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ACYLATION OF OXAZOLO[4,5-*b*]PYRIDIN-2(3*H*)-ONES, 2-PHENYLOXAZOLO[4,5-*b*]PYRIDINES AND PYRROLO[2,3-*b*]PYRIDIN-2(2*H*)-ONES

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Abstract : Acetylation and benzoylation of oxazolo[4,5-*b*]pyridin-2(3*H*)-ones, 2-phenyloxazolo-[4,5-*b*]pyridines and pyrrolo[2,3-*b*]pyridin-2(2*H*)-ones were realised *via* reactions catalyzed with palladium. © 1997 Published by Elsevier Science Ltd.

The three main groups of analgesics on the market are the opioids such as morphine, codeine and dextropropoxyphen, the nonsteroidal anti-inflammatory agents including aspirin, ibuprofen, indomethacin and paracetamol.[1] The main objective in current pain research is to develop new, improved non opioid analgesics which are as effective as the opioids but without their side effects such as respiratory depression, physical dependency, tolerance and constipation.[2] Previous studies realised by Lesieur et al have shown that 6-benzoyl benzoxazolinone (figure 1) have high analgesic activity comparable to indomethacin.[3]

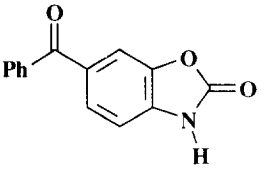

Figure 1

With regard to the bioisosteric relationships, which are very important in therapeutic chemistry, we have considered replacing the benzene ring (figure 1) by a pyridinic structure. Thereby, in connection with our studies on heterocyclic compounds with analgesical activity[4], we have investigated the acylation of oxazolo[4,5-*b*]pyridin-2(3*H*)-ones (compounds A, figure 2). In addition, we have explored the acylation of analogues which possess in the 2 position a phenyl group (compounds **B**) and also isosteric derivatives with a methylene group instead of the oxygen (compounds **C**).

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For the elaboration of these acylated structures **A**, **B** and **C**, we have applied Stille's reaction[5] and organozinc methodology[6] using palladium as catalyst.

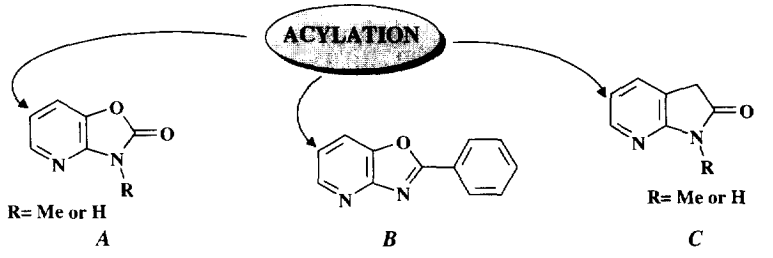
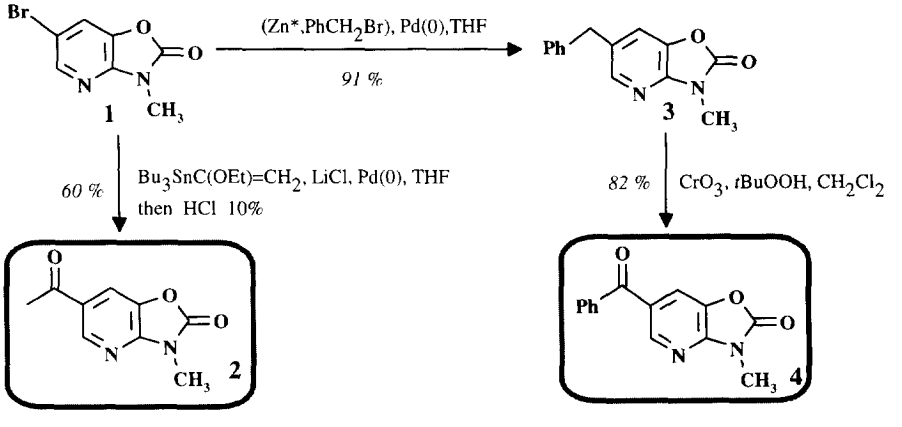


Figure 2

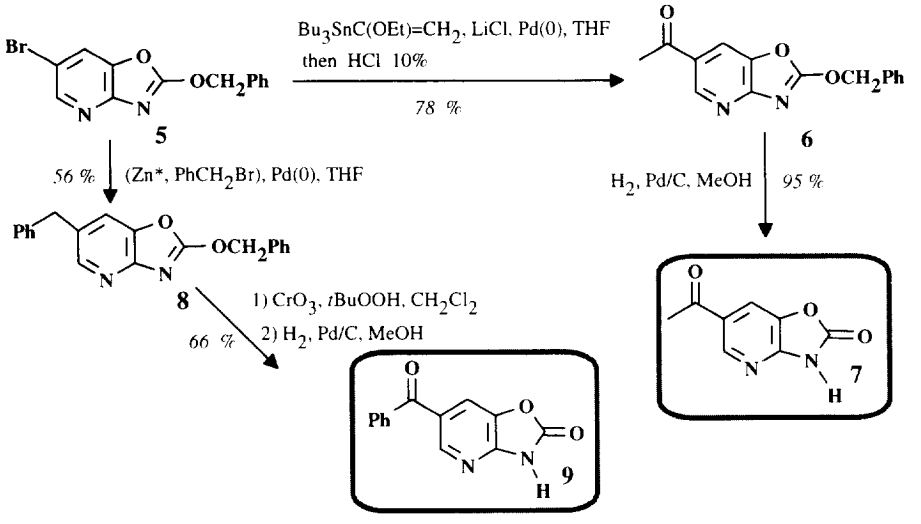
Compound **2** was obtained with a satisfactory yield starting from the brominated derivative **1**[7] using (1-ethoxyvinyl)tributyltin as reagent in terahydrofuran followed by an acid hydrolysis (scheme 1). The benzoylated derivated **4** was obtained in two steps (scheme 1). The first step involved a reaction of the organozinc halide obtained from benzyl bromide with compound **1** under palladium catalysis. The second step required an oxidation of the benzylic function using commercial aqueous 70 % *tert*-butyl hydroperoxide and catalytic amount of chromium(VI) oxide[8].

SCHEME 1



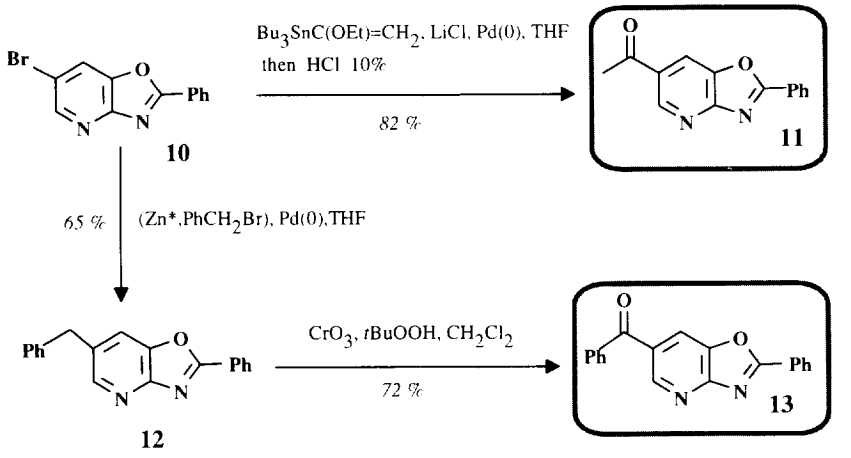
In order to prepare nitrogen unsubstituted analogs, we have used compound **5**[9] as starting derivative following the same experimental procedure as described in scheme 1. The presence of the benzyl moiety on **5** can afford, after O-debenzylation in methanol under hydrogen pressure, compounds **7** and **9** in good yields (scheme 2).

SCHEME 2



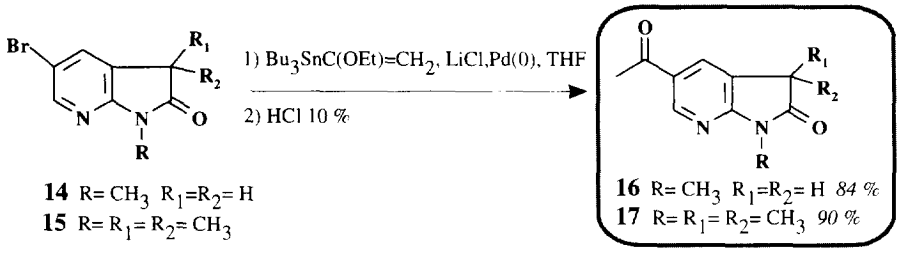
Compounds **11** and **13** respectively acetylated and benzoylated at 6 position and belonging to the family of 2-phenyloxazolo[4,5-*b*]pyridin-2(3*H*)-one were prepared according to the sequence described in previous schemes using product **10**[10] as starting material (scheme 3).

SCHEME 3



The acetylation reaction was also run on pyrrolo[2,3-*b*]pyridin-2(2*H*)-ones. According to the methodology previously described, compounds **16** and **17** were obtained in good yields starting respectively from the derivatives **14**[11] and **15**[12] (scheme 4).

SCHEME 4

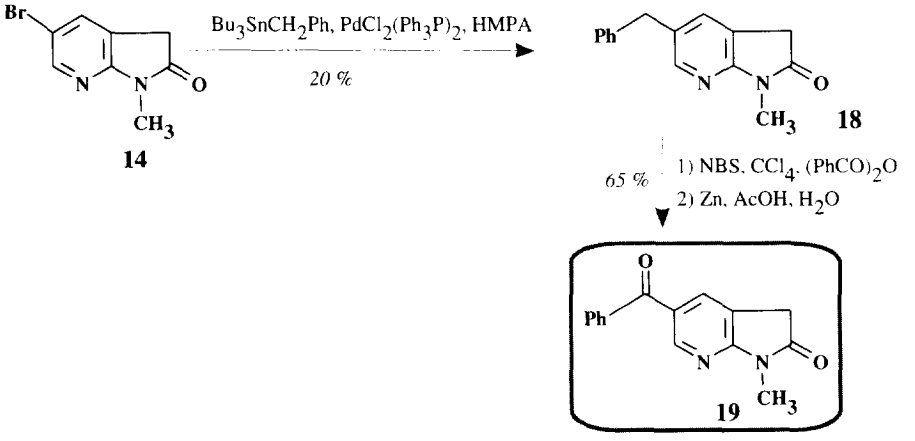


14 R= CH_3 R_1=R_2= H
15 R= R_1= R_2= CH_3

16 R= CH_3 R_1=R_2= H *84 %*
17 R= R_1= R_2= CH_3 *90 %*

With the aim of preparation of benzoylated compounds in this series of pyrrolo[2,3-*b*]pyridin-2(2*H*)-one derivatives, the organozinc reaction was applied but without success. Consequently to solve this problem, the benzyl group was introduced *via* the benzyltributyltin reagent, prepared according to a modified literature procedure[10]. This reaction lead to compound **18** in 20% yield but predominantly to degradation products. Amide **18** was submitted, after purification, to a bromination reaction with *N*-bromosuccinimide followed by a treatment using zinc in acetic acid and water. This sequence furnished compound **19** benzoylated at the 5-position with a yield of 65% (scheme 5).

SCHEME 5



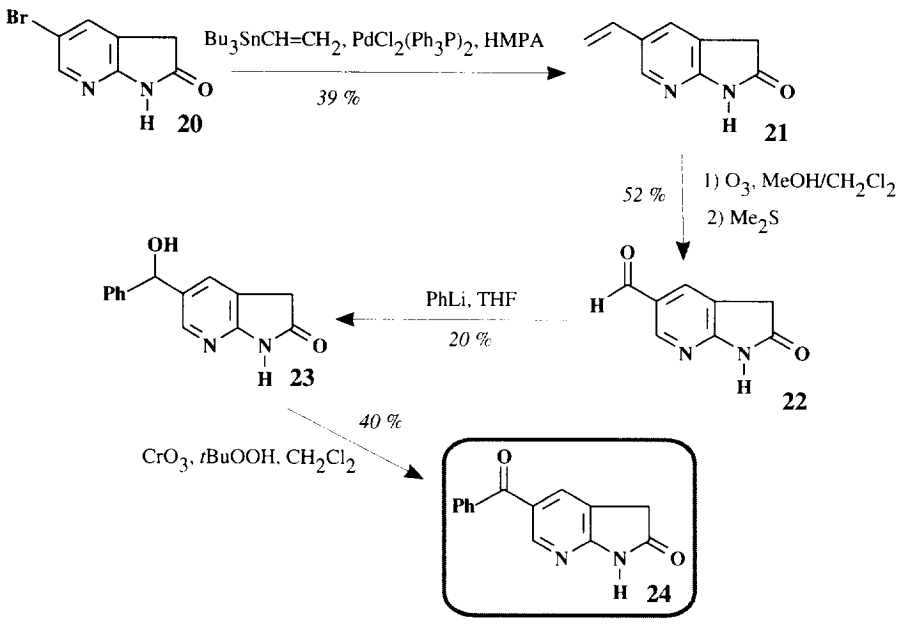
14

18

19

The analogue of compound **19**, without the methyl group on nitrogen, was prepared from compound **20**[11] according to scheme 6. Numerous attempts at benzylation using organozinc reagents as well as Stille's methodology were unsuccessful. To solve this problem, we have introduced at the 5-position the vinyl chain using vinyltributyltin as reagent and palladium as catalyst. Compound **21**, obtained with a yield of 39%, was submitted to ozonolysis using the standard procedure giving the aldehyde **22** in 52% yield. Treatment of **22** with phenyllithium in THF gave the secondary alcohol **23** with a poor yield. Finally, compound **24** was obtained by oxidation with commercial aqueous 70% *tert*-butyl hydroperoxide and a catalytic amount of chromium(VI) oxide[8].

SCHEME 6



In conclusion, several acetylated and benzoylated oxazolo [4,5-*b*]pyridin-2(3*H*)-ones, 2-phenyloxazolo[4,5-*b*]pyridines and pyrrolo[2,3-*b*]pyridin-2(2*H*)-ones have been obtained by using palladium complexes as catalyst. The analgesic properties of the elaborated compounds have been studied. These compounds were first evaluated on mice for their analgesic activity *via* a screening procedure with the phenylquinone (PBQ) induced writhing test and then, for the most active of them, also in rat with the acetic acid (AA) induced writhing test. Among these derivatives, compound **16** possess potent antinociceptive activity (ED_{50} in PBQ test = 26.7 mg/kg ; ED_{50} in AA test = 16 mg/kg) with moderate anti-inflammatory properties.

Complementary safety pharmaceutical evaluation is currently under investigation to determine if this compound could be a good candidate for clinical development.

Acknowledgments: We are grateful to A.D.I.R. Company (Courbevoie, France) for their multiform support and also to Ms Le Floch for the typing.

EXPERIMENTAL

Melting points are uncorrected. ^1H NMR (300 MHz) spectra was run on a Bruker AM 300 WB spectrometer with TMS as internal standard. IR spectra of liquid films or KBr pellets were recorded on a Perkin-Elmer 297 instrument. Mass spectra were registered on a Nermag R-10-10-C apparatus. Microanalysis were performed on a Perkin-Elmer 240 C instrument. Analytical thin layer chromatography was performed on Merck $60F_{254}$ silica gel plate. Column chromatography was performed using silica gel 60 (0.063-0.0200 mm, E. Merck) and flash

chromatography was conducted with silica gel (0.040-0.063 mm, E. Merck). All air- and moisture-sensitive reactions were conducted under argon atmosphere in flame-dried glassware. Anhydrous solvents or reagents were transferred *via* syringe. Tetrakis(triphenylphosphine)palladium (0) was prepared by using the literature procedure[13].

6-Acetyl-3-methyl-2-oxooxazolo[4,5-*b*]pyridin-2-(3*H*)-one 2: (General procedure A). To a stirred solution of 6-bromo-3-methyloxazolo[4,5-*b*]pyridin-2(3*H*)-one **1** (700 mg, 3,05 mmol) in THF (20 ml) was added successively (1-ethoxyvinyl)tributyltin (1.06 ml, 3.14 mmol), tetrakis(triphenylphosphine)palladium (0) (0.180 g, 0.15 mmol), lithium chloride (0.380 g, 8.84 mmol). After 8 h of reflux, the solution was hydrolysed with a solution of HCl (10 %) and stirring was maintained during one hour. The solvent was removed under reduce pressure, after hydrolysis and extraction with CH_2Cl_2 (2x10 ml), the organic layers were dried over magnesium sulfate and evaporated. Then, the crude mixture was purified by flash chromatography (eluent CH_2Cl_2/AcOEt : 8/2) to provide compound **2** (60 %, 352 mg), m.p. 162-163°C; IR(KBr) 1790, 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.53 (s, 3H, CH_3), 3.63 (s, 3H, NCH_3), 7.91 (d, 1H, J=1.5 Hz, H_7), 8.72 (d, 1H, J=1.5 Hz, H_5). MS *m/z* 210 (M+18). Anal. Calcd. for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58 . Found : C, 56.15; H, 4.00; N, 14.50.

6-Benzyl-3-methyloxazolo[4,5-*b*]pyridin-2-(3*H*)-one 3 : (General procedure B).

To a suspension of zinc (227 mg, 3.48 mmol) in THF (10 ml) was added 1,2-dibromoethane (0.02 ml, 0.02 mmol). The mixture was heated at 60 °C during 3 min., then chlorotrimethylsilane (0.06 ml, 0.5 mmol) was added after cooling to 35 °C. After 30 min. of stirring, benzylbromide (0.11 ml, 0.9 mmol) was added. Thirty minutes later, compound **1** (200 mg, 0.87 mmol) and tetrakis (triphenylphosphine) palladium (0) (4 mg, 0.003mmol) were added. This mixture was heated at 50 °C during 20 min. The crude mixture was filtered, the residue was treated with a solution of HCl 10 % then extracted with CH_2Cl_2. After drying over $MgSO_4$ followed by evaporation of the solvent, the crude product was purified on silica gel (eluent : CH_2Cl_2). Compound **3** was obtained in a 91 % yield (191 mg), m.p. 127-128 °C; IR (KBr) 1780 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.46 (s, 3H, NCH_3), 4.00 (s, 2H, CH_2), 7.14-7.35 (m, 6H, H_7+H_{arom}), 8.02 (d, 1H, J= 1.5 Hz, H_5). Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C,69.99; H, 5.03; N, 11.66. Found : C, 69.90; H, 5.00; N, 11.50.

6-Benzoyl-3-methyl-2-oxazolo[4,5-*b*]pyridin-2-(3*H*)-one 4 : (General procedure C).

In a flask containing a stirred mixture of CrO_3 (5 mg, 0.05 mmol) in CH_2Cl_2 (25 ml) was added sequentially commercial aqueous 70 % *t*BuOOH (1.08 ml, 8 mmol) and 6-benzyl-3-methyloxazolo[4.5-*b*]pyridin-2(3*H*)-one **3** (236 mg, 1 mmol). When the colour of the mixture became yellow more CrO_3 (5 mg, 0.05 mmol) and 70 % *t*BuOOH (1.08 ml, 8 mmol) were added. After 24 h of stirring, the mixture was filtered through celite. After evaporation of solvents, the crude product was purified by chromatography on silica gel (eluent CH_2Cl_2). Compound **4** was obtained in a 82 % yield (205 mg), m.p. 131-132 °C; IR (KBr) : 1790, 1635 cm^{-1}. ^{1}H-NMR

($CDCl_3$, 300 MHz), δ: 3.55 (s, 3H, NCH_3), 7.48-7.56 (m, 2H, H_{arom}), 7.60-7.67 (m, 1H, H_{arom}), 7.78 (d, 2H, J=7,4 Hz, H_{arom}), 7.89 (d, 1H, J=1.5 Hz, H_7), 8.58 (d, 1H, J=1.5 Hz, H_5). MS *m/z* 255 (M+1). Anal. Calcd. for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02. Found : C, 66.02; H, 3.90; N, 11.02.

6-Acetyl-2-benzyloxyoxazolo[4,5-*b*]pyridin-2-(3*H*)-one 6. This compound was obtained in a 78 % yield according to the general procedure (**A**), using **5** as starting material, m.p. 180-181 °C; IR (KBr) 1750, 1670 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ: 2.50 (s, 3H, CH_3), 5.48 (s, 2H, OCH_2), 7.53 (d, 1H, J=1.5 Hz, H_7), 7.35-7.48 (m, 5H, H_{arom}), 7.96 (d, 1H, J=1,5 Hz, H_5). Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found : C, 67.10; H, 4.50; N, 10.40.

6-Acetyl-2-oxazolo[4,5-*b*]pyridin-2-(3*H*)-one 7. Compound **6** (1 g, 4 mmol) was dissolved in methanol (25 ml) then palladium on charcoal (10 %) (100 mg) was added. The solution was kept under hydrogen pressure at 40 psi during 18 hours. The catalyst was removed by filtration, then the solvent was evaporated under reduce pressure followed by a purification using silica gel (eluent : CH_2Cl_2/MeOH : 95/5). Compound **7** was obtained in a 95 % yield (631 mg), m.p. 222-223 °C; IR (KBr) 3500-3200, 1750, 1670 cm^{-1}, ^1H-NMR (DMSO+D_2O, 300 MHz) δ: 2.22 (s, 3H, CH_3), 7.87 (s, 1H, H_7), 8.66 (s, 1H, H_5). MS *m/z* 179 (M+1). Anal. Calcd. for $C_8H_6N_2O_3$: C, 53.94; H, 3.39; N, 15.72. Found : C, 53.90; H, 3.35; N, 15.70.

6-Benzyl-2-(benzyloxy)oxazolo[4,5-*b*]pyridine 8. This compound was prepared according to the same experimental procedure described for compound **3** using **5** as starting derivatives (general procedure **B**). Compound **8** was obtained in a 56 % yield, m.p. 212-213 °C; IR (KBr) 1740 cm^{-1}. ^1H-NMR ($CDCl_3$, 300 MHz), δ: 3.82 (s, 2H, CH_2), 5.39 (s, 2H, NCH_2), 6.90 (d, 1H, J=1.5 Hz, H_7), 7.00 (d, 1H, J=1.5 Hz, H_5), 7.10 (d, 2H, J=6.6 Hz, H_{arom}), 7.25-7.33 (m, 3H, H_{arom}), 7.38 (s, 5H, H_{arom}). Anal. Calcd. for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.85. Found : C, 75.90; H, 5.00; N, 8.80.

6-Benzoyl-2-oxazolo[4,5-*b*]pyridin-2-(3*H*)-one 9. Compound **8** was treated with CrO_3 and 70 % *t*BuOOH similarly as general procedure (**C**). The resulting crude product was submitted to hydrogenation as described for compound **8**. Compound **9** was obtained in a 66 % yield, m.p. 196-197 °C; IR (KBr): 3300-2800, 1800, 1640 cm^{-1}. ^1H-NMR (DMSO+D_2O, 300 MHz) δ: 7.47-7.62 (m, 2H, H_{arom}), 7.67-7.79 (m, 3H, H_{arom}), 7.94 (d, 1H, J= 1.5 Hz, H_7), 8.38 (d, 1H, J=1.5 Hz, H_5). MS *m/z* 241 (M+1). Anal. Calcd. for $C_{13}H_8N_2O_3$: C, 65.00; H, 3.36; N, 11.66. Found : C, 64.90; H, 3.35; N, 11.50.

6-Acetyl-2-phenyloxazolo[4,5-*b*]pyridine 11. Compound **11** was obtained in a similar manner to the general procedure (**A**) using **10** as starting product and obtained in a 82 % yield. m.p. 192-193°C; IR (KBr) 1680, 1605 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz), δ: 2.72 (s, 3H, CH_3), 7.54-7.66 (m, 3H, H_{arom}), 8.35 (d, 2H, J =7.7 Hz, H_{arom}), 8.42 (d, 1H, J=1.7 Hz, H_7), 9.18 (d, 1H, J=1.7 Hz, H_5). MS *m/z* 239 (M+1). Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found : C, 70.50; H, 4.20; N, 11.75.

6-Benzyl-2-phenyloxazolo[4,5-*b*]pyridine 12. This compound was prepared from **10** according to the general procedure (**B**) and was obtained in a 65% yield, m.p. 175-176 °C; IR (KBr) 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz), δ: 4.14 (s, 2H, CH_2), 7.20-7.36 (m, 5H, H_{arom}), 7.49-7.58 (m, 5H, H_{arom}), 7.62 (d, 1H, J=1.5 Hz, H_7), 8.28 (d, 1H, H_{arom}), 8.50 (d, 1H, J=1.5 Hz, H_5). Anal. Calcd. for $C_{19}H_{14}N_2O$: C, 79.68; H, 4.90; N, 9.70. Found : C, 79.68; H, 4.90; N, 9.70.

6-Benzoyl-2-phenyloxazolo[4,5-*b*]pyridine 13. This compound was obtained from **12** in a 72 % yield using general procedure (**C**), m.p.189-190 °C; IR (KBr) 1650, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz), δ: 7.46-7.63 (m, 6H, H_{arom}), 7.77-7.82 (m, 2H, H_{arom}), 8.29-8.33 (m, 3H, H_7, H_{arom}), 8.95 (d, 1H, J=1.5 Hz, H_5). MS *m/z* 301 (M+1). Anal. Calcd. for $C_{19}H_{12}N_2O_2$: C, 75.99; H, 4.03; N, 9.33. Found : C, 75.90; H, 4.00; N, 9.30.

5-Acetyl-1-methyl-1,3-dihydro-pyrrolo[2,3-*b*]pyridin-2-one 16. This compound was obtained in a 84 % yield according to the general procedure (**A**) using **14** as starting compound, m.p. 200-201 °C; IR (KBr) 1705, 1670 cm^{-1}.^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.58 (s, 3H, CH_3CO), 3.32 (s, 3H, NCH_3), 3.58 (s, 2H, CH_2), 8.04 (s, 1H, H_4), 8.78 (s, 1H, H_6). MS *m/z* 191 (M+1). Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found : C, 63.10; H, 5.20; N, 14.65.

5-Acetyl-1,3,3-trimethyl-1,3-dihydro-pyrrolo[2,3-*b*]pyridin-2-one 17. This compound was obtained in a 90 % yield starting from **15** according to the general procedure (**A**). m.p. 99-100 °C; IR (KBr) 1732 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz), δ: 1.43 (s, 6H, 2×CH_3), 2.62 (s, 3H, CH_3CO), 3.35 (s,3H, NCH_3), 8.00 (s, 1H, H_4), 8.78 (s, 1H, H_6). MS *m/z* 219 (M+1). Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found : C, 65.90; H, 6.40; N, 12.75.

5-Benzyl-1-methyl-1,3-dihydro-pyrrolo[2,3-*b*]pyridin-2-one 18. To a stirred solution of **14** (100 mg, 0.47 mmol) in HMPA (0.5 ml) benzyltributyltin (0.187 g, 0.49 mmol) and bis(triphenylphosphine)palladium (II) chloride (13 mg, 0.02 mmol) were added and the mixture was heated to 65 °C for 6 h. After cooling, the reaction was diluted with water (10 ml) and extracted with AcOEt (20 ml). The organic phase was dried over $MgSO_4$ and was concentrated, the crude product was purified by a column of chromatography (eluent : CH_2Cl_2/ACOEt 95/5) to give compound **18** in a 20 % yield (21 mg) as an oil; IR (film) 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz), δ: 3.30 (s, 3H, NCH_3), 3.48 (s, 2H, CH_2), 3.94 (s, 2H, CH_2), 7.15-7.33 (m, 6H, H_{arom}, H_4), 8.08 (s, 1H, H_6). Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found : C, 75.58; H, 5.90; N, 11.70.

5-Benzoyl-1-methyl-1,3-dihydro-pyrrolo[2,3-*b*]pyridin-2-one 19. Compound **18** (40 mg, 0.17 mmol) was dissolved in anhydrous CCl_4 and was added to *N*-bromosuccinimide (60 mg, 0.34 mmol) and a trace of benzoyl peroxyde. This reaction was kept under reflux for one hour. The resulting bromide derivative was dissolved in acetic acid (2 ml) and zinc powder (50 mg, 0.76 mmol) was added. After 30 min of stirring

followed by filtration, the crude mixture was diluted with water (5 ml) and extracted with CH_2Cl_2 (10 ml). After drying and evaporation, the mixture was purified by chromatography (petroleum ether/AcOEt 6:4) and compound **19** was obtained in a 65 % yield (28 mg) as an oil; IR (film) 1735, 1647 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.37 (s, 3H, NCH_3), 3.64 (s, 2H, CH_2), 7.53 (t, 2H, J=7.4 Hz, H_{arom}), 7.64 (d, 1H, J=7.35 Hz, H_{arom}), 7.79 (d, 2H, J=7.4 Hz, H_{arom}), 8.02 (d, 1H, J=1.2 Hz, H_4), 8.63 (d, 1H, J=1.2 Hz, H_6). MS *m/z* 253 (M+1). Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found : C, 71.30; H, 4.65; N, 11.00.

5-Vinyl-1,3-dihydro-pyrrolo[2,3-*b*]pyridin-2-one 21. Compound **20** (1.62 g, 7.60 mmol) was dissolved in HMPA (7.6 ml). Vinyltributyltin (2.3 ml, 7.91 mmol) and bis(triphenylphosphine)palladium (II) chloride (213 mg, 0.3 mmol) were added successively to this solution. After 25 h at 65 °C, the solvent was removed and the crude product was purified by chromatography (eluent petroleum ether/AcOEt 1/1). Compound **21** was obtained in a 39 % yield (475 mg). m.p. 164-165 °C; IR (KBr) 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.65 (s, 2H, CH_2), 5.40 (d, 1H, J=11.0 Hz, H_{vinyl}), 5.81 (d, 1H, J=17.7 Hz, H_{vinyl}), 6.81 (dd, 1H, J=11.0, 17.7 Hz, H_{vinyl}), 7.70 (s, 1H, H_4), 8.18 (s, 1H, H_6), 9.15 (s, 1H, NH). Anal. Calcd. for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found : C, 67.38; H, 4.99; N, 17.40.

2-Oxo-1,3-dihydro-pyrrolo[2,3-*b*]pyridin-5-carboxaldehyde 22. Compound **21** (470 mg, 2.93 mmol) was dissolved in a solution of CH_2Cl_2 and MeOH (4/1) (10 ml) at -78 °C and placed in an ozonolysis apparatus (Trailigaz LI). After 10 min of reaction, the excess of ozone was removed by nitrogen stream and methyl sulfide (1 ml) was added to the solution, which was then allowed to warm up to room temperature. The solvents were evaporated. Chromatography (eluent AcOEt) of the residue gave compound **22** in a 52 % yield (247 mg). m.p.>230 °C; IR (KBr) 1727, 1686 cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ: 3.62 (s, 2H, CH_2), 7.90 (s, 1H, H_4), 8.63 (s, 1H, H_6), 9.92 (s, 1H, CHO), 11.51 (s, 1H, NH). Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found : C, 59.01; H, 3.68; N, 17.22.

5-(Hydroxyphenylmethyl)-1,3-dihydro-pyrrolo[2,3-*b*]pyridin-2-one 23. Compound **22** (250 mg, 1.5 mmol) was dissolved in THF (25 ml) then phenyllithium (1,8 M in solution in THF, 2.3 ml, 4.12 mmol)was added at -78 °C. The mixture was stirred at -78 °C to room temperature during 1.5 h then was hydrolyzed with 2N HCl and extracted with CH_2Cl_2. After drying and evaporation, chromatography (eluent AcOEt) gave **23** in a 20 % yield (74 mg). m.p.148-149 °C ; IR (KBr) 3300-3000, 1715 cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ: 3.30 (s, 2H, CH_2), 5.62 (s, 1H, CH), 5.91 (s, 1H, OH), 7.12-7.42 (m, 6H, H_{arom} + H_4), 8.00 (s, 1H, H_6), 10.91 (s, 1H, NH). Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found : C, 69.90; H, 4.95; N, 11.52.

5-Benzoyl-1,3-dihydro-pyrrolo[2,3-*b*]pyridin-2-one 24. Compound **24** was obtained in a 40 % yield similarly as **4** starting from compound **23** according to the general procedure **C**. m.p. 150-151 °C; IR (KBr) 1735, 1647 cm^{-1}. ^{1}H-NMR (DMSO, 300 MHz) δ: 3.67 (s, 2H, CH_2), 7.55-7.78 (m, 5H, H_{arom}), 7.92 (s, 1H,

H_4), 8.43 (s, 1H, H_6), 11.45 (s, 1H, NH). MS *m/z* 239 (M+1). Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N,11.76. Found :C, 70.50; H, 4.20; N, 11.68.

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9. **6-Bromo-(2-benzyloxy)oxazolo[4,5-*b*]pyridine 5.** To a solution of ethanol (60 ml) sodium (385 mg, 16.38 mmol) was first added by portions then 6-bromooxazolo[4,5-*b*]pyridin-2(3*H*)-one (3g, 13.9 mmol). After one hour at room temperature, the solvent was evaporated and *N,N*-dimethylformamide (50 ml) was added to the crude product. After complete dissolution, a solution of benzyl bromide (2.5ml, 20.85 mmol) was transferred dropwise to the solution. After 2 hours under reflux, then evaporation of DMF, the residue was hydrolyzed and extracted with CH_2Cl_2 (2×20 ml). The organic layers were dried over magnesium sulfate and evaporated. Then, the crude mixture was purified by flash chromatography (eluent petroleum ether/ AcOEt) to provide compound **5** in a 38 % yield (1.95g), m.p. 222-223°C; IR (KBr) 1740 cm^{-1}. 1H-NMR ($CDCl_3$, 300 MHz) δ: 5.40 (s, 2H, OCH_2), 7.16 (d, 1H, J= 2.2 Hz, H_7), 7.34 (s, 5H, H_{arom}) 7.42 (d, 1H, J= 2.2 Hz, H_5). MS(IC) *m/z* 307 (M+1). Anal. Cald. for $C_{13}H_9BrN_2O_2$: C, 51.17; H, 2.97; N, 9.18. Found : C, 51.10; H, 2.90; N, 9.15. During this reaction the 3-benzyl-6-bromooxazolo [4,5-*b*]pyridin-2(3*H*)-one[7] was also obtained in a 53 % yield (2.70g).
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