SYNTHESIS OF FUSED SYSTEMS IN THE ISOQUINOLINE SERIES : OXAZOLO- AND PYRROLO[3,2-*c*]ISOQUINOLINES

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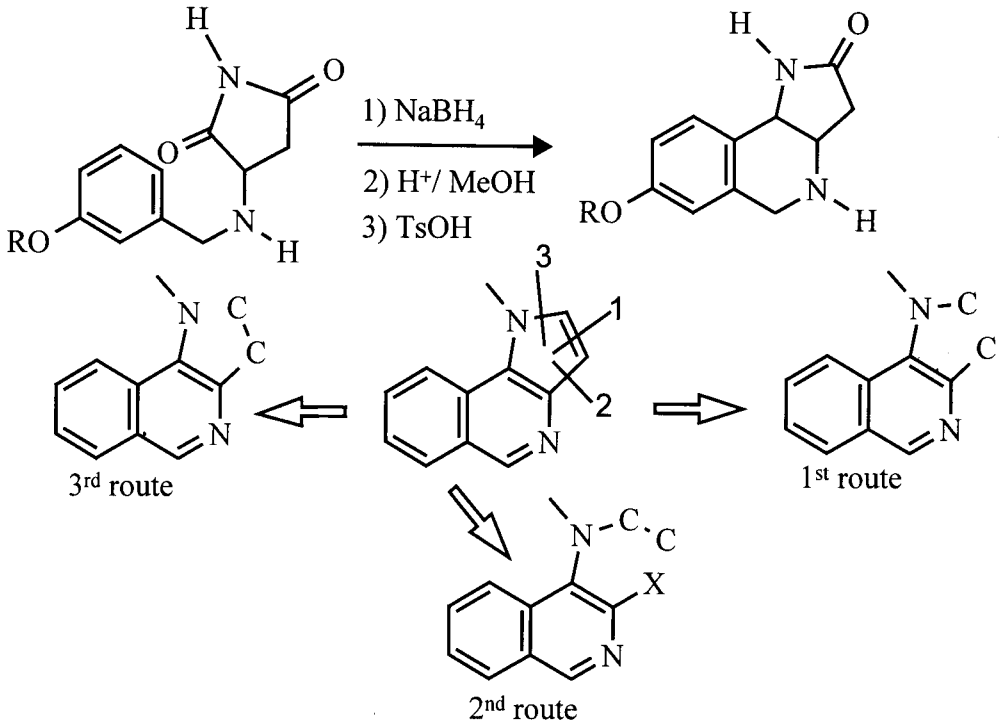
Abstract-In order to synthesize the pyrrolo[3,2-*c*]isoquinoline structure, three different routes starting from readily available isoquinolines were tried. The ring closure reaction of a malonic derivative of 4-amino-3-bromoisoquinoline led to an oxazolo[3,2-*c*]isoquinoline instead of the target molecule. This latter was obtained *via* Sonagashira coupling reaction followed by ring closure under basic conditions. A study of the lithiation of the *N*-sulfonated pyrrolo[3,2-*c*]isoquinoline was undertaken. After optimization of the lithiation conditions, various 2-substituted pyrrolo[3,2-*c*]isoquinolines were obtained and their oxidation reactions studied.

INTRODUCTION

During the course of our investigations to design potential receptors for carboxylic acids and amines we were concerned by the synthesis of pyrrolo[3,2-*c*]isoquinoline derivatives.[1] Whereas some papers describing the synthesis of pyrrolo[3,2-*c*]quinolines have recently appeared[2] only one was devoted to the parent isoquinoline structure.[3] We recently described a synthetic route starting from 3-aminosuccinimides.[4]

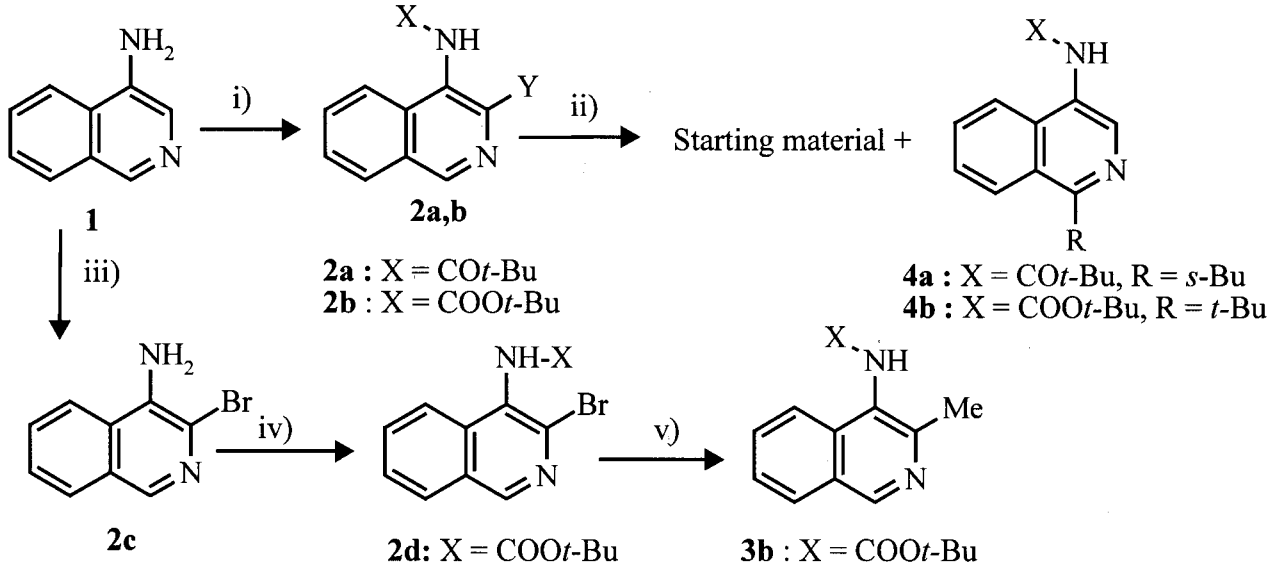


Scheme 1: The previous route[4] and three other strategies

In this route, the fused isoquinoline ring was constructed *via* an electrophilic cyclisation[4] leading to the pyrrolo[3,2-*c*]isoquinoline skeleton (Scheme 1).The main drawback of this strategy is that the cyclization could be successfully realized, only if, an electron-donating group is present (*i.e.* a methoxy or a benzyloxy group) at the phenyl ring *para* to the electrophilic attack. Another approach to this ring system would consist to build the pyrrole ring on the appropriate substituted isoquinoline derivatives. A simple retrosynthetic analysis shows that the pyrrolo[3,2-*c*]isoquinoline skeleton could be achieved by the three routes outlined in Scheme 1. In these three routes, the key step is the obtention of the appropriate 3,4-disubstituted isoquinoline derivatives starting from the readily available 4-aminoisoquinoline.[5] This latter compound is easily obtained *via* bromination of isoquinoline and subsequent copper salts promoted amination.[5]
The aim of this paper is to report the results of the various strategies outlined in the retrosynthetic Scheme 1 in order to synthesize pyrrolo[3,2-*c*]isoquinoline derivatives.

RESULTS AND DISCUSSION

1) Metalation of isoquinoline derivatives
Our objective was, starting from a 4-acylaminoisoquinoline, to substitute the 3 position with a one carbon atom electrophile and then to perform the ring closure (first route on Scheme 1). In the benzene series similar ring closure reactions were reported[6] starting from acylated *o*-toluidines.



(i) ClCO*t*-Bu, NEt_3, THF for **2a**. $(Boc)_2O$, NaHMDS, THF for **2b**. (ii) 1) RLi, TMEDA, THF; 2) Ethanol-*d*. (iii) NBS, DMF, rt, 1 h. (iv) NaHMDS, $(Boc)_2O$, THF. (v) 1) 1.2 eq MeLi, ether; 2) 1.1 eq *n*-BuLi; 3) MeI

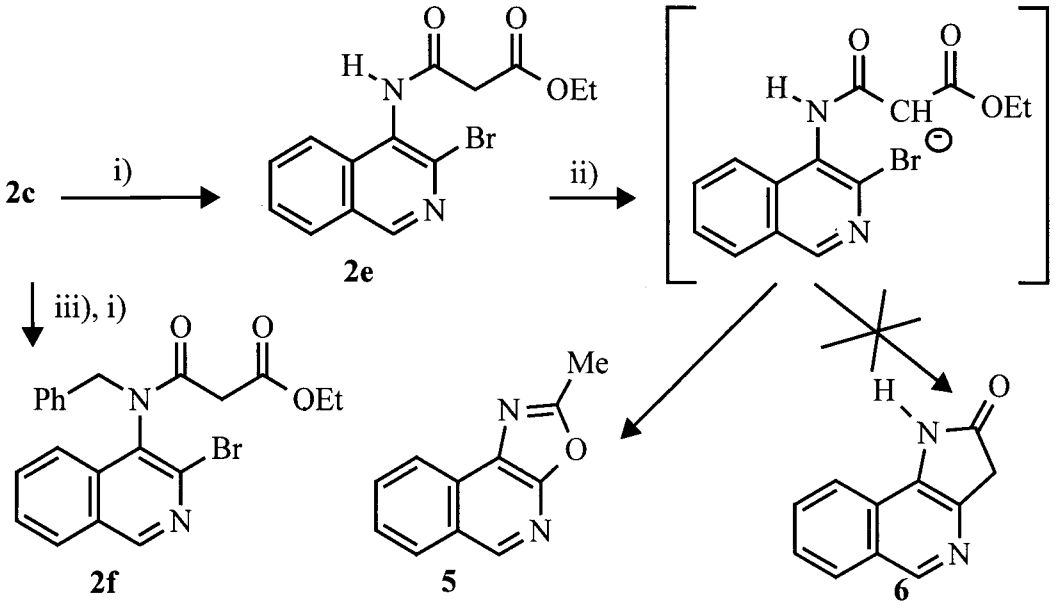
Scheme 2

We first tried metalation reactions on 4-acylaminoisoquinolines expecting that the acylamino group would play a directing metalation role (Scheme 2). Very little is known about the direct lithiation of isoquinolines.[7] Nucleophilic addition at the 1-position was often reported.[7] However, in the quinoline series, 3-acylamino derivatives were successfully metalated with LDA.[8]
Starting from the 4-pivaloylamino derivative (**2a**) or from the 4-*tert*-butyloxycarbonylamino derivative (**2b**), we tested various sterically hindered alkyllithium reagents (with a view to lowering the addition reaction at the 1 position). The reaction mixture was then quenched with ethanol-*d* before hydrolysis. Whatever the conditions no metalation occurred (no deuterium incorporation was observed) but in some cases the 1-alkyl substituted isoquinoline resulting from the oxidation of the intermediate addition product during the work-up was observed besides starting material. Two 1,4-disubstituted derivatives

(**4a**) or (**4b**) were thus obtained but not purified. We also tried the halogen-metal exchange route starting from 4-amino-3-bromoisoquinoline (**2c**). This latter compound was obtained *via* bromination of 4-aminoisoquinoline (**1**) with bromonium acetate.[9] However the yield was poor (40 %) and not reproducible. So we performed the bromination with *N*-bromosuccinimide (NBS) in dimethylformamide under conditions described for bromination of electron-rich aromatic compounds[10] and the yield was improved (80 %). The structure was confirmed by the observation of a nuclear Overhauser effect between protons at 1 and 8 positions (6.2 % NOE). The direct halogen metal exchange of bromoanilines can be achieved with a large excess of *n*-BuLi.[11] We used a 4-fold excess of *n*-BuLi in THF followed by quenching with EtOD. The sole product was 4-aminoquinoline probably resulting from a prototropic process which could be either intra- or intermolecular.[12] To avoid this prototropic process, the 3-bromo-4-*tert*-butyloxycarbonylamino derivative (**2d**) (obtained from **2c** by conventional method) was first submitted to the N-H deprotonation with methyllithium poorly efficient for halogen metal exchange.[13] Further reaction with *n*-BuLi (-55 °C) and methyl iodide as an electrophile led to **3b** in a 45 % yield. First attempts using BuLi as a base in ether gave a little addition on the ring even at -55 °C. So we used more hindered bases. Generation of carbanion of a 3-methylisoquinoline was reported by action of lithium amides affording the expected derivatives after reaction with various electrophiles.[14] Under similar conditions : LDA, LDA/HMPA, and also PhLi we did not obtain the expected cyclised coumpound. We can assume that the anionic species did not form as no deuterated compound could be isolated after quenching of the presumed carbanion with EtOD.

2) Ethyl (3-bromo-4-aminocarbonylisoquinolin-2-yl)acetate route.

Our strategy (2nd route in Scheme 1) was to generate the anion at active methylene position and to realize the ring closure by well documentated methods described in the litterature.[15] In this case, it could be expected that the nucleophilic ring closure would be easy since the carbon-bromine bond bore by an electron deficient ring is more reactive than in the benzene series. Effectively, reaction occurred but unfortunately we did not obtain compound (**6**) or its precursor (Scheme 3). Instead, we obtained, the 2-methyloxazolo[5,4-*c*]isoquinoline[16] which was identified by microanalysis, MS, IR, ^1H and ^{13}C NMR spectroscopies.[17] This result is surprising because similar compounds in the homoaromatic series gave mainly the pyrrolo derivative.[18]



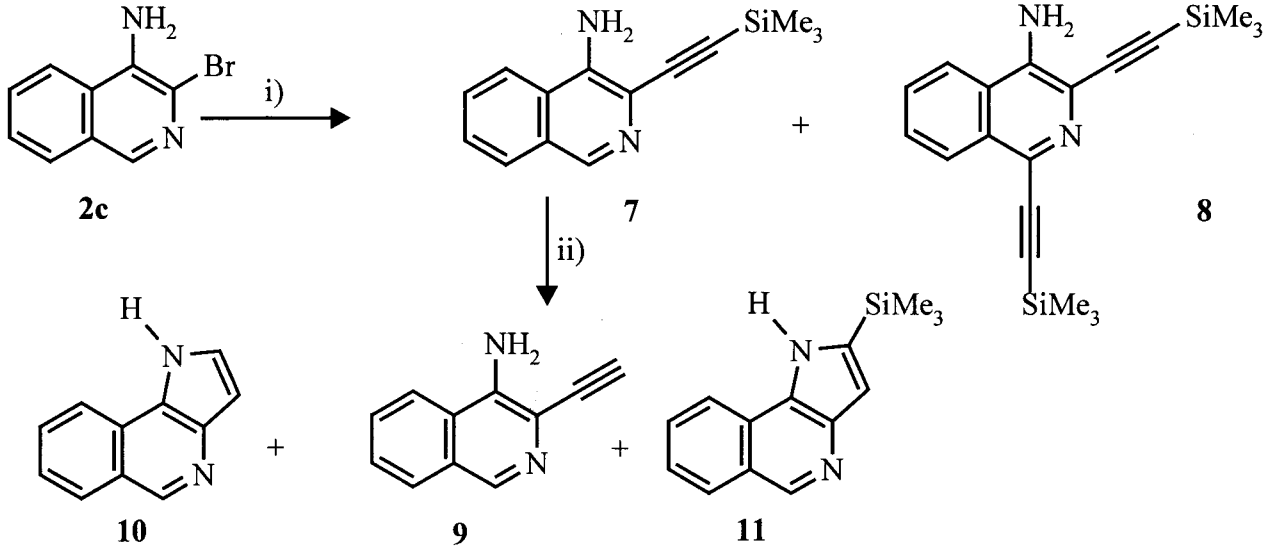
(i) $ClCOCH_2COOEt$, CH_2Cl_2, NEt_3, 0 °C --> rt. (ii) CuI, DMF, NaH, 120 °C. iii) NaHMDS, THF, rt then $PhCH_2Cl$.

Scheme 3

It must be mentioned that for compound (**5**) the above cyclisations could proceed through benzyne formation instead of nucleophilic aromatic substitution. We performed the same reaction with the *N*-benzyl derivative (**2f**) but only tarry material could be isolated.

3) Cross coupling route

The third strategy described in Scheme 1 was successful *via* Pd° promoted cross coupling reaction[19] between trimethylsilylacetylene (TMSA) and 4-amino-3-bromoisoquinoline (**2c**).The ethynyl derivative (**7**) was obtained in a 53 % yield besides 18 % of the bis-coupled product (**8**). The temperature had no influence on the amount of **8**. Under appropriate conditions, it was reported that such aminoethylnyl derivatives could be cyclized into pyrrole rings.[20] Under CuI catalysis, the pyrrolo[3,2-*c*]isoquinoline was obtained in 53 % yield besides small amounts of compounds (**9**) and (**11**) whereas with $NaNH_2$ the yield was 73 % starting from **7** (no cyclization from **9**). The overall yield for **10** was 35 % within three steps whereas the previously reported method[3] (based on Fischer indole synthesis) required four steps and the yield was 4%.

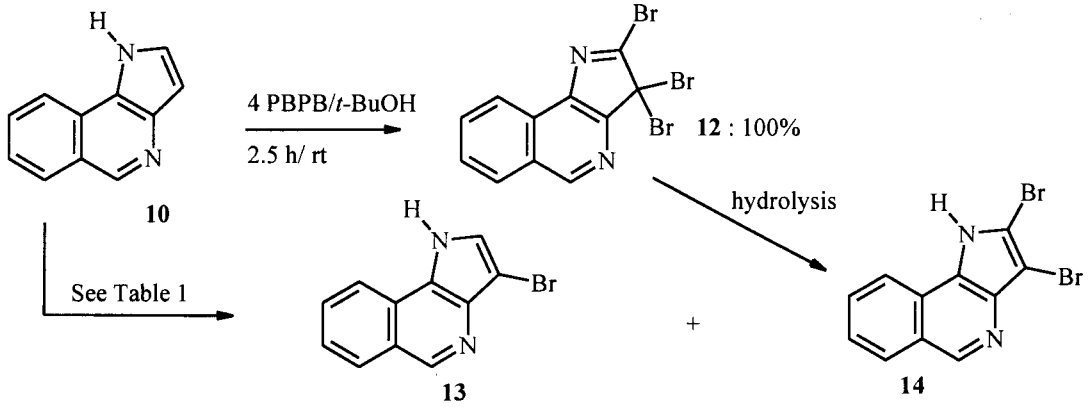


(i) 1.5 eq TMSA, 1 % CuI, 1 % $PdCl_2(PPh_3)_2$, DMF/NEt_3, 100 °C, 16 h. (ii) 2.5 eq $NaNH_2$, DMF, reflux, 16 h.

Scheme 4

4) Some properties of the pyrroloisoquinoline structure

a) Direct oxidation reactions. Bromination reagents like NBS are known to oxidise indoles into oxindoles.[21] Under non-aqueous conditions, these reagents led to the bromination of the pyrrole part of the indoles whereas in aqueous medium or in alcohol the oxidation reaction is the main process.[22] Marfat *et al.*[23] have published an efficient method leading to 7-azaoxindoles *via* oxidation of azaindoles with pyridinium bromide perbromide (PBPB).



Scheme 5

Under these conditions, the pyrrolo[3,2-*c*]isoquinoline (**10**) afforded in a quantitative yield the tribrominated derivative (**12**) instead of the expected azaoxindole. The structure of **12** was established by comparison with similar compounds in the 7-azaindole series[23] and by analysis of its MS and ^{1}H NMR spectra. We decided then to use the Hinman and Bauman method[21] with *N*-bromosuccinimide in *tert*-butanol and to control the amount of bromonium ions involved (Table 1).

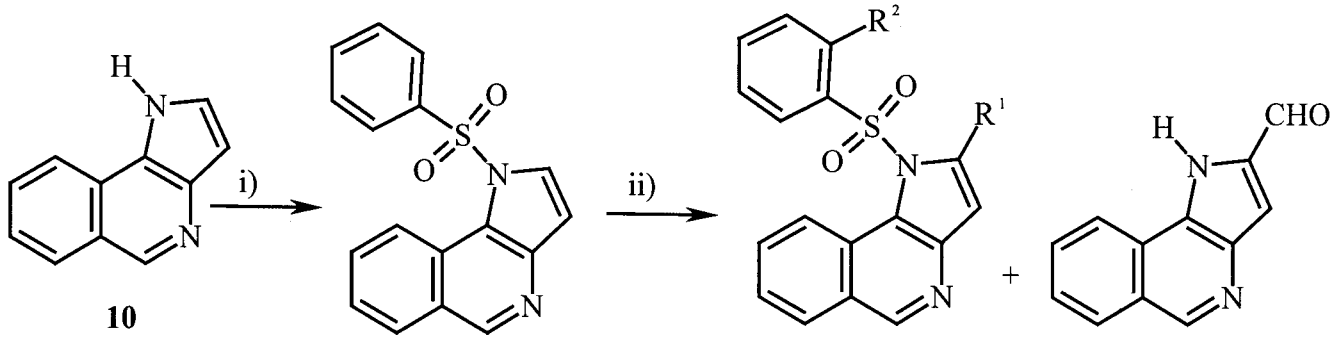
Entry	Reagent	Conditions	Result[a]
1[21]	1 NBS	*t*-BuOH/H_2O/rt/6.5 h	40% **13** + 5% **14**
2[21]	2 NBS	*t*-BuOH/H_2O/rt/3.5 h	11% **14**
3[24]	DMSO/HCl	H_2O/80°C/5 h	**10**
4	2 NBS	DMSO/rt/1 h	86% **14**
5	3 NBS	DMSO/rt/18 h	Complex mixture

(a) yields obtained after purification of the crude reaction mixture.

Table 1: Oxidation attempts

Only brominated products were obtained (Entries 1, 2, 4) whereas no oxidation product could be detected. However, it was possible to define conditions affording the dibromo compound (**14**) in good yield (Entry 4) or mainly the monobromo compound (**13**). In order to carry out the hydrolysis of the tribromo compound (**12**), we tried various conditions (KOH/EtOH/reflux, MeOH/H_2O/reflux,[25] 3N H_2SO_4/dioxane/reflux[22]) known to convert bromoindoles into oxindoles or isatines. Whatever the conditions, large degradation was observed but under acidic or neutral conditions, various amounts of the dibromo compound (**14**) could be isolated. The bromination reactions described above did not lead to the targeted oxidation product, but they afforded new brominated derivatives in the *1H*-pyrrolo[3,2-*c*]isoquinoline series.

b) Metallation of 1-phenylsulfonyl-*1H*-pyrrolo[3,2-*c*]isoquinoline. The metallation reaction has been largely used to functionalise the 2-position of indoles or azaindoles.[26] Appropriate regents are able to convert the intermediate lithio species into oxindoles. In order to avoid addition reactions on the isoquinoline part, we used directly hindered lithiation reagents like *tert*-butyllithium and LDA. We selected the *N*-phenylsulfonyl moiety as a protecting group of the pyrrole moiety.[27]



10

15: 61%

16 : R^1=D ; R^2=H
17 : R^1=$SiMe_3$; R^2=H
18 : R^1=$SiMe_3$; R^2=$SiMe_3$
19 : R^1=CHO ; R^2=H

20

(i): 2.5 eq $PhSO_2Cl$, 10% HSO_4,Bu_4N, NaOH, H_2O, toluene, rt 7 h. (ii): Metallation conditions, see Table 2.

Scheme 5

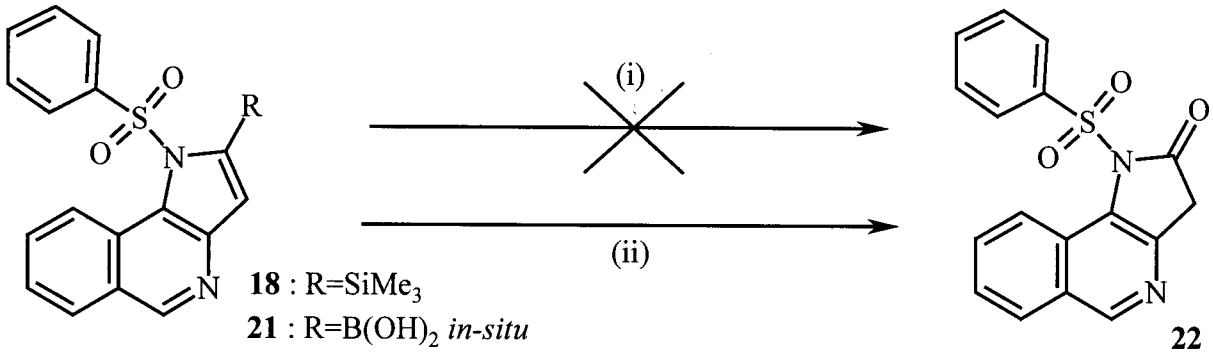
This latter group was introduced under the phase transfer conditions described by Illi[28] and the so-obtained compound (**15**) was submitted to lithiation experiments. The expected intermediate lithio species was quenched with methanol-*d*.

Entry	Base	Conditions	Electrophile	Result[a]
1	1.1 *t*-BuLi	THF/-73 °C/1 h	6 MeOD	**10**
2	2 LDA	THF/-18 °C/ 30 min	6 MeOD	73% **16**
3	2 LDA	THF/-18 °C/1.5 h	6 MeOD	65% **16**
4	2 LDA	THF/-18 °C/30 min	1 Me_3SiCl	43% **17** + 6% **15**
5	2 LDA + 1 TMEDA	THF/-18 °C/30 min	1 Me_3SiCl	41% **17** + 14% **15**
6	2 LDA + 1 Me_3SiCl	THF/rt/1.5 h	1 Me_3SiCl	? + 11% **15**
7	2 LTMP	THF/-18 °C/30 min	1 Me_3SiCl	11% **17** + 16% **15** 10% **18**
8	2 LDA	THF/-18 °C/30 min	6 HCOOEt	27% **19** + 13% **20**

(a): yields obtained after purification by flash chromatography of the crude reaction mixture.

Table 2 : Metallation experiments

No metallation reaction was observed with *tert*-butyllithium, at low temperature (Table 2, Entry 1). An excess of LDA to deplace the equilibrium,[26b,c] and subsequent quenching with methanol-*d* led to the deuterated compound (**16**) (Entry 2) in a 73 % yield besides desulfonylated product (**10** < 10%) and unreacted material (**15** < 10%). Since it was not possible to improve the yield with increasing of the reaction time (Entry 3), we selected the metallation conditions of Entry 2 and we used electrophiles able to afford the targeted azaoxindole after oxidation. Chlorotrimethylsilane led to a 43 % yield (Entry 4) and addition of TMEDA did not improve this yield[26a,b] (Entry 5). We also tried equilibrium displacement by simultaneous introduction of the electrophile and the lithiation reagent (Entry 6)[29] but we observed only the formation of unidentified side products. The more basic LTMP led to a decreased yield (11% **17**; Entry 7) due to the formation of the disilyl species (**18**) (10%) *via* metallation of both the pyrrole and phenyl ring of the benzene sulfonyl moiety.[30] Quenching with ethyl formate afforded the aldehyde (**19**) (Entry 8) besides a small amount of the deprotected compound (**20**). The boronic acid (**21**) was also synthesized as an intermediate and was subsequently oxidised into (**22**) under the conditions described by Mongin *et al*[31] in the pyridine series. The silylated compound (**17**) afforded only degradation products.



(i) 4 eq $MeCO_3H$, 16 eq $MeCO_2Na$, CH_2Cl_2, 0°C-->rt, 4 days. (ii) 1.1 eq $MeCO_3H$, THF, -18 °C to 0 °C, 1 h.

Scheme 6

CONCLUSION

During the course of this work, we have explored several routes for the obtention of the pyrroloisoquinoline structure. The synthesis of 4-amino-3-bromoisoquinoline (**2c**) has been improved and bromine-lithium exchanges or coupling reactions were studied. Two new routes leading to 2-methyloxazolo[5,4-*c*]isoquinoline (**5**) and pyrrolo[3,2-*c*]isoquinoline (**10**) were described. The metallation reaction of the *N*-sulfonated pyrrolo[3,2-*c*]isoquinoline and subsequent quenching with some electrophiles afforded 2-substituted derivatives.

EXPERIMENTAL

The IR spectra were recorded on a Beckmann IR 4250 spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded either on a 200 MHz or a 400 MHz Bruker apparatus. Spectra were recorded in $CDCl_3$ or in DMSO-d_6). Chemicals were purchased from Aldrich Co. and Janssen Co. and, unless ortherwise stated, were used without further purification. Flash chromatographies were performed with silica gel 60 (70-230 mesh from Merck) and monitored by TLC with silica gel plates (Merck, Kieselgel 60 F_{254}). General remark : The 4 protons of the benzene part of isoquinoline derivatives generally appeared at chemical shifts in the following decreasing order : H_5-H_8 and H_6-H_7. The values of the chemical shifts are closely related, so the corresponding signals are sometimes difficult to be interpreted because some signals are superimposed. As a consequence, in some cases an expected doublet of doublet will appear as a triplet (with identical coupling constants) and will be noted t_{app} (apparent triplet) or as a doublet (with two different coupling constants) and will be noted dd_{app} (apparent doublet of doublet).

4-*tert*-Butylcarbonylaminoisoquinoline (2a)

To a solution of 4-aminoisoquinoline (**1**)[5] (0.4 g, 2.8 mmol) and triethylamine (0.4 mL, 2.8 mmol) in THF (10 mL) was added dropwise pivaloyl chloride (0.36 mL, 2.8 mmol.) at a temperature below 5 °C. The mixture was then stirred at rt for 4 h and water (6 mL) was added. The pH was adjusted to 8-9 with a satured solution of sodium carbonate, and the solution was extracted with dichloromethane. The organic phases were dried on $MgSO_4$ and evaporated to dryness under reduced pressure. The crude product was purified by chromatography (silica gel, acetone/cyclohexane 2/1, $R_f = 0.5$). The yield was 0.22 g (34 %). Brown oil. ^1H NMR (200 MHz, $CDCl_3$) : 1.41 (9H, s) ; 7.5-7.72 (3H, m) ; 7.80 (1H, m) ; 7.95 (1H, d, J = 7.9 Hz) ; 8.75 (1H, s) ; 9.05 (1H, s). IR (cm^{-1}) : 1650 (C=O). Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.64; H, 7.08; N, 12.27. Found : C, 73.50; H, 6.99; N, 12.11.

4-*tert*-Butyloxycarbonylaminoisoquinoline (2b)

To a solution of 4-aminoisoquinoline (**1**) (0.5 g, 3.5 mmol) in THF (10 mL) was added dropwise, at rt, a solution of NaHMDS (1 M in THF, 7.7 mL, 7.7 mmol). The mixture was stirred for 15 min at this temperature. A solution of di-*tert*-butyl dicarbonate (0.772 g, 3.5 mmol) in THF (10 mL) was added under argon. After 2.5 h, aqueous hydrochloric acid (0.25 M, 48 mL) was added. The mixture was extracted with ethyl acetate (3 x 20 mL) and the organic phases were dried ($MgSO_4$) and evaporated to dryness. The residue was purified by chromatography (silica gel, ethyl acetate/cyclohexane 3/1, Rf = 0.5). A brown solid was obtained. Yield 0.64 g (75 %). mp 162 °C (ethanol/water). ^1H NMR (200 MHz, $CDCl_3$) : 1.59 (9H, s); 6.84 (1H, m); 7.66 (1H, dd_{app}, J = 9.1 and 8.1 Hz); 7.78 (1H, t_{app}, J = 6.9 Hz); 7.94 (1H, d_{app}, J = 8.4 Hz); 8.03 (1H, d_{app}, J = 7.8 Hz); 8.92 (1H, s); 9.11 (1H, s). IR (cm^{-1}) : 1674 (C=O). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.82 ; H, 6.61 ; N, 11.47. Found : C, 68.93 ; H, 6.97 ; N, 11.36.

4-Amino-3-bromoisoquinoline (2c)

To a solution of 4-aminoisoquinoline (**1**) (8.53 g, 59.2 mmol) in DMF (30 mL) cooled at 10 °C, was added *N*-bromosuccinimide (10.54 g, 59.2 mmol). The mixture was stirred at rt until complete disappearence of reagent (**1**) (followed by TLC, $R_f = 0.8$ in ethyl acetate, about 1 h). Water (300 mL) was then added and the solution was extracted with ethyl acetate (5 x 140 mL). The organic phase was washed with water (3 x 300 mL), dried ($MgSO_4$) and evaporated to dryness to afford a brown solid. Yield 10.96 g (83 %). mp 139 °C (ethanol/water) (lit.,[7] 140-141 °C). ^1H NMR (200 MHz, $CDCl_3$): 4.70 (2H, m); 7.58 (1H, dt, J = 1.1 and 8.1 Hz); 7.66 (1H, dt, J = 1.4 and 8.4 Hz); 7.76 (1H, dd, J = 0.6 and 8.4 Hz); 7.88 (1H, d, J = 8.1 Hz); 8.48 (1H, s). Anal. Calcd for $C_9H_7N_2Br$: C, 48.45; H, 3.17; N, 12.56. Found : C, 48.66; H, 3.05; N, 12.41.

3-Bromo-4-*tert*-butyloxycarbonylaminoisoquinoline (2d)

To a solution of 4-amino-3-bromoisoquinoline (**2c**) (6 g, 26.9 mmol) in THF (15 mL) under argon, was added dropwise, at rt, a solution of NaHMDS (2M solution in THF, 29 mL, 58 mmol). The mixture was stirred for 15 min, then di-*tert*-butyl dicarbonate (5.93 g, 26.9 mmol) in THF (25 mL) was added. After stirring for 4 h, the solvent was evaporated to dryness. The residue was dissolved in aqueous hydrochloric acid (0.25 M solution, 250 mL) and extracted with ethyl acetate (5x100 mL). The organic phase was dried ($MgSO_4$), evaporated to dryness and the solid recrystallized from toluene to afford 6.52 g (75 %) of a beige solid. TLC: Rf = 0.2 (dichloromethane/cyclohexane 1/1). mp 149 °C. ^1H NMR (200 MHz, $CDCl_3$): 1.55 (9H, s); 7.45 (1H, m); 7.68 (1H, td, J = 8.1 and 1.2 Hz); 7.82 (1H, td, J = 6.9 and 1.3 Hz); 8.02 (2H, d, J = 9.3 Hz). IR (cm^{-1}) 1716 (C=O). Anal. Calcd for $C_{14}H_{15}N_2O_2Br$: C, 52.02 ; H, 4.69 ; N, 8.67. Found C, 52.21; H, 4.34 ; N, 8.84.

3-Methyl-4-*tert*-butyloxycarbonylaminoisoquinoline (3b)

A solution of methyllithium (0.8 M in ether, 4.6 mL, 3.7 mmol) was added under argon, at -70°C, to a solution of compound (**2d**) (1.004 g, 3.1 mmol) in ether (90 mL). After stirring for 45 min, a solution of *n*-butyllithium (2.5 M in hexanes, 1.3 mL, 3.25 mmol) was added dropwise and the mixture was stirred for 75 min at -55 °C. Methyl iodide (2.9 mL, 46.1 mmol) was then added and the mixture was stirred at rt for 12 h. Water (100 mL) was added, the mixture was extracted with dichloromethane (4 x 40 mL). The organic phase was dried ($MgSO_4$) and evaporated to dryness. The obtained oil was purified by chromatography (silica gel, ethyl acetate/dichloromethane 1/2, R_f = 0.2). Yield 0.32 g (44 %). Yellow solid. mp 155 °C (ethanol/water). ^1H NMR (200 MHz, $CDCl_3$): 1.56 (9H, m); 2.72 (3H, s); 6.30 (1H, m); 7.62 (1H, dd, J = 7.0 and 8.0 Hz); 7.76 (1H, ddd : J = 1.2, 8.4 and 6.8 Hz); 7.96 (1H, d, J = 6.2 Hz); 8.00 (1H, d, J = 7.2 Hz); 9.30 (1H, s). IR (cm^{-1}) : 1708 (C=O). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.73 ; H, 7.03 ; N, 10.85. Found : C, 69.56; H, 7.09; N, 10.70.

Ethyl *N*-2-[(3-bromoisoquinolin-4-yl)aminocarbonyl]acetate (2e)

To a solution of monoethyl malonate[32] (1.48 g, 11.2 mmol) in benzene (20 mL) containing 2 drops of DMF, oxalyl chloride (1.09 mL, 12.3 mmol) was added dropwise at 0 °C. The mixture was stirred at rt for 2 h and the volatile products and solvent were eliminated under vacuum. The resulting crude acid chloride was dissolved in dicholoromethane (15 mL).

A solution of 4-amino-3-bromoisoquinoline (**2c**) (0.5 g, 2.2 mmol) and triethylamine (0.37 mL ; 2,7 mmol) in dichloromethane (20 mL) was then dropwise added, at 0 °C for 1 h to the above acid chloride under argon. The solution was stirred for 12 h at rt, then washed with water (2 x 10 mL) and a saturated aqueous sodium carbonate solution (2 x 10 mL). The organic phase was dried ($MgSO_4$) then evaporated to dryness. The obtained crude solid was recrystallized from ethyl acetate/cyclohexane. Yield 0.55 g (74 %). Beige solid. mp 169 °C (decomp). TLC: R_f = 0.3 (ethyl acetate/cyclohexane 1/1). ^1H NMR (200 MHz, $CDCl_3$): 1.45 (3H, t, J = 7.1 Hz); 3.71 (2H, s); 4.39 (2H, q, J = 7.1 Hz); 7.69 (1H, t, J = 6.8); 7.75 (1H, dd, J = 8.4 and 6.7 Hz); 7.89 (1H, d, J = 8.3 Hz); 8.04 (1H, d, J = 8.1 Hz); 9.02 (1H, s); 9.25 (1H, m). IR (cm^{-1}) : 1729 and 1660 (C=O ester and C=O amide). Anal. Calcd for $C_{14}H_{13}N_2O_3Br$: C, 49.87; H, 3.89; N, 8.31. Found : C, 49.95; H, 3.58; N, 8.39.

Ethyl *N*-benzyl-*N*-2-[(3-bromoisoquinolin-4-yl)aminocarbonyl]acetate (2f)

A solution of NaHMDS (2 M in THF, 3.1 mL, 6.2 mmol) was added dropwise at rt under argon, to a solution of 4-amino-3-bromoisoquinoline (**2c**) (1.36 g, 6.1 mmol) in THF (30 mL). After stirring for 15 min at rt, a solution of benzyl bromide (1.15 g, 6.7 mmol) in anhydrous THF (30 mL) was added. The solution was stirred at rt for 12 h, then treated with a saturated aqueous solution of ammonium chloride (110 mL). After evaporation of THF under vacuum, the aqueous phase was extracted with dichloromethane (3 x 50 mL), the organic phase was dried ($MgSO_4$) and concentrated. The residual oil was purified by column chromatography (silica gel, dichloromethane, R_f = 0.4) giving 4-*N*-

benzylamino-3-bromoisoquinoline as a yellow oil. Yield 1.1 g (58 %). ^{1}H NMR (200 MHz, $CDCl_3$): 4.30 (1H, m); 4.50 (2H, s); 7.30-7.55 (5H, m); 7.66 (1H, dt_{app}, J = 1.3 and 8.1 Hz); 7.75 (1H, dt_{app}, J = 1.7 and 8.4 Hz); 8.00 (1H, d_{app}, J = 7.6 Hz); 8.21 (1H, d_{app}, J = 8.2 Hz); 8.73 (1H, s). Anal. Calcd for $C_{16}H_{13}N_2Br$: C, 61.35; H, 4.19; N, 8.94. Found : C, 61.73; H, 4.27; N, 9.18 .

The so-obtained *N*-benzylamino derivative was condensed with 9 eq of ethyl malonyl chloride as described for the obtention of compound (**2e**). Purification by column chromatography. Yield 1.19 g (80 %). White solid. mp 94 °C (ethanol/water). TLC: R_f = 0.2 (ethylacetate/cyclohexane). ^{1}H NMR (200 MHz, $CDCl_3$) : 1.19 (3H, t, J = 7.2 Hz); 2.95 (1H, d, J = 15.5 Hz); 3.18 (1H, d, J = 15.5 Hz); 4.05 (2H, 2 q, J = 3.4 and 7.2 Hz) ; 4.55 (1H, d, J = 13.9 Hz); 5.52 (1H, d, J = 13.9 Hz); 7.51-7.67 (2H, m); 7.35 (1H, dd_{app}, J = 7.6 Hz); 8.02 (1H, dd_{app}, J = 7.3 and 1.1 Hz); 9.08 (1H, s); IR (cm^{-1}) : 1744 and 1675 (C=O ester and C=O amide). Anal. Calcd for $C_{21}H_{19}N_2O_3Br$: C, 59.87; H, 4.56; N, 6.65. Found : C, 59.76; H, 4.49; N, 6.52.

2-Methyloxazolo[5,4-*c*]isoquinoline (5)

To a solution of compound (**2e**) (0.1 g, 0.3 mmol) in DMF (5 mL), under argon at rt, was added sodium hydride (80 % suspension, 0.029 g, 0.9 mmol). When hydrogen did not evolved, cuprous iodide (0.087 g, 0.45 mmol) was added and the mixture was warmed at 120 °C for 5 h. After cooling, water (60 mL) was added and the aqueous phase was extracted with ethyl acetate (4x40 mL). The organic phase was dried ($MgSO_4$) and evaporated to dryness. The residual solid was purified by column chromatography (silica gel, ethyl acetate/dichloromethane 1/30, R_f = 0.3). Yield 0.024 g (44 %). Yellow solid. mp 116-118 °C.(lit.,[16] 127 °C). ^{1}H NMR (200 MHz, $CDCl_3$): 2.79 (3H, s); 7.64 (1H, dt_{app}, J = 1.1 and 8.1 Hz); 7.86 (1H, dt_{app}, J = 1.2 and 8.2 Hz); 8.13 (1H, d_{app}, J = 8.4 Hz); 8.42 (1H, d_{app}, J = 8.3 Hz); 8.98 (1H, s). ^{13}C NMR ($CDCl_3$): 14.88; 121.06-125.86-128.34-131.06; 126.80-127.22-129.64; 155.73; 164.44. I.R (cm^{-1}): 1637 (oxazole ring). MS (EI) 184. Anal. Cacd for $C_{11}H_8N_2O$: C, 71.72; H, 4.39; N, 15.21. Found: C, 71.59; H, 4.15; N, 15.12. Under the same conditions, no reaction occurred with compound (**2f**).

Sonagashira reaction

A mixture of 4-amino-3-bromoisoquinoline (**2c**) (2 g, 9 mmol), cuprous iodide (0.017 g, 0.09 mmol), $PdCl_2(PPh_3)_2$ (0.056 g, 0.09 mmol), trimethylsilylacetylene (2.6 mL, 18 mmol) in THF (7 mL) and triethylamine (42 mL) was heated at 100 °C under argon for 16 h. After cooling at rt, the mixture was evaporated to dryness and the residue was purified by column chromatography (silica gel, ethyl acetate/cyclohexane 1/5). Two products were obtained :

4-Amino-3-trimethylsilylethynylisoquinoline (7) R_f= 0.1. Yield 1.16 g (54 %). Yellow solid. mp : 152 °C (ethanol/water). ^{1}H NMR (200 MHz, $CDCl_3$): 0.32 (9H, s); 4.78 (2H, m); 7.55-7.70 (2H, m); 7.80 (1H, d_{app}, J = 8.4 Hz); 7.91 (1H, d_{app}, J = 8.4 Hz); 8.67 (1H, s). IR (cm^{-1}): 2140 (ethyne). Anal. Calcd for $C_{14}H_{16}N_2Si$: C, 69.94; H, 6.72; N, 11.66. Found : C, 69.98; H, 6.72; N, 11.29.

4-Amino-1,3-bis(trimethylsilylethynyl)isoquinoline (8) R_f = 0.2. Yield 0.42 g (14 %). Yellow solid. mp 195 °C (ethanol/water). ^{1}H NMR (200 MHz, $CDCl_3$) : 0.32 (s, 18H); 4.96 (m, 2H); 7.6-7.8 (m, 3H); 8.37 (d, 1H). Anal. Calcd for $C_{14}H_{16}N_2Si$: C, 69.94; H, 6.72; N, 11.66. Found : C, 69.98; H, 6.72; N, 11.29.

Cyclization with cuprous iodide

The above ethynylisoquinoline (7) (0.484 g, 2 mmol) and cuprous iodide (0.005 g, 0.025 mmol) were dissolved in freshly distilled DMF (15 mL) was heated to reflux for 24 h. The solvent was removed under vacuum and the residue dissolved in dichloromethane (70 mL) and ammonia (25 mL, 32 % aqueous solution). After decantation, the organic layer was dried ($MgSO_4$) and concentrated to dryness. The residual dark oil was purified by column chromatography on silica gel (ethyl acetate/cyclohexane 2/3). Three compounds were isolated:

Pyrroloisoquinoline (10)
Yield 0.17 g (51 %).(R_f = 0.1 : ethyl acetate/cyclohexane 2/3). Pale yellow solid. mp 206 °C (ethanol/water). ^{1}H NMR (200 MHz, $CDCl_3$): 6.96 (1H, dd, J = 2.1 and 3.2 Hz); 7.43 (1H, dd_{app}, J = 2.9 and 3.2 Hz); 7.54 (1H, dd_{app}, J = 8.2 and 7.1 Hz); 7.78 (1H, dt_{app}, J = 1.2 and 8.2 Hz); 8.07 (2H, t_{app}, J = 8.1 Hz); 9.07 (1H, s); 9.70 (1H, m). Anal. Calcd for $C_{11}H_8N_2$: C, 78.54; H, 4.80; N, 16.65. Found: C, 77.7; H, 4.7; N, 16.3.

Trimethylsilylpyrroloisoquinoline (11)
Yield 0.034 g (7 %). Yellow solid. mp >205 °C (decomp, ether). R_f = 0.15 (ethyl acetate/cyclohexane : 2/3). ^{1}H NMR (200 MHz, $CDCl_3$): 0.42 (9H, s); 7.1 (1H, d, J =2.2 Hz); 7.54 (1H, dd, J= 8.1 and 7.0 Hz); 7.75 (1H, dd, J = 5.9 and 6.9 Hz); 8.06 (1H, 1H, J = 8.5 Hz); 8.10 (1H, d, J = 7.4 Hz); 9.04 (2H,s).

4-amino-3-ethylnylisoquinoline (9)
Yield 0.013 g (4 %). White solid. mp 228 °C (decomp, ethanol/water). R_f = 0.2 (ethyl acetate/cyclohexane : 2/3). ^{1}H NMR (200MHz, $CDCl_3$): 3.61 (1H, s); 4.86 (2H, m); 7.54-7.77 (2H, m); 7.84 (1H, d, J = 7.8 Hz); 7.89 (1H, d, J = 7.4 Hz). 8.64 (1H, s).

Cyclization with sodium amide
A mixture of the trimethylsilylisoquinoline (**7**) (0.87 g, 3.6 mmol) and sodium amide (0.37 g, 9 mmol) in freshly distilled DMF (35 mL) was heated to reflux under an argon atmosphere for 16 h. The solvent was eliminated under vacuum and the residue was triturated in water. The aqueous layer was extracted with dichloromethane. After usual work-up, the residual dark oil was purified by column chromatography on silica gel (ethyl acetate/cyclohexane : 2/3) giving 0.46 g (76 %) of the required pyrroloisoquinoline as a sole product.

2,3,3-Tribromo-*3H*-pyrrolo[3,2-*c*]isoquinoline (12)
To a stirred solution of the pyrrolo[3,2-*c*]isoquinoline (**10**) (0.05 g, 0.3 mmol) in *tert*-butanol (3 mL) was added pyridinium bromide perbromide (PBPB, 0.31 g, 0.92 mmol) within 25 min. The reaction mixture was allowed to stir at rt with occasionnal warming (to prevent *tert*-butanol from freezing) over a period of 3 h. An additional amount of PBPB (0.1g, 0.3 mmol) was added and the reaction mixture was stirred for an additional 1 h. *tert*-Butanol was removed *in vacuo* and the resulting residue dissolved in ethyl acetate/water (20 mL of a 1/1 mixture). The organic layer was separated and the aqueous layer was extracted with an additional 8 mL of ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give 0.122 g (quantitative yield) of a green solid. mp > 250 °C (decomp, ethyl acetate). ^{1}H NMR ($CDCl_3$, 200 MHz): 7.72 (1H, ddd, J = 9.4, 8.2 and 1.1 Hz); 7.89 (1H, ddd, J = 9.2, 8.2 and 1.2 Hz); 8.10 (1H, dd, J=8.4 and 1.0 Hz); 8.4 (1H, d, J = 10.4 Hz); 9.23 (1H, s). MS (EI): 406 and typical fragments 325, 245 and 165 displaying three bromine atoms.

3-Bromo-*1H*-pyrrolo[3,2-*c*]isoquinoline (13)
To a solution of the pyrrolo[3,2-*c*]isoquinoline (**10**) (0.05 g, 0.3 mmol) in *tert*-butanol (2 mL) containing water (0.1 mL), *N*-bromosuccinimide (0.06 g, 0.33 mmol) was added in small portions within 15 min. The resulting mixture was stirred at rt for 7 h. The solvent was removed under reduced pressure, the residue triturated with water (4 mL) and extracted with dichloromethane. A brown solid was obtained (0.109 g). The crude product was purified by flash chromatography (silica gel, ethyl acetate/cyclohexane 3/1). Yield 0.03 g (40 %). mp >260 °C (decomp, ethyl acetate). ^{1}H NMR ($CDCl_3$, 200 MHz): 7.45 (1H, s); 7.59 (1H, dd_{app}, J = 8.1 and 7.0 Hz); 7.78 (1H, dd_{app}, J=7.07 and 8.3 Hz); 8.04 (1H, d_{app}, J = 7.6 Hz); 8.12 (1H, d_{app}, J = 8.1 Hz); 9.1 (1H, s); 9.19 (1H, m). IR (cm^{-1}): 1635 (C=C). Anal. Calcd for $C_{11}H_7N_2Br$: C, 53.46; H, 2.86; N,11.34. Found: C, 53.1; H, 2.6; N, 11.0.

2,3-Dibromo-*1H*-pyrrolo[3,2-*c*]isoquinoline (14)

To a solution of pyrrolo[3,2-*c*]isoquinoline (**10**) (0.05 g, 0.3 mmol) in DMSO (1 mL), *N*-bromosuccinimide (0.11 g, 0.62 mmol) was added in small portions within 15 min. The resulting mixture was stirred at rt for 1 h. After addition of water, the precipitated material was filtered, washed with a small amount of water and then with cyclohexane. A brown solid was obtained (0.083 g, 86 %) after drying. This solid was crystallized from ethanol/water. mp 252 °C (decomp, ethanol). ^{1}H NMR ($CDCl_3$, 200 MHz): 7.59 (1H, ddd, J = 1.1, 7.1 and 8.0 Hz); 7.78 (1H, ddd, J = 1.2, 7.0 and 8.2 Hz); 8.01 (1H, d_{app}, J = 8.1 Hz); 8.10 (1H, d_{app}, J = 8.0 Hz); 9.09 (1H, s); 9.61 (1H, m). IR (cm^{-1}) : 3630 (NH); 1633 (C=C). Anal. Calcd for $C_{11}H_6N_2Br_2$: C, 40.52; H, 1.86; N, 8.60. Found: C, 40.63; H, 1.44; N, 8.5.

1-Phenylsulfonyl-*1H*-pyrrolo[3,2-*c*]isoquinoline (15)

A mixture of 1*H*-pyrrolo[3,2-*c*]isoquinoline (**10**) (0.523 g, 3.1 mmol), tetrabutylammonium hydrogensulfate (0.11 g, 0.32 mmol) in toluene (80 mL) and 50 % aqueous sodium hydroxide (26 mL) was vigourously stirred for 5 min at rt. Benzenesulfonyl chloride (0.64 mL, 5 mmol) was then added dropwise within 15 min. The resulting slurry was vigourously stirred for 5.5 h. An other amount of benzenesulfonyl chloride (0.40 mL, 3.1 mmol) was added and the solution stirred vigourously for 1.5 h. Water (105 mL) was then added and the organic layer was collected. The aqueous layer was extracted with dichloromethane (3×70 mL). The organic layers were washed with water (3×70 mL) and dried on $MgSO_4$. Removal of the solvent led to a yellow oil which was purified by flash chromatography on silica gel (ethyl acetate/cyclohexane: 1/2, R_f=0.25). The yield was 0.58 g (61 %) of a yellow solid. mp 136 °C. IR (cm^{-1}):1619 (aromatics); 1370. 1326. 1188 (NSO_2Ph). ^{1}H NMR ($CDCl_3$, 200 MHz): 7.11 (1H, d, J = 3.7 Hz); 7.30-7.59 (4H, m); 7.69-7.81 (3H, m); 8.02 (1H, d, J = 8.1 Hz); 8.05 (1H, d, J = 3.7 Hz); 9.04 (1H, d, hidden by the signal at 9.07 ppm); 9.07 (1H, s). Anal. Calcd for $C_{17}H_{12}N_2O_2S$: C, 66.21; H, 3.93; N, 9.09. Found: C, 66.15; H, 3.96; N, 8.71.

General procedure for the metallation reaction of 1-phenylsulfonylpyrrolo[3,2-*c*]isoquinoline

The volumes of solvents and amounts of reagents are mentioned for each reaction. A solution of freshly distilled diisopropylamine or 2,2,6,6-tetramethylpiperidine in THF under an argon atmosphere was cooled to –78 °C. A solution of *n*-butyllithium (2.5 M in hexane) was added dropwise. The mixture was stirred for 15 min at this temperature and then warmed to –18°C (ice-salt bath). A solution of 1-phenylsulfonylpyrrolo[3,2-*c*]isoquinoline (**15**) in THF at –18°C under an argon.atmosphere was added dropwise on the lithium amide prepared above and the reaction mixture was stirred for 30 min at this temperature. The quenching with electrophiles and the hydrolysis are described for each molecule. The product was extracted with dichloromethane and the organic layers dried on $MgSO_4$ before removal of the solvent under reduced pressure. The residue was purified by flash chromatography on silica gel.

2-Deuterio-1-phenylsulfonyl-*1H*-pyrrolo[3,2-*c*]isoquinoline (16)

According to the general procedure, 1-phenylsulfonylpyrrolo[3,2-*c*]isoquinoline (**15**) (0.0492 g, 0.16 mmol) in THF (3 mL) was reacted with LDA prepared from diisopropylamine (0.045 mL, 0.32 mmol) in THF (3 mL) and *n*-butyllithium (2.5 M solution in hexane, 0.13 mL). The reaction mixture was quenched with methanol-*d* (0.3 mL, slow addition at –18 °C). The solution was stirred for 30 min at this temperature and then for 30 min at rt. The yield was 0.036 g (73 %) of a white solid. TLC: R_f=0.25 (ethyl acetate/cyclohexane : 1/2). ^{1}H NMR ($CDCl_3$): 7.30-7.59 (4H, m); 7.69-7.81 (3H m); 8.02 (1H, d, J = 8.1 Hz); 8.05 (1H, s); 9.04 (1H, s); 9.07 (1H, s).

2-Trimethylsilyl-1-phenylsulfonyl-*1H*-pyrrolo[3,2-*c*]isoquinoline (17)

According to the general procedure, 1-phenylsulfonylpyrrolo[3,2-*c*]isoquinoline (**15**) (0.063 g, 0.21 mmol) in THF (3 mL) was reacted with LDA prepared from diisopropylamine (0.060 mL, 0.44 mmol) in THF (3 mL) and *n*-butyllithium (2.5 M solution in hexane, 0.175 mL). The reaction mixture was quenched with chlorotrimethylsilane (0.027 mL, 0.21 mmol, slow addition at –18°C). The solution was

stirred for 2 h at -18°C and hydrolysis was carried out with aqueous 5% sodium hydrogencarbonate at 0 °C. The yield was 0.034 g (43 %) of a yellow oil. TLC: R_f=0.2 (ethyl acetate/cyclohexane: 1/4). IR (cm^{-1}): 1619 (aromatic); 1362, 1348, 1172 (NSO_2Ph); 846, 753 ($SiMe_3$). MS: 380 [$M^{+\bullet}$]. ^1H NMR ($CDCl_3$, 200 MHz): 0.51 (3H, s); 7.40 (1H, s); 7.29-7.72 (6H, m); 7.68 (1H, ddd, J = 1.6, 6.9 and 8.5 Hz); 8.00 (1H, dd, J = 1.0 and 7.9 Hz); 8.93 (1H, dd, J = 0.8 and 8.7 Hz); 9.06 (1H, s).

2-Trimethylsilyl-1-[2-(trimethylsilyl)phenylsulfonyl]-*1H*-pyrrolo[3,2-*c*]isoquinoline: (18)
According to the general procedure, 1-phenylsulfonylpyrrolo[3,2-*c*]isoquinoline (**15**) (0.05 g, 0.16 mmol) in THF (3 mL) was reacted with LTMP prepared from 2,2,6,6-tetramethylpiperidine (0.056 mL, 0.32 mmol) in THF (3 mL) and *n*-butyllithium (2.5 M solution in hexane, 0.13 mL). The reaction mixture was quenched with freshly distilled chlorotrimethylsilane (0.022 mL, 0.17 mmol, slow addition at –18 °C). The solution was stirred for 2 h at –18 °C and then decomposed with an aqueous solution of sodium hydrogencarbonate (5%) at 0 °C. The product was purified by flash chromatography on silica gel (R_f=0.2, ethyl acetate/cyclohexane: 1/10). The yield was 0.007 g (10 %) of a white solid. This side-product was not further purified. IR (cm^{-1}): 1624 (aromatic): 1357, 1175 (NSO_2Ph); 844, 754 ($SiMe_3$). MS (E.I.): 452 [$M^{+\bullet}$]. ^1H NMR ($CDCl_3$): 0.44 (9H, s); 0.65 (9H, s); 6.74 (1H, d, J = 8 Hz); 7.13 (1H, dd, J = 7.3 and 7.5 Hz); 7.47 (4H, m); 7.90 (1H, dd, J = 1.2 and 7.5); 8.03 (1H, m); 8.33 (1H, m).

1-Phenylsulfonyl-*1H*-pyrrolo[3,2-c]isoquinoline-2-carboxaldehyde: (19) and *1H*-Pyrrolo[3,2-*c*]isoquinoline-2-carboxaldehyde: (20)
According to the general procedure, 1-phenylsulfonylpyrrolo[3,2-*c*]isoquinoline (**15**) (0.500 g, 1.6 mmol) in THF (15 mL) was reacted with LDA prepared from diisopropylamine (0.45 mL, 0.32 mmol) in THF (15 mL) and *n*-butyllithium (2.5 M solution in hexane, 0.13 mL). The reaction mixture was quenched with ethyl formate (0.65 mL, 8 mmol, slow addition at –18 °C). The solution was stirred at –18 °C for 1 h and then 1 h at rt. Hydrolysis was carried out with a saturated solution of ammonium chloride at 0 °C. Purification was achieved by flash chromatography on silica gel (first elution with dichloromethane, ethyl acetate/cyclohexane: 2/3.3 and finally with ethyl acetate/cyclohexane: 5/1 in which R_f=0.3).

Product (19): The yield was 0.145 g (27 %) of a red solid. mp 248 °C (ethanol/water). IR (cm^{-1}): 3152, 1620, 1375, 1350, 1174 (NSO_2Ph). MS 336 [$M^{+\bullet}$] ; [$M^{+\bullet}$-28 : - CHO-1]. ^1H NMR ($CDCl_3$) : 7.04 (1H, s); 7.19-7.62 (6H, m); 7.76 (1H, dd, J = 7.0 and 7.4 Hz); 8.02 (1H, d, J = 7.8 Hz); 8.92 (1H, d, J = 8.8 Hz); 9.05 (1H, s). ^1H NMR (DMSO-d_6) : 6.95 (1H, s); 7.25-7.70 (6H, m); 7.81 (1H, dd, J = 8.7 and 7.6 Hz); 8.20 (1H, d, J = 7.5 Hz); 8.77 (1H, d, J = 8.6 Hz); 9.15 (1H, s). Whatever the solvent, no signal corresponding to the formyl group could be observed. Anal. Calcd for $C_{18}H_{12}N_2O_3S$: C, 64.61; H, 3.60; N, 8.33. Found: C, 64.70; H, 3.93; N, 8.22
Product (20) : The yield was 0.04 g (13 %) of a yellow solid. mp > 216 °C (decomp). TLC: R_f=0.3 (ethyl acetate/cyclohexane: 2/3). IR (cm^{-1}) :1670 (C=O aldehyde); 3096, 3026, 2929 (NH pyrrole). ^1H NMR ($CDCl_3$): 7.63 (1H, s); 7.71 (1H, dd, J = 7.6 and 7.0 Hz); 7.86 (1H, dd, J = 7.6 and 7.0 Hz); 8.12 (1H, d, J = 8.8 Hz); 8.24 (1H, d, J = 7.5 Hz); 9.94 (1H, s); 10.25 (1H, m).

REFERENCES AND NOTES

1. P. Charpentier, J. F. Brière, G. Dupas, G. Quéguiner, and J. Bourguignon, *Tetrahedron*, 1996, **52**, 10441.
2. S. K. Kang, S. S. Park, S. S. Kim, J. K. Choi, and E. K. Yum, Tetrahedron Lett., 1999, **40**, 4379 and references cited therein.
3. T. R. Govindachari and V. Sudarsanam, *Indian J. Chem.*, 1966, **5**, 16.
4. J. F. Brière, P. Charpentier, G. Dupas, G. Quéguiner, and J. Bourguignon, *Tetrahedron*, 1997, **53**, 2075.

5. J. J. Craig and W. E. Cass, *J. Am. Chem. Soc.*, 1942, **64**, 783.
6. E. M. Kaiser and J. D. Petty, *Synthesis*, 1975, 705.
7. M. D. Nair and M. S. Premila, 'The Chemistry of Heterocyclic Compounds: Isoquinolines part two,' Vol. 38, ed. by F. G. Kathawala, G. M. Coppola, and H. F. Schuster, J. Wiley and Sons, New York, 1990, p. 65.
8. a) A. Godard, J. M. Jacquelin, and G. Quéguiner, *J. Organomet. Chem.*, 1988, **354**, 273. b) An example of chlorine directed *ortho*-lithiation has been recently reported with LDA on 1-aryl-3-chloroisoquinolines: A. Ford, E. Sinn, and S. Woodward, *J. Chem. Soc., Perkin Trans. 1*, 1997, 927.
9. G. M. Sanders, M. Van Dijk, and H. J. den Hertog, *Rec. Trav. Chim. Pays-Bas*, 1974, **93**, 298.
10. R. H. Mitchell, Y. H. Lai, and R. V. Williams, *J. Org. Chem.*, 1979, **44**, 4733.
11. P. Beak, T. J. Musick, C. Liu, T. Cooper, and D. J. Gallagher, *J. Org. Chem.*, 1993, **58**, 7330.
12. N. S. Narashimhan, N. Sunder, R. Ammanamanchi, and B. D. Bonde, *J. Am. Chem. Soc.*, 1990, **112**, 4431.
13. T. R. Kelly and M. H. Kim, *J. Am. Chem. Soc.*, 1994, **116**, 7072.
14. G. P. Gisby, P. G. Sammes, and R. A. Watt, *J. Chem. Soc., Perkin Trans. 1*, 1982, 249.
15. a) M. F. Semmelhack, B. P. Chong, R. D. Satuffer, T. D. Rogerson, A. Chong, and L. D. Jones, *J. Am. Chem. Soc.*, 1975, **97**, 2507. b) T. Kume, K. Shimohara, H. Fujishima, S. Hara, and T. Shimoda, *Heterocycles*, 1990, **31**, 459.
16. E. B. Mullock, and H. Suschitzky, *J. Chem. Soc. (C)*, 1968, 1937. In the paper, compound (**10**) was obtained by pyrolysis of 4-azidoisoquinoline in a mixture of polyphosphoric acid and acetic acid.
17. a) I. Tikk, G. Deak, P. Sohar, and J. Tamas, *J. Chem Res. (S)*, 1987, 95. b) I. Tikk, G. Deak, P. Sohar, and J. Tamas, *J. Chem Res. (M)*, 1987, 1101.
18. J. F. Bunnett, T. Kato, R. R. Flynn, and J. A. Skorcz, *J. Org. Chem.*, 1963, **28**, 1
19. T. Sakamoto and Y. Kondo, *Chem. Pharm. Bull.*, 1987, **35**, 1823.
20. a) K. Iritani, S. Matsubara, and K. Utimoto, *Tetrahedron Lett.*, 1988, **29**, 1799. b) T. Sakamoto, Y. Kondo, S. Iwashita, and H. Yamanaka, *Chem. Pharm. Bull.*, 1987, **35**, 1823. c) D. Villemin and D. Goussu, *Heterocycles*, 1989, **29**, 1255. d) V. Kumar, J. A. Dority, E. R. Bacon, B. Singh, and G. Y. Lesher, *J. Org. Chem.*, 1992, **57**, 6995.
21. R. L. Hinman and C. P. Bauman, *J. Org. Chem.*, 1964, **29**, 1206.
22. W. B. Lawson, A. Patchornik, and B. Witkop, *J. Am. Chem. Soc.*, 1960, **82**, 5918.
23. A. Marfat and M. P. Carta, *Tetrahedron Lett.*, 1987, **28**, 4027.
24. K. Szabo-Pusztay and L. Szabo, *Synthesis*, 1979, 276.
25. J. Patrick, A. Yahya, and Y. Jim, *Tetrahedron Lett.*, 1984, **25**, 3099.
26. a) R. J. Sundberg, 'Best Synthetic Methods, Key Systems and Functional Groups: Indoles,'ed. by O. Meth-Cohn, Academic Press, London, 1996. b) A. S. Bourlot, E. Désarbre, and J. Y. Mérour, *Synthesis*, 1994, 411. c) J-R. Dormoy and A. Heymes, *Tetrahedron*, 1993, **49**, 2885.
27. a) R. J. Sunberg and H. F. Russell, *J. Org. Chem.*, 1973, **38**, 3324. b) G. W. Gribble, M. G. Saulnier, J. A. Obaza-Nutaitis, and D. M. Ketcha, *J. Org. Chem.*, 1992, **57**, 5891.
28. V. O. Illi, *Synthesis*, 1979, 136.
29. G. W. Gribble and S. C. Conway, *Synth. Commun.*, 1992, **22**, 2129.
30. R. J. Sundberg, R. Broome, C. P. Walters, and D. Schnur, *J. Heterocycl. Chem.*, 1981, **18**, 807.
31. a) S. C. Conway and G. W. Gribble, *Heterocycles*, 1990, **30**, 627. b) F. Trécourt, M. Mallet, O. Mongin, and G. Quéguiner, *J. Org. Chem.*, 1994, **59**, 6173.
32. D. S. Breslow and E. Baumgarden, *J. Am. Chem. Soc.*, 1944, **66**, 1286.

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