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Synthesis of 2-Substituted-1*H*-Pyrrolo[2,3-*b*]Pyridines: Preparation of 7-Azaolivacine Analogue and 7-Azaindolopyridopyrimidine Derivatives.

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Abstract: 2-Substituted-1*H*-pyrrolo[2,3-*b*]pyridines have been prepared from 7-azaindole by lithiation followed by addition of various electrophiles. A 7-azaolivacine analogue and a pyrido[3'2':4,5]pyrrolo[1,2-*c*]pyrido[3,2-*d*]pyrimidine have also been prepared.

2-Substituted indoles, such as 2-phenylindole[3] or indomethacine,[4] are pharmacologically important substances and are precursors for the preparation of alkaloids such as vindorosine.[5] The standard synthetic methods of indoles[6] (Fischer, Madelung or Reissert) are generally used to prepare the 2-substituted indolic framework. Neverthless, for two decades the metalation of the 2-position of *N*-protected-indoles has been developed[7]. This method allows for the introduction of various substituents and often has been used for the synthesis of tetracyclic compounds like ellipticine derivatives.[8]

Recently there has arisen considerable interest in azaindole chemistry due to the importance of polyaza tetracyclic compounds as DNA intercalators and possible anticancer agents. In our research program devoted to the reactivity of 1*H*-pyrrolo[2,3-*b*]pyridine or 7-azaindole[9], we planned to prepare new derivatives based on the 7-azaindole framework. To reach this target, we required 2-substituted-7-azaindole compounds; but the direct syntheses of these derivatives by Fischer, Madelung or Reissert methods often give bad results.[10] The low reactivity of the π-deficient ring of the pyridine or the drastic basic conditions with high reaction temperatures were the principal reasons for the low yields during the formation of 7-azaindole from pyridine derivatives. Recently, the Madelung procedure has been performed at low temperature and led to several azaindolic derivatives.[11] The lithiation method, already widely studied for other bisheterocyclic structures such as 1*H*-pyrrolo[3,2-*c*] pyridines (5-azaindoles)[12,13] or furo[3,2-*c*] pyridines,[14] has been scarcely[15] used in the 7-azaindole series .

This paper describes the preparation of 2-substituted-7-azaindoles by lithiation of the 2-position of the 7-azaindole followed by the addition of a large range of electrophiles. Palladium cross-coupling reactions have been applied for the 2-stannyl derivative. These methodologies could lead to the synthesis of a 7-azaolivacine analogue and pyrido[3'2':4,5]pyrrolo[1,2-*c*]pyrido[3,2-*d*]pyrimidine derivatives.

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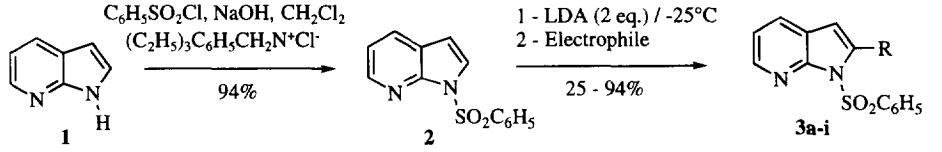
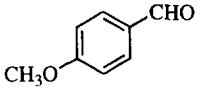
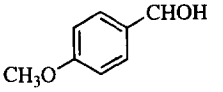
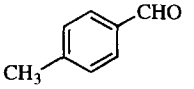
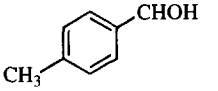
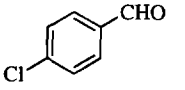
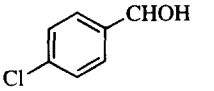
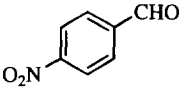
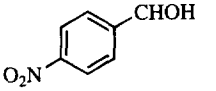
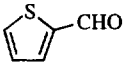
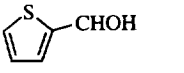
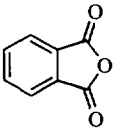
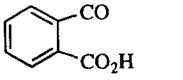
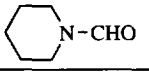
To prepare the 2-lithio-7-azaindole, we need a removable Directing Metalation Group (DMG) in the 1-position usually used in indolic series like $SO_2C_6H_5$,[16] $SO_2N(CH_3)_2$,[17] $OCH_2O(CH_2)_2Si(CH_3)_3$,[18] COOH,[19] $CO_2C(CH_3)_3$,[20] or $CON(C(CH_3)_3)_2$.[21] We have chosen the phenylsulfonyl group as DMG in the 1-position for practical reasons. The 1-phenylsulfonyl-7-azaindole (**2**)[22] has been easily prepared from the commercially available 7-azaindole (**1**) and phenylsulfonyl chloride by a phase transfer reaction in 94% yield (Scheme 1). The lithiation of the 2-position is performed with 2 equivalents of LDA at -25°C for 30 min. With only 1 equivalent of LDA and subsequent addition of various electrophiles we observed the formation of the desired compounds **3** but in low yield. Longer time than 30 min at -25°C for the preparation of the anionic derivative decreased the yield; no reaction occurred when the lithiation was performed at -78°C whatever the time of the reaction (Scheme 1).

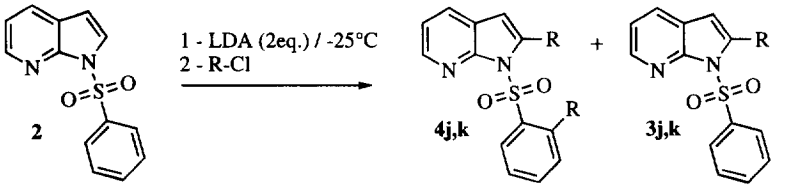


Entry	3	Electrophiles	Amount of electrophile (eq.)	R	Yield (%)
1	**a**	CH_3I	1.1	CH_3	94
2	**b**		1.1		62
3	**c**		1.1		50
4	**d**		1.1		62
5	**e**		1.1		62
6	**f**		1.1		60
7	**g**		1.1		25
8	**h**	CO_2	1.1	COOH	60
9	**i**		4	CHO	33

Scheme 1

The addition of various electrophiles was performed at -25°C during 2h-16h (Scheme 1), the best result being obtained with iodomethane. The 2-methyl-1-phenylsulfonyl-7-azaindole (**3a**) was prepared in 94% yield (Entry 1) and the alcohols **3b-f** were obtained in 50 - 62 % yield from the corresponding aldehydes (Entries 2-6). We observed the presence of two rotamers on the ^{1}H-NMR spectra of compounds **3b,c**. The use of phthalic anhydride or dry ice as electrophiles led to carboxylic acid derivatives **3g,h** in 25 and 60% yields (Entries 7, 8). The preparation of the 2-formyl-1-phenylsulfonyl-7-azaindole (**3i**) (Entry 9), obtained in only 33% yield, required 4 equivalents of *N*-formylpiperidine. The yield could not be increased by using DMF instead of *N*-formylpiperidine whatever amount of electrophile used. The addition of a chelating agent such as TMEDA was ineffective for increasing the yield.

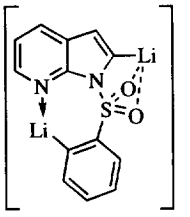
The use of trimethylsilyl chloride or trimethyltin chloride as electrophiles led to the formation of two derivatives (Scheme 2); the disubstituted compounds **4j,k** and the monosubstituted compounds **3j,k**. The yield of disubstituted-7-azaindoles **4j,k** (Entries 10, 11 and 13, 14) increased when the amount of electrophile also increased. A selective monosubstitution was performed by using TMEDA (1eq / 7-azaindole) as chelating agent in the mixture. Compounds **3j,k** were obtained in 69% and 70% yields respectively (Entries 12, 16).



Entry	3-4	R	Amount of electrophile(eq.)	TMEDA	Yield of **4** (%)	Yield of **3** (%)
10	**j**	$Si(CH_3)_3$	1.2	No	29	53
11	**j**	$Si(CH_3)_3$	2.2	No	37	45
12	**j**	$Si(CH_3)_3$	1.2	Yes	-	69
13	**k**	$Sn(CH_3)_3$	1.2	No	28	4
14	**k**	$Sn(CH_3)_3$	2.2	No	57	23
15	**k**	$Sn(CH_3)_3$	1.2	Yes	-	56
16	**k**	$Sn(CH_3)_3$	2.2	Yes	-	70

Scheme 2

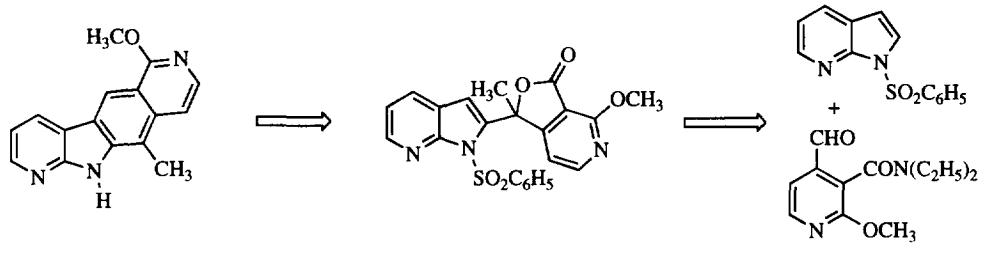
In the indolic series, the substitution of the phenylsulfonyl group itself, used as DMG during the synthesis of 2-substituted-1-phenylsulfonylindole, had already been reported by some authors when the reaction was performed with 2 equivalents of lithium amide[23] or *tert*-butyllithium.[24] In our case, a dianionic intermediate **A** (Figure 1) could be expected and the presence of the nitrogen atom in 7-position of 7-azaindole probably increases the stabilization of the dianionic species. It is well-known that nitrogen heterocycles derivatives could be used in lithiation process to stabilize anionic derivatives.[7,25] This fact could explain the relative high yield of disubstituted compounds **4**.



A

Figure 1

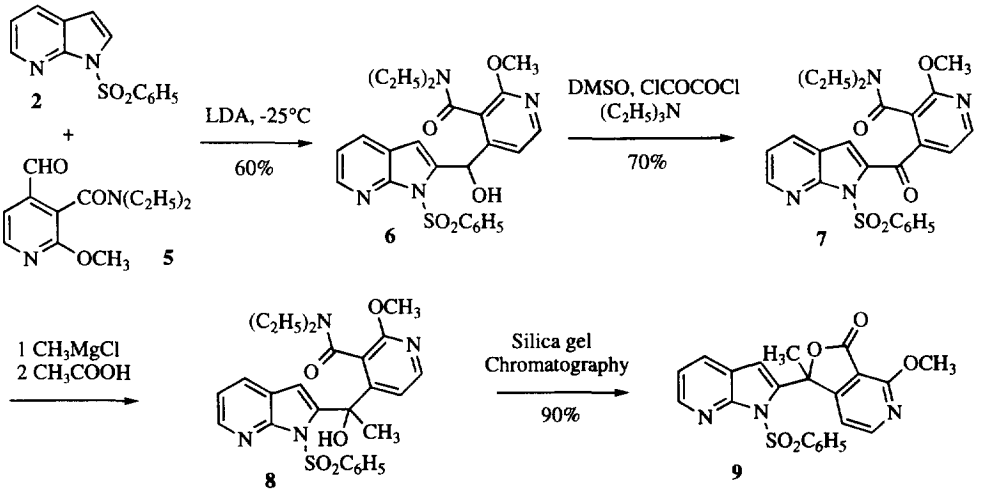
We applied this strategy to prepare a 7-azaolivacine analogue from 7-azaindole by lithiation of the 2-position. We have chosen a similar retrosynthetic synthesis *via* a lactonic intermediate, reported in Scheme 3, as Heymes and Dormoy described for 5-azaellipticine.[13] Only Bisagni's group prepared some 7-azaellipticine derivatives by cyclization of triazolopyridines.[26]



Scheme 3

According to the preparation described by Heymes and Dormoy,[13] aldehyde **5** has been obtained from 2-chloronicotinic acid by amidification with diethylamine, then substitution of chlorine by methoxyl and finally, addition of DMF by a lithiation procedure

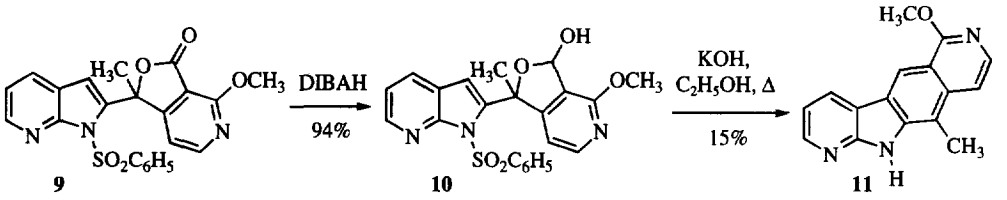
The aldehydic compound **5** was condensed with the 2-lithio-7-azaindole, prepared as described above, to give compound **6** (Scheme 4) which showed 2 rotamers by ^{1}H-NMR. In 5-azaindole series, a similar observation has also been reported.[13]



Scheme 4

Swern oxidation was performed to give the ketone **7** in 70% yield. Manganese oxidation (MnO_2) failed for compound **6** but has been effective for the alcohol **3b**. Ketone **7** was treated with methylmagnesium chloride and, after refluxing in acetic acid, did not give the expected lactone **9**. The ^{1}H-NMR spectrum of the crude reaction showed only the formation of alcohol **8**. Fortunately, lactonisation occurred during the purification of alcohol **8** on silica gel and compound **9** was obtained in 90% yield from **7** (Scheme 4).

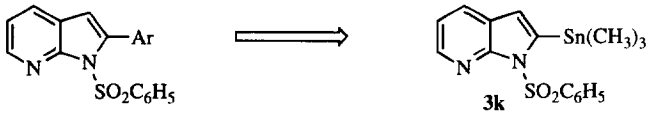
The lactone function of compound **9** was reduced with DIBAH at low temperature (-78°C) and afforded the lactol **10** in 94% yield. This compound was treated with KOH in refluxing ethanol to lead to the tetracyclic compound **11** in only 15% yield (Scheme 5).



Scheme 5

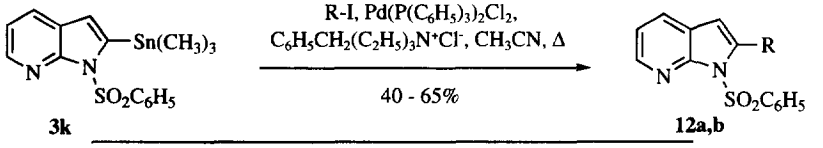
Compound **11** may be an useful intermediate since anchoring a chain *via* a displacement of the labile OCH_3 can give access to potential antitumor agents.

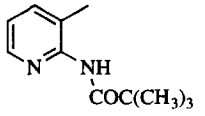
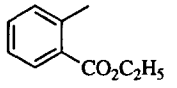
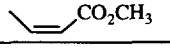
2-Substituted indoles may also be obtained *via* other metallic derivatives than the lithium species. Heck, Stille or Suzuki coupling reactions, using metallic group (Zn[27], B[28] or Sn[18,20,29]) or triflate[30] as substituent in the 2-position of indole, also gave 2-substituted indoles. These methods generate great interest for the synthesis of 2-aryl-7-azaindoles and the compound **3k** seems to be a good candidate to perform Stille reaction (Scheme 6).



Scheme 6

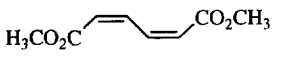
We have performed some palladium catalysed cross-coupling reactions between 2-(trimethylstannyl)-7-azaindole (**3k**) and iodo derivatives in CH_3CN with $Pd(P(C_6H_5)_3)_2Cl_2$ as catalyst and $C_6H_5CH_2(C_2H_5)_3N^+Cl^-$ to prepare 2-substituted-7-azaindoles **12a,b** in 65 and 40% yields, respectively. During the course of these reactions, we have also observed the formation of 1-phenylsulfonyl-7-azaindole (**2**) (Scheme 7).



12	R	Time reaction	Yield
a		24 h	65%
b		24 h	40%
c		24h	-

Scheme 7

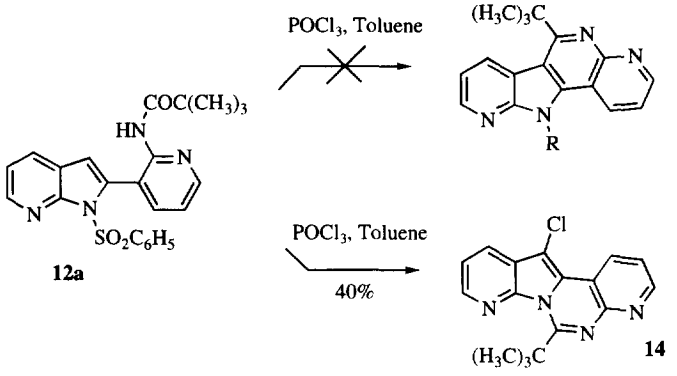
With methyl 3-iodopropenoate, the compound **12c** has not been obtained as expected. Using other palladium catalysts under different conditions was unfruitful. In toluene at reflux with $Pd(P(C_6H_5)_3)_4$ as catalyst, we have observed the coupling of two molecules of methyl 3-iodopropenoate to give the diene derivative **13**[31] in 30% yield (Figure 2).



13

Figure 2

In order to prepare new γ-carbolines, compound **12a** was treated with $POCl_3$ in toluene to perform a Bischler-Napieralski cyclisation (Scheme 8).



Scheme 8

Surprisingly, the cyclisation did not occur in the 3-position but in the 1-position to lead to the tetracyclic compound **14** (Scheme 8). Performing the reaction with PPSE,[32] the starting material was recovered. The formation of **14** may be explained by a dephenylsulfonylation of the nitrogen atom in 1-position. Then a nucleophilic attack of this azaindolic nitrogen atom on the chloroiminoether, formed by the reaction of $POCl_3$ with amide, could lead to the cyclised product (Scheme 8).

It is however difficult to know exactly when the chlorination step in 3-position happens; the halogenation could occur after the dephenylsulfonylation step (when the 1-position is not substituted) as well as after the formation of the pyrimidine ring. In the indolic series, halogenation of the 3-position of indolo[1,2-*c*] quinazoline is well-known.[33] Joule[34] has also reported on the chlorination of the 3-position of 2-methylindole during phenylsulfonylation.

Lithiation at the 2-position of 1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (**2**) can lead to 2-substituted-7-azaindoles **3a-k** in good yields. Some derivatives, prepared with this strategy, have been used to obtain the 7-azaolivacine analogue **11** or 2-aryl-7-azaindoles **12a-b** *via* palladium cross-coupling process. Pyrido [3',2':4,5]pyrrolo[1,2-*c*]pyrido[3,2-*d*]pyrimidine **14**, a new azaindolo framework,[33] has been prepared and opens a field of new derivatives.

Acknowledgements: We would like to thank the société Sanofi and Dr. Dormoy for providing us samples of compound **5** and Dr. L. Savelon and Dr. S. Piroëlle for helpful discussions. We would like to thank Professor J. Joule for providing us with a copy of the experimental section of the thesis of Dr. L. Dalton.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1310 instrument. NMR spectra were obtained on a Bruker AM 300 instrument using TMS as internal standard. Mass spectra were obtained on a Nermag R 10C instrument (chemical ionization with ammonia). 3-Diethylaminocarbonyl-4-formyl-2-methoxypyridine (**5**) has been prepared as described by Heymes and Dormoy.[13]

1-Phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (2).

Finely powdered sodium hydroxide (0.625 g, 15.62 mmol) was added to a solution of CH_2Cl_2 (10 mL) containing benzyltriethylammonium chloride (0.030 g, 0.13 mmol) and 1*H*-pyrrolo[2,3-*b*]pyridine (**1**) (0.590 g, 5.0 mmol). Benzenesulfonyl chloride (0.670 g, 6.25 mmol) was slowly added at 0°C and the resulting suspension was stirred at this temperature for 15 min and 2 h at room temperature. The suspension was filtered through celite, washed with CH_2Cl_2 and the filtrate was evaporated *in vacuo*. The residue was chromatographed on a silica gel column (eluent: CH_2Cl_2) to give **2** in 94% yield; mp 129-131°C (CH_3OH) (lit.[22] 132°C). IR (KBr), ν: 1370, 1170 (SO_2) cm^{-1}. ^{1}H-NMR (300MHz, $CDCl_3$), δ: 6.54 (d, 1H, H_3, J = 4.0 Hz), 7.12 (dd, 1H, H_5, J = 4.4, 8.1 Hz), 7.43 (m, 2H, H_{arom}), 7.51 (m, 1H, H_{arom}), 7.68 (d, 1H, H_2, J = 4.0 Hz), 7.78 (dd, 1H, H_4, J= 1.5, 8.1 Hz), 8.14 (d, 2H, H_{arom}, J = 7,3 Hz), 8.37 (dd, 1H, H_6, J = 1.5, 4.4 Hz).

Lithiation of 1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine (2) and addition of electrophiles (without addition of TMEDA): general procedure.

n-Butyllithium (1.6 M in hexane) (1.30 mL, 2.0 mmol) was added dropwise to a solution of diisopropylamine (0.280 mL, 2.0 mmol) in anhydrous THF (3 mL) under argon at -78°C. This solution was stirred for 30 min at -78°C before using. Then the LDA solution was warmed at -25°C and a solution of anhydrous THF (5 mL) containing 1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine **2** (0.258 g, 1.0 mmol) was added dropwise. After the addition, the resulting solution was stirred for 30 min at -25°C to lead to a brown solution. Then the electrophile (1 - 4 mmol), dissolved in anhydrous THF (2 - 8 mL), was added dropwise and the end of the reaction was determinated by tlc control (2h - 16h). Hydrolysis was performed at room temperature.

Workup for compounds **3a-f,i**.

After neutralization, the mixture was extracted with CH_2Cl_2 (4 x 15 mL), the organic layers were dried ($MgSO_4$), and the solvent was evaporated *in vacuo*. The residue was chromatographed (eluent: CH_2Cl_2) on a silica gel column to give compounds **3a-f,i** (Spectroscopic data are reported in Table 1).

3a: Anal. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.98; H, 4.26; N, 10.47. **3b**: Anal. Calcd for $C_{21}H_{18}N_2O_4S$: C, 63.95; H, 4.60; N, 7.10. Found: C, 64.23; H, 4.82; N, 6.92. **3c**: Anal. Calcd for $C_{21}H_{18}N_2O_3S$: C, 66.65; H, 4.79; N, 7.40. Found: C, 66.98; H, 4.60; N, 7.22. **3d**: Anal. Calcd for $C_{20}H_{15}ClN_2O_3S$: C, 60.23; H, 3.79; N, 7.02. Found: C, 60.05; H, 3.99; N, 7.24. **3e**: Anal. Calcd for $C_{20}H_{15}N_3O_5S$: C, 58.67; H, 3.69; N, 10.26. Found: C, 58.82; H, 3.55; N, 10.09. **3f**: Anal. Calcd for $C_{18}H_{14}N_2O_3S_2$: C, 58.36; H, 3.81; N, 7.56. Found: C, 58.65; H, 3.63; N, 7.38. **3i**: Anal. Calcd for $C_{14}H_{10}N_2O_3S$: C, 58.73; H, 3.52; N, 9.78. Found: C, 58.54; H, 3.67; N, 9.61.

Workup for compounds **3g,h**.

The aqueous layer was acidified until pH = 1 with an aqueous solution of HCl 10%. Extraction was performed with ethyl acetate (3 x 15 mL). The organic layers were dried ($MgSO_4$), and the solvent was evaporated *in vacuo*. The residue was chromatographed on a silica gel column to give the desired compounds **3g,h** (Spectroscopic data are reported in Table 1). Eluent for compound **3g**: CH_2Cl_2 / CH_3OH, 95 / 5, v/v. Anal. Calcd for $C_{21}H_{14}N_2O_5S$: C, 62.06; H, 3.47; N, 6.89. Found: C, 61.79; H, 3.12; N, 6.95. Eluent for compound

3h: CH_2Cl_2 / CH_3OH, 80 / 20, v/v. Anal. Calcd for $C_{14}H_{10}N_2O_4S$: C, 55.62; H, 3.33; N, 9.27. Found: C, 55.38; H, 3.58; N, 9.11.

Table 1: Spectroscopic Data of Compounds **3a-i**.

3	mp (°C)	IR cm^{-1}	^{1}H-NMR, δ, J (Hz)	MS (IE, NH_3)
a	100-102[h]	1360, 1170.[a]	2.74 (s, 3H, CH_3), 6.30 (s, 1H, H_3), 7.12 (dd, 1H, H_5, J = 4.8, 7.9), 7.46 (m, 2H, H_{arom}), 7.55 (m, 1H, H_{arom}), 7.69 (dd, 1H, H_4, J = 1.5, 7.9), 8.14 (d, 2H, H_{arom}, J = 7,4), 8.37 (dd, 1H, H_6, J = 1.5, 4.8).[c]	273 (M^++1)
b[g]	156-158[i]	3400, 1370, 1170.[a]	3.80 (s, 3H, CH_{3a}), 3.84 (s, 3H, CH_{3A}), 6.32 (s, 2H, H_{3A+a}), 6.49 (s, 2H, CH_{A+a}), 6.80-7.00 (m, 4H, $H_{aromA+a}$), 7.13 (dd, 2H, H_{5A+a}, J = 4.4, 7.4), 7.30-7.60 (m, 10H, H_{arom}), 7.71 (dd, 2H, H_{4A+a}, J = 1.5, 7.4), 7.90-8.00 (m, 4H, H_{arom}), 8.37 (dd, 2H, H_{6A+a}, J = 1,5, 4.4).[d]	395 (M^++1)
c[g]	oil	3500-3200, 1370, 1170.[b]	2.33 (s, 3H, CH_{3a}), 2.38 (s, 3H, CH_{3A}), 6.28 (s, 2H, H_{3A+a}), 6.49 (s, 2H, CH_{A+a}), 7.05-7.40 (m, 6H, H_{arom}), 7.30-7.60 (m, 10H, H_{arom}), 7.69 (dd, 2H, H_{4A+a}, J = 1.5, 7.4), 7.94 (m, 4H, H_{arom}), 8.36 (dd, 2H, H_{6A+a}, J = 1.5, 5.1).[d]	-
d	171-173[i]	3440-3420, 1370, 1170.[a]	6.25 (s, 1H, H_3), 6.49 (s, 1H, CH), 7.14 (dd, 1H, H_5, J = 5.2, 8.1), 7.00-7.44 (m, 6H, H_{arom}), 7.56 (m, 1H, H_{arom}), 7.72 (dd, 1H, H_4, J = 1.5, 8.1), 7.98 (m, 2H, H_{arom}), 8.40 (dd, 1H, H_6, J = 1.5, 5.2).[d]	-
e	194-196[i]	3150-3300, 1370, 1170.[a]	6.16 (s, 1H, H_3), 6.60 (s, 1H, CH), 7.16 (dd, 1H, H_5, J = 5.2, 8.1), 7.44 (m, 2H, H_{arom}), 7.58 (m, 1H, H_{arom}), 7.66 (m, 2H, H_{arom}), 7.71 (dd, 1H, H_4, J = 1.5, 8.1), 8.06 (m, 2H, H_{arom}), 8.24 (m, 2H, H_{arom}), 8.41 (dd, 1H, H_6, J = 1.5, 5.2).[d]	-
f	oil	3500-3300, 1370, 1170.[b]	6.53 (s, 1H, H_3), 6.80 (s, 1H, CH), 7.00 (m, 2H, H_{arom}), 7.14 (dd, 1H, H_5, J = 5.2, 7.4), 7.31 (d, 1H, H_{arom}, J = 5.1), 7.38 (m, 2H, H_{arom}), 7.51 (m, 1H, H_{arom}), 7.75 (dd, 1H, H_4, J = 1.5, 7.4), 7.96 (m, 2H, H_{arom}), 8.37 (dd, 1H, H_6, J = 1.5, 5.2).[d]	-
g	155-157[j]	3300-2900, 1710, 1655.[a]	6.98 (s, 1H, H_3), 7.38 (dd, 1H, H_5, J = 4.4, 8.1), 7.60-7.90 (m, 7H, H_{arom}), 8.11 (dd, 1H, H_4, J = 1.5, 8.1), 8.41 (m, 2H, H_{arom}), 8.55 (dd, 1H, H_6, J = 1,5, 4.4).[e]	-
h	188-190[j]	3320, 1740, 1370, 1150.[a]	7.70 (s, 1H, H_3), 7.80 (dd, 1H, H_5, J = 4.4, 8.1), 8.10 (m, 2H, H_{arom}), 8.20 (m, 1H, H_{arom}), 8.60 (dd, 1H, H_4, J = 1.5, 8.1), 8.85 (m, 2H, H_{arom}), 8.95 (dd, 1H, H_6, J = 1.5, 4.4).[f]	-
i	140-145[h]	1670, 1370, 1170.[a]	7.27 (dd, 1H, H_5, J = 4.4, 8.1), 7.39 (s, 1H, H_3), 7.48 (m, 2H, H_{arom}), 7.59 (m, 1H, H_{arom}), 7.97 (dd, 1H, H_4, J = 1.5, 8.1), 8.17 (m, 2H, H_{arom}), 8.62 (dd, 1H, H_6, J = 1.5, 4.4), 10.64 (s, 1H, CHO).[c]	287 (M^++1)

IR: [a] KBr, [b] Film.

^{1}H-NMR: [c] $CDCl_3$, [d] $CDCl_3$ + D_2O, [e] DMSO-d_6, [f] Acetone-d_6.

[g] Ratio of Rotamers (A/a): for **3b**, 80/20; for **3c**, 50/50. [h] CH_3OH; [i] CH_2Cl_2/$(C_2H_5)_2O$, [j] CH_3OH/H_2O.

1-Phenylsulfonyl-2-trimethylsilyl-1*H*-pyrrolo[2,3-*b*]pyridine (3j) and 2-trimethylsilyl-1-[2'-(trimethyl silyl)phenylsulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridine (4j).

Compounds **3j** and **4j** were prepared according to conditions reported for compound **3a** using 2.2 equivalents of trimethylsilyl chloride. Eluent: CH_2Cl_2

3j: yield: 45%; mp 140-142°C (CH_3OH). IR (KBr), ν: 1360, 1160 (SO_2) cm^{-1}. ^{1}H-NMR (300MHz, $CDCl_3$), δ: 0.50 (s, 9H, 3xCH_3), 6.85 (s, 1H, H_3), 7.11 (dd, 1H, H_5, J = 4.4, 8.1 Hz), 7.45 (m, 2H, H_{arom}), 7.52 (m, 1H, H_{arom}), 7.78 (dd, 1H, H_4, J = 1.5, 8.1 Hz), 8.13 (m, 2H, H_{arom}), 8.35 (dd, 1H, H_6, J = 1.5, 4.4 Hz); Anal. Calcd for $C_{16}H_{18}N_2O_2SSi$: C, 58.15; H, 5.49; N, 8.48. Found: C, 58.43; H, 5.35; N, 8.69.

4j: yield: 37%; mp 102-104°C (CH_3OH). IR (KBr), ν: 1350, 1160 (SO_2) cm^{-1}. ^{1}H-NMR (300MHz, $CDCl_3$), δ: 0.42 (s, 9H, 3xCH_3), 0.58 (s, 9H, 3xCH_3), 6.87 (d, 1H, H_{arom}, J = 8.1 Hz), 6.91 (s, 1H, H_3), 7.09 (dd, 1H, H_5, J = 4.8, 8.1 Hz), 7.17 (m, 1H, H_{arom}), 7.43 (m, 1H, H_{arom}), 7.75-7.90 (m, 2H, H_{arom}), 8.20 (dd, 1H, H_6, J = 1.5, 4.8 Hz).

1-Phenylsulfonyl-2-trimethylstannyl-1*H*-pyrrolo[2,3-*b*]pyridine (3k) and 2-trimethylstannyl-1-[2'-(trimethylstannyl)phenylsulfonyl]-1*H*-pyrrolo[2,3-*b*]pyridine (4k).

Compounds **3k** and **4k** were prepared according to conditions reported for compound **3a** using 2.2 equivalents of trimethylstannyl chloride. Eluent: CH_2Cl_2.

3k: yield: 23%; mp 140-142°C (CH_3OH). IR (KBr), ν: 1360, 1160 (SO_2) cm^{-1}. ^{1}H-NMR (300MHz, $CDCl_3$), δ: 0.49 (s, 9H, 3xCH_3), 6.73 (s, 1H, H_3), 7.10 (dd, 1H, H_5, J = 5.2, 8.1 Hz), 7.45 (m, 2H, H_{arom}), 7.53 (m, 1H, H_{arom}), 7.76 (dd, 1H, H_4, J = 1.5, 8.1 Hz), 8.11 (m, 2H, H_{arom}), 8.32 (dd, 1H, H_6, J = 1.5, 5.2 Hz); Anal. Calcd for $C_{16}H_{18}N_2O_2SSn$: C, 45.64; H, 4.31; N, 6.65 Found: C, 45.35; H, 4.19; N, 6.87.

4k: yield: 57%; oil. IR (KBr), ν: 1350, 1160 (SO_2) cm^{-1}. ^{1}H-NMR (300MHz, $CDCl_3$), δ: 0.44 (s, 9H, 3xCH_3), 0.50 (s, 9H, 3xCH_3), 6.77 (s, 1H, H_3), 7.03 (dd, 1H, H_5, J = 4.4, 8.1 Hz), 7.10-7.30 (m, 2H, H_{arom}), 7.42 (m, 1H, H_{arom}), 7.70-7.80 (m, 2H, H_{arom}), 8.09 (dd, 1H, H_6, J = 1.5, 4.4 Hz); MS (NH_3): m/z = 585 (M^++1).

Lithiation of 1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridine and addition of electrophiles (with addition of TMEDA).

Same procedure as for the reported general procedure, with addition of a solution of THF (5 mL) containing **2** (0.258g, 1.0 mmol) and TMEDA (0.150 mL, 1.0 mmol), at -25°C. Yields are reported in Scheme 2.

(3-Diethylaminocarbonyl-2-methoxypyridin-4-yl)(1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl) methanol (6).

The compound **6** was obtained in 60% yield according to the procedure used for the synthesis of compound **3b**. Aldehyde **5** was used as electrophile (1.5 eq.) and the time of reaction has been 3 h. Eluent: ethyl acetate / petroleum ether , 90 / 10, v/v. Mp 190-192°C (CH_2Cl_2 / $(C_2H_5)_2O$). IR (KBr), ν: 3350-3250 (OH), 1640 (CO) (large) cm^{-1}. ^{1}H-NMR (300MHz, $CDCl_3$ + D_2O) (2 rotamers A / a: 75 / 25) ; δ: 0.68 (t, 3H, CH_{3a}, J = 7.1 Hz), 1.10 (t, 3H, CH_{3a}, J = 7.1 Hz), 1.20 (t, 3H, CH_{3A}, J = 7.1 Hz), 1.30 (t, 3H, CH_{3A}, J = 7.1 Hz), 2.40-3.20 (m, 4H, CH_{2a}), 3.21-3.85 (m, 4H, CH_{2A}), 3.95 (s, 3H, CH_{3a}), 4.05 (s, 3H, CH_{3A}), 6.38 (s, 1H, CH_a), 6.45-6.60 (m, 4H, CH_A + H_{3a} + 2H_{arom}), 6.96 (s, 1H, H_{3A}) 7.13 (dd, 1H, H_{5a}, J = 5.2, 7.4 Hz), 7.19 (dd, 1H, H_{5A}, J = 5.2, 7.4 Hz), 7.35-7.80 (m, 7H, H_{4a}+ H_{arom}), 7.84 (dd, 1H, H_{4A}, J= 1.5, 7.4 Hz), 7.97 (m, 4H, H_{arom}), 8.08 (d, 1H, H_{aromA}, J = 5.5 Hz), 8.30-8.35 (m, 2H, H_{6a} +H_{aroma}), 8.40 (dd, 1H, H_{6A}, J = 1.5, 5.2 Hz); Anal. Calcd for $C_{25}H_{26}N_4O_5S$: C, 60.71; H, 5.30; N, 11.33. Found: C, 60.45; H, 5.51; N, 11.12

(3-Diethylaminocarbonyl-2-methoxypyridin-4-yl)(1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl) Ketone (7).

Under an inert atmosphere, DMSO (0.367 mL, 4.960 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise to a solution of dry CH_2Cl_2 (6 mL) containing oxalyl chloride (0.216 mL, 2.480 mmol) at -60°C. Then the alcohol **6** (1.080 g, 2.190 mmol) in dry CH_2Cl_2 was added and followed, after 15 min, by the addition of triethylamine (1.15 mL, 11.260 mmol) to the mixture. The solution was stirred for 10 min at -60°C, then at room temperature for 2 h. H_2O was added to the mixture and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), the organic layers were dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The residue was chromatographed on a silica gel column (eluent: ethyl acetate / petroleum ether, 90 / 10, v / v) to give 754 mg of compound **7** (70% yield). Mp 96-98°C (CH_2Cl_2/ $(C_2H_5)_2O$). IR (KBr), ν: 1670, 1630 cm^{-1}. ^{1}H-NMR (300MHz, $CDCl_3$) δ: 1.16 (t, 6H, CH_3, J = 7.1 Hz), 3.20-3.90 (m, 4H, CH_2), 4.02 (s, 3H, CH_3), 6,97 (s, 1H, H_3), 7.20-7.30 (m, 2H, H_5 + H_{arom}), 7.50-7.65 (m, 3H, H_{arom}), 7.89 (dd, 1H, H_4, J= 1.5, 8.1 Hz), 8.33 (d, 1H, H_{arom}, J = 5.1 Hz), 8.47 (m, 2H, H_{arom}), 8.61 (dd, 1H, H_6, J = 1.5, 5.2 Hz); Anal. Calcd for $C_{25}H_{24}N_4O_5S$: C, 60.96; H, 4.91; N, 11.37. Found: C, 61.29; H, 5.19; N, 10.99.

1-(3-Diethylaminocarbonyl-2-methoxypyridin-4-yl)-1-(1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl) ethanol (8) and 4-methoxy-1-methyl-1-(1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-1,3-dihydro-3-oxo-furo [3,4-*c*] pyridine (9)

Under an inert atmosphere at room temperature the ketone **7** (0.495 g, 1.0 mmol), dissolved in dry THF (6 mL), was treated with CH_3MgCl (3M in THF, 0.365 mL, 1.10 mmol). The mixture was stirred for 1 h then acetic acid (1 mL) was added dropwise and the solution was heated at reflux for 1h. After evaporation *in vacuo*, the residue was treated with ethyl ether (3 mL) until a brown precipitate appeared. The compound **8** was filtered (0.60 g) and after purification on a silica gel column (eluent: ethyl acetate / petroleum ether, 90 / 10, v/v) gave compound **9** in 90% yield.

8: ^{1}H-NMR (300MHz, DMSO-d_6 + D_2O) δ: 1.06 (t, 6H, CH_3, J = 7.0 Hz), 2.13 (s, 3H, CH_3), 2.74 (m, 4H, CH_2), 4.05 (s, 3H, CH_3), 7.24 (d, 1H, H_{arom}, J = 5.2 Hz), 7.27 (s, 1H, H_3), 7.32 (dd, 1H, H_5 , J = 4.3, 7.7 Hz), 7.50-7.67 (m, 3H, H_{arom}), 7.97 (m, 2H, H_{arom}), 8.06 (d, 1H, H_4, J= 7.7 Hz), 8.41 (d, 1H, H_6, J = 4.3 Hz), 8.50 (d, 1H, H_{arom}, J = 5.2 Hz).

9: mp 98-100°C (CH_2Cl_2 / $(C_2H_5)_2O$). IR (KBr), ν: 1770 (CO) cm^{-1}. ^{1}H-NMR (300MHz, DMSO-d_6) δ: 2.10 (s, 3H, CH_3), 4.06 (s, 3H, CH_3), 7.20 (d, 1H, H_{arom}, J = 5.2 Hz), 7.25 (s, 1H, H_3), 7.29 (dd, 1H, H_5 , J = 4.3, 7.7 Hz), 7.45-7.65 (m, 3H, H_{arom}), 7.94 (m, 2H, H_{arom}), 8.03 (d, 1H, H_4, J= 7.7 Hz), 8.38 (d, 1H, H_6, J = 4.3 Hz), 8.46 (d, 1H, H_{arom}, J = 5.2 Hz); MS (NH_3): m/z = 436 (M^++1); Anal. Calcd for $C_{22}H_{17}N_3O_5S$: C, 60.68; H, 3.94; N, 9.65. Found: C, 60.83; H, 3.81; N, 9.43.

3-Hydroxy-4-methoxy-1-methyl-1-(1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)-1,3-dihydro-3-oxo-furo[3,4-*c*]pyridine (10).

Compound **9** (0.520 g, 1.20 mmol) was stirred at -78°C in CH_2Cl_2 (20 mL) under an inert atmosphere. Then DIBAH was added dropwise (5x1.2 mL, 5x1.2 mmol, 1 eq each 10 min) until the starting product disappeared (tlc control). After warming to -30°C, acetone (2 mL) and an aqueous solution of acetic acid (20%) (5mL) were added. When the mixture had risen to room temperature, H_2O (30 mL) was added. After collecting the organic layer by decantation, the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The residue was chromatographed on a silica gel column (eluent: 99.5 / 0.5, CH_2Cl_2 / CH_3OH, v/v) to give compound **10** in 94% yield. Mp 68-70°C (CH_2Cl_2 / $(C_2H_5)_2O$). IR (KBr), ν: 3400-3200 (OH) cm^{-1}. ^{1}H-NMR (300MHz, DMSO-d_6 +D_2O) (2 diastereomers, A/a, 60/40) δ: 2.05 (s, 3H, CH_{3a}), 2.07 (s, 3H, CH_{3A}), 3.91 (s, 3H, CH_{3A}), 3.93 (s, 3H, CH_{3a}),

6.25 (s, 1H, H_{3a}), 6.45 (s, 1H, CH_A), 6.50 (s, 1H, CH_a), 6.85 (d, 1H, H_{aromA}, J = 5.1 Hz), 7.00 (s, 1H, H_{3A}), 7.10-7.30 (m, 3H, H_{arom}), 7.35-7.65 (m, 7H, H_{arom}), 7.80 (d, 1H, H_{4a}, J= 7.7 Hz), 7.90 (m, 2H, H_{arom}), 7.96 (d, 1H, H_{4A}, J= 7.7 Hz), 8.12 (d, 1H, H_{arom}, J = 5.1 Hz), 8.15-8.30 (m, 4H, H_{arom}); Anal. Calcd for $C_{22}H_{19}N_3O_5S$: C, 60.40; H, 4.38; N, 9.61. Found: C, 60.13; H, 4.72; N, 9.43.

1-Methoxy-5-methyl-6*H*-pyrido[3',2':4,5]pyrrolo[2,3-*g*]isoquinoline (11).

Potassium hydroxide (0.168 g, 3.0 mmol) and compound **10** (0.090 g, 0.026 mmol) were refluxed in ethanol 95% (2 mL) for 1 h. After evaporation of C_2H_5OH *in vacuo*, H_2O (3 mL) was added. The mixture was neutralised, extracted with CH_2Cl_2 (5 x 3 mL). The organic layers were dried ($MgSO_4$). After evaporation of the solvent *in vacuo*, the residue was chromatographed on a silica gel column (eluent: 99 / 1; CH_2Cl_2 / CH_3OH, v/v) to give compound **11** in 15% yield. Mp > 250°C (CH_3OH). IR (KBr), v: 3150 (NH) cm^{-1}. ^1H-NMR (300MHz, DMSO-d_6) δ: 2.80 (s, 3H, CH_3), 4.11 (s, 3H, CH_3), 7.24 (dd, 1H, H_9, J = 5.4, 7.8 Hz), 7.54 (d, 1H, H_4, J = 5.5 Hz), 7.98 (d, 1H, H_3, J = 5.5 Hz), 8.49 (d, 1H, H_8, J= 5.4 Hz), 8.72 (d, 1H, H_{10}, J= 7.8 Hz), 8.94 (s, 1H, H_{11}), 11.98 (s, 1H, NH); SM (NH_3): m/z = 264 (M^++1); Anal. Calcd for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 73.29; H, 4.68; N, 16.08.

Palladium cross coupling: general procedure:

1-Benzenesulfonyl-2-trimethylstannyl-7-azaindole (**3k**) (0.210 g, 0.50 mmol), the iodo derivative (0.550 mmol), triethylbenzyl ammonium chloride (0.114 g, 0.550 mmol), and $Pd[P(C_6H_5)_3]_4$ (0.020 g, 0.025 mmol) were refluxed in CH_3CN (3 mL) for 24 h. After evaporation of CH_3CN *in vacuo*, the residue was chromatographed on a silica gel column to give the desired compound.

2,2-Dimethyl-*N*-[3-(1-phenylsulfonyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)pyridin-2-yl]propanamide (12a).

Eluent: 99.5 / 0.5; CH_2Cl_2 / CH_3OH, v / v. yield: 65%. Mp 128-130°C (CH_3OH). IR (KBr), v: 3220-3120 (NH), 1670 (CO) cm^{-1}. ^1H-NMR (300MHz, $CDCl_3$) δ: 1.11 (s, 9H, 3 x CH_3), 6.67 (s, 1H, H_3), 7.19 (dd, 1H, H_5, J = 5.2, 8.1 Hz), 7.25-7.60 (m, 4H, H_{arom}), 7.70-7.85 (m, 4H, H_{arom}), 7.96 (s, 1H, NH), 8.45 (dd, 1H, H_{arom}, J = 2.2, 5.2 Hz), 8.60 (dd, 1H, H_{arom}, J = 2.2, 5.2 Hz); Anal. Calcd for $C_{23}H_{22}N_4O_3S$: C, 63.58; H, 5.10; N, 12.89. Found: C, 63.37; H, 5.26; N, 12.97.

Ethyl 2-(1-phenyl-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl) benzoate (12b).

Eluent: CH_2Cl_2. yield: 40%. Mp 148-150°C (C_2H_5OH). IR (KBr), v: 1700 (CO) cm^{-1}. ^1H-NMR (300MHz, $CDCl_3$) δ: 0.88 (s, 3H, CH_3), 3.90-4.15 (m, 2H, CH_2), 6.40 (s, 1H, H_3), 7.18 (dd, 1H, H_5 , J = 5.2, 8.1 Hz), 7.35-7.70 (m, 6H, H_{arom}), 7.80 (dd, 1H, H_4, J = 2.2, 8.1 Hz), 8.04 (d, 2H, H_{arom}, J = 7.4 Hz), 8.17 (m, 1H, H_{arom}), 8.45 (dd, 1H, H_6, J = 2.2, 5.2 Hz); Anal. Calcd for $C_{22}H_{18}N_2O_4S$: C, 65.01; H, 4.46; N, 6.89. Found: C, 65.37; H, 4.40; N, 6.99.

5-Chloro-11-(2-methylpropan-2-yl)pyrido[3', 2':4,5]pyrrolo[1,2-*c*]pyrido[3,2-*d*]pyrimidine (14).

Compound **12a** (0.070 g, 0.16 mmol) and $POCl_3$ (0.045 mL, 0.50 mmol) in toluene (2 mL) were heated for 3h at reflux. The solvent was evaporated *in vacuo* and H_2O (3mL) was added. After neutralisation, extraction was performed with CH_2Cl_2 (3 x 5 mL). After drying ($MgSO_4$), CH_2Cl_2 was evaporated *in vacuo* and the residue was chromatographed on a silica gel column (eluent: CH_2Cl_2) to give compound **14** in 40% yield. Mp 212-214°C (CH_3OH). IR (KBr), v: 1610 (C=N) cm^{-1}. ^1H-NMR (300MHz, $CDCl_3$) δ: 1.87 (s, 9H, 3 x CH_3), 7.43-7.51 (m, 2H, H_{arom}), 8.16 (dd, 1H, H_{arom}, J = 1.5, 8.1 Hz), 8.65 (dd, 1H, H_{arom}, J = 1.5, 4.4 Hz), 8.82 (dd, 1H, H_{arom}, J = 1.5, 4.4 Hz), 9.28 (dd, 1H, H_{arom}, J = 1.5, 8.1 Hz). SM (NH_3): m/z = 311 (M^++1), 313 (M^++3); Anal. Calcd for $C_{17}H_{15}ClN_4$: C, 65.70; H, 4.86; N, 18.03. Found: C, 65.63; H, 4.97; N, 18.23.

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