Pergamon

Tetrahedron, Vol. 53, No. 37, pp. 12505-12524, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00771-0

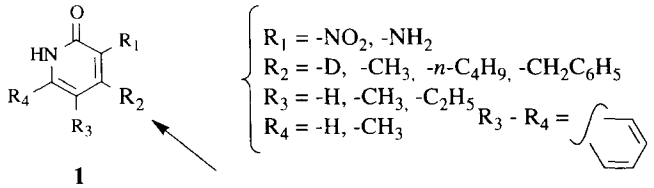
Studies towards 4-C-Alkylation of Pyridin-2(*1H*)-one Derivatives.

Valérie Dollé, Chi Hung Nguyen and Emile Bisagni*

UMR 176 CNRS-Institut Curie, Section de Recherche,
15 rue Georges Clémenceau, 91405 Orsay, France.

Abstract : In order to obtain 4-C-alkylated pyridin-2(*1H*)-ones, two strategies were studied : nucleophilic substitution of 4-chloro-3-nitropyridinone derivatives which essentially failed and lithiations of 2-methoxy-3-pivaloylaminopyridines which gave the expected products. © 1997 Elsevier Science Ltd.

With a view to obtaining biologically active compounds related to the pyridinone family of HIV-1 Reverse Transcriptase inhibitors which we recently described[1], we now wish to obtain different 4-C-alkylated pyridin-2(*1H*)-ones of general formula **1** (Figure 1). To this end, two strategies have been studied. First, since we have previously reported the substitution reactions of 4-chloro-5-methyl-3-nitropyridin-2(*1H*)-one[2] (**2**) and 4-chloro-3-nitroquinolin-2(*1H*)-one[1] respectively (**3**) with thiophenol and aniline[1], leading to the corresponding 4-thiophenyl and 4-anilino derivatives[1], we tried to extend this methodology by the nucleophilic substitutions of **2** and **3** with various carbanions. Secondly, we studied the lithiation and subsequent alkylation of 2-methoxy-3-pivaloylaminopyridines. In this paper, we report the results of our studies in this field.



1

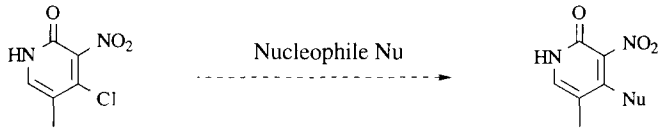
Figure 1 : How to 4-C-alkylate 3-substituted- and 3,5,6-trisubstituted-pyridin-2(*1H*)-ones ?

A) Nucleophilic substitutions of 4-chloro-3-nitropyridinone derivatives

As a model (Table 1) we studied the reaction of chloronitropyridinone **2** with methylmagnesium iodide and methyllithium. All starting material was completely consumed at -78°C and in the presence of 2.5-3

Fax : 01.69.07.53.81 - E. mail : bisagni@curie.u-psud.fr

equivalents of CH_3Li and CH_3MgI. From the large cocktail of compounds observed by TLC, only two compounds could be isolated ; structures **6** and **7** were assigned on the basis of ^1H NMR. Clearly two main reactions took place : i) the normal chlorine atom substitution by methylmagnesium iodide, leading to 4,5-dimethyl-3-nitropyridin-2(*1H*)-one (**6**) ; ii) the 1,6-Michaël type addition of methylmagnesium iodide giving the compound **7** (**7** is rather unstable, but could be isolated by rapid flash chromatography; for example, it decomposes at room temperature within 30 min. in a dilute chloroform solution, as observed during ^1H NMR spectrum acquisition). This 1,6-Michaël addition was the only reaction observed when methyllithium was used and the yield was then improved to 25 %. Subsequent manganese dioxide oxidation of derivative **7** allowed the isolation of the stable 4-chloro-5,6-dimethyl-3-nitropyridin-2(*1H*)-one (**8**) (Table 1).



2[2] **4**

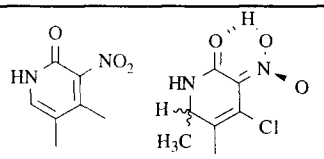
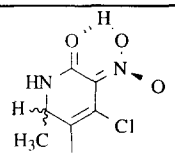
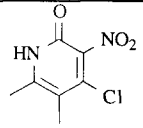
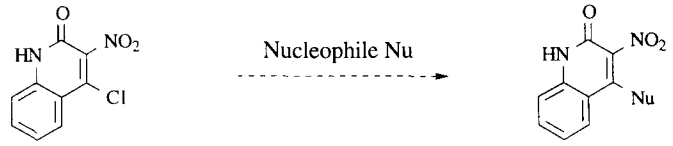
Nucleophile	Experimental Conditions	Products	Yields
MeMgI (3.0 eq) in ether	THF, -78°C	 **6** **7**	8 % (**6**) and 8 % (**7**)
MeLi (2.5 eq) in ether	THF, -78°C	 **7** (unstable)	25 %
a. MeLi (2.5 eq) in ether b. MnO_2 (10.0 eq)	1) THF, -78°C 2) CH_2Cl_2, r.t.	 **8**	9 %

Table 1 : Nucleophilic substitutions of 4-chloro-5-methyl-3-nitropyridin-2(*1H*)-one (**2**) with methylmagnesium iodide and methyllithium

Similar reactions using both methylmagnesium iodide and methyllithium were then performed using 4-chloro-3-nitroquinolin-2(*1H*)-one (**3**) as the starting compound. The results are summarized in Table 2. Under the usual conditions, methylmagnesium iodide and methyllithium led directly to a low yield of 4,4-

dimethyl-3-nitro-3,4-dihydroquinolin-2(*1H*)-one (**9**) corresponding to a 4-C-bis-methylation (Table 1, entries 1 and 3). This probably arises from an 1,4-addition-elimination and new addition reaction of methylmagnesium iodide or methyllithium on the compound **3**. The monomethylated derivative **10** was never observed under these experimental conditions. However, treatment of **3** with a fourfold excess of a 2:1 mixture of Grignard reagent/copper bromide[3] salt (Table 1, entry 2) gave the expected 4-methyl-3-nitroquinolin-2(*1H*)-one (**10**), with a yield which did not exceed 6 %. Attempts to react compound **3** with 3 equivalents of dimethylzinc in toluene at reflux led only to recovered starting compound **3**.



3[1] **5**

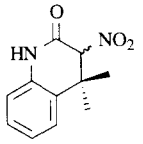
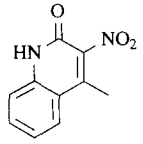
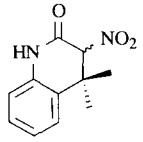
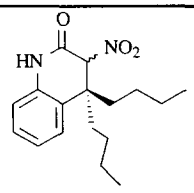
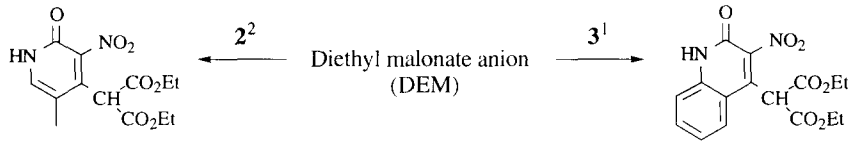
Entry	Nucleophile	Experimental Conditions	Products	Yields
1	MeMgI (3.0 eq) in ether	THF, -78°C	 **9**	6 %
2	MeMgI (8.0 eq) in ether	$CuBr^3$ (4.0 eq), THF, -78°C	 **10**	6 % (**10**) and 15 % (**3**)
3	MeLi (2.2 eq) in ether MeLi (3.5 eq) in ether	THF, -78°C THF, -78°C	 **9**	20 % 31 %
4	*n*-BuLi (2.2 eq) in hexane *n*-BuLi (3.5 eq) in hexane *n*-BuLi (3.3 eq) in hexane	THF, -78°C THF, -78°C THF, 0°C	 **11**	34 % 34 % 18 %

Table 2 : Nucleophilic substitutions of 4-chloro-3-nitroquinolin-2(*1H*)-one (**3**)

In the case of *n*-butyllithium, the reaction was studied at -78°C with 2.2 and 3.5 equivalents of *n*-BuLi and at 0°C with 3.3 equivalents of the same reagent. As can be seen in Table 2 entry 4, the use of 3.5 equivalents of *n*-BuLi did not improve the 34 % yield obtained at -78°C with 2.2 equivalents and a higher temperature (0°C) led to a markedly lowered yield of the 4,4-dibutyl-3-nitro-3,4-dihydroquinolin-2(*1H*)-one (**11**), the formation of which can be explained as above.

Thus, the use of methylmagnesium iodide, methyllithium and *n*-butyllithium did not seem to be an appropriate way of obtaining the desired 4-C-monoalkylated pyridin-2(*1H*)-ones **4** or **5**. On the other hand, nucleophilic substitutions of compounds **2** and **3** were studied with the more hindered and stabilized diethyl malonate[4-6], benzylcyanide and ethyl phenylacetate anions under various experimental conditions. Only diethyl malonate gave the expected compounds. However, compound **2** led to diethyl-(5-methyl-3-nitropyridin-2(*1H*)-on-4-yl)malonate (**12**) with a low yield (6 %). Chloroquinolinone **3** again gave better results, diethyl malonate derivative **13** being obtained in a yield of 37 %, after optimization (Table 3, entry 5).



12 **13**

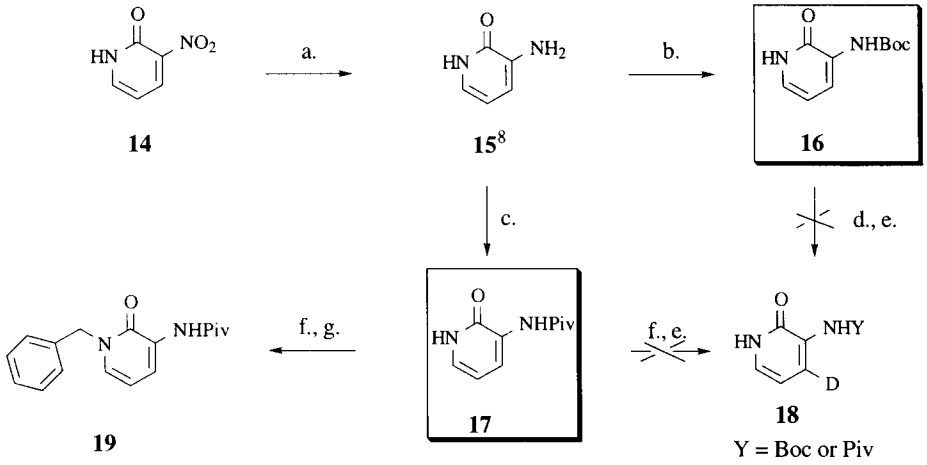
Entry	Starting material	Experimental Conditions	Yield (expected compound)	% recoveredstarting material
1	**2**	DEM[4,5] (7.0 eq), NaH (7.0 eq), DMF 6.5 h, Δ_{reflux}	-	recovered
2	**2**	DEM (3.0 eq), NaH (3.0 eq), THF/HMPA cat 3.5 h r.t. and then 12 h Δ_{reflux}	4 % (**12**)	57 %
3	**2**	DEM (6.0 eq), NaH (6.0 eq), THF/DMF 5 h 80°C and then 48 h 40°C	6 % (**12**)	61 %
4	**3**	DEM[4,5] (2.0 eq), NaH (2.0 eq), THF 5 h r.t. and then 15 h Δ_{reflux}	13 % (**13**)	-
5	**3**	DEM (7.5 eq), NaH (7.5 eq), THF/DMF 4 h 100°C and then 48 h r.t.	37 % (**13**)	-
6	**3**	a. HMDS[6] (excess), TMSCl cat, Δ_{reflux} b. DEM (5.0 eq), NaH (5.0 eq), THF/DMF, 70°C, 3.5 h	25 % (**13**)	17 %

Table 3 : Nucleophilic substitutions of **2** and **3** by diethyl malonate

These disappointing results led us to study the lithiation and subsequent electrophilic substitution of suitably substituted pyridines.

B) Lithiations and electrophilic substitutions of 2-methoxy-3-pivaloylaminopyridines

As is well known, the lithiation of polysubstituted aromatics generally requires an *ortho*-directing group[7]. Therefore, starting from the commercially available 3-nitropyridin-2(*1H*)-one (**14**), we prepared[8] 3-aminopyridinone **15** and its *N*-Boc and *N*-pivaloylamino derivatives **16** and **17**. Attempts to obtain the 4-lithiated pyridine from compound **16** by using *tert*-butyllithium, as described in the literature in the case of *N*-Boc aniline[9] and *N*-Boc pyridines[10], totally failed. We turned to the study of **17**, but attempts at lithiation[11,12] with *n*-BuLi at -10°C in the presence of tetramethylethylenediamine (TMEDA) also failed. In both cases, no traces of the corresponding 4-deuteropyridines **18** were observed when quenching was performed with D_2O. Only 1-*N*-benzyl-3-pivaloylaminopyridin-2(*1H*)-one (**19**) was isolated from **17** after reaction with benzyl bromide (Scheme 1).

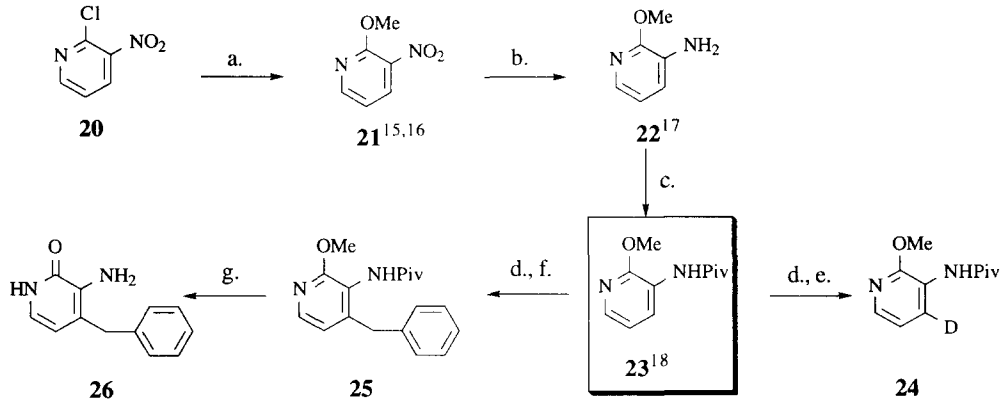


a H_2, Pd/C 10 %, MeOH/THF (1/1), r.t., 97 %; b. $(Boc)_2O$ (1.1 eq), NEt_3 (2.2 eq), CH_2Cl_2, r.t. to Δ_{reflux}, 25 % (and 47 % starting material **15**); c. *t*-BuCOCl (1.1 eq), NEt_3 (1.1 eq), CH_2Cl_2, 0°C to r.t., 81 %; d. *t*-BuLi[9,10] (3.3 eq), THF, -78°C; e. D_2O; f. *n*-BuLi[11,12] (3.5 eq), TMEDA (3.5 eq), THF, -78°C to -10°C; g. Benzyl bromide (4.5 eq), 69 %.

Scheme 1 : Lithiation studies of protected 3-aminopyridin-2(*1H*)-ones **16** and **17**

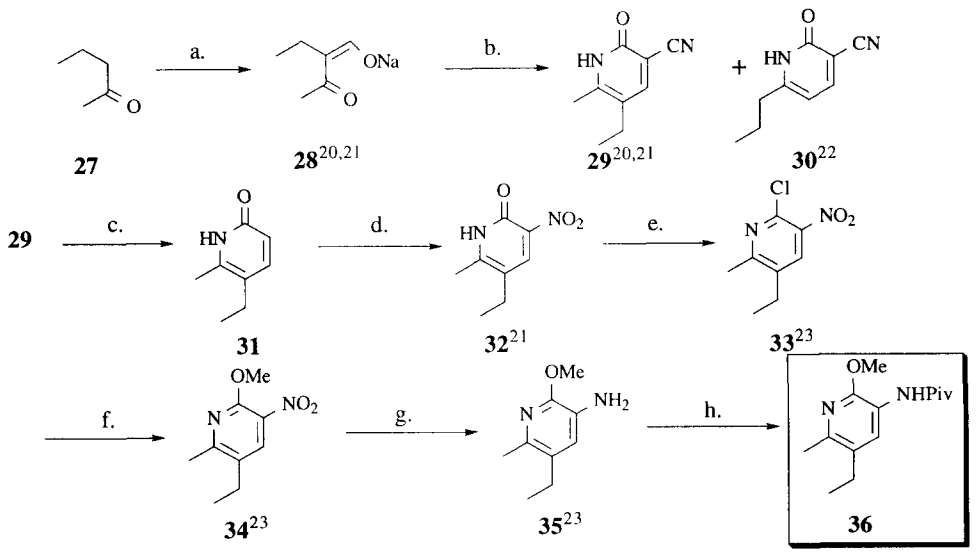
Although the presence of the lactam function in the cases of furo- and pyrrolo-[3,2-c]pyridinones did not prevent the formation of the corresponding lithiatied derivatives in moderate yields[13], it seemed that in our case the protection of the NHCO pyridinone function of **16** and **17** was necessary[14]. Starting from 2-chloro-3-nitropyridine (**20**), we prepared the known nitropyridine **21**[15,16], then the corresponding amine **22**[17] and 2-methoxy-3-pivaloylaminopyridine[18] (**23**) (Scheme 2). In this study, an appreciable improvement of the preparation of **23** was obtained (93 % overall yield) compared to that described in the literature. Lithiation of compound **23** by *n*-BuLi at -10°C in the presence of TMEDA took place quantitatively, as verified by D_2O hydrolysis which gave 4-deutero derivative **24**. This high yield was fully in agreement with results recently reported by Quéguiner *et al.*[11,19]. When reacted with benzyl bromide, the lithio derivative led to 4-benzyl-2-

methoxy-3-pivaloylaminopyridine (**25**), the acidic hydrolysis[11] of which (regeneration of the NHCO function) provided the expected 3-amino-4-benzylpyridin-2(*1H*)-one (**26**) (Scheme 2).



a. MeONa (1.3 eq), MeOH, r.t.; b. H_2, Pd/C 10 %, MeOH/THF (1/1), r.t.; c. *t*-BuCOCl (1.1 eq), NEt_3 (1.1 eq), CH_2Cl_2, 0°C to r.t., (93 % overall yield for 3 steps); d. *n*-BuLi[11,19] (3.5 eq), TMEDA (3.5 eq), THF, -78°C to -10°C; e. D_2O, 99 %; f. Benzyl bromide (4.5 eq), 68 % and 10 % of starting material **23**; g. HCl 3M[11], H_2O, Δ_{reflux}, 70 %.

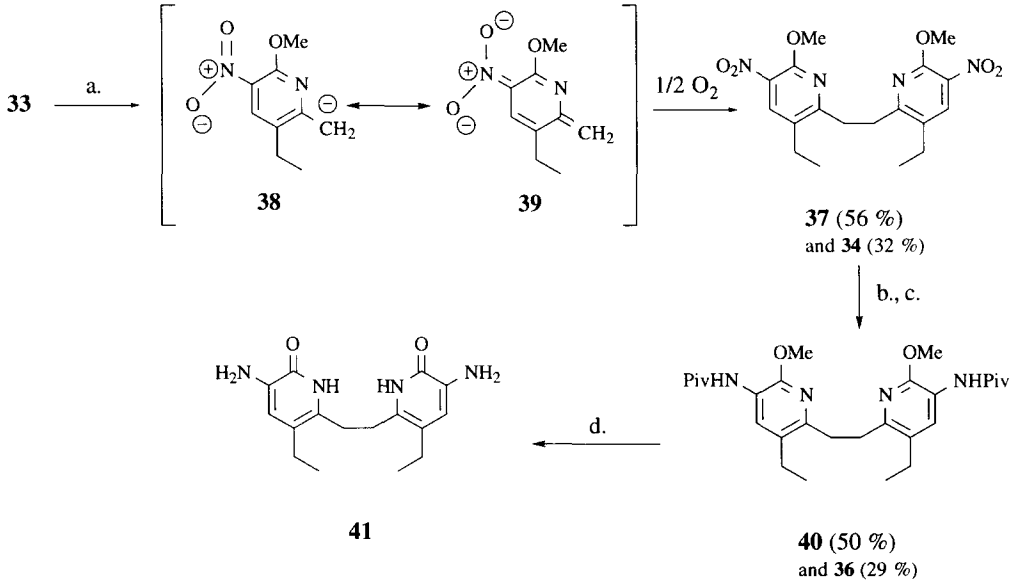
Scheme 2 : Synthesis and lithiation of compound **23**



a. HCO_2Et (1.08 eq), MeONa (1.00 eq), EtOH, Et_2O, N_2, 0°C to r.t., >39 %; b. Cyanoacetamide (1.00 eq), piperidine (0.75 eq), AcOH (0.75 eq), H_2O, Δ_{reflux}, 61 % (**29**) and 1.5 % (**30**); c. HCl 6N, 2 days, Δ_{reflux}, 88 %; d. H_2SO_4 (d=1.80) (25.00 eq), HNO_3 (d=1.52) (2.00 eq), 0°C, 81 %; e. $POCl_3$ (30.00 eq), $BnEt_3NCl$ (4.00 eq), Δ_{reflux}, 88 %; f. MeONa (3.00 eq), MeOH, r.t., 64 h, 99 %; g. H_2, Pd/C 10 %, MeOH/THF (1/1), 99 %; h. *t*-BuCOCl (1.10 eq), NEt_3 (1.10 eq), CH_2Cl_2, 0°C, 96 %.

Scheme 3 : Synthesis of **36**

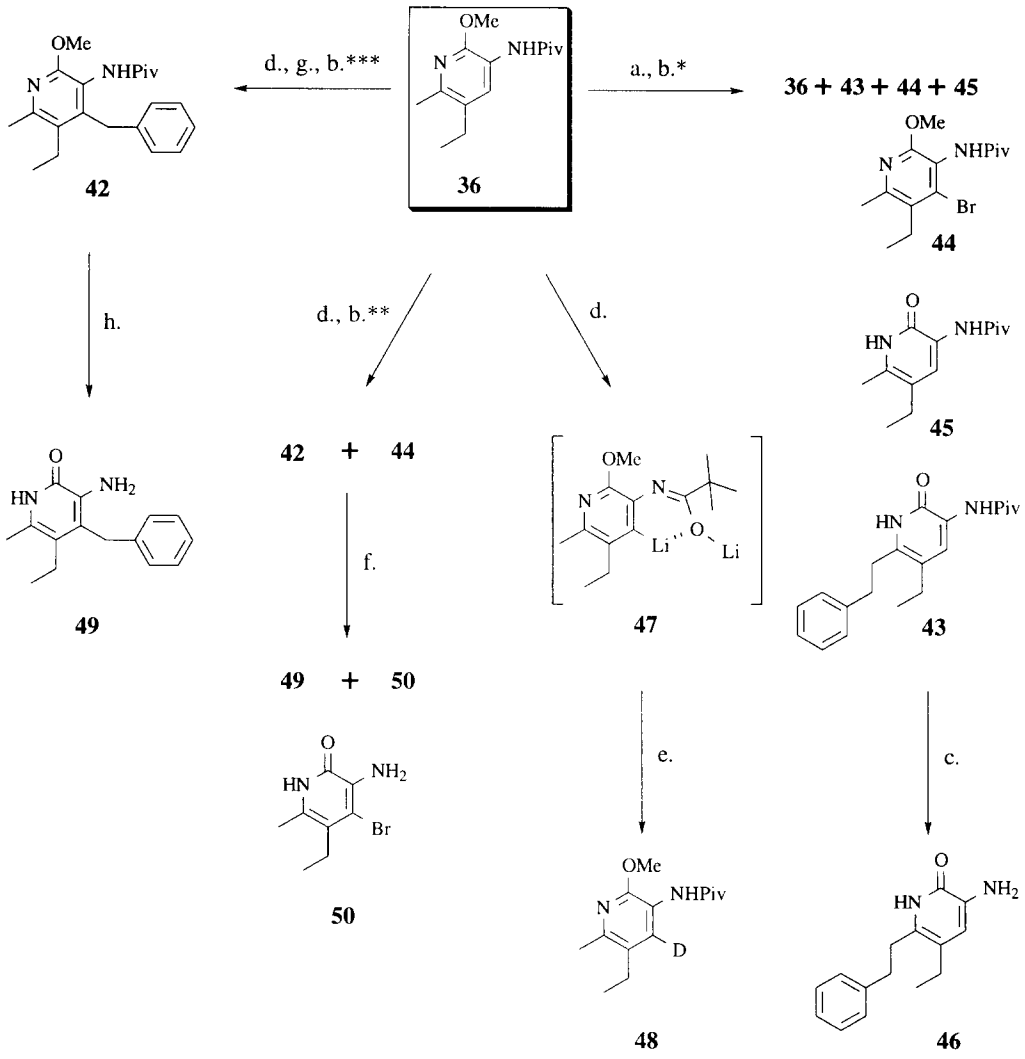
These encouraging results led us to consider this route as suitable for the synthesis of related 5,6-disubstituted pyridinone derivatives. Therefore 5-ethyl-6-methyl-3-pivaloylamino derivative **36** was prepared from 2-pentanone (**27**) according to the pathway depicted in Scheme 3. Base-catalysed ethylformate formylation of **27** gave mainly the intermediate **28** from which **29** was produced by cyclocondensation with cyanoacetamide[20,21]. However, the concomitant formation of 3-cyano-6-propylpyridin-2(*1H*)-one (**30**) ; which had already been prepared by another route[22], showed that partial 1-formylation of 2-pentanone (**27**) can not be avoided. Hydrolysis and decarboxylation of nitrile **29** provided 5-ethyl-6-methylpyridin-2(*1H*)-one (**31**) the nitration of which gave nitropyridinone **32**, already prepared from **28** and nitroacetamide[21]. The synthesis of **32** starting from cyanoacetamide is a convenient and safe alternative to the use of the rather expensive nitroacetamide which requires a hazardous preparation. Successive transformations into **33**[23], **34**[23], **35**[23] and **36** proceeded as described for the synthesis of analogue **23** (Scheme 3).



a. MeONa (3.00 eq), MeOH, r.t., 144 h; b. H_2, Pd/C 10 %, MeOH/THF (1/1); c. *t*-BuCOCl (1.10 eq), NEt_3 (1.10 eq), CH_2Cl_2, 0°C; d. HCl[11] 3M, AcOH, H_2O, Δ_{reflux}, 93 %.

Scheme 4 : Dimerization reaction of **33**

It is worth noting that when the transformation **33** to **34** was performed, over 144 h instead of 64 h, a dimerized compound **37** was isolated with a 56 % yield. Formation of a radical arising from monoelectronic oxidation of transient species **38** or **39** probably accounts for this result which corresponds to the already described dimerization of *p*-nitrotoluene[24,25] (Scheme 4). The dimer **37** was further transformed into **40** and **41**, successively, under the usual experimental conditions.



a. *t*-BuLi (3.5 eq), TMEDA (3.5 eq), THF, -78°C to -10°C; b. Benzyl bromide (4.5 eq), *28 % (**43**), 11 % (**44**), 7 % (**45**) and 8.5 % **36** recovered, **56 % (**42** + **44** : 6/4) and 24 % **36** recovered, ***53 % (**42**) and 34.5 % **36** recovered; c. HCl 3M[11], H_2O, AcOH, Δ_{reflux} to r.t., 74%; d. *n*-BuLi (3.5 eq), TMEDA (3.5 eq), THF, -78°C to 0°C; e. D_2O, ≈100 %; f. HCl 3M[11], H_2O, Δ_{reflux}, 52 % (6/4); g. $Cu^{I}I$:DMS[26-29] (3.5 eq), THF, -78°C to 0°C; h. HCl 3M[11], H_2O, Δ_{reflux} to r.t., 95 %.

Scheme 5 : Lithiations and substitutions of pyridine derivative **36**

It was hoped that the conditions used successfully for the lithiation and substitution of **23** could be applied to **36**. However, treatment with *n*-BuLi at -10°C in the presence of TMEDA followed by addition of benzyl bromide led to recovered starting material and did not give the expected pyridine **42**. Surprisingly, using *t*-BuLi under similar conditions gave 28 % of 6-phenethylpyridinone **43**, 11 % of 4-bromo derivative **44**, 8 % of recovered starting material **36** and 7 % of partially deprotected starting compound **45** ; no traces of the expected product **42** were observed. These results clearly showed that in both cases, the 4-lithio derivative **47** was certainly not efficiently formed. Acidic hydrolysis of **43** gave corresponding pyridinone **46** (Scheme 5).

In order to get specific lithiation at the 4-position of compound **36**, a study of lithiation conditions of this compound was planned, using *n*-BuLi at various temperatures with and without TMEDA. The results of this study are summarized in Table 4, where the yields correspond to the percentage of deuterated pyridinone **48** obtained after D_2O hydrolysis of lithio derivative **47**.

Entry	a. *n*-BuLi (3.5 eq), THF with TMEDA (3.5 eq) b. D_2O			Entry	a. *n*-BuLi (3.5 eq), THF without TMEDA b. D_2O		
	Temperature/ Time	Deuteration percentage*	Observations		Temperature /Time	Deuteration percentage*	Observations
1	not performed	-	-	1'	-40°C / 30 min.	0%	Yellow Solution
2	-10°C / 1 h	0%	Yellow Solution	2'	-10°C / 30 min.	50%	Orange Solution
3	0°C / 1 h	~100%	Orange Precipitate	3'	0°C / 30 min.	25%	Yellow Light Precipitate
4	25°C / 30 min.	50%	Yellow Precipitate	4'	25°C / 30 min.	0%	Orange Solution

Table 4 : Deuteration Studies of **36** with *n*-BuLi as a function of the Temperature
(*Defined by ^1H NMR)

As can be seen, 4-lithiations were performed both in the presence (entries 1 to 4) and absence (entries 1' to 4') of TMEDA. As expected, yields were higher in the presence of TMEDA (except entry 2'). At -10°C (entry 2), no lithiation occurred. At 0°C (entry 3), a quantitative lithiation of compound **36** was observed. At higher temperature (entry 4), the yield decreased, probably due to the degradation of the lithio derivative **47**. Using the optimum conditions for lithiation followed by benzyl bromide quenching then provided 4-benzyl-pyridinone **42** and bromo derivative **44** in a ratio 3/2 and with a 56 % overall yield (**42** + **44**) together with recovered compound **36** (24 %) (Scheme 5). Complete hydrolysis of the inseparable **42** + **44** mixture was performed by boiling with dilute hydrochloric acid to give another inseparable mixture of pyridinones **49** and **50**. The formation of the bromo derivative **44** can be explained by a metal/halogen exchange in the reaction of the *ortho*-lithio derivative **47** with benzyl bromide. The lithium/bromide exchange observed is clearly

facilitated by the ability to form stabilized benzylic anionic species. Finally, in order to avoid the formation of this undesired 4-bromopyridine **44**, the intermediate lithium derivative **47** was turned into the corresponding organocopper reagent by $Cu^{I}I$:dimethyl sulfide complex[26-29]. C-alkylation with benzyl bromide then provided 4-benzyl-5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (**42**) with a 53 % yield and 34 % of recovered starting material **36**.

Although we finally succeeded in synthesing the desired 4-C-alkylated pyridin-2(*1H*)-one derivatives **26** and **49** *via* the lithiation strategy, it is obvious that the experimental conditions generally need specific optimization for each new example if the required efficiency is to be obtained. Biological studies of the new compounds are in progress and results will be reported elsewhere.

In conclusion, this study led to some general remarks which must be pointed out :

The direct nucleophilic substitutions of 4-chloro-3-nitropyridin-2(*1H*)-one **2** or the equivalent chloronitroquinolone **3** provided various compounds arising either from direct substitution or from 1,6 or 1,4-Michaël type addition-elimination and new addition reactions. Moreover, when the expected compounds were obtained, the yields were generally low.

On the contrary, lithiation of 2-methoxy-3-pivaloylaminopyridine derivatives allowed their electrophilic substitution. Under normal conditions, however, a 4-bromo derivative appeared as a by product and in order to improve the yields by avoiding the side reactions, an organocopper reagent was used successfully .

Experimental

TLC was carried out on pre-coated plates of silica gel 60F254 (Merck). In order to reveal the compounds, TLC plates were exposed to UV-light. Purifications were performed on silica gel (40-60 µm, SDS) columns by medium pressure chromatography. In all experiments involving lithium and magnesium derivatives, the glassware was dried in the oven for a 24 h period before use. Tetrahydrofuran (THF) was systematically freshly distilled from sodium/benzophenone. All melting points were measured on an Electrothermal 9200 apparatus and were uncorrected. NMR spectra were recorded at 294 °K in the given solvents on a Bruker AC 200 and a Bruker AMX 300 apparatus using the hydrogenated residue of the deuteriated solvents ($CHCl_3$, δ = 7.25 ppm and DMSO, δ = 2.54 ppm) as internal standards for ^1H NMR as well as the deuteriated solvents ($CHCl_3$, δ = 77.0 ppm ; DMSO, δ = 39.6 ppm and CH_2Cl_2, 54.1 ppm) as internal standards for ^{13}C NMR (*, $^\#$ = interchangeable assignments). Chemical shifts (δ) were reported in ppm units, downfield either from TMS (s, d, t, q, m, dd, td, br s for singlet, doublet, triplet, quadruplet, multiplet, doublet of doublet, triplet of doublet and broad respectively) and coupling constants (J) were given in hertz (Hz). Multiplicity's for ^{13}C NMR were obtained using DEPT spectroscopy. Elemental analysis, performed by the "Service Central de Microanalyses du CNRS", 91190 Gif-sur-Yvette, France, were within 0.3 % or the theoretical values calculated for C, H, N, O and Cl. Mass spectra (MS) were obtained on a AEI MS-50 spectrometer for the electronic impact (IE) and on a NERMAG R10-10-C by direct introduction for the chemical ionization (DCI/NH_4^+). For some products obtained with a low yield (< 10 %), only ^1H NMR and/or MS spectra were recorded.

CAUTIONS : Because of the strong allergic effects on the skin of the chloro-nitropyridinone derivative **2** and chloro-nitroquinolone **3**, their manipulation should be carried out in a well ventilated hood and the use of gloves is strongly recommanded.

Since dimethyl sulfide is very toxic and very irritating for eyes, this reagent must be used very cautiously and with an appropriate respirator.

4,5-Dimethyl-3-nitropyridin-2(*1H*)-one (6) : Methylmagnesium iodide (1.78 M in ether ; 0.30 ml ; 0.53 mmol) was added dropwise to a solution of 4-chloro-3-nitro-5-methylpyridin-2(*1H*)-one[2] (**2**) (100 mg ; 0.53 mmol) in THF (10 ml) cooled at -78°C. The mixture was stirred at -78°C under a nitrogen atmosphere for a 15 min. period. Two other eq of methylmagnesium iodide (1.78 M in ether ; 0.60 ml ; 1.06 mmol) were added and the solution was stirred at room temperature during 18 h. The mixture was poured in 15 ml of a saturated aqueous solution of ammonium chloride. The aqueous layer was extracted with 3 x 10 ml of chloroform. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using cyclohexane:ethyl acetate = 1:1 to 0:1 as eluant giving the unstable product **7** (9.0 mg ; 8 %) and the product **6** (7.0 mg ; 8 %) as a yellow solid. Rf = 0.28 (dichloromethane:ethanol = 8:2) ; ^{1}H NMR ($CDCl_3$) δ : 2.09 (s, 3H, CH_3-5), 3.09 (s, 3H, CH_3-4), 6.68 (s, 1H, H-6).

4-Chloro-5,6-dimethyl-3-nitro-1,6-dihydropyridin-2(*1H*)-one (7) : The reaction was performed as above using 2.5 eq of methyllithium (1.6 M in ether) and 4-chloro-3-nitro-5-methylpyridin-2(*1H*)-one[2] (**2**) (100 mg ; 0.53 mmol). After usual treatment, the residue was quickly purified by column chromatography using cyclohexane:ethyl acetate = 1:1 as eluant giving the product **7** (22 mg ; 25 %) which is unstable in solution. Rf = 0.53 (dichloromethane:ethanol = 95:5) ; ^{1}H NMR ($CDCl_3$) δ : 1.45 (d, 3H, J = 6.7 Hz, CH_3-6), 2.04 (s, 3H, CH_3-5), 4.14 (qd, 1H, J_1 = 6.5 Hz, J_2 = 1.0 Hz, H-6), 6.44 (br s, 1H, NH), 15.16 (s, 1H, OH).

4-Chloro-5,6-dimethyl-3-nitropyridin-2 (*1H*)-one (8) : The reaction was performed as above using 2.5 eq of methyllithium (1.6 M in ether) and 4-chloro-3-nitro-5-methylpyridin-2(*1H*)-one[2] (**2**) (100 mg ; 0.53 mmol). After usual treatment, the residue was quickly purified by column chromatography using cyclohexane:ethyl acetate = 1:1 as eluant giving the product **7** (23.0 mg). Then manganese oxide (97 mg ; 1.12 mmol) was added to a solution of **7** (23 mg ; 0.11 mmol) in 20 ml of dichloromethane. The mixture was stirred at room temperature under a nitrogen atmosphere during 48 h. The catalyst was filtered off on celite and the solvent was evaporated under reduced pressure to give **8** (3 mg ; 9 %). Rf = 0.24 (cyclohexane:ethyl acetate = 1:1) ; MS (IE) : 202 [M].

4,4-Dimethyl-3-nitro-3,4-dihydroquinolin-2(*1H*)-one (9) : Starting from 4-chloro-3-nitroquinolin-2(*1H*)-one[1] (**3**) (100 mg ; 0.44 mmol) and methyllithium (1.6 M in ether ; 0.98 ml ; 1.56 mmol), the reaction was performed as above (for **7**). After treatment, the residue was purified by column chromatography using dichloromethane:ethanol = 1:0 to 95:5 as eluant giving the product **9** (30 mg ; 31 %) as an orange solid. m.p. 136-137°C ; Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99 ; H, 5.49 ; Found : C, 60.49 ; H, 5.74 ; Rf = 0.42 (hexane:ethyl acetate = 1:1) ; MS (IE) : 220 [M] ; 174 [M-NO_2] ; ^{1}H NMR ($CDCl_3$) δ : 1.75 (s, 3H, CH_3-4*), 1.85 (s, 3H, CH_3-4*), 5.45 (s, 1H, H-3), 7.17-7.27 (m, 1H, H-6#), 7.41-7.53 (m, 1H, H-7#), 7.55-7.59 (m, 2H, H-5 and H-8), 9.70 (s, 1H, NH).

4-Methyl-3-nitroquinolin-2(*1H*)-one (10) : A mixture of 255 mg (1.78 mmol) of anhydrous copper[(1)] bromide, anhydrous THF (5 ml) and 2.0 ml of ethereal methylmagnesium iodide (1.78 M ; 3.56 mmol) was stirred under a nitrogen atmosphere at -78°C for 20 min. 4-Chloro-3-nitroquinolin-2(*1H*)-one[1] (**3**) (100 mg ; 0.44 mmol), dissolved in THF (5 ml) was added dropwise and the reaction mixture was stirred for 1 h at -78°C, 1.5 h at 0°C and then 16 h at room temperature. The mixture was poured in 20 ml of a saturated aqueous solution of ammonium chloride. The aqueous layer was extracted with 3 x 50 ml of chloroform. The combined organic layers were washed with 20 ml of water and 20 ml of brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using cyclohexane:ethyl acetate = 95:5 to 1:1 as eluant giving the product **10** (6.0 mg ; 6 %) as a white solid and the starting material **3** (15.0 mg ; 15 %). **10** : Rf = 0.37 (cyclohexane:ethyl acetate = 1:1) ; ^{1}H NMR ($CDCl_3$) δ : 3.27 (s, 3H, CH_3-4), 7.25-7.30 (m, 1H, H-6*), 7.30-7.34 (m, 1H, H-7*), 7.80-7.87 (m, 2H, H-5 and H-8).

4,4-Dibutyl-3-nitro-3,4-dihydroquinolin-2(*1H*)-one (11) : Starting from 4-chloro-3-nitroquinolin-2(*1H*)-one[1] (**3**) (100 mg ; 0.44 mmol) and *n*-butyllithium (1.6 M solution in hexane ; 0.98 ml ; 1.56 mmol), the reaction was performed in THF at -78°C as above (for **6**). After treatment, the residue was purified by column chromatography using dichloromethane as eluant giving the product **11** (46 mg ; 34 %) as a pale yellow solid. m.p. 130-132°C ; Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08 ; H, 7.95 ; N, 9.20 ; Found : C, 66.92 ; H, 7.75 ; N, 8.91 ; Rf = 0.61 (dichloromethane:ethanol = 95:5) ; MS (IE) : 304 [M] ; 201 [M-NO_2-butyl] ; 189 [M-2 *n*-C_4H_9-H] ; ^{1}H NMR (DMSO-d_6) δ : 0.80-2.13 (m, 18H, 2 *n*-C_4H_9), 5.90 (s, 1H, H-3), 7.00 (d, J = 7.6 Hz, 1H, H-6*), 7.10 (t, J = 7.6 Hz, 1H, H-7*), 7.27 (m, 2H, H-5 and H-8), 10.91 (s, 1H, NH).

Diethyl-(5-methyl-3-nitropyridin-2(*1H*)-on-4-yl)malonate (12) : Dimethylformamide was dried on 4 Å molecular sieves. The starting material **2** was dried in the presence of phosphorus pentoxide under vacuum at room temperature. To a solution of freshly distilled diethyl malonate (0.48 ml ; 3.18 mmol) in dry THF (5 ml) was added sodium hydride (60 % dispersion in mineral oil) (127 mg ; 3.18 mmol). The mixture was stirred at room temperature for a 30 min. period. 4-Chloro-5-methyl-3-nitropyridin-2(*1H*)-one[2] (**2**) (100 mg ; 0.53 mmol), dissolved in 10 ml of dry dimethylformamide, was added dropwise. Stirring was pursued under a nitrogen atmosphere at 80°C for 5 h and further at 40°C for 48 h. After cooling, the organic layer was neutralized by addition of a 10 % aqueous solution of acetic acid and evaporated under reduced pressure. The residue was taken up in 10 ml of ethyl acetate and washed with 10 ml of water. The aqueous layer was extracted with 10 ml of ethyl acetate. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using dichloromethane:ethanol = 1:0 to 98:2 as eluant giving the starting material **2** (61 mg ; 61 %) and the product **12** (10 mg ; 6 %) as a yellow solid. Rf = 0.54 (dichloromethane:ethyl acetate:ethanol = 1:1:0.1) ; ^{1}H NMR ($CDCl_3$) δ : 1.29 (t, 6H, J = 7.0 Hz, 2 CH_2CH_3), 2.14 (s, 3H, CH_3-5), 4.26 (q, 4H, J = 7.2 Hz, 2 CH_2CH_3), 4.65 (s, 1H, CH-4), 7.41 (s, 1H, H-6), 13.30 (br s, 1H, NH).

Diethyl-(3-nitroquinolin-2(*1H*)-on-4-yl)malonate (13) : Starting from diethyl malonate (0.50 ml ; 3.30 mmol), 60 % sodium hydride (132 mg ; 3.30 mmol) and 4-chloro-3-nitroquinolin-2(*1H*)-one[1] (**3**) (100 mg ; 0.44 mmol), the reaction was performed as above (for **12**). The solvents were evaporated under reduced pressure and water (10 ml) was added. The aqueous layer was neutralized by addition of a saturated aqueous solution of ammonium chloride and extracted

with 3 x 10 ml of ethyl acetate. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using dichloromethane:ethanol = 1:0 to 95:5 as eluant giving the product **13** (58 mg ; 37.5 %) as pale yellow crystals (after recrystallisation from ethanol). m.p. 159-160°C ; Anal. Calcd for $C_{16}H_{16}N_2O_7$: C, 55.17 ; H, 4.63 ; N, 8.04 ; O, 32.15 ; Found : C, 55.21 ; H, 4.51 ; N, 7.99 ; O, 32.42 ; Rf = 0.41 (dichloromethane:ethanol = 95:5) ; ^{1}H NMR ($CDCl_3$) δ : 1.21 (t, 6H, J = 7.2 Hz, 2 CH_3), 4.24 (q, 4H, J = 7.1 Hz, 2 CH_2), 4.90 (s, 1H, CH-4), 7.31 (td, 1H, J_1 = 7.0 Hz, J_2 = 1.2 Hz, H-7'*), 7.50 (dd, 1H, J_1 = 7.4 Hz, J_2 = 0.9 Hz, H-6'#), 7.64 (td, 1H, J_1 = 7.0 Hz, J_2 = 1.0 Hz, H-8'*), 7.86 (dd, 1H, J_1 = 7.5 Hz, J_2 = 0.8 Hz, H-9'#), 13.01 (br s, 1H, NH).

3-*tert*-Butoxycarbonylaminopyridin-2(*1H*)-one (16) : The mixture of di-*tert*-butyl dicarbonate (2.75 ml ; 12.0 mmol) and triethylamine (1.67 ml ; 12.0 mmol) was added to a suspension of **15**[8] (1.20 g ; 10.9 mmol) in 50 ml of dichloromethane. The mixture was stirred at room temperature for 1 h and refluxed during 30 min.. Triethylamine (1.67 ml ; 12.0 mmol) was still added and the mixture was refluxed during 30 min. Stirring at room temperature was pursued 12 h further. The organic layer was washed with 50 ml of water and 50 ml of brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using dichloromethane:ethanol:triethylamine = 1:0:0 to 78:15:5 as eluant giving the product **16** (0.58 g ; 25 %) as a green-blue solid and starting material **15** (0.57 g ; 47 %). **16** : m.p. 148-149°C ; Anal. Calcd for $C_{10}H_{14}N_2O_3$: C, 57.13 ; H, 6.71 ; N, 13.33 ; O, 22.83 ; Found : C, 56.81 ; H, 6.41 ; N, 13.21 ; O, 23.05 ; Rf = 0.49 (dichloromethane:ethanol = 95:5) ; ^{1}H NMR (DMSO-d_6) δ : 1.49 (s, 9H, $COOC(CH_3)_3$), 6.25 (t, 1H, J = 7.0 Hz, H-5), 7.08 (d, 1H, J = 7.1 Hz, H-4), 7.72 (s, 1H, NH-3), 7.82 (d, 1H, J = 7.2 Hz, H-6), 11.90 (br s, 1H, NH-1).

3-Pivaloylaminopyridin-2(*1H*)-one (17) : Triethylamine (0.70 ml ; 4.99 mmol) was added to a solution of **15**[8] (500 mg ; 4.54 mmol) in 50 ml of dichloromethane. The mixture was cooled at 0°C and 0.61 ml of trimethylacetyl chloride (4.99 mmol) was added dropwise. The solution was stirred at room temperature for a 3 h period and washed with 20 ml of water. The aqueous layer was extracted with 3 x 20 ml of dichloromethane. The combined organic layers were washed with 20 ml of brine, dried over magnesium sulfate and concentrated under reduced pressure. The resulting solid was washed with cyclohexane, filtrated and dried giving the product **17** (715 mg ; 81 %) as a white solid. m.p. 180-181°C ; Anal. Calcd for $C_{10}H_{14}N_2O_3$: C, 61.84 ; H, 7.27 ; O, 16.47 ; Found : C, 62.19 ; H, 7.52 ; O, 16.09 ; Rf = 0.21 (dichloromethane:ethanol = 95:5) ; ^{1}H NMR (DMSO-d_6) δ : 1.23 (s, 9H, $COC(CH_3)_3$), 6.27 (t, 1H, J = 6.6 Hz, H-5), 7.13 (dd, 1H, J_1= 1.1 Hz, J_2 = 6.3 Hz, H-4*), 8.22 (dd, 1H, J_1= 1.8 Hz, J_2= 7.3 Hz, H-6*), 8.65 (br s, 1H, NH-3), 12.10 (br s, 1H, NH-1).

1-*N*-Benzyl-3-pivaloylaminopyridin-2(*1H*)-one (19) : The starting material **17** was dried in the presence of phosphorus pentoxide under vacuum at room temperature during 48 h. 3-Pivaloylaminopyridin-2(*1H*)-one (**17**) (300 mg ; 1.54 mmol) and freshly distilled (on calcium hydride) TMEDA (0.82 ml ; 5.41 mmol) were added to anhydrous THF (6 ml) and the mixture was cooled at -78°C under a nitrogen atmosphere. *n*-Butyllithium (1.6 M in hexane ; 3.38 ml ; 5.41 mmol) was then slowly added. The mixture was stirred for 2 h at -10°C, cooled at -78°C and freshly distilled benzyl bromide (0.83 ml ; 6.95 mmol) was added dropwise. After 2.5 h at -10°C, the solution was allowed to reach room temperature, stirred for 12 h and water (15 ml) was then added. The aqueous layer was extracted with 3 x 40 ml of ethyl acetate. The combined organic layers were washed with 15 ml of brine, dried over magnesium sulfate and

concentrated under reduced pressure. The residue was purified by column chromatography using dichloromethane:ethanol = 1:0 to 95:5 as eluant to give the product **19** (303 mg ; 69 %) as a violet oil. Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81 ; H, 7.09 ; N, 9.85 ; O, 11.25 ; Found : C, 71.63 ; H, 6.97 ; N, 9.62 ; O, 11.29 ; Rf = 0.68 (dichloromethane:ethanol = 95:5) ; ^{1}H NMR (DMSO-d_6) δ : 1.25 (s, 9H, COC $(CH_3)_3$), 5,21 (s, 2H, CH_2), 6.39 (t, 1H, J = 7.2 Hz, H-5), 7.29-7.36 (m, 5H, C_6H_5), 7.53 (dd, 1H, J_1 = 1.6 Hz, J_2= 6.9 Hz, H-4*), 8.21 (dd, 1H, J_1= 1.5 Hz, J_2= 7.4 Hz, H-6*), 8.67 (s, 1H, NH-3).

2-Methoxy-3-nitropyridine (21) : Sodium methoxide (0.44 g ; 8.20 mmol) was slowly dissolved in 10 ml of methanol. **20** (commercial, can be pursached from Aldrich) (1.00 g ; 6.31 mmol), dissolved in 10 ml of methanol, was added dropwise. The mixture was stirred for a 8 h period at room temperature. Sodium chloride was filtrated and evaporation of the solvent under reduced pressure provided the known product **21**[15,16] in quantitative yield (1.00 g) as a yellow solid m.p. 149-150°C.

3-Amino-2-methoxypyridine (22) : 2-Methoxy-3-nitropyridine (**21**) (925 mg ; 6.0 mmol) was dissolved in 30 ml of a mixture of methanol:THF = 1:1. The catalyst (10 % palladized charcoal) (92 mg) was added and the mixture was stirred at room temperature under hydrogen atmosphere for 1 h. The catalyst was filtered off. The solvents were evaporated under reduced pressure giving the product **22** (740 mg ; 99 %) as a violet solid. m.p. 49-50°C, in agreement with the litterature[17].

4-Deutero-2-methoxy-3-pivaloylaminopyridine (24) : The starting material **23** was dried in the presence of phosphorus pentoxide under vacuum at room temperature during 24 h. 2-Methoxy-3-pivaloylaminopyridine[18] (**23**) (50 mg ; 0.24 mmol) and freshly distilled (on calcium hydride) TMEDA (0.13 ml ; 0.84 mmol) were added to anhydrous THF (1 ml) and the mixture was cooled at -78°C under a nitrogen atmosphere. *n*-Butyllithium (1.6 M in hexane ; 0.53 ml ; 0.84 mmol) was then slowly added. Dry ice bath was removed, the mixture was stirred for 2 h at -10°C and deuterium oxide (1.0 ml) and then water (2.0 ml) were added. The aqueous layer was extracted with 3 x 10 ml of ether. The combined organic layers were washed with 5 ml of brine, dried over magnesium sulfate and concentrated under reduced pressure giving the product **24** (49 mg ; 99 %) as a colourless oil. Anal. Calcd for $C_{11}H_{15}DN_2O_2$: C, 63.13 ; H, 7.22 ; Found : C, 63.18 ; H, 7.68 ; Rf = 0.29 (cyclohexane:ethyl acetate = 9:1) ; ^{1}H NMR (DMSO-d_6) δ : 1.26 (s, 9H, $COC(CH_3)_3$), 3.96 (s, 3H, CH_3O), 7.01 (d, 1H, J = 4.9 Hz, H-5), 7.94 (d, 1H, J = 5.3 Hz, H-6), 8.51 (s, 1H, NH-3).

4-Benzyl-2-methoxy-3-pivaloylaminopyridine (25) : Starting from 2-methoxy-3-pivaloylaminopyridine[18] (**23**) (500 mg ; 2.40 mmol), TMEDA (1.27 ml ; 8.40 mmol) and *n*-butyllithium (1.6 M in hexane ; 5.25 ml ; 8.40 mmol), the reaction was performed as above (for **24**). The mixture was stirred for 2 h at -10°C, cooled again at -78°C and freshly distilled benzyl bromide (1.28 ml ; 10.80 mmol) was added dropwise. After 2.5 h at -10°C, the solution was warmed to room temperature, stirred for 12 h and water (20 ml) was then added. The aqueous layer was extracted with 3 x 60 ml of ether. The combined organic layers were washed with 20 ml of brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using cyclohexane:ethyl acetate = 1:0 to 7:3 as eluant giving the product **25** (487 mg ; 68 %) as a white solid and 50 mg of starting material **23** (10 %). **25** : m.p. 110-111°C ; Anal. Calcd for $C_{18}H_{22}N_2O_2 \cdot 0.6\ H_2O$: C, 69.92 ; H, 7.56 ; N, 9.06 ; Found : C, 69.86 ; H, 7.26 ; N, 9.31 ; Rf = 0.08 (cyclohexane:ethyl acetate = 9:1) ; ^{1}H NMR (DMSO-d_6) δ : 1.25 (s, 9H, $COC(CH_3)_3$), 3.84 (s, 2H, CH_2),

3.86 (s, 3H, CH_3O), 6.72 (d, 1H, J = 5.2 Hz, H-5), 7.20-7.31 (m, 5H, C_6H_5), 7.96 (d, 1H, J = 5.2 Hz, H-6), 8.87 (s, 1H, NH-3).

3-Amino-4-benzylpyridin-2(*1H*)-one (26) : To a suspension of 4-benzyl-2-methoxy-3-pivaloylaminopyridine (**25**) (200 mg ; 0.67 mmol) in water (30 ml), 3M aqueous hydrochloric acid (15 ml) was added. The mixture was refluxed for 3.5 h. The yellow solution was neutralized by addition of concentrated aqueous ammonium hydroxide and extracted with 3 x 80 ml of ethyl acetate. The combined organic layers were washed with 10 ml of brine, dried over magnesium sulfate and concentrated under reduced pressure. Column chromatography using dichloromethane:ethanol = 1:0 to 95:5 as eluant gave the product **26** (94 mg ; 70 %) as a white solid. m.p. 166-167°C : Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98 ; H, 6.04 ; N, 13.99 ; O, 7.99 ; Found : C, 71.88 ; H, 6.03 ; N, 14.05 ; O, 7.72 ; Rf = 0.23 (dichloromethane:ethanol = 95:5) ; ^{1}H NMR (DMSO-d_6) δ : 3.75 (s, 2H, CH_2), 4.93 (s, 2H, NH_2), 5.86 (d, 1H, J = 6.8 Hz, H-5), 6.61 (d, 1H, J = 6.8 Hz, H-6), 7.22-7.36 (m, 5H, C_6H_5), 11.29 (br s, 1H, NH-1).

3-Cyano-5-ethyl-6-methylpyridin-2(*1H*)-one[20,21] **(29) and 3-cyano-6-propylpyridin-2(*1H*)-one**[22] **(30)** : After heating in the presence of calcium hydride for 1 h, piperidine was distilled. The aqueous solution of piperidinium acetate was prepared by dropwise addition at 0°C of glacial acetic acid (39.00 ml ; 0.68 mol) to piperidine (67.40 ml ; 0.68 mol) in 90 ml of water. 2-Ethyl-3-oxobutanal sodium salt[20,21] (**28**) (123.72 g ; 0.91 mol), cyanoacetamide (76.40 g ; 0.91 mol) and water (2100 ml) were then added. The resulting mixture was refluxed for 16 h, cooled to 0°C and glacial acetic acid (150 ml) was added cautiously. The precipitate was collected by filtration, washed with 800 ml of water and dried in the presence of calcium chloride under vacuum at 50°C to give the product[20,21] **29** (90.30 g ; 61 %) as a pale yellow solid m.p. 243-244°C. The aqueous layer was extracted with 3 x 600 ml of dichloromethane. The combined organic layers were concentrated under reduced pressure. The residue was purified by column chromatography using dichloromethane:ethanol = 1:0 to 9:1 as eluant giving the product[22] **30** (2.20 g ; 1.5 %) as a pale yellow solid m.p. 150-151°C.

5-Ethyl-6-methylpyridin-2 (*1H*)-one (31) : 3-Cyano-5-ethyl-6-methylpyridin-2(*1H*)-one[20,21] (**29**) (10.0 g ; 61.66 mmol) was dissolved in 440 ml of 6N aqueous hydrochloric acid. The mixture was refluxed under stirring during 48 h. After cooling at 0°C, the aqueous layer was basified by addition of 200 ml of a concentrated aqueous ammonium hydroxide solution and extracted with 3 x 350 ml of dichloromethane. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure giving the product **31** (7.5 g ; 88 %) as a white solid. m.p. 155-156°C ; Anal. Calcd for $C_8H_{11}NO$: C, 70.04 ; H, 8.08 ; N, 10.21 ; O, 11.66 ; Found : C, 69.75 ; H, 7.89 ; N, 9.99 ; O, 11.57 ; Rf = 0.75 (dichloromethane:ethanol = 95:5) ; ^{1}H NMR ($CDCl_3$) δ : 1.09 (t, 3H, J = 7.5 Hz, CH_3CH_2), 2.32 (s, 3H, CH_3-6), 2.38 (q, 2H, J = 7.6 Hz, CH_3CH_2), 6.39 (d, 1H, J = 9.1 Hz, H-3*), 7.28 (d, 1H, J = 9.2 Hz, H-4*), 13.25 (br s, 1H, NH-1).

5-Ethyl-6-methyl-3-nitropyridin-2(*1H*)-one (32) : 5-Ethyl-6-methylpyridin-2(*1H*)-one (**31**) (6.0 g ; 44.0 mmol) was dissolved in concentrated sulfuric acid (58.6 ml ; 1093.0 mmol). The mixture was cooled at 0°C and nitric acid (d = 1.52 ; 3.5 ml ; 88.0 mmol) was cautiously added dropwise. The colour of the solution changed from red to yellow-orange. The resulting mixture was stirred at 0°C for 1.5 h, then poured in 400 ml of ice water and extracted with 3 x 1.0

l of dichloromethane. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure giving the product[21] **32** (6.4 g ; 81 %) as a yellow solid, m.p. 247-248°C.

5-Ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (36) : 3-Amino-5-ethyl-2-methoxy-6-methylpyridine[23] (**35**) (3.68 g ; 22.14 mmol) was dissolved in the mixture of dichloromethane (260 ml) and triethylamine (3.39 ml ; 24.35 mmol). The mixture was cooled at 0°C and 3.00 ml of trimethylacetyl chloride (24.35 mmol) was added dropwise. The solution was stirred at 0°C for 15 min. and then washed with 100 ml of water. The aqueous layer was extracted with 3 x 200 ml of dichloromethane. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using dichloromethane as eluant to provide the product **36** (5.31 g ; 96 %) as a colourless oil. Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17 ; H, 8.86 ; N, 11.19 ; O, 12.78 ; Found : C, 67.11 ; H, 8.56 ; N, 10.91 ; O, 12.67 ; Rf = 0.88 (dichloromethane:ethanol = 95:5) ; ^{1}H NMR ($CDCl_3$) δ : 1.16 (t, 3H, J = 7.4 Hz, CH_3CH_2), 1.28 (s, 9H, $COC(CH_3)_3$), 2.32 (s, 3H, CH_3-6), 2.49 (q, 2H, J = 7.5 Hz, CH_3CH_2), 3.93 (s, 3H, CH_3O), 7.83 (br s, 1H, NH-3), 8.39 (s, 1H, H-4) ; ^{13}C NMR (CH_2Cl_2) δ : 15.2 (CH_3CH_2), 21.5 (CH_3-6), 26.0 (CH_3CH_2), 28.1 ($COC(CH_3)_3$), 40.5 ($COC(CH_3)_3$), 54.1 (CH_3O), 121.3 (C-5), 127.8 (CH-4), 130.6 (C-3), 146.8 (C-6), 151.3 (C-2), 177.4 ($COC(CH_3)_3$).

5-Ethyl-6-[2'-(5-ethyl-2-methoxy-3-nitropyridin-6-yl)ethyl]-2-methoxy-3-nitropyridine (37) : Sodium methoxide (4.04 g ; 75.0 mmol) was slowly dissolved in 60 ml of methanol at 0°C. 2-Chloro-5-ethyl-6-methyl-3-nitropyridine[23] (**33**) (5.00 g ; 25.0 mmol), dissolved in 65 ml of methanol, was added dropwise. The mixture was stirred at room temperature for a 144 h period and concentrated under reduced pressure. Water (300 ml) was added. The aqueous layer was extracted with 3 x 250 ml of ethyl acetate. The combined organic layers were washed with 100 ml of brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using cyclohexane:ethyl acetate = 1:0 to 1:1 as eluant giving the product[23] **34** (1.57 g ; 32 %) as an orange solid and the dimer **37** (2.71 g ; 56 %) as an orange solid. Rf = 0.33 (cyclohexane:ethyl acetate = 9:1) ; MS (IC) : 391 [M + H] ; 375 [M + H - O] ; 359 [M + H - 2 O] ; 197 [M/2 + H] ; ^{1}H NMR ($CDCl_3$) δ : 1.32 (t, 6H, J = 7.5 Hz, 2 CH_3CH_2), 2.85 (q, 4H, J = 7.5 Hz, 2 CH_3CH_2), 3.94 (s, 4H, 2 CH_2), 4.18 (s, 6H, 2 CH_3O), 8.08 (s, 1H, H-4*), 8.18 (s, 1H, H-4'*).

5-Ethyl-6-[2'-(5-ethyl-2-methoxy-3-pivaloylaminopyridin-6-yl)ethyl]-2-methoxy-3-pivaloylaminopyridine (40) : The preceding crude compound (9.40 g, without purification by column chromatography) was dissolved in 460 ml of a mixture of methanol:THF = 1:1. The catalyst (10 % palladized charcoal) (0.94 g) was added and the mixture was stirred at room temperature under hydrogen atmosphere for 2.5 h. The catalyst was filtered off and the solvent evaporated under reduced pressure. The resulting residue (7.40 g) was dissolved in dichloromethane (570 ml) and triethylamine (6.81 ml ; 48.8 mmol). The mixture was cooled at 0°C and trimethylacetyl chloride (6.00 ml ; 48.8 mmol) was added dropwise. The solution was stirred at 0°C for 15 min and then washed with 200 ml of water. The aqueous layer was extracted with 3 x 400 ml of dichloromethane. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using dichloromethane:ethanol = 1:0 to 99:1 giving **36** (3.22 g ; 29 %) as a colourless oil and **40** (5.50 g ; 50 %) as a yellow solid. **40** : m.p. 170-170.5°C ; Anal. Calcd for $C_{28}H_{42}N_4O_4$: C, 67.44 ; H, 8.49 ; N, 11.24 ; O, 12.83 ; Found : C, 67.14 ; H, 8.59 ; N, 11.09 ; O, 12.98 ; Rf = 0.11 (dichloromethane) ; MS (IC) : 499 [M + H] ; 251 [M/2 + 2H] ; ^{1}H NMR ($CDCl_3$) δ : 1.16 (t, 6H, J = 7.4 Hz, 2 CH_3CH_2), 1.30 (s, 18H, 2 $COC(CH_3)_3$), 2.57 (q, 4H, J = 7.5 Hz, 2

CH_3CH_2), 3.06 (s, 4H, 2 CH_2), 3.94 (s, 6H, 2 CH_3O), 7.86 (s, 2H, H-4 and 4'), 8.41 (s, 2H, 2 NH-3) ; ^{13}C NMR (CH_2Cl_2) δ : 15.9 (CH_3CH_2), 25.6 (CH_3CH_2), 28.1 ($COC(CH_3)_3$), 33.4 (CH_2), 40.5 ($COC(CH_3)_3$), 54.1 (CH_3O), 121.2 (C-5), 128.0 (CH-4), 130.5 (C-3), 150.0 (C-6), 151.5 (C-2), 177.4 ($COC(CH_3)_3$).

3-Amino-6-[2'-(3-amino-5-ethyl-pyridin-2(*1H*)-on-6-yl)ethyl]-5-ethylpyridin-2(*1H*)-one (41) : 3M aqueous hydrochloric acid (28 ml) and glacial acetic acid (20 ml) were added to a suspension of 5-ethyl-6-[2'-(5-ethyl-2-methoxy-3-pivaloylaminopyridin-6-yl)ethyl]-2-methoxy-3-pivaloylaminopyridine (**40**) (300 mg ; 0.60 mmol) in 56 ml of water. The mixture was refluxed for 17 h. The solution was basified at 0°C by addition of concentrated aqueous ammonium hydroxide. The solid was filtered off giving **41** (170 mg ; 93 %) of a beige solid. m.p. 300°C ; Anal. Calcd for $C_{16}H_{22}N_4O_2 \cdot 0.65\ H_2O$: C, 61.19 ; H, 7.48 ; N, 17.84 ; Found : C, 60.95 ; H, 7.18 ; N, 17.63 : Rf = 0.14 (dichloromethane:ethanol = 95:5) ; ^1H NMR (DMSO-d_6) δ : 0.98 (t, 6H, J = 7.3 Hz, 2 CH_3CH_2), 2.20 (q, 4H, J = 7.5 Hz, 2 CH_3CH_2), 4.84 (s, 4H, 2 NH_2), 6.32 (s, 2H, H-4 and 4'), 11.02 (br s, 2H, NH-1 and 1'). The 2 CH_2 signals were overlapped by DMSO signal.

4-Benzyl-5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (42) : The starting material **36** and copper iodide (Cu^II) were dried in the presence of phosphorus pentoxide under vacuum respectively at room temperature and at 60°C during 24 h. 5-Ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (**36**) (200 mg ; 0.80 mmol) and freshly distilled (on calcium hydride) TMEDA (0.42 ml ; 2.80 mmol) were added to dry THF (10 ml) and the mixture was cooled at -78°C under a nitrogen atmosphere. *n*-Butyllithium (1.6 M in hexane ; 1.75 ml ; 2.80 mmol) was added dropwise. Dry ice bath was removed and the mixture was stirred for 1 h at 0°C. An orange-yellow precipitate was observed. In another hand, the Cu^II:dimethyl sulfide complex was prepared at -78°C under a nitrogen atmosphere by addition of dimethyl sulfide (2.64 ml ; 35.95 mmol) to a suspension of copper iodide (532 mg ; 2.80 mmol) in anhydrous THF (20 ml). The Cu^II:dimethyl sulfide complex was then added dropwise to the mixture at -78°C. The grey mixture was stirred at 0°C for a 30 min. period and cooled again at -78°C to allow the addition of benzyl bromide (0.43 ml ; 3.60 mmol). The resulting mixture was stirred at 0°C for 2 h and at room temperature for 12 h. Water (4 ml) and 28 % aqueous ammonium hydroxide (4 ml) were added. The blue aqueous layer was extracted with 3 x 20 ml of ether. The combined organic layers were washed with 10 ml of brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using cyclohexane:ethyl acetate = 1:0 to 8:2 as eluant to give the product **42** (143 mg ; 53 %) as a white solid and 69 mg (34.5 %) of starting material **36**. **42** : m.p. 186-187°C ; Anal. Calcd for $C_{21}H_{28}N_2O_2 \cdot 0.1\ H_2O$: C, 73.73 ; H, 8.25 ; N, 8.19 ; O, 9.83 ; Found : C, 73.51 ; H, 8.01 ; N, 7.93 ; O, 9.84 ; Rf = 0.27 (cyclohexane:ethyl acetate = 8:2) ; ^1H NMR ($CDCl_3$) δ : 1.00 (t, 3H, J = 7.5 Hz, CH_3CH_2), 1.18 (s, 9H, $COC(CH_3)_3$), 2.46 (s, 3H, CH_3-6), 2.56 (q, 2H, J = 7.5 Hz, CH_3CH_2), 3.89 (s, 3H, CH_3O), 3.99 (s, 2H, $CH_2C_6H_5$), 6.60 (br s, 1H, NH-3), 6.94-6.97 (m, 2H, C_6H_5), 7.17-7.22 (m, 3H, C_6H_5).

5-Ethyl-6-(2-phenethyl)-3-pivaloylaminopyridin-2(*1H*)-one (43) and 5-ethyl-6-methyl-3-pivaloylaminopyridin-2(*1H*)-one (45) : The starting material **36** was dried in the presence of phosphorus pentoxide under vacuum at room temperature during 24 h. 5-Ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (**36**) (200 mg ; 0.80 mmol) and freshly distilled (on calcium hydride) TMEDA (0.42 ml ; 2.80 mmol) were added to dry THF (6 ml) and the mixture was cooled to -78°C under a nitrogen atmosphere. *t*-Butyllithium (1.6 M in pentane ; 1.64 ml ; 2.80 mmol) was then slowly added. Dry ice bath was removed and the mixture was stirred for 2.75 h at -10°C. An orange precipitate was observed.

The mixture was cooled at -78°C and freshly distilled benzyl bromide (0.43 ml ; 3.60 mmol) was added dropwise. After 2 h at -10°C, the solution was warmed to room temperature and stirred for 12 h. Water (10 ml) was then added and the aqueous layer was extracted with 3 x 20 ml of ether. The combined organic layers were washed with 10 ml of brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using dichloromethane:ethanol = 1:0 to 98:2 as eluant giving 15 mg of starting material **36** (8.5 %), **44** (29 mg ; 11 %) as a yellow solid, **43** (64 mg ; 28 %) as a pale yellow solid and **45** (11 mg ; 7 %) as a yellow solid. **43** : m.p. 168-169°C ; Anal. Calcd for $C_{20}H_{26}N_2O_2$: C, 73.59 ; H, 8.03 ; N, 8.58 ; O, 9.80 ; Found : C, 73.58 ; H, 8.12 ; N, 8.25 ; O, 10.03 ; Rf = 0.56 (dichloromethane:ethanol = 99:1) ; ^{1}H NMR ($CDCl_3$) δ : 1.10 (t, 3H, J = 7.4 Hz, CH_3CH_2), 1.28 (s, 9H, $COC(CH_3)_3$), 2.36 (q, 2H, J = 7.6 Hz, CH_3CH_2), 2.86-2.96 (m, 4H, CH_2CH_2), 7.17-7.25 (m, 5H, C_6H_5), 8.42 (s, 1H, H-4), 8.56 (br s, 1H, NH-3), 12.93 (br s, 1H, NH-1) ; **45** : m.p. 200-201°C ; Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07 ; H, 8.53 ; O, 13.54 ; Found : C, 66.22 ; H, 8.31 ; O, 13.49 ; Rf = 0.40 (dichloromethane:ethanol = 99:1) ; ^{1}H NMR ($CDCl_3$) δ : 1.11 (t, 3H, J = 7.6 Hz, CH_3CH_2), 1.31 (s, 9H, $COC(CH_3)_3$), 2.27 (s, 3H, CH_3-6), 2.39 (q, 2H, J = 7.5 Hz, CH_3CH_2), 8.39 (s, 1H, H-4), 8.54 (br s, 1H, NH-3), 12.56 (br s, 1H, NH-1).

4-Bromo-5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (44) : The starting material **36** was dried in the presence of phosphorus pentoxide under vacuum at room temperature during 24 h. 5-Ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (**36**) (400 mg ; 1.60 mmol) and freshly distilled (on calcium hydride) TMEDA (0.84 ml ; 5.60 mmol) were added to dry THF (12 ml) and the mixture was cooled at -78°C under a nitrogen atmosphere. *n*-Butyllithium (1.6 M in hexane ; 3.50 ml ; 5.60 mmol) was added dropwise. Dry ice bath was removed and the mixture was stirred for 1 h at 0°C. An orange-yellow precipitate was observed. The mixture was cooled at -78°C to allow the addition of benzyl bromide (0.86 ml ; 7.19 mmol). The pale yellow mixture was stirred at 0°C for 2 h and at room temperature for 12 h. Water (20 ml) was added and the blue aqueous layer was extracted with 3 x 40 ml of ether. The combined organic layers were washed with 20 ml of brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using cyclohexane:ethyl acetate = 1:0 to 8:2 as eluant giving a mixture of **42** and **44** (6 : 4) (303 mg ; 56 %) and 97 mg (24 %) of starting material **36**. **44** : Rf = 0.27 (cyclohexane:ethyl acetate = 8:2) ; MS (IE) : 330/328 [M] ; 249 [M - Br] ; 244 [M - Piv] ; ^{1}H NMR ($CDCl_3$) δ : 1.10 (t, 3H, J = 7.4 Hz, CH_3CH_2), 1.32 (s, 9H, $COC(CH_3)_3$), 2.46 (s, 3H, CH_3-6), 2.74 (q, 2H, J = 7.5 Hz, CH_3CH_2), 3.88 (s, 3H, CH_3O), 6.89 (br s, 1H, NH-3). These ^{1}H NMR assignments were obtained from the pure **44** compound (obtained from **36** and *t*-BuLi, see Scheme 5) spectra.

3-Amino-5-ethyl-6-(2-phenethyl)-pyridin-2(*1H*)-one (46) : 3M aqueous hydrochloric acid (6 ml) was added to a suspension of 5-ethyl-6-(2-phenethyl)-3-pivaloylaminopyridin-2(*1H*)-one (**43**) (40 mg ; 0.12 mmol) in water (12 ml) and glacial acetic acid (5 ml). The mixture was refluxed for 1 h and then stirred at room temperature for 16 h. The solution was basified by addition of concentrated aqueous ammonium hydroxide and extracted with 3 x 15 ml of ethyl acetate. The combined organic layers were washed with 8 ml of brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography using dichloromethane:ethanol = 1:0 to 95:5 as eluant giving the product **46** (22 mg ; 74 %) as an orange light solid. m.p. 160-161°C ; Rf = 0.62 (dichloromethane:ethanol = 95:5) ; ^{1}H NMR ($CDCl_3$) δ : 0.90-1.10 (m, 3H, CH_3CH_2), 2.10-2.59 (m, 4H, 2 CH_2), 2.84 (q, 2H, J = 8.3 Hz, CH_3CH_2), 3.90 (br s, 2H, NH_2), 6.53 (s, 1H, H-4), 7.11-7.27 (m, 5H, C_6H_5).

4-Deutero-5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (48) : Starting from 5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (**36**) (200 mg ; 0.80 mmol), TMEDA (0.42 ml ; 2.80 mmol) and *n*-butyllithium (1.6 M in hexane ; 1.75 ml ; 2.80 mmol), the reaction was performed as above (for **44**). The mixture was stirred for 1 h at 0°C. 1.0 ml of deuterium oxide and then 3.0 ml of water were added. The aqueous layer was extracted with 3 x 10 ml of ether. The combined organic layers were washed with 4 ml of brine, dried over magnesium sulfate and concentrated under reduced pressure to give the product **48** in quantitative yield (200 mg) as a colourless oil. Anal. Calcd for $C_{14}H_{21}DN_2O_2$: C, 66.90 ; H, 8.42 ; Found : C, 67.11 ; H, 8.88 ; Rf = 0.88 (dichloromethane:ethanol = 95:5) ; ^{1}H NMR ($CDCl_3$) δ : 1.15 (t, 3H, J = 7.7 Hz, CH_3CH_2), 1.29 (s, 9H, $COC(CH_3)_3$), 2.35 (s, 3H, CH_3-6), 2.52 (q, 2H, J = 7.5 Hz, CH_3CH_2), 3.96 (s, 3H, CH_3O), 7.85 (br s, 1H, NH-3).

3-Amino-4-benzyl-5-ethyl-6-methylpyridin-2(*1H*)-one (49) : Starting from 4-benzyl-5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (**42**) (200 mg ; 0.59 mmol) and 3M aqueous hydrochloric acid (13 ml), the reaction was performed as above (for **26**) to give the product **49** (135 mg ; 95 %) as violet crystals (after recrystallisation from ethanol). m.p. 223-224°C ; Anal. Calcd for $C_{15}H_{18}N_2O$. 0.1 H_2O : C, 73.80 ; H, 7.51 ; N, 11.48 ; O, 7.21 ; Found : C, 73.78 ; H, 7.61 ; N, 11.29 ; O, 6.99 ; Rf = 0.77 (dichloromethane:ethanol = 1:1) ; ^{1}H NMR ($CDCl_3$) δ : 1.00 (t, 3H, J = 7.5 Hz, CH_3CH_2), 2.30 (s, 3H, CH_3-6), 2.41 (q, 2H, J = 7.5 Hz, CH_3CH_2), 3.86 (br s, 2H, NH_2), 3.91 (s, 2H, $CH_2C_6H_5$), 7.15-7.28 (m, 5H, C_6H_5), 11.80 (br s, 1H, NH-1).

Attempt to obtain **3-amino-4-bromo-5-ethyl-6-methylpyridin-2(*1H*)-one (50)** : Starting from a mixture (6:4) of 4-benzyl-5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (**42**) and 4-bromo-5-ethyl-2-methoxy-6-methyl-3-pivaloylaminopyridine (**43**) (200 mg ; 0.59 mmol) and 3M aqueous hydrochloric acid (13 ml), the reaction was performed as above (for **26**). The residue was purified by column chromatography using dichloromethane:ethanol = 1:0 to 95:5 as eluant giving 74 mg (52 %) of an unseparable mixture (6:4) of **49 + 50**. **50** : Rf = 0.77 (dichloromethane:ethanol = 1:1) ; ^{1}H NMR ($CDCl_3$), beside the signals of compound **49** (see above), the signals of **50** can be recorded at δ : 1.08 (t, 3H, J = 7.5 Hz, CH_3CH_2), 2.29 (s, 3H, CH_3-6), 2.58 (q, 2H, J = 7.5 Hz, CH_3CH_2), 4.42 (br s, 2H, NH_2), 12.00 (br s, 1H, NH-1).

Acknowledgments

We thank the "Agence Nationale de Recherches sur le SIDA" (ANRS) for its financial support and English speaking reviewer for advisible language corrections.

References

1. a. Bisagni, E. ; Dollé, V. ; Nguyen, C.-H. ; Legraverend, M. ; Aubertin, A.-M. ; Kirn, A. ; Andreola, M.L. ; Tarrago-Litvak, L. Fr. Demande Appl. 9509323, 30 Jul **1995** ; b. Dollé, V. ; Fan, E ; Nguyen C.H. ; Aubertin, A.-M. ; Kirn, A. ; Andreola, M.L. ; Jamieson, G. ; Tarrago-Litvak, L. ; Bisagni, E. *J. Med. Chem.* **1995**, *38*, 4679-4686.
2. Nguyen, C.H. ; Bisagni, E. ; Lavelle, F. ; Bissery, M.-C. ; Huel, C. *Anti-Cancer Drug Des.* **1992**, *7*, 219-233.
3. Bell, T.W. ; Hu, L.-Y. ; Patel, S.V. *J. Org. Chem.* **1987**, *52*, 3847-3850.

4. Leffek, K.T. ; Matinopoulos-Scordou, A.E. *Can. J. Chem.* **1977**, *55*, 2656-2663.
5. Scobie, M. ; Tennant, G. *J. Chem. Soc., Chem. Commun.* **1993**, 1756-1757.
6. Legraverend, M. ; Nguyen, C.H. ; Zerial, A. ; Bisagni, E. *Nucleosides & Nucleotides* **1986**, *5* (2), 125-134.
7. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879-933.
8. Anderson, W.K. ; Davrie, D.K. *J. Heterocycl. Chem.* **1993**, *30* (6), 1533-1536.
9. Muchowski, J.M. ; Venuti, M.C. *J. Org. Chem.* **1980**, *45*, 4798-4801.
10. Venuti, M.C. ; Stephenson, R.A. ; Alvarez, R. ; Bruno, J.J. ; Strosberg, A.M. *J. Med. Chem.* **1988**, *31*, 2136-2145.
11. a. Gangor, T. ; Marsais, F. ; Quéguiner, G. *Synthesis* **1982**, 499 ; b. Godard, A. ; Rovera, J.-C. ; Marsais, F. ; Plé, N. ; Quéguiner, G. *Tetrahedron* **1992**, *48*, n° 20, 4123-4134.
12. Turner, J.A. *J. Org. Chem.* **1983**, *48*, 3401-3408.
13. a. Bisagni, E. ; Chi Hung, N. ; Lhoste, J.M. *Tetrahedron* **1983**, *39*, n° 10, 1777-1781 ; b. Meghani, P. ; Joule, J.A. *J. Chem. Soc. Perkin Trans. I* **1988**, *1*, 1-8.
14. Gros, Ph. ; Fort, Y. ; Quéguiner, G. ; Caubère, P. *Tet. Lett.* **1995**, *36*, n° 27, 4791-4794.
15. Singh, B. ; Lesher, G.Y. ; Brundage, R.P. *Synthesis* **1991**, 894-896.
16. a. Gruber, W. *Can. J. Chem.* **1953**, *31*, 1181-1187 ; b. Ahmed, H.J. *J. Chem. Soc.* **1954**, 4516-4520.
17. Binz, A. ; Schickh, O.v. *Ber.* **1935**, *68B*, 315-324.
18. Estel, L. ; Linard, F. ; Marsais, F. ; Godard, A. ; Quéguiner, G. *J. Heterocycl. Chem.* **1989**, *26*, 105-112.
19. Marsais, F. ; Rovera, J-C. ; Turck, A. ; Godard, A. ; Quéguiner, G. *J. Chem. Soc. Perkin Trans.* **1990**, 2611-2612.
20. Hoffman, J.M. ; Wai, J.S. ; Thomas, C.M. ; Levin, R.B. ; O'Brien, J.A. ; Goldman, M.E. *J. Med. Chem.* **1982**, *35*, 3784-3791.
21. Saari, W.S. ; Hoffman, J.M. ; Wai, J.S. ; Fisher, T.E. ; Rooney, C.S. ; Smith, A.M. ; Thomas, C.M. ; Goldman, M.E. ; O'Brien, J.A. ; Nunberg, J.H. ; Quintero, J.C. ; Schleif, W.A. ; Emini, E.A. ; Stern, A.M. ; Anderson, P.S. *J. Med. Chem.* **1991**, *34*, 2922-2925.
22. Mosti, L. ; Menozzi, G. ; Scherone, P. ; Dorigo, P. ; Gaion, R.M. *Eur. J. Med. Chem. Chim. Ther.* **1989**, *24*, 517-530.
23. Hoffman, J.M. ; Smith, A.M. ; Rooney, C.S. ; Fisher, T.E. ; Wai, J.S. ; Thomas, C.M. ; Bamberger, D.L. ; Barnes J.L. ; Williams, T.M. ; Jones, J.H. ; Olson, B.D. ; O'Brien, J.A. ; Goldman, M.E. ; Nunberg, J.H. ; Quintero, J.C. ; Schleif, W.A. ; Emini, E.A. ; Anderson, P.S. *J. Med. Chem.* **1993**, *36*, 953-966.
24. Green, A.G. ; Davies, A.H. ; Horsfall, R.S. *J. Chem. Soc.* **1907**, *91*, 2076-2083.
25. House, H.O. *Org. Synth.* **1963**, *IV*, 367-368.
26. Corey, E.J. ; Naef, R. ; Hannon, F.J. *J. Am.Chem. Soc.* **1986**, *108*, 7114-7116.
27. Ellefson, C.R. *J. Org. Chem.* **1979**, *44*, n° 9, 1533-1536.
28. Sato, T. ; Kawara, T. ; Kokubu, Y. ; Fujisawa, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 945-946.
29. Casas, R. ; Cavé, C. ; d'Angelo, J. *Tet. Lett.* **1995**, *36*, n° 7, 1039-1042.

(*Received in Belgium* 28 *April* 1997; *accepted* 3 *July* 1997)