-2.7 (m, 6 H, 3 x NCH_2), 3.0-3.6 (m, 4 H, 2 x NCH_2), 6.2-6.5 (d, 2 H, J = 5 Hz, H_{arom}), 7.8-8.2 (d, 2 H, J = 5 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 11.2 (CH_3), 44.2, 46.8, 47.8, 49.2 (5 x NCH_2), 105.6 (C_{arom}), 147.5 (C_{arom}), 152 (C_{arom}); MS 221. *Anal.* Calcd for $C_{13}H_{23}N_3$: C, 70.54; H, 10.47; N, 18.99. Found: C, 70.86; H, 10.43; N, 18.71.

***N,N,N'*-Triethyl-*N'*-(3-pyridyl)-1,2-ethanediamine (6 $R^1 = R^2 = R^3 = H$; $R^4 = Et$; $R^5 = (CH_2)_2NEt_2$):** Eluent: 50% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) (60 MHz) δ 0.6-1.2 (m, 9 H, 3 x CH_3), 2.2-2.7 (m, 6 H, 3 x NCH_2), 3.0-3.6 (m, 4 H, 2 x NCH_2), 6.8-7.0 (m, 2 H, H_{arom}), 7.7-8.0 (m, 2 H,

H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 10.9 (CH_3), 44, 46.6, 47.9, 49.2 (5 NCH_2), 113.7-122.6 (C_{arom}), 133.2-135.6 (C_{arom}), 142.6 (C_{arom}); MS 221. *Anal.* Calcd for $C_{13}H_{23}N_3$: C, 70.54; H, 10.47; N, 18.99. Found: C, 70.12; H, 10.42; N, 19.46.

2-Ethoxy-4-piperidinopyridine (5 R^1 = EtO; R^2 = R^3 = H; R^4, R^5 = $(CH_2)_5$): Eluent: 10% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 0.9-1.8 (m, 9 H, CH_3, 3 x CH_2), 2.8-3.3 (m, 4 H, 2 x NCH_2), 3.9-4.4 (q, 2 H, J = 7 Hz, OCH_2), 5.7-5.9 (d, 1 H, J = 2 Hz, H_{arom}), 6.0-6.3 (dd, 1 H, J_1 = 2 Hz, J_2 = 5 Hz, H_{arom}), 7.5- 7.8 (d, 1 H, J_2 = 5 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 14.1 (CH_3), 23.6 (CH_2), 24.3 (CH_2), 46.7 (NCH_2), 60.3 (OCH_2), 92.2 (C_{arom}), 103.4 (C_{arom}), 146.2 (C_{arom}), 156.8 (C_{arom}), 164.9 (C_{arom}); MS 206. *Anal.* Calcd for $C_{12}H_{18}N_2O$: C, 69.86; H, 8.79; N, 13.58. Found: C, 69.86; H, 8.93; N, 13.64.

2-Ethoxy-3-piperidinopyridine (6 R^1 = EtO; R^2 = R^3 = H; R^4, R^5 = $(CH_2)_5$): Eluent: 10% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ 1.0-1.9 (m, 9 H, CH_3, 3 x CH_2), 2.5-3.1 (m, 4 H, 2 x NCH_2), 4.0-4.5 (q, 2 H, OCH_2), 6.3- 6.9 (m, 2 H, H_{arom}), 7.3-7.6 (d, 1 H, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ 14.5 (CH_3), 24.2 (CH_2), 25.9 (CH_2), 51.3 (NCH_2), 61.4 (OCH_2), 116.6-124.4 (C_{arom}), 137.1 (C_{arom}), 138.3 (C_{arom}), 156.5 (C_{arom}); MS 206. *Anal.* Calcd for $C_{12}H_{18}N_2O$: C, 69.86; H, 8.79; N, 13.58. Found: C, 69.88; H, 8.97; N, 13.30.

2-Ethoxy-4-diethylaminopyridine (5 R^1 = EtO; R^2 = R^3 = H; R^4 = R^5 = Et): Eluent: 10% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 0.7-1.2 (t, 6 H, J = 9 Hz, 2 x CH_3), 1.2-1.4 (t, 3 H, J = 7 Hz, OCH_2CH_3), 2.8-3.4 (q, 4 H, J = 9Hz, 2 x NCH_2), 3.9-4.4 (q, 2 H, J = 7 Hz, OCH_2), 5.6 (d, 1 H, J = 2 Hz, H_{arom}), 5.8-6.1 (dd, 1 H, J_1 = 2 Hz, J_2 = 5 Hz, H_{arom}), 7.6-7.9 (d, 1 H, J = 5 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 11.5 (CH_3), 14 (CH_3), 42.9 (NCH_2), 60.1 (OCH_2), 89.4 (C_{arom}), 101.3 (C_{arom}), 146 (C_{arom}), 153.6 (C_{arom}), 164.7 (C_{arom}); MS 194. *Anal.* Calcd for $C_{11}H_{18}N_2O$: C, 68.00; H, 9.36; N, 14.42. Found: C, 68.16; H, 9.46; N, 14.32.

3-Ethoxy-4-diethylaminopyridine (6 R^1 = EtO; R^2 = R^3 = H; R^4 = R^5 = Et): Eluent: 10% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 0.5-1.1 (t, 6 H, J = 9 Hz, 2 x CH_3), 1.2-1.5 (t, 3 H, J = 7 Hz, OCH_2CH_3), 2.7-3.3 (q, 4 H, J = 9 Hz, 2 x NCH_2), 3.9-4.4 (q, 2 H, J = 7 Hz, OCH_2), 6.3-6.9 (m, 2 H, H_{arom}), 7.3- 7.5 (d, 1 H, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 12 (CH_3), 14.5 (CH_3), 45.1 (NCH_2), 61.3 (OCH_2), 116.2 (C_{arom}),126.8 (C_{arom}), 133.9 (C_{arom}), 137.9 (C_{arom}), 157.2 (C_{arom}); MS 194. *Anal.* Calcd for $C_{11}H_{18}N_2O$: C, 68.00; H, 9.36; N, 14.42. Found: C, 68.31; H, 9.34; N, 14.58.

2-Ethoxy-4-dipropylaminopyridine (5 R^1 = EtO; R^2 = R^3 = H; R^4 = R^5 = Pr): Eluent: 10% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 0.6-1.1 (t, 6 H, J = 7 Hz, 2 x CH_3), 1.1-1.8 (m, 7 H, 2 x

CH_2CH_3, OCH_2CH_3), 2.8-3.3 (t, 4 H, J = 7 Hz, 2 x NCH_2), 3.9-4.4 (q, 2 H, J = 7 Hz, OCH_2), 5.7 (d, 1 H, J = 2 Hz, H_{arom}), 5.9-6.1 (dd, 1 H, J_1 = 2 Hz, J_2 = 5 Hz, H_{arom}), 7.6 (d, 1 H, J = 5 Hz, C_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 10.6 (CH_3), 14.3 (CH_3), 19.7 (CH_2), 51.5 (NCH_2), 60.4 (OCH_2), 89.9 (C_{arom}), 101.7 (C_{arom}), 146.2 (C_{arom}), 154.4 (C_{arom}), 164.9 (C_{arom}); MS 222. *Anal.* Calcd for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 69.87; H, 9.60; N, 12.69.

2-Ethoxy-3-dipropylaminopyridine (6 R^1 = EtO; R^2 = R^3 = H; R^4 = R^5 = Pr): Eluent: 10% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 0.6-1.1 (t, 6 H, J = 7 Hz, 2 x CH_3), 1.1-1.8 (m, 7 H, 2 x CH_2CH_3, OCH_2CH_3), 2.8-3.2 (t, 4 H, J = 7 Hz, 2 x NCH_2), 4.1-4.6 (q, 2 H, J = 7 Hz, OCH_2), 6.3-7.0 (m, 2 H, H_{arom}), 7.3-7.7 (d, 1 H, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 11.4 (CH_3), 14.5 (CH_3), 20.3 (CH_2), 53.8 (NCH_2), 61.2 (OCH_2), 116.2 (C_{arom}), 126.2 (C_{arom}), 134.6 (C_{arom}), 137.4 (C_{arom}), 157.07 (C_{arom}); MS 222. *Anal.* Calcd for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 70.06; H, 9.77; N, 12.60.

2-Ethoxy-4-diisopropylaminopyridine (5 R^1 = EtO; R^2 = R^3 = H; R^4 = R^5 = *i*-Pr): Eluent: 10% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 0.8-1.5 (m, 15 H, 5 x CH_3), 3.4-3.9 (m, 2 H, 2 x NCH), 3.9-4.4 (q, 2 H, J = 7 Hz, OCH_2), 5.8 (d, 1 H, J = 2 Hz, H_{arom}), 5.9-6.2 (dd, 1 H, J_1 = 2 Hz, J_2 = 5 Hz, C_{arom}), 7.6 (d, 1 H, J = 5 Hz, C_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 14.5 (CH_3), 20.2 (CH_3), 46.6 (CH), 60.7 (OCH_2), 93.1 (C_{arom}), 105 (C_{arom}), 145.7 (C_{arom}), 154.5 (C_{arom}), 164.8 (C_{arom}); MS 222. *Anal.* Calcd for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 70.31; H, 10.14; N, 12.53.

2-Ethoxy-3-diisopropylaminopyridine (6 R^1 = EtO; R^2 = R^3 = H; R^4 = R^5 = *i*-Pr): Eluent: 10% AcOEt/PE); Liquid; ^{1}H-NMR (CCl_4) δ: 0.7-1.1 (s, 12 H, 4 x CH_3), 1.1-1.6 (t, 3 H, J = 7 Hz, CH_2CH_3), 3.2-3.8 (m, 2 H, 2 x NCH), 4.1-4.6 (q, 2 H, J = 7 Hz, OCH_2), 6.4-6.8 (dd, 1 H, J_1 = 7 Hz, J_2 = 4 Hz, H_{arom}), 7.1-7.4 (d, 1 H, J = 7 Hz, H_{arom}), 7.6-7.9 (d, 1 H, J = 4 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 14.6 (CH_3), 21.8 (CH_3), 49 (CH), 61.1 (OCH_2), 115.8 (C_{arom}), 139.4 (C_{arom}), 130.5 (C_{arom}), 142.1 (C_{arom}), 162.6 (C_{arom}).

***N*-[3-(2-Ethoxy-4-pyridyl)pentyl]-*N*,*N*-diethylamine (5 R^1 = EtO; R^2 = R^3 = H; R^4 = Et; R^5 = $(CH_2)_2NEt_2$):** Eluent: 10% AcOEt/PE; Liquid; ^{1}H-NMR (Ccl_4) δ: 0.7-1.5 (m, 12 H, 4 x CH_3), 2.1-2.7 (m, 6 H, 3 x NCH_2CH_3), 2.9-3.5 (t, 4 H, J = 7 Hz, 2 x NCH_2), 3.9-4.4 (q, J = 7 Hz, 2 H, OCH_2), 5.7 (d, 1 H, J = 2 Hz, H_{arom}), 5.8-6.1 (dd, 1 H, J_1 = 2 Hz, J_2 = 5 Hz, H_{arom}), 7.4-7.7 (d, 1 H, J_2 = 5 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 11.4 (CH_3), 11.6 (CH_3), 14.4 (CH_3), 44.4, 47, 48, 49.7 (NCH_2), 60.6 (OCH_2), 89.8 (C_{arom}), 101.7 (C_{arom}), 146.4 (C_{arom}), 154.2 (C_{arom}), 165 (C_{arom}); MS 265. *Anal.* Calcd for $C_{15}H_{27}N_3O$: C, 67.88; H, 10.25; N, 15.83. Found: C, 67.81; H, 10.26; N, 15.85.

2-Methoxy-4-(4-morpholyl)pyridine (5 R^1 = MeO; R^2 = R^3 = H; R^4, R^5 = $O(CH_2CH_2)_2$): Eluent: 10% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 2.9-3.3 (m, 4 H, 2 x NCH_2), 3.4-3.7 (m, 4 H, 2 x OCH_2), 3.8 (s, 3 H, OCH_3), 5.9-6 (d, 1 H, J = 2 Hz, H_{arom}), 6.2-6.4 (dd, 1 H, J_1 = 2 Hz, J_2 = 5 Hz, H_{arom}), 7.6-7.9 (d, 1 H, J = 5 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 46.4 (NCH_2), 53.1 (CH_3), 66.2 (OCH_2), 93 (C_{arom}), 104 (C_{arom}), 147 (C_{arom}), 157.9 (C_{arom}), 165.8 (C_{arom}); MS 194. *Anal.* Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.26; N, 14.42. Found: C, 61.98; H, 7.26; N, 14.11.

2-Methoxy-3-(4-morpholyl)pyridine (6 R^1 = MeO; R^2 = R^3 = H; R^4, R^5 = $O(CH_2CH_2)_2$): Eluent: 10% AcOEt/PE; Liquid; ^{1}H-NMR ($CDCl_3$) δ: 2.7-3.1 (m, 4 H, 2 x NCH_2), 3.4-3.9 (m, 4 H, 2 x OCH_2), 4.0 (s, 3 H, OCH_3), 6.5-6.7 (d, 1 H, J = 2 Hz, H_{arom}), 7.1-7.3 (m, 1 H, H_{arom}), 7.6-7.7 (m, 1 H, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 49.9 (NCH_2), 52.9 (CH_3), 66.4 (OCH_2), 116.6 (C_{arom}), 123.9 (C_{arom}), 135.4 (C_{arom}), 138.7 (C_{arom}), 156.2 (C_{arom}); MS 194. *Anal.* Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.26; N, 14.42. Found: C, 61.82; H, 7.28; N, 13.98.

2-(2,2-Dimethylpropyloxy)-4-(4-morpholyl)pyridine (5 R^1 = *tert*-$BuCH_2O$; R^2 = R^3 = H; R^4, R^5 = $O(CH_2CH_2)_2$): Eluent: 10% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 1 (s, 9 H, 3 x CH_3), 2.9-3.3 (m, 4 H, 2 x NCH_2), 3.4-3.8 (m, 4 H, 2 x OCH_2), 3.8 (s, 2 H, OCH_2), 5,8-5,9 (d, 1 H, J = 2 Hz, H_{arom}), 6-6.3 (dd, 1 H, J_1 = 2 Hz, J_2 = 5 Hz, H_{arom}), 7.5-7.8 (d, 1 H, J = 5 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 26.2 (CH_3), 31.1 (C), 46.1 (NCH_2), 65.8 (OCH_2), 74.9 (OCH_2), 92.8 (C_{arom}), 103.3 (C_{arom}),146.5 (C_{arom}), 157.4 (C_{arom}), 165.7 (C_{arom}); MS 250. *Anal.* Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 66.82; H, 8.77; N, 10.87.

2-(2,2-Dimethylpropyloxy)-3-(4-morpholyl)pyridine (6 R^1 = *tert*-$BuCH_2O$; R^2 = R^3 = H; R^4, R^5 = $O(CH_2CH_2)_2$): Eluent: 10% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 1.0 (s, 9 H, 3 x CH_3), 2.7-3.1 (m, 4 H, 2 x NCH_2), 3.4-3.8 (m, 4 H, 2 x OCH_2), 3.9 (s, 2 H, OCH_2), 6.4-6.9 (m, 2 H, H_{arom}), 7.4-7.7 (m, 1 H, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 26.8 (CH_3), 31.4 (C), 50.3 (NCH_2), 66.8 (OCH_2), 77.5 (OCH_2), 116.6 (C_{arom}), 124 (C_{arom}), 135.7 (C_{arom}), 138.6 (C_{arom}), 156.8 (C_{arom}); MS 250. *Anal.* Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.45; H, 9.28; N, 11.10.

2,4-Di-(4-morpholyl)pyridine (5 R^1 = $O(CH_2CH_2)_2N$; R^2 = R^3 = H; R^4, R^5 = $O(CH_2CH_2)_2$): Eluent: 30% AcOEt/PE; mp 96°C (AcOEt/PE); ^{1}H-NMR (CCl_4) δ: 2.9-3.4 (m, 8 H, 4 x NCH_2), 3.4-3.9 (m, 8 H, 4 x OCH_2), 5.6-5.8 (d, 1 H, J = 2 Hz, H_{arom}), 5.8-6.1 (dd, 1 H, J_1 = 2 Hz, J_2 = 5 Hz, H_{arom}), 7.6-7.8 (d, 1 H, J = 5 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 45.6-46.3 (NCH_2), 66-66.3 (OCH_2), 90.1 (C_{arom}), 100.9 (C_{arom}), 147.9 (C_{arom}), 156.9 (C_{arom}), 160.8 (C_{arom}); MS 249. *Anal.* Calcd for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68; N, 16.85. Found: C, 62.48; H, 7.72; N, 16.88.

2,4-Bis-(dipropylamino)pyridine (5 R^1 = Pr_2N; R^2 = R^3 = H; R^4 = R^5 = Pr): Eluent: 30% AcOEt/PE; mp 95°C (AcOEt/PE); ^{1}H-NMR ($CDCl_3$) δ: 0.9-1.3 (t, 12 H, J = 7 Hz, 4 x CH_3), 1.3-2.1 (m, 8 H, 4 x CH_2CH_3), 2.9-3.7 (m, 8 H, 4 x NCH_2), 5.4 (d, 1 H, J = 2 Hz, H_{arom}), 5.8-6.1 (dd, 1 H, J_1 = 2 Hz, J_2 = 5 Hz, H_{arom}), 7.4-7.8 (d, 1 H, J = 5 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 10.6 (CH_3), 19.9, 20 (CH_2CH_3), 51.7, 52.3 (NCH_2), 84.9 (C_{arom}), 98.4 (C_{arom}), 136.7 (C_{arom}), 150.5 (C_{arom}), 155.3 (C_{arom}); MS 277. *Anal.* Calcd for $C_{17}H_{31}N_3$: C, 73.59; H, 11.26; N, 15.15. Found: C, 73.72; H, 11.27; N, 15.01.

2-Ethoxy-5-(4-morpholyl)pyridine (6 R^1 = R^2 = H; R^3 = EtO; R^4, R^5 = $O(CH_2CH_2)_2$): Eluent: 10% AcOEt/PE; mp 52°C (AcOEt/PE); ^{1}H-NMR ($CDCl_3$) δ: 1.2-1.5 (t, 3 H, J = 7 Hz, CH_3), 2.7-3.1 (m, 4 H, 2 x NCH_2), 3.4-3.8 (m, 4 H, 2 x OCH_2), 3.9-4.4 (q, 2 H, J = 7 Hz, OCH_2CH_3), 6.2-6.6 (d, 1 H, J = 9 Hz, H_{arom}), 6.8-7.1 (dd, 1 H, J_1 = 9 Hz, J_2 = 3 Hz, H_{arom}), 7.3-7.7 (d, 1 H, J = 3 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 14.2 (CH_3), 50 (NCH_2), 61 (OCH_2), 66.3 (OCH_2), 110.4 (C_{arom}), 128.6 (C_{arom}), 133.8 (C_{arom}), 141.6 (C_{arom}), 158.2 (C_{arom}); MS 208. *Anal.* Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.40; H, 7.50; N, 13.20.

2,5-Di-(4-morpholyl)pyridine (6 R^1 = R^2 = H; R^3 = $O(CH_2CH_2)_2N$; R^4, R^5 = $O(CH_2CH_2)_2$): Eluent: 30% AcOEt/PE; mp 134°C (AcOEt/PE); ^{1}H-NMR ($CDCl_3$) δ: 2.8-3.6 (m, 8 H, 4 x NCH_2), 3.5-4.0 (m, 8 H, 4 x OCH_2), 6.5-6.7 (d, 1 H, J = 9 Hz, H_{arom}), 7.0-7.5 (dd, 1 H, J_1 = 2 Hz, J_2 = 3 Hz, H_{arom}), 7.8-8.0 (d, 1 H, J = 3 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 46.3-50.4 (NCH_2), 66.6-66.7 (OCH_2), 107.5 (C_{arom}), 127.4 (C_{arom}), 136.5 (C_{arom}), 140.2 (C_{arom}), 154.9 (C_{arom}); MS 249. *Anal.* Calcd for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68; N, 16.85. Found: C, 62.88; H, 7.77; N, 17.08.

2,5-Bis-(dipropylamino)pyridine (6 R^1 = R^2 = H; R^3 = Pr_2N; R^4 = R^5 = Pr): Eluent: 30% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 0.9-1.1 (t, 12 H, J = 7 Hz, 4 x CH_3), 1.3-1.8 (m, 8 H, 4 x CH_2CH_3), 2.7-3.5 (m, 8 H, 4 x NCH_2), 6.0-6.3 (d, 1 H, J = 9 Hz, H_{arom}), 5.8-6.1 (dd, 1 H, J_1 = 9 Hz, J_2 = 3 Hz, H_{arom}), 7.4-7.8 (d, 1 H, J = 3 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 11.4 (CH_3), 20.4, 20.8 (CH_2CH_3), 50.7, 54.6 (NCH_2), 106 (C_{arom}), 123.3 (C_{arom}), 126.8 (C_{arom}), 135.8 (C_{arom}), 151.9 (C_{arom}); MS 277. *Anal.* Calcd for $C_{17}H_{31}N_3$: C, 73.59; H, 11.26; N, 15.15. Found: C, 73.76; H, 11.53; N, 14.71.

3-Ethoxy-5-(4-morpholyl)pyridine (6 R^1 = R^3 = H; R^2 = EtO; R^4, R^5 = $O(CH_2CH_2)_2$): Eluent: 10% AcOEt/PE; mp 65°C (AcOEt/PE); ^{1}H-NMR ($CDCl_3$) δ: 1.2-1.6 (t, 3 H, J = 7 Hz, CH_3), 2.8-3.3 (m, 4 H, 2 x NCH_2), 3.5-4.2 (m, 6 H, 3 x OCH_2), 6.4-6.7 (m, 1 H, H_{arom}), 7.6-7.9 (s, 2 H, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 14.4 (CH_3), 48.2 (NCH_2), 63.4 (OCH_2), 66.2 (OCH_2), 108 (C_{arom}),

127.8 (C_{arom}), 130.5 (C_{arom}), 147.5 (C_{arom}), 155.1 (C_{arom}); MS 208. *Anal.* Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.38; H, 7.88; N, 13.38.

3,5-Di-(4-morpholyl)pyridine (6 R^1 = R^3 = H; R^2 = $O(CH_2CH_2)_2N$; R^4, R^5 = $O(CH_2CH_2)_2$): Eluent: (30% AcOEt/PE; mp 177°C (AcOEt/PE); ^{1}H-NMR ($CDCl_3$) δ: 2.9-3.3 (m, 8 H, 4 x NCH_2), 3.6-4.0 (m, 8 H, 4 x OCH_2), 6.4-6.7 (m, 1 H, H_{arom}), 7.7 (d, 2 H, *J* = 3 Hz, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 48.6 (NCH_2), 66.4 (OCH_2), 108.8 (C_{arom}), 129.9 (C_{arom}), 147.1 (C_{arom}); MS 316. *Anal.* Calcd for $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68; N, 16.85. Found: C, 62.55; H, 7.62; N, 16.61.

3,5-Bis-(dipropylamino)pyridine (6 R^1 = R^3 = H; R^2 = Pr_2N; R^4 = R^5 = Pr): Eluent: 30% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 0.6-1.1 (t, 12 H, *J* = 7 Hz, 4 x CH_3), 1.1-2 (m, 8 H, 4 x CH_2CH_3), 2.8-3.4 (m, 8 H, 4 x NCH_2), 5.9 (s, 1 H, H_{arom}), 7.2 (s, 2 H, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 109 (CH_3), 20.1 (CH_2 CH_3), 52.4 (NCH_2), 100.3 (C_{arom}), 122.4 (C_{arom}),144.1 (C_{arom}); MS 277. *Anal.* Calcd for $C_{17}H_{31}N_3$: C, 73.59; H, 11.26; N, 15.15. Found: C, 73.64; H, 11.10; N, 15.26.

Scheme 3

3-Bromo-5-(4-morpholyl)pyridine (8 R^4, R^5 = $O(CH_2CH_2)_2$): Eluent: 30% AcOEt/PE; mp 77°C (AcOEt/PE); ^{1}H-NMR ($CDCl_3$) δ: 2.8-3.2 (m, 4 H, 2 x NCH_2), 3.5-3.9 (m, 4 H, 2 x OCH_2), 7.0-7.2 (m, 1 H, H_{arom}), 7.9-8.2 (m, 2 H, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 47.7 (NCH_2), 66.1 (OCH_2), 113.5 (C_{arom}), 116.7 (C_{arom}), 128.7 (C_{arom}), 133.8 (C_{arom}), 140.4 (C_{arom}); MS 243. *Anal.* Calcd for $C_9H_{11}N_2OBr$: C, 44.46; H, 4.56; N, 11.52; Br, 32.87. Found: C, 44.66; H, 4.74; N, 11.35; Br, 32.72.

3-Bromo-4-(4-morpholyl)pyridine (9 R^4, R^5 = $O(CH_2CH_2)_2$): Eluent: 10% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 2.8-3.2 (m, 4 H, 2 x NCH_2), 3.5-3.9 (m, 4 H, 2 x OCH_2), 6.5-6.8 (d, 1 H, *J* = 5 Hz, H_{arom}), 8.0-8.2 (d, 1 H, *J* = 5 Hz, H_{arom}), 8.3 (s, 1 H, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 50.2 (NCH_2), 66.3 (OCH_2), 114.6 (C_{arom}), 114.9 (C_{arom}), 149.1 (C_{arom}), 152.9 (C_{arom}), 156.1 (C_{arom}); MS 243. *Anal.* Calcd for $C_9H_{11}N_2OBr$: C, 44.46; H, 4.56; N, 11.52; Br, 32.87. Found: C, 44.51; H, 4.67; N, 11.42; Br, 32.86.

3-Bromo-5-dipropylaminopyridine (8 R^4 = R^5 = Pr): Eluent: 10% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 0.6-1.1 (t, 6 H, *J* = 7 Hz, 2 x CH_3), 1.1-1.8 (m, 4 H, 2 x CH_2CH_3), 2.9-3.3 (m, 4 H, 2 x NCH_2), 6.7-6.9 (m, 1 H, H_{arom}), 7.6-7.9 (m, 2H, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 11.1 (CH_3), 19.9 (CH_2CH_3), 52.2 (NCH_2), 119.5 (C_{arom}), 120.8 (C_{arom}), 132.3 (C_{arom}), 136.5 (C_{arom}), 144.7 (C_{arom}); MS 257. *Anal.* Calcd for $C_{11}H_{17}N_2Br$: C, 51.37; H, 6.66; N, 10.90; Br, 31.07. Found: C, 51.33; H, 6.71; N, 10.79, Br, 31.17.

3-Bromo-4-dipropylaminopyridine (9 R^4 = R^5 = Pr): Eluent: 10% AcOEt/PE; Liquid; ^{1}H-NMR (CCl_4) δ: 0.6-1.1 (t, 6 H, *J* = 7 Hz, 2 x CH_3), 1.1-1.9 (m, 4 H, 2 x CH_2CH_3), 2.9-3.4 (m, 4 H, 2 x

NCH_2), 6.5-6.9 (d, 1 H, J = 5 Hz, H_{arom}), 7.9-8.2 (d, 1 H, J = 5 Hz, H_{arom}), 8.3 (s, 1 H, H_{arom}); ^{13}C-NMR ($CDCl_3$) δ: 11.1 (CH_3), 20.3 (CH_2CH_3), 52.9 (NCH_2), 113.4 (C_{arom}), 115.4 (C_{arom}), 147.9 (C_{arom}), 153.4 (C_{arom}),155.1 (C_{arom}); MS 257. *Anal.* Calcd for $C_{11}H_{17}N_2Br$: C, 51.37; H, 6.66; N, 10.90; Br, 31.07. Found: C, 51.02; H, 6.53; N, 11.26; Br, 31.19.

Scheme 4

4-(4-Morpholyl)-2-pyridinol (12 R^4, R^5 = $O(CH_2CH_2)_2$): Eluent: 10% MeOH/CH_2Cl_2; mp 201°C (AcOEt/PE); IR ν: 3700-3000 cm^{-1} (OH); UV (MeOH): λmax (log ε) : 229.4 (4.55), 275.1 (4,26); ^{1}H-NMR ($CDCl_3$) δ: 3.2-3.3 (m, 4 H, 2 x NCH_2), 3.7-3.8 (m, 4 H, 2 x OCH_2), 5.7 (d, 1 H, J = 2 Hz, H_{arom}), 5.9 (dd, 1 H, J_1 = 2 Hz, J_2 =5 Hz, H_{arom}), 7.1-7.2 (d, 1 H, J =7 Hz, H_{arom}), 12.6 (s, 1 H, OH); ^{13}C-NMR ($CDCl_3$) δ: 45.7 (NCH_2), 65.8 (OCH_2), 94.6 (C_{arom}), 97.4 (C_{arom}), 133.9 (C_{arom}), 158.8 (C_{arom}), 165.2 (C_{arom}); MS 180. *Anal.* Calcd for $C_9H_{12}N_2O_2$ (hydrated 2.58% H_2O): C, 58.43; H, 6.50; N, 15.06. Found: C, 58.52; H, 6.38; N, 14.82.

3-(4-Morpholyl)-1,2-dihydro-2-pyridinone (13 R^4, R^5 = $O(CH_2CH_2)_2$): Eluent: 10% MeOH/ CH_2Cl_2; mp 195°C (AcOEt/PE); IR ν: 3400-3000 cm^{-1} (NH), 1648 cm^{-1} (C=O); UV (MeOH): λmax (log ε) : 232.3 (3.79), 263.6 (3,73), 314.4 (4,08); ^{1}H-NMR ($CDCl_3$) δ: 3.0-3.3 (m, 4 H, 2 x NCH_2), 3.8-4.0 (m, 4 H, 2 x OCH_2), 6.1-6.3 (t, 1 H, J = 7 Hz, H_{arom}), 6.7-6.8 (dd, 1 H, J_1 = 7 Hz, J_2 = 2 Hz, H_{arom}), 7.1-7.2 (dd, 1 H, J_1 = 7 Hz, J_2 = 2 Hz, H_{arom}), 13.1 (s, 1 H, NH); ^{13}C-NMR ($CDCl_3$) δ 49.3 (NCH_2), 66.7 (OCH_2), 106.7 (C_{arom}), 122.3 (C_{arom}), 126.9 (C_{arom}), 142 (C_{arom}), 161.3 (C_{arom}); MS 180. *Anal.* Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.71; H, 6.71; N, 15.81.

4-Dipropylamino-2-pyridinol (12 R^4 = R^5 = Pr): Eluent: 10% MeOH/CH_2Cl_2; mp 130°C (AcOEt/PE); IR ν: 3600-2400 cm^{-1} (OH); UV (MeOH): λmax (log ε) : 232.8 (4.12), 277.0 (4.01); ^{1}H-NMR ($CDCl_3$) δ: 0.6-1.1 (t, 6 H, J = 7 Hz, 2 x CH_3), 1.1-1.9 (m, 4 H, 2 x CH_2CH_3), 2.9-3.5 (m, 4 H, 2 x NCH_2), 5.3 (d, 1 H, J = 2 Hz, H_{arom}), 5.5-5.8 (dd, 1 H, J_1 = 2 Hz, J_2 = 5 Hz, H_{arom}), 6.9-7.2 (d, 1 H, J = 5 Hz, H_{arom}), 13.0 (s, 1 H, OH); ^{13}C-NMR ($CDCl_3$) δ: 10.6 (CH_3), 19.9 (CH_2CH_3), 51.7 (NCH_2), 91.8 (C_{arom}), 95.8 (C_{arom}), 133.8 (C_{arom}), 155.9 (C_{arom}), 165.8 (C_{arom}); MS 194. *Anal.* Calcd for $C_{11}H_{18}N_2O$: C, 68.00; H, 9.34; N, 14.42. Found: C, 67.69; H, 9.71; N, 14.24.

3-(Dipropylamino)-1,2-dihydro-2-pyridinone (13 R^4 = R^5 = Pr): Eluent: 10% MeOH/CH_2Cl_2; mp 34°C (AcOEt/PE); IR ν: 3400-3000 cm^{-1} (NH), 1641 cm^{-1} (C=O); UV (MeOH): λmax (log ε) : 238.4 (3.68), 275.2 (3,69), 325.0 (3.92); ^{1}H-NMR ($CDCl_3$) δ: 0.6-1.2 (t, 6 H, J = 7 Hz, 2 x CH_3), 1.2-1.8 (m, 4 H, 2 x CH_2CH_3), 2.8-3.6 (m, 4 H, 2 x NCH_2), 5.7-6.1 (m, 1 H, H_{arom}), 6.2-6.6 (d, 1 H, H_{arom}),

6.6-7.0 (d, 1 H, $\mathbf{H_{arom}}$), 13.0 (s, 1 H, NH); ^{13}C-NMR ($CDCl_3$) δ: 11.3 (CH_3), 19.4 (CH_2CH_3), 52.2 (NCH_2), 106.4 ($\mathbf{C_{arom}}$), 123.3 ($\mathbf{C_{arom}}$), 125.2 ($\mathbf{C_{arom}}$), 140.3 ($\mathbf{C_{arom}}$), 161.9 ($\mathbf{C_{arom}}$); MS 194. *Anal.* Calcd for $C_{11}H_{18}N_2O$: C, 68.00; H, 9.34; N, 14.42. Found: C, 67.83; H, 9.45; N, 13.93.

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