Two alternatives for the synthesis of pyrrolo[1,2-*a*]quinoxaline derivatives

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Dedicated to Professor Joan Bosch on the occasion of his 60th anniversary

Abstract
The 4,5-dihydropyrrolo[1,2-*a*]quinoxaline system was prepared through two different reaction sequences. The first method is based on the intramolecular reductive amination of the corresponding nitrophenylpyrrole-carbaldehyde intermediate, whereas an alternative synthesis involves as key step, the intramolecular substitution of an aromatic fluoride by a secondary amine.

Keywords: Pyrroles, pyrrolo-quinoxaline, defluoro-cyclization, polycyclic heterocyclic compounds

Introduction

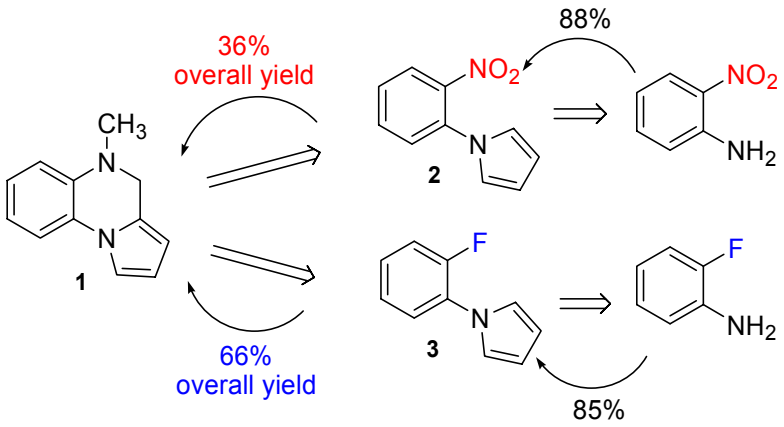
The pyrrolo[1,2-*a*]quinoxaline system is the skeleton of several heterocyclic compounds possessing interesting biological activity. This nucleus substituted at the C-4 with alkylpiperazines gives highly selective agonist affinity for the serotonine receptors.[1] Pyrrolo[1,2-*a*]quinoxaline-2- or -4-carboxylic acid hydrazide derivatives[2] showed high anti-tuberculosis activity, while 2-(aminomethyl)-4-phenylpyrrolo[1,2-*a*]quinoxalines revealed a central dopamine antagonist activity.[3] More recently, *N*-sulfonyl-pyrrolo[1,2-*a*]quinoxalines were prepared as estrogenic receptor modulators[4] and 4-hydrazino-pyrroloquinoxalines demonstrated anticancer activity and therapeutic properties influencing the angiogenesis function.[5]

Whereas the preparation of pyrrolo[1,2-*a*]quinoxalin-4-ones has been described,[6] a bibliographical search for the pyrrolo[1,2-*a*]quinoxalines revealed surprisingly that only a few synthetic procedures have been reported previously for these heterocyclic analogues, *i.e.* reduction of the lactam derivatives,[7] 1,3-dipolar cycloaddition of quinoxalium *N*-ylides to alkenes[8] and alkynes[9] or reaction of 1-(2-aminophenyl)pyrroles with aldehydes.[10]

As part of a program aimed at the discovery of novel polycyclic compounds with therapeutic potential and following our previous interest in the synthesis of tricyclic pyrrole condensed systems such as pyrrolo[2,1-*c*][1,4]benzoxazines,[11] we now wish to report two different sequences for the synthesis of its bioisosteric heterocycle pyrrolo[1,2-*a*]quinoxaline; both pyrrolo-benzoxazines and pyrrolo-quinoxalines are considered useful scaffolds in medicinal chemistry.

Results and Discussion

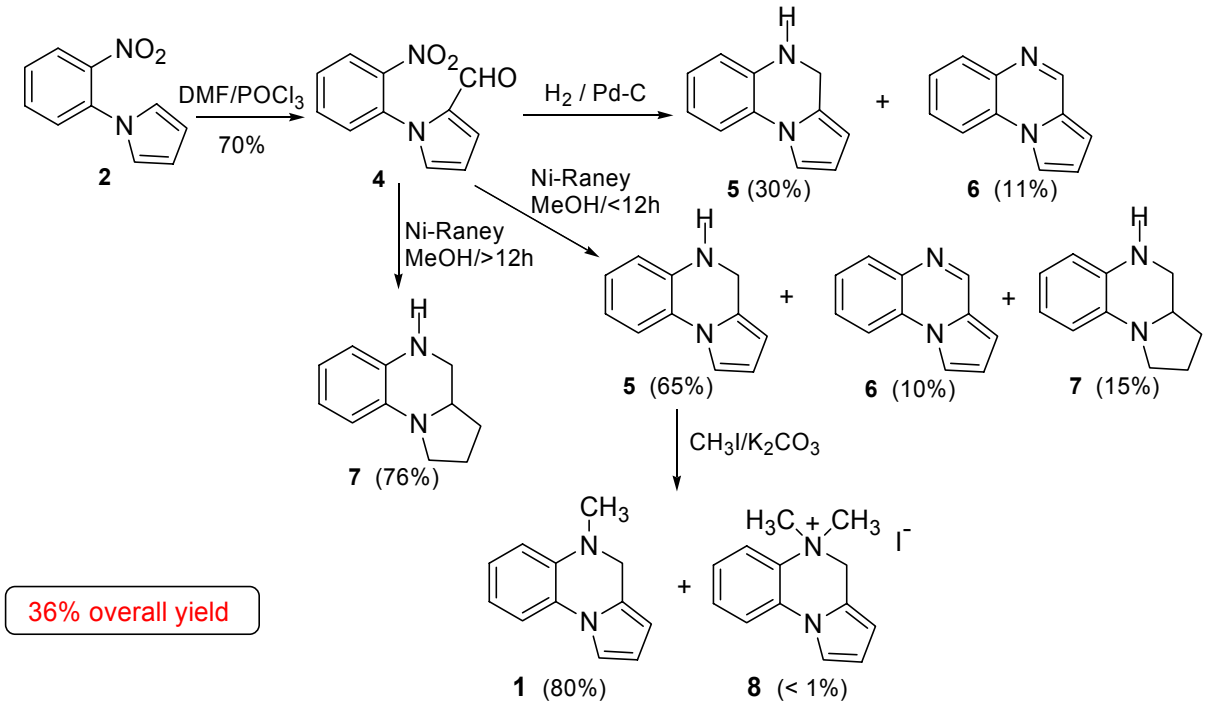
Following previous work of our laboratory on the synthesis of pyrrolo[2,1-*c*][1,4]benzoxazines[11] we report here two different and useful synthetic approaches to the synthesis of pyrrolo[1,2-*a*]quinoxalines from the corresponding commercially available 2-substituted anilines (Scheme 1).



Scheme 1

The key starting intermediates **2** and **3**[11] were prepared by reacting 2-nitroaniline or 2-fluoroaniline with 2,5-dimethoxytetrahydrofuran (DMTHF) in the presence of glacial acetic acid by a modified Paal-Knorr procedure[12-13] known as the Clauson-Kaas reaction[14] in 88% and 85% yield, respectively. The introduction of a formyl group at C-2 of the condensed heterocyclic system, under Vilsmeier-Haak conditions, affords the aldehydes **4** and **9** in acceptable yields (70% for **4** and 85% for **9**) (Scheme 2 and 3).

Method 1



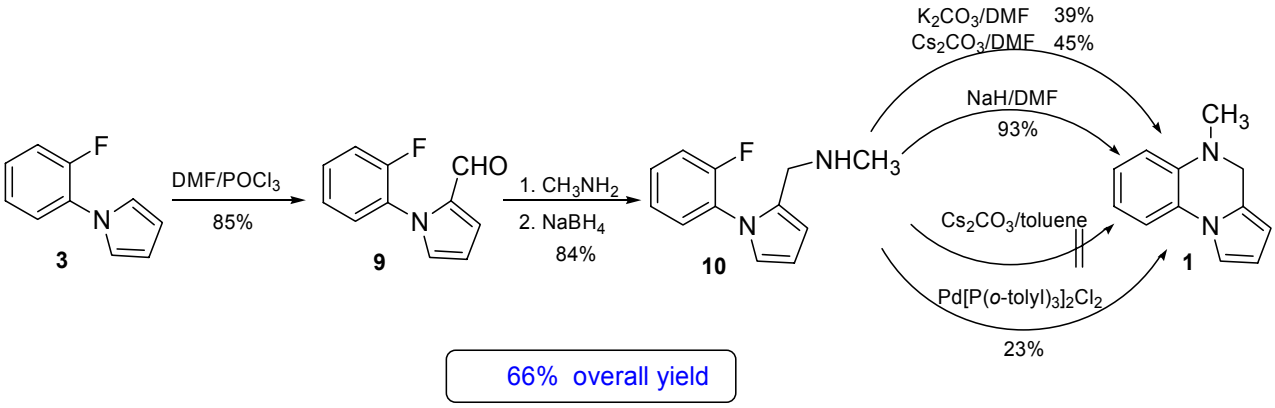
Scheme 2

The nitroaldehyde **4** was reductively cyclized using catalytic hydrogenation; optimum yield (65% for compound **5**) was obtained using Ni-Raney in methanol, under hydrogen atmosphere, for a period of time less than 12 h. Prolonged hydrogenation reaction time (more than 12 h) leads exclusively to reduced hexahydropyrroloquinoxaline **7** in 76% yield. When 10% Pd/C was used as catalyst in ethyl acetate, a mixture of the desired pyrrolo-quinoxaline **5** (30%) and the analogue **6** (11%) was obtained (Scheme 2).

Methylation of the pyrrolo-quinoxaline **5** was carried out in acetone with CH_3I in the presence of K_2CO_3 at room temperature to give the *N*-methylquinoxaline **1** in good yield (80%). In this alkylation process, traces of the corresponding quinoxalium iodide were also isolated (**8**). It is noteworthy that the compound **1** was previously prepared by Mannich reaction from *N*-(2-(methylamino)phenyl)pyrrole in only 22% yield.[15]

The pyrrolo-quinoxaline **1** was preferably prepared in higher yields by an alternative synthesis (*method 2*) in which 2-fluoroaniline was chosen as starting material. The formylation of the *N*-(2-fluorophenyl)pyrrole **3** and subsequent treatment with methylamine, followed by reduction of the intermediate imine with $NaBH_4$ provided the secondary amine **10** in good yield (Scheme 3).

Method 2



Scheme 3

Several attempts were made to optimize the intramolecular cyclization: first treatment of the methylamine **10** in refluxing toluene under the coupling reaction conditions[16] catalyzed by $Pd[P(o\text{-tolyl})_3]_2Cl_2$/BINAP/ Cs_2CO_3 gave the pyrrolo-quinoxaline **1** in low yields (< 30 %). Further insight into this reaction was obtained by treatment of the amine **10** with Cs_2CO_3 (1 eq) as a base without catalyst. The absence of reaction under these conditions suggests the implication of catalyst and ligand in the cyclization process or that the solvent is inadequate for the nucleophilic aromatic substitution.

The pyrrolo-quinoxaline **1** was successfully obtained by treatment of the methylamine **10** with NaH in DMF by direct intramolecular nucleophilic displacement of the fluoride anion by the secondary amine (93%). Other bases as anhydrous Cs_2CO_3 and K_2CO_3 in excess (5 eq) in DMF gave the quinoxaline in low yields (45% and 39% respectively). These results revealed that an excess of base is necessary and that DMF is the appropriate solvent for the intramolecular aromatic nucleophilic substitution.

Conclusion

The two synthetic methods described herein allow the preparation of the pyrrolo-quinoxaline **1** in each three steps, but whereas the *method 1* provide the pyrrolo-quinoxaline in 36% overall yield, the second sequence involving formylation, reductive amination and cyclization give the desired compound in 66% overall yield. It is interesting to note that *method 1* provides next to the desired dihydropyrrolo-quinoxaline, also the pyrrolo-quinoxaline **6** and the hexahydropyrrolo-quinoxaline **7**, interesting and useful intermediates in organic synthesis and in medicinal chemistry.

Experimental Section

General Methods. Melting points were obtained on an MFB-595010M Gallenkamp apparatus in open capillary tubes and are uncorrected. IR spectra were obtained using a FTIR Perkin-Elmer 1600 Infrared Spectrophotometer. Only noteworthy IR absorptions are listed (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini-200 (200 and 50.3 MHz respectively) or Varian Gemini-300 (300 and 75.5 MHz) Instrument using $CDCl_3$ as solvent with tetramethylsilane as internal standard or $(CD_3)_2CO$. Other ^{1}H-NMR spectra and heterocorrelation ^{1}H-^{13}C (HMQC and HMBC) experiments were recorded on a Varian VXR-500 (500 MHz). Mass spectra were recorded on a Helwett-Packard 5988-A. Column chromatography was performed with silica gel (E. Merck, 70-230 mesh). Reactions were monitored by TLC using 0.25 mm silica gel F-254 (E. Merck). Microanalysis was determined on a Carlo Erba–1106 analyser. All reagents were of commercially quality or were purified before use. Organic solvents were of analytical grade or were purified by standard procedures. Commercial products were obtained from Sigma-Aldrich.

Method 1. *N*-Methyl-4,5-dihydropyrrolo[1,2-*a*]quinoxaline (1). 5,5-Dimethyl-4*H*-pyrrolo[1,2-*a*]quinoxalium iodide (8). To a solution of quinoxaline **5** (250 mg, 1.47 mmol) in 30 mL of dry acetone was added K_2CO_3 (305 mg, 2.2 mmol) and methyl iodide (0.18 mL, 2.94 mmol). The resulting mixture was stirred at room temperature for 10 h. Then, acetone was removed and the residue was diluted with water (20 mL) and extracted with ether (3 x 15 mL). The organic phases were dried over Na_2SO_4, filtered and the solvent removed under vacuum to give a yellow solid, which was purified by silica gel column chromatography eluting with a mixture of hexane/ethyl acetate 90:10 affording the title compound as a yellow solid (216 mg, 1.18 mmol, 80 % yield). (See the reference 15 for experimental details reported previously for **1**, such as mp: 65-66 (methanol)).

Mp: 67-68 ºC (hexane / ethyl acetate). IR (KBr) υ cm^{-1}: 1645 (C=H); 1517 (C=C); 1377 (C-N). ^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm), 2.38 (s, 3H, CH_3-N); 3.63 (s, 2H, CH_2-N); 5.98 (m, 1H, H-3); 6.30 (m, 1H, H-2); 7.06-7.10 (m, 1H, H-6); 7.11 (m, 2H, H-7, H-8); 7.14 (dd, J_1 = 3, J_2 = 1.4 Hz, 1H, H-1), 7.28 (dd, J_1 = 7.8, J_2 = 1.4 Hz, 1H, H-9). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ(ppm), 38.4 (CH_3); 49.1 (CH_2); 103.6 (CH, C-3); 109.9 (CH, C-2); 112.7 (CH, C-6); 113.8 (CH, C-1); 114.4 (CH, C-9); 118.5 (CH, C-7); 124.7 (CH, C-8'); 125.7 (C, C-3a); 126.4 (C, C-5a); 138.2 (C, C-9a). Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21%. Found: C, 78.59; H, 6.23; N, 15.58%.

Finally, the column chromatography was eluted with ethyl acetate 100% to give only traces of the quinoxalium salt **8**, which was assigned structure by ^{1}H NMR spectroscopy and mass spectra. SM (EI) m/z (%): 327 (22) [MH+]. ^{1}H NMR (DMSO-d_6, 300 MHz) δ(ppm), 3.42 (s, 3H, CH_3-N); 3.52 (s, 3H, CH_3-N); 5,12 (s, 2H, CH_2-N); 6.44 (m, 2H, H-2, H-3); 7.41 (t, J = 8 Hz, 1H, H-8); 7.62 (t, J = 8 Hz, 1H, H-7); 7.76 (m, 1H, H-1); 8.01 (dd, J_1 = 8.6 Hz, J_2 = 1.6 Hz, 2H, H-6, H-9).

***N*-(2-Nitrophenyl)pyrrole (2).** Following the general procedure reported previously by V. Nacci *et al.*[17] after purification by column chromatography, the nitropyrrole **2** was obtained as a yellow oil in 88% yield. Nacci et all. reported only the ^{1}H NMR data for **2** and these are incomplete.
IR (KBr) υ cm^{-1}: 1530 (C=C); 1355 (C=N). ^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm), 6.37 (t, *J* = 2.2 Hz, 2H, H-3, H-4); 6.80 (t, *J* = 2.2 Hz, 2H, H-2, H-5); 7.50 (m, 1H, H-4'); 7.62 (d, *J* = 8 Hz, 1H, H-6'); 7.85 (dd, J_1 = 8, J_2 = 1.8 Hz, 1H, H-5'); 8.06 (d, *J* = 1.8 Hz, 1H, H-3'). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ(ppm), 110.9 (CH, C-3, C-4); 121.2 (CH, C-2, C-5); 124.9 (CH, C-6'); 127.5* (CH, C-3'); 127.7* (CH, C-4'); 133.2 (CH, C-5'); 134.0 (C, C-1'); 145.0 (C, C-2').
* interchangeable

***N*-(2-Fluorophenyl)pyrrole (3).** For the experimental procedure and analytical data, see reference 11.

***N*-(2-Nitrophenyl) pyrrole-2-carbaldehyde (4).** To a solution of distilled DMF (0.43 mL, 5.84 mmol) and $POCl_3$ (895 mg, 5.84 mmol) was added the nitrophenylpyrrole **2** (1 g, 5.31 mmol). The resulting mixture was stirred at room temperature for 3 h. The crude reaction was treated with saturated solution of Na_2CO_3 and extracted with ether (3x20mL). The organic phase was dried over Na_2SO_4, filtered and the filtrate was evaporated. The crude of reaction was purified by column chromatography of silica gel eluting with hexane/ethyl acetate to give the aldehyde **4** in 70% yield (805 mg, 3.72 mmol). Mp: 128-130 ºC (hexane/ethyl acetate). IR (KBr) υ cm^{-1}: 1652 (C=O); 1530 (C=C); 1354 (C-NO_2). ^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm), 6.49 (m, 1H, H-4); 7.02 (m, 1H, H-3); 7.13 (m, 1H, H-5); 7.43 (d, *J* = 8.8 Hz, 1H, H-6'); 7.68 (m, 2H, H-4', H-5'); 8.20 (d, *J* = 8.8 Hz, 1H, H-3'); 9.51 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ(ppm), 111.6 (CH, C-4); 123.9 (CH, C-2); 124.8 (CH, C-5); 125.2 (CH, C-3); 129.4 (CH, C-6'); 129.5 (CH, C-3'); 131.1 (CH, C-4'); 133.5 (C, C-1'); 133.6 (CH, C-5'); 146.0 (C, C-2'); 178.6 (C, CHO).

4,5-Dihydropyrrolo[1,2-*a*]quinoxaline (5). Pyrrolo[1,2-*a*]quinoxaline (6). 1,2,3,3a,4,5-Hexahydropyrrolo[1,2-*a*]quinoxaline (7). A solution of nitrocarbaldehyde **4** (500 mg, 2.31 mmol) in methanol (30 mL) was introduced in a hydrogenation flask and Ni-Raney (300 mg, 50% in water) was added. The resulting mixture was stirred under a hydrogen atmosphere during 4h. Then, the suspension was filtered and the methanol of the liquid phase was removed under vacuum. The crude product was purified by silica gel column chromatography and eluted with a mixture of hexane and ethyl acetate (90:10) to give a white solid (255 mg, 1.5 mmol, 65 % yield) corresponding to the 4,5-dihydropyrrolo[1,2-*a*]quinoxaline (**5**). Using a mixture of hexane and ethyl acetate (85:15), the 1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoxaline (**7**) (60 mg, 0.34 mmol, 15 %) was obtained as a white solid and finally, the elution with a mixture of hexane and ethyl acetate (80:20) gave the pyrrolo[1,2-*a*]quinoxaline (**6**) as a white solid (39 mg, 0.23 mmol, 10%).
Compound **7** was obtained in 76% yield, following the same conditions, after a prolonged reaction time (more than 12 h).
Using 10% Pd/C as a catalyst in ethyl acetate, a mixture of the pyrroloquinoxaline **5** (30%) and the pyrroloquinoxaline **6** (11%) was obtained after purification by column chromatography eluting with hexane/ethyl acetate.

4,5-Dihydropyrrolo[1,2-*a*]quinoxaline (5). Mp: 114-116 ºC (hexane/ethyl acetate). IR (KBr) υ cm^{-1}: 3368 (NH); 1490 (C=C); 1294 (C-N). ^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm), 3.90 (bs, 1H, NH); 4.40 (s, 2H, CH_2-N); 5.98(m, 1H, H-3); 6.30 (t, J_1 = 3 Hz, 1H, H-2); 6.72 (dd, J_1 = 7.8, J_2 = 1.4 Hz, 1H, H-6); 6.80 (dt, J_1 = 7.8, J_2 = 1.6 Hz, 1H, H-7); 6.95 (dd, J_1 = 7.2, J_2 = 1.4 Hz, 1H, H-8); 7.14 (dd, J_1 = 3, J_2 = 1.4 Hz, 1H, H-1); 7.28 (dd, J_1 = 7.8, J_2 = 1.6 Hz, 1H, H-9). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ(ppm), 40.8 (CH_2-N); 110.0 (CH, C-2); 114.1 (CH, C-1); 114.7 (CH, C-9); 115.3 (CH, C-6); 119.0 (CH, C-7); 124.4 (CH, C-8); 125.4 (C, C-3a); 125.6 (C, C-5a); 136.3 (C, C-9a). Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46%. Found: C, 77.97; H, 5.65; N, 16.84%.

Pyrrolo[1,2-*a*]quinoxaline (6). Mp: 137-139 ºC (hexane/ethyl acetate). IR (KBr) υ cm^{-1}: 1546 (C=N); 1454 (C=C); 1233 (C-N). ^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm), 6.93 (m, 2H, H-2, H-3); 7.48 (m, 3H, H-7, H-8); 7.94 (m, 3H, H-1, H-6, H-9); 8.82 (s, 1H, H-4). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ(ppm), 107.1 (CH, C-3); 113.7 (CH, C-2); 114.1 (CH, C-6); 125.1 (CH, C-1); 126.3 (CH, C-7); 127.7 (CH, C-8); 127.9 (C, C-3a); 130.0 (C, C-5a); 135.7 (C, C-9a); 145.7 (CH, C-4). Anal. Calcd for $C_{11}H_8N_2$: C, 78.55; H, 4.79; N, 16.66%. Found: C, 78.77; H, 4.65; N, 16.34%.

1,2,3,3a,4,5-Hexahydropyrrolo[1,2-*a*]quinoxaline (7). Mp: 99-101 ºC (hexane/ethyl acetate). IR (KBr) υ cm^{-1}: 3341 (NH); 1597 (C=CH); 1518 (C=C); 1318 (C-N). ^{1}H NMR ($CDCl_3$, 200 MHz) δ(ppm), 1.42 (m, 1H, H-3); 2.02 (m, 3H, 2 x H-2, H-3); 2.80 (bs, 1H, H-3a); 3.23 (m, 2H, 2 x H-1); 3.51 (m, 2H, H-4); 6.41 (d, J = 8.4Hz, H-9); 6.54 (m, 2H, H-7, H-8); 6.62 (m, 1H, H-6). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ(ppm), 23.6 (C-3); 29.9 (C-2); 46.1 (C-1); 47.3 (C-4); 56.7 (CH, C-3a); 110.9 (CH, C-6); 113.5 (CH, C-9); 116.3 (CH, C-8); 119.4 (CH, C-7); 132.6 (C, C-5a); 135.0 (C, C-9a). Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08%. Found: C, 75.54; H, 7.91; N, 16.42%.

***N*-(2-Fluorophenyl)pyrrole-2-carbaldehyde (9).** For the experimental procedure and analytical data, see reference 11.

***N*-(2-Fluorophenyl)-2-(2-methylaminomethyl)pyrrole (10).** To a solution of 1 g (4.90 mmol) of *N*-(2-fluorophenyl)pyrrole-2-carbaldehyde **9** in toluene (10 mL), methylamine (5 mL) and a catalytic amount of *p*-toluenesulfonic acid (PTSA) were added. The mixture was stirred at reflux using a refrigerant and a Dean Stark system for 24 h. The reaction was monitored by TLC using hexane/ethyl acetate 7:3 as eluent. After complete consumption of the starting aldehyde, the mixture was cooled to room temperature and the solvent was removed under vacuum. Then, methanol (12 mL) and 100 mg (2.64 mmol) of $NaBH_4$ were added to the crude reaction mixture and the resulting mixture was stirred at room temperature for 2 h. Methanol was removed, water (15 mL) and dichloromethane (20 mL) were added. The crude reaction mixture was extracted with dichloromethane, the organic layers were dried over Na_2SO_4, filtered and the solvent evaporated. The residue was purified by silica gel column chromatography using hexane/ethyl acetate 90/10 as eluent. Finally the residue was recollected in methanol and the solvent was removed under vacuum to give 0.840 mg (4.11 mmol, yield 84 %) of the methylamine **10** as colorless oil.

IR (KBr) υ (cm-1): 3424 (NH), 1511 (C=C), 1372 (C-N); 742 (C-F). ^{1}H NMR ($CDCl_3$, 300 MHz) δ(ppm), 2.97 (s, 3H, CH_3-N); 4.25 (s, 2H, CH_2-N); 6.08 (m, 1H, H-4); 6.40 (m, 1H, H-3); 6.85 (m, 1H, H-5'); 6.92 (m, 1H, H-3'); 7.22 (t, *J* = 6 Hz, H-4'); 7.24 (m, 1H, H-5); 7,36 (m, 1H, H-6'). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ(ppm), 36.6 (CH_3); 49.4 (CH_2); 103.9 (CH, C-3); 112.6 (CH, C-4); 113.0 (CH, C-5); 114.1 (CH, *J* = 22 Hz, C-3'); 114.6 (CH, *J* = 14 Hz, C-4'); 118.7 (CH, C-5'); 125.0 (CH, C-6'); 125.8 (C, C-2); 138.5 (C, C-1'); 155,0 (C, *J* = 254 Hz, C-2'). Anal. Calcd for $C_{12}H_{13}FN_2$. ½ CH_3OH: C, 63.53; H, 6.40; N, 11.86%. Found: C, 63.88; H, 6.02; N, 11.51%.

Method 2. *N*-Methyl-4,5dihydropyrrolo[1,2-*a*]quinoxaline (1). *Procedure a).* To a suspension of Cs_2CO_3 (130 mg, 0.40 mmol), BINAP (0.5 mol %) and Pd[P(*o*-tolyl)$_3$]$_2$Cl$_2$ (0.1 mol %) in toluene (1 mL) the corresponding methylamine **10** (80 mg, 0.39 mmol) was added and the resulting mixture was stirred and heated at 100 ºC under argon for 12 h.

The mixture was cooled to room temperature, the solvent was removed and the crude product was purified by silica gel column chromatography using hexane / ethyl acetate 90:10 as eluent. The title compound was isolated as a white solid in 23 % yield (17 mg, 0.02 mmol).

Procedure b). To a solution of methylamine **10** (160 mg, 0.78 mmol) in freshly distilled DMF (4 mL), NaH (50 mg, 2.08 mmol) was slowly added under an argon atmosphere. The resulting mixture was heated at 100 ºC for 48 h. The crude reaction mixture was cooled to room temperature and diluted with water and ice (30 mL), and then 2N HCl was added until *pH* 5-6. The mixture was extracted with ether (3x20 mL). Then the organic phase was washed with water, dried over Na_2SO_4, filtered and the solvent was removed under vacuum. The crude reaction mixture was purified by silica gel chromatography column using a mixture of hexane/ethyl acetate 90:10 as eluent. An amount of 133.5 mg (0.73 mmol) 93% of the title compound as a white solid was obtained.

Following the above indicated conditions and using Cs_2CO_3 or K_2CO_3 (excess 5 equiv) instead of NaH the same quinoxaline **1** was obtained in 45 and 39% yield, respectively.

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