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A NEW RING-FORMING METHODOLOGY FOR THE SYNTHESIS OF BIOACTIVE PYRROLOQUINOLINE DERIVATIVES

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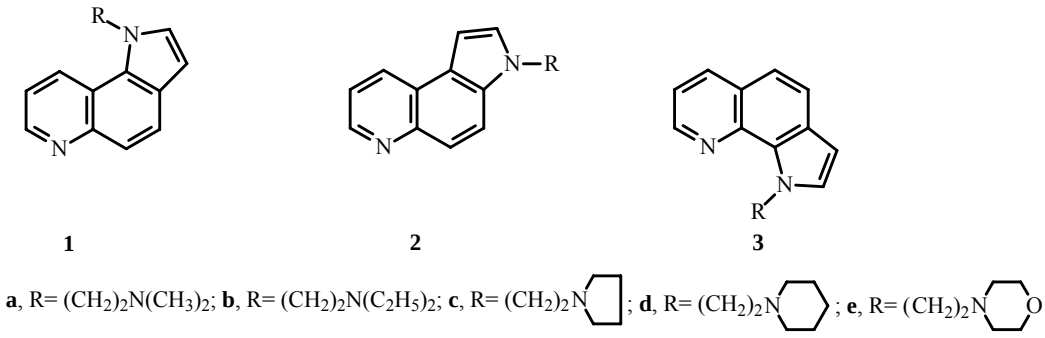
Abstract - A new, efficient, two-step method for the synthesis of bioactive pyrroloquinolines is described. Readily available nitroquinolines, bearing the nitro moiety in the carbocyclic ring, are treated with 4-chlorophenoxyacetonitrile in the presence of potassium *tert*-butoxide/THF to give the analogous vicarious nucleophilic substitution products (**5**, **8** and **11**). These, in turn, are subjected to catalytic hydrogenation to produce 1*H*-pyrrolo[2,3-*f*]quinoline (**6**), 3*H*-pyrrolo[3,2-*f*]quinoline (**9**) and 1*H*-pyrrolo[3,2-*h*]quinoline (**12**) in good yields and relatively short reaction times. The differential activity of two *N*-alkylated 1*H*-pyrrolo[2,3-*f*]quinolines (**1)** in cisplatin resistant cell lines compared to the corresponding parent lines suggests that these might be useful leads for developing agents for use in drug resistant diseases.

The cytotoxic properties of polycyclic aromatic compounds are well documented.[1] Previously, we and others have published[2-5] the synthesis of aromatic heterocycles which, by forming molecular complexes with DNA, inhibit its processing. In the course of our program directed towards the development of novel DNA interactive agents (**e.g. 1**-**3**) (**Figure 1**), we were faced with the problem of preparing 1*H*-pyrrolo[2,3-*f*]quinoline (**6**) and its positional isomers 3*H*-pyrrolo[3,2-*f*]quinoline (**9**) and 1*H*-pyrrolo[3,2-*h*]quinoline (**12**) (**Scheme 1**).

Figure 1



Almost all of the known methods for the construction of these heterocyclic structures are laborious and multi step.[6-8] The only promising one pot reaction, which utilizes vinylmagnesium bromide and nitroarenes, proceeds well only with 5-nitroquinoline (**5**).[9] Implementation of this method on 6-nitroquinoline (**7**) led to the formation of the expected 3*H*-pyrrolo[3,2-*f*]quinoline (**9)** but in very low yield. When the reaction was performed on 8-nitroquinoline (**10**) none of the desired product (**12**) was isolated.

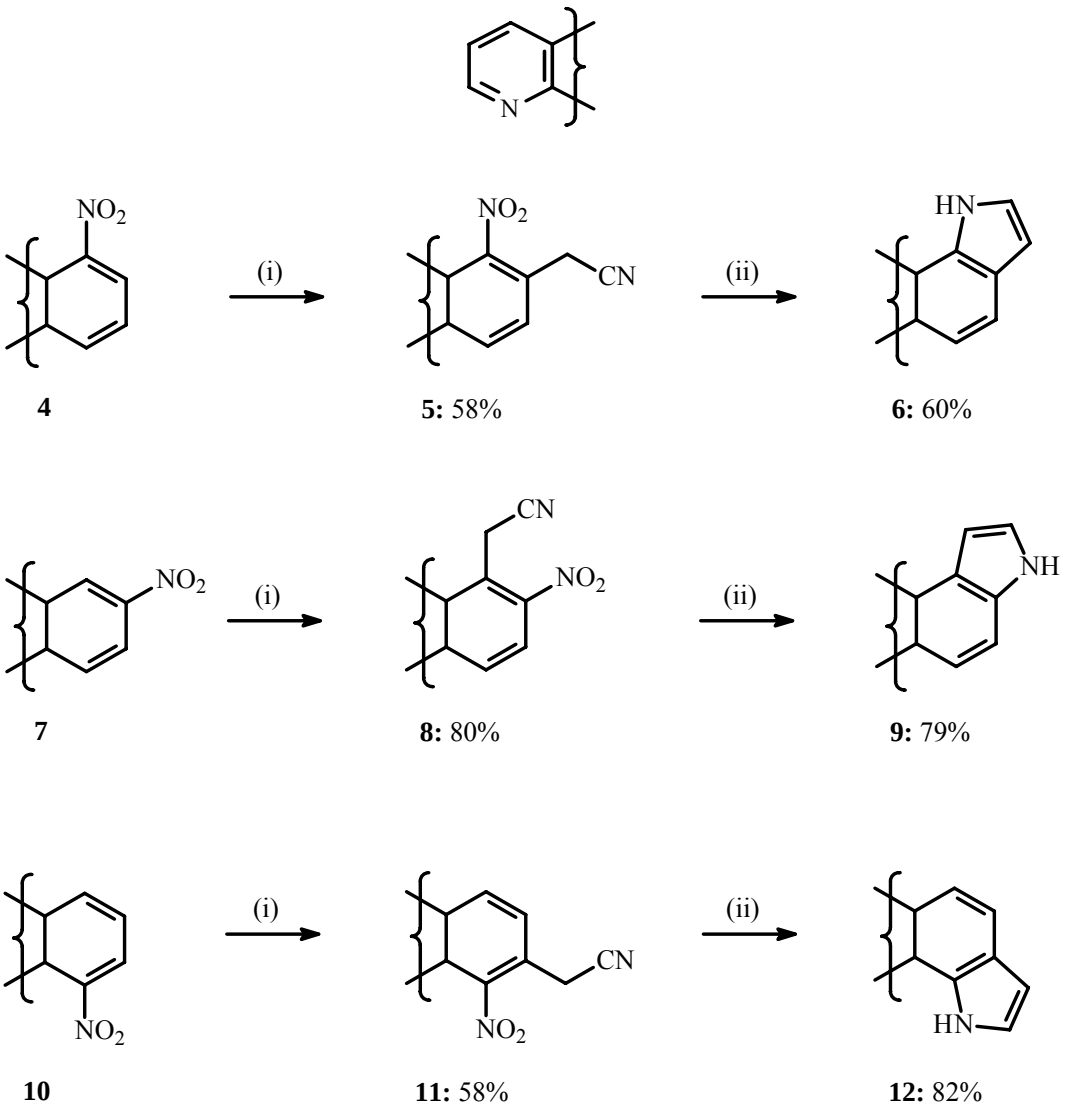
In lieu of this deficiency in methods of preparation of these pyrroloquinolines,[8,10,11] we report here a new, general two-step procedure. As shown in **Scheme 1**, our approach is simple, highly efficient and suitable for the preparation of all positional isomers. After experimentation with Makosza's vicarious nucleophilic substitution method, we found that when readily available nitroquinolines bearing the nitro moiety in the carbocyclic ring are treated with 4-chlorophenoxyacetonitrile (1.1 equiv.) and potassium *tert*-butoxide (2.2 equiv.) in dry tetrahydrofuran at –10 ^{o}C under an argon atmosphere the acetonitriles (**5**, **8** and **11**) are formed in 58-80 % yield.[12,13]

Following the method of Bromidge *et al.*[14] for the construction of the indole nucleus, the *o*-nitroquinolinylacetonitriles (**5**, **8** and **11**) are catalytically hydrogenated at 50 psi using (10% Pd) on activated carbon in the presence of ethanol/water (7:1) and a catalytic quantity of acetic acid to give the desired pyrroloquinolines (**6**, **9** and **12**), respectively in 60-82 % yield.[6,8,9]

The target molecules (**1-3**) are prepared in good yield by *N*-alkylation of the corresponding pyrroloquinolines (**6, 9** and **12**), using the appropriate 2-chloro-*N*,*N*-dialkylethylamine hydrochloride in the presence of sodium hydride in dimethylformamide (**Figure 1**).

Two of the new *N*-alkylated pyrroloquinolines exhibit significant cytotoxicity in an ovarian carcinoma cell line panel (**Table 1**). It is interesting that both compounds (**1b**) (R=$(CH_2)_2N(C_2H_5)_2$) and (**1d**) (R=$(CH_2)_2N(CH_2)_5$) are more active in the cisplatin resistant CH1CisR cell line compared to the corresponding parent CH1 line. This suggests that these molecules may represent new leads in the search for agents effective in drug resistant diseases.

Scheme 1



Reagents and conditions: i: *p*-$ClC_6H_4OCH_2CN$, *t*-BuOK, THF, -10 °C, 25 min; ii: H_2, 10% Pd/C, 50 psi, AcOH, $EtOH/H_2O$, rt, 1-3.5 h.

Table 1. Cytotoxic activity (IC_{50} in μM)[a] of two derivatives of 1*H*-pyrrolo[2,3-*f*]quinoline (**1**) in five ovarian carcinoma cell lines

Compound	A2780	A2780CisR	CH1	CH1CisR	SKOV-3
1b	12.0	>25	>25	17.0	>25
1d	15.8	>25	>25	16.5	>25

[a]Dose of agent required to inhibit cell growth by 50% compared with PBD-free controls as measured by the sulforhodamine B (SRB) growth delay assay. The cells were incubated with the compounds for 96 h at 37 °C.

EXPERIMENTAL

Melting points were determined on a Büchi 530 apparatus and are uncorrected. ^1H (200 MHz) and ^{13}C (50 MHz) NMR spectra were taken in $CDCl_3$ and recorded on a Bruker AC200 MHz spectrometer. The

spectra are reported in ppm values and tetramethylsilane was used as internal standard. *J*-Values are given in Hz. The solvents used were dried as follows: *N*,*N*-dimethylformamide over molecular sieves (4Å) and tetrahydrofuran over calcium hydride. DC-Alufolien plates (Kieselgel 60 F_{254}, Schichtdicke 0.2 mm, Merck) were used for analytical TLC and were visualized with ultraviolet light or developed with iodine or phosphomolybdic acid. Microanalyses were carried out by the Microanalytical Section of the Institute of Organic and Pharmaceutical Chemistry, NHRF-Greece.

5-Nitroquinoline (**4**), 6-nitroquinoline (**7**) and 8-nitroquinoline (**10**) were purchased from Aldrich Chemical Company (Gillingham, Dorset, UK).

The procedures given below for the synthesis of **5** and **6** were utilized in the formation of their respective positional isomers (**8**, **11**) and (**9**, **12**). Similarly, the procedure described for the synthesis of **1b** was followed for the preparation of its congeners (**1a**, **1c-e**, **2a-e** and **3a-e**).

To a stirred mixture of potassium *tert*-butoxide (0.71 g, 6.32 mmol) in tetrahydrofuran (6 mL) was added dropwise a solution of 5-nitroquinoline (0.50 g, 2.87 mmol) and 4-chlorophenoxyacetonitrile (0.53 g, 3.16 mmol) in tetrahydrofuran (9 mL) at –10 °C. The resulting red suspension was left stirring at this temperature for 25 min and then quenched with 5 mL of hydrochloric acid (5 %). The mixture was then extracted with ethyl acetate, the extract was washed with water and dried over sodium sulfate. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (cyclohexane : EtOAc = 7 : 3, v/v) to give 0.35 g (58%) of **5**, mp 120-121 °C, lit.,[12] 112 °C; the ^{1}H NMR spectral data are in agreement with those reported by Makosza *et al*.[12]

5-Nitro-6-quinolinylacetonitrile (**5**) (0.25 g, 1.17 mmol) in ethanol/water (7 : 1, 24 mL) and glacial acetic acid (0.18 mL) were hydrogenated over 10% palladium on carbon (0.18 g) at 50 psi for 2 h. The reaction mixture was filtered through Celite and evaporated *in vacuo*. The residue was partitioned between 10% potassium carbonate (10 mL) and ethyl acetate (2 x 25 mL), the combined organic extract was dried over sodium sulfate and evaporated under reduced pressure to give after trituration with a mixture of ethyl acetate/cyclohexane (8 : 2, v/v) 0.12 g (60%) of **6**, mp (ethanol) 175-176 °C, lit.,[8] 178-180 °C; the ^{1}H NMR spectral data are in agreement with those reported.[6,8]

To a solution of **6** (0.10 g, 0.60 mmol) in dimethylformamide (1 mL) was added, portionwise, sodium hydride (60%) (0.03 g, 0.66 mmol) and the mixture was subsequently stirred for 30 min at rt. To this suspension a solution of diethylaminoethyl chloride (prepared from diethylaminoethyl chloride hydrochloride (0.10 g, 0.60 mmol), sodium hydride (60%) (0.02 g, 0.60 mmol) and dimethylformamide (2.5 mL) was added and the mixture was stirred at 55 °C for 2 h. Afterwards, dimethylformamide was removed *in vacuo* and the residue was dissolved in ethyl acetate (30 mL), washed with water (20 mL), brine (20 mL) and dried over sodium sulfate. Concentration under reduced pressure afforded the crude

product, which was purified by flash chromatography (EtOAc : methanol = 8 : 2, v/v) to give 0.12 g (74%) of **1b** as a viscous oil; ^{1}H NMR δ 2.55 (q, *J* = 7.3 Hz, 6H, NCH_2CH_3), 2.85 (t, *J* = 7.3 Hz, 2H, NCH_2CH_2), 4.08 (q, *J* = 7.3 Hz, 4H, NCH_2CH_3), 4.57 (t, *J* = 7.3 Hz, 2H, NCH_2CH_2), 6.60 (d, *J* = 3.2 Hz, 1H, 2-H), 7.15 (d, *J* = 2.9 Hz, 1H, 3-H), 7.40 (dd, *J* = 8.6, 4.1 Hz, 1H, 8-H), 7.75 (d, *J* = 8.6 Hz, 1H, 4-H), 7.89 (d, *J* = 8.6 Hz, 1H, 5-H), 8.62 (d, *J* = 8.3 Hz, 1H, 9-H), 8.80 (dd, *J* = 4.5, 1.6 Hz, 1H, 7-H); ^{13}C NMR δ 11.6, 47.6, 49.6, 52.8, 102.7, 117.9, 119.9, 122.2, 124.7, 126.1, 127.7, 128.6, 129.7, 146.7, 146.9. *Anal*. Calcd for $C_{17}H_{21}N_3$: C, 76.37; H, 7.92; N, 15.72. Found: C, 76.29; H, 7.91; N, 15.69.

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