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First synthesis of arylpyrrolo- and pyrazolopyrrolizinones as useful agents with potential biological interest

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Abstract—Novel arylpyrrolo- and pyrazolopyrrolizinones were prepared in three or four steps starting from aminoarylpyrrole and pyrazole carboxylates through the cyclisation of a Vilsmeier–Haack intermediate. This synthesis was enhanced by diverse *N*-protections of the aza-heterocycle and furnish new series with potential biological interest.

We recently reported the synthesis and the biological evaluation of novel thienopyrrolizinones among which derivative MR 22388 exhibited a potent antiproliferative activity in relation with an antitubulin action.[1] With the aim to increase the structural diversity of these compounds, we wish to describe herein the first synthesis of their aza-analogs belonging to the pyrrolo **1** and pyrazolo **2** series (Fig. 1).

Using the route elaborated in the thiophene series, the starting materials we needed to reach this goal were aminoarylpyrrole and pyrazole carboxylates. We very recently described the synthesis of methyl 3-amino-4-aryl-1*H*-pyrrole-2-carboxylates **3** in three steps starting from commercial arylacetonitriles (Scheme 1).[2] We used

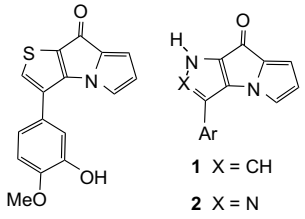
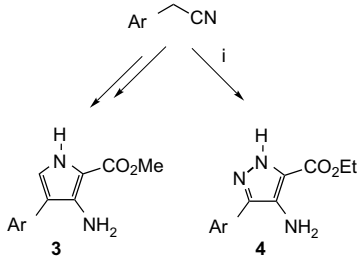


Figure 1.



Scheme 1. Reagents and conditions: (i) N_2CHCO_2Et, EtONa, EtOH, 25 °C.

the same starting materials and ethyl diazoacetate to prepare ethyl 4-amino-5-aryl-1*H*-pyrazole-3-carboxylates **4** according to Tarzia's method.[3]

The methyl aminopyrrolecarboxylates **3** were first involved in a four steps sequence beginning with a Clauson-Kaas and Zdenek[4] reaction leading to **5** (Scheme 2).[5] The latter was then treated with refluxing pyrrolidine to form the carboxamide **6**[6] before cyclisation under Vilsmeier conditions (refluxing $POCl_3$) to an iminium salt, which was finally hydrolysed under alkaline conditions to give the pyrrolopyrrolizinones **1** in moderate to low yields (Table 1).[7,8]

N-Substitution of the pyrrole ring of **6** improved the cyclisation yield since methyl **8**, ethyl **9** and benzyl **10** derivatives led to the corresponding pyrrolizinones **12**, **13** and **14**, respectively in excellent yields (Table 1).

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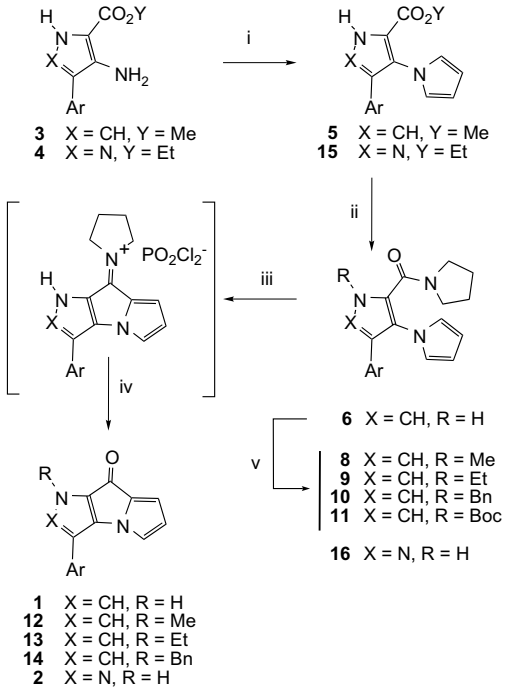


Scheme 2. Reagents and conditions: (i) 2,5-dimethoxyTHF, 4-chloropyridine hydrochloride, dioxane, 100 °C; (ii) pyrrolidine, 87 °C; (iii) $POCl_3$, 70 °C; (iv) 10% NaOH; (v) NaH, RX, DMF, 0–25 °C or $(Boc)_2O$, TEA, DMAP, CH_2Cl_2, 25 °C.

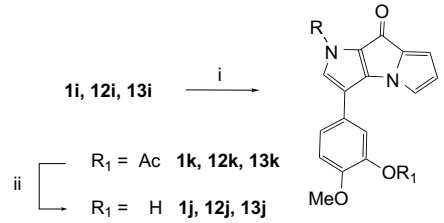
Table 1. Preparation of **1a–i**, **12d,i**, **13d,i**, **14d,i** and **2d,i** from corresponding carboxamides

Compd	Ar	R	X	Yield (%) (from)[a]
1a	2-Thienyl	H	CH	28 (**6a**)
1b	3-Thienyl	H	CH	4 (**6b**)
1c	Phenyl	H	CH	5 (**6c**)
1d	4-Cl-phenyl	H	CH	16 (**6d**)
1e	4-F-phenyl	H	CH	32 (**6e**)
1f	4-Me-phenyl	H	CH	23 (**6f**)
1g	4-MeO-phenyl	H	CH	10 (**6g**)
1h	3,4-DiCl-pheyl	H	CH	14 (**6h**)
1i	3-BnO,4-MeO-phenyl	H	CH	2 (**6i**); 32 (**11i**)
12d	4-Cl-phenyl	Me	CH	72 (**8d**)
12i	3-BnO,4-MeO-phenyl	Me	CH	95 (**8i**)
13d	4-Cl-phenyl	Et	CH	66 (**9d**)
13i	3-BnO,4-MeO-phenyl	Et	CH	66 (**9i**)
14d	4-Cl-phenyl	Bn	CH	82 (**10d**)
14i	3-BnO,4-MeO-phenyl	Bn	CH	61 (**10i**)
2d	4-Cl-phenyl	H	N	42 (**16d**)
2i	3-BnO,4-MeO-phenyl	H	N	6 (**16i**)

[a] Isolated yields after column chromatography.

In the case of the *N*-Boc derivative **11i**, *N*-deprotection occurred under the cyclisation conditions leading directly to **1i** in 32% yield.

The analogs of MR 22388, **1j**, **12j** and **13j**, bearing a *m*-hydroxy, *p*-methoxyphenyl ring in 3-position were finally obtained by *O*-debenzylation of **1i**, **12i** and **13i**, respectively, under treatment with HBr in acetic acid



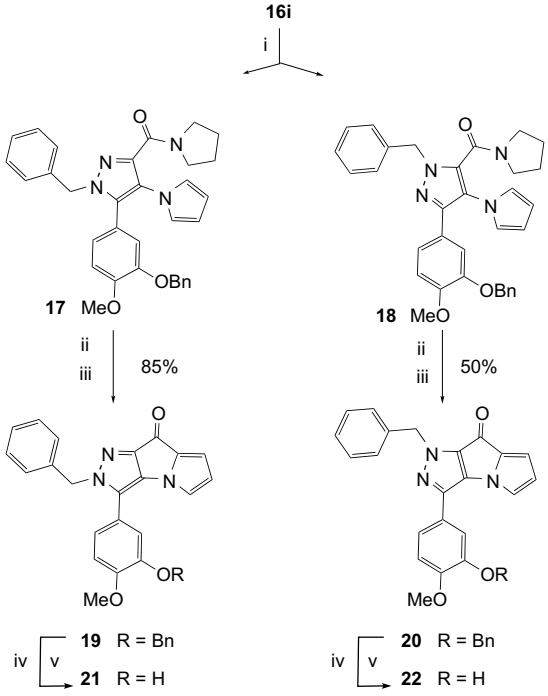
Scheme 3. Reagents and conditions: (i) 33% HBr in AcOH, 25 °C; (ii) NaOH 1 N, MeOH, 25 °C.

followed by alkaline hydrolysis of the resulting acetoxyderivatives **1k**, **12k**, **13k** (Scheme 3).

The same chemical pathway was used to achieve the synthesis of the pyrazolopyrrolizinones **2** (Scheme 2). The aminoesters **4** led successively to **15** and **16**, which were cyclised under treatment with boiling $POCl_3$ followed by hydrolysis to give ketones **2**.

As for the pyrrole series, the yield of the cyclisation was improved by *N*-protection of the pyrazole ring. However, benzylation of **16i** (NaH in DMF) took place equally on N1 and N2, due to the delocalisation of the negative charge between the two pyrazole nitrogens under treatment with NaH (Scheme 4).

The regioisomers **17** and **18** were separated, cyclised and hydrolysed as previously into **19** and **20** in 85% and 50% yield, respectively. *O*-Debenzylation was achieved as above with respect of the *N*-benzyl group of **21** and **22**.



Scheme 4. Reagents and conditions: (i) BnBr, NaH, DMF, 0–25 °C; (ii) $POCl_3$, 70 °C; (iii) 10% NaOH, 80 °C; (i) 33% HBr in AcOH, 25 °C; (ii) NaOH 1 N, MeOH, 25 °C; (iv) 33% HBr in AcOH, 25 °C; (v) NaOH 1 N, MeOH, 25 °C.

Other alkylation conditions[9] are under investigation in order to achieve a more selective *N*-benzylation.

In conclusion, we have developed an efficient synthesis of the first arylpyrrolo- and pyrazolopyrrolizinones whose suitability as biologically active agents, particularly in the antineoplastic domain, is currently under investigation.

Acknowledgements

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5. *Typical Clauson-Kaas reaction procedure*. A solution of 2,5-dimethoxytetrahydrofuran (0.61 mL, 4.7 mmol) in dioxane (25 mL) was stirred for 15 min with 4-chloropyridine hydrochloride (0.705 g, 4.7 mmol). The aminoester **3e** (0.9 g, 3.84 mmol) was added and the reaction mixture was refluxed for 1.5 h and filtered through a small pad of Celite. The solvent was evaporated to give a brown residue that was dissolved in methylene chloride (100 mL). The solution was washed with an 1 N aqueous hydrochloric acid solution (2×100 mL), dried ($MgSO_4$) and evaporated to give **5e** as a beige solid (980 mg, 90%) that was crystallised from Et_2O. Mp 172 °C. IR (KBr): *v* 3295, 3139, 3043, 2951, 1671 (CO), 1570, 1443, 1383, 1159, 1137, 726 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.38 (br s, 1H, N*H*), 7.07 (d, $J = 3.4$ Hz, 1H, C*H*N), 6.90 (m, 4H, $H_{aromatic}$), 6.66 (m, 2H, $H_{pyrrole}$), 6.26 (m, 2H, $H_{pyrrole}$), 3.77 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.85 (d, $J = 246$ Hz), 160.54, 128.31 (d, $J = 7$ Hz), 129.29, 128.01, 122.88, 122.76, 118.92, 117.26, 115.45 (d, $J = 21$ Hz), 108.97, 51.79. MS (EI^+) *m*/*z*: 284.0.
6. *Typical amidification reaction procedure*. A solution of **5e** (850 mg, 2.99 mmol) in pyrrolidine (20 mL) was refluxed for 12 h. After the mixture was cooled and evaporated, the yellow oil was dissolved in chloroform (100 mL) and the solution was washed with an 1 N aqueous hydrochloric acid solution (2×100 mL), dried ($CaCl_2$) and evaporated to give a brown solid. This residue was purified by silica gel chromatography, eluting by cyclohexane–ethyl acetate (1:2) to furnish carboxamide **6e** as a beige solid (490 mg, 47%). Mp 222 °C. IR (KBr): *v* 3215, 2970, 2880, 1598 (CO), 1474, 1212, 837, 729 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 10.03 (br s, 1H, N*H*), 6.99 (d, $J = 3.1$ Hz, 1H, C*H*N), 6.90 (m, 4H, $H_{aromatic}$), 6.59 (m, 2H, $H_{pyrrole}$), 6.20 (m, 2H, $H_{pyrrole}$), 3.56 (m, 2H, $H_{pyrrolidine}$), 2.53 (m, 2H, $H_{pyrrolidine}$), 1.78 (m, 2H, $H_{pyrrolidine}$), 1.61 (m, 2H, $H_{pyrrolidine}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.33, 160.31 (d, $J = 241$ Hz), 129.09, 128.63 (d, $J = 9$ Hz), 128.45, 123.58, 122.08, 120.77, 117.73, 115.28 (d, $J = 23$ Hz), 109.71, 46.45, 46.32, 26.07, 23.89. MS (EI^+) *m*/*z*: 323.2.
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8. *Typical cyclisation reaction procedure*. A solution of the carboxamide **6e** (400 mg, 1.24 mmol) in phosphorous oxychloride (20 mL) was stirred at 70 °C for 3 h. After cooling, the reaction mixture was concentrated to give the intermediary iminium salt, which was slowly added to an 10% aqueous sodium hydroxide solution (100 mL) and heated at 80 °C for 3 h. After cooling, the resulting suspension was extracted with ethyl acetate (2×50 mL) and the combined organic layers were washed with water (2×100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated to give a dark red solid. This residue was purified by silica gel chromatography, eluting by cyclohexane–ethyl acetate (1:1) to furnish thienopyrrolizinone **1e** as a red solid (260 mg, 32%). Mp 252 °C. IR (KBr): *v* 3175, 2990, 2965, 2932, 1663 (CO), 1586, 1534, 1522, 1385, 1224, 1150, 826, 720 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 10.32 (br s, 1H, NH), 7.44 (d, $J = 8.5$ Hz, 2H, $H_{aromatic}$), 7.13 (d, $J = 8.5$ Hz, 2H, $H_{aromatic}$), 6.93 (d, $J = 2.9$ Hz, 1H, CHN), 6.84 (d, $J = 2.8$ Hz, 1H, H-7), 6.56 (d, $J = 3.7$ Hz, 1H, H-5), 5.97 (dd, $J = 2.8$, 3.7 Hz, 1H, H-6). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.78, 167.89, 161.75 (d, $J = 246$ Hz), 136.13, 128.73, 128.25 (d, $J = 8$ Hz), 125.57, 125.25, 120.78, 115.92 (d, $J = 21$ Hz), 113.26, 111.83, 111.56. HRMS (EI^+) *m*/*z*: 252.0699 (M^+, 100, $C_{15}H_9N_2OF$ required 252.0699).
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