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A short route to the synthesis of pyrroloacridines via Ullmann–Goldberg condensation

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ABSTRACT

A concise method for the preparation of pyrroloacridines was reported via CuI mediated Ullmann–Goldberg condensation of 5-amino-2-methylindoles and *o*-halobenzoic acid derivatives followed by cyclization with $POCl_3$.

Pyrroloacridines and pyrroloacridones are of particular interest because they have a variety of interesting biological activities. Significantly, members of this family are active in assays for antihelmintic,[1] antitumor,[1,2] antifungal,[3] and DNA binding.[4–6] These abilities are specifically important in inhibiting the growth of cancerous cells, making these compounds ideal for developing novel anticancer drugs. To date, the only pyrroloacridines that have been published from marine sources are plakinidines A–E and alpkinidine.[1,7–10] Only a few reports[11] are available for the synthesis of pyrroloacridines and therefore the synthetic versatility of these compounds needs to be explored.

As a result of their significant potential as therapeutics, a considerable synthetic attention has been directed at the development of efficient methods toward the construction of pyrroloacridine moiety. So, we became interested in synthesizing pyrroloacridines which are isomeric analogues of bioactive pyrroloacridines such as those shown in Figure 1. Our method is based on CuI mediated N-arylation of 5-amino-2-methylindole with *o*-halobenzoic acids by Ullmann–Goldberg condensation[12] followed by intramolecular Friedel–Crafts cyclization[13] with $POCl_3$.

As shown in Scheme 1, 5-amino-2-methylindole **1a** was subjected to Ullmann–Goldberg condensation with 2-iodobenzoic acid **2a** in the presence of CuI (10 mol %) and K_2CO_3 (1.0 equiv) at 80 °C in DMSO to give the condensation product[14] **3a**. Due to the activation of halogens by the ortho-substituted carboxylic group, a facile condensation occurred. The results, presented in Table 1, indicate the condensation products are obtained in good yield. 2-Bromobenzoic and 2-chlorobenzoic acid required relatively longer reaction time than their iodo analogue due to the order of halogen displacement I > Br > Cl. Due to the further activation of iodide by the strong electron-withdrawing nitro group, **2f** requires only half of the reaction time compared to **2c**.

The condensation products **3a–i** are subjected to cyclization with $POCl_3$ which results in the corresponding pyrroloacridones[15] and pyrroloacridines[15] depending on the reaction temperature. As shown in Scheme 1, the condensation products **3a–f** have produced the corresponding pyrroloacridones **4a–f** after being treated with an excess of $POCl_3$ in good yields at 60 °C. The results are summarized in Table 1. The condensation products **3g–i** could not give the corresponding pyrroloacridones at 60 °C. This may be due to the strong electron-withdrawing nature of phenylsulphonyl group.

When the reaction was performed at 120 °C, the condensation products **3a–i** gave the corresponding pyrroloacridines **5a–i**. The absence of two singlets (due to 4th and 7th position protons of indole) in the aromatic region of ^1H NMR spectrum, clearly reveals the exclusive formation of regioisomeric pyrroloacridines **5a–i**. This is further confirmed by the characterization of the structure of **5g** by the single crystal X-ray analysis.[16] The ORTEP diagram of **5g** is shown in Figure 2.

In summary, we have developed a simple and efficient two-step method for the synthesis of pyrroloacridones and pyrroloacridines via N-arylation of 5-amino-2-methylindole derivatives with 2-halobenzoic acids by Ullmann–Goldberg condensation followed by intramolecular Friedel–Crafts cyclization with $POCl_3$. This method provides a new entry to the synthesis of pyrroloacridone and pyrroloacridine derivatives of biological importance.

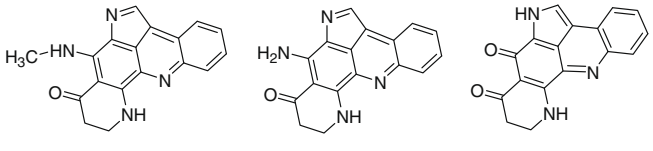

Figure 1. Representative pyrroloacridines isolated from marine sources.

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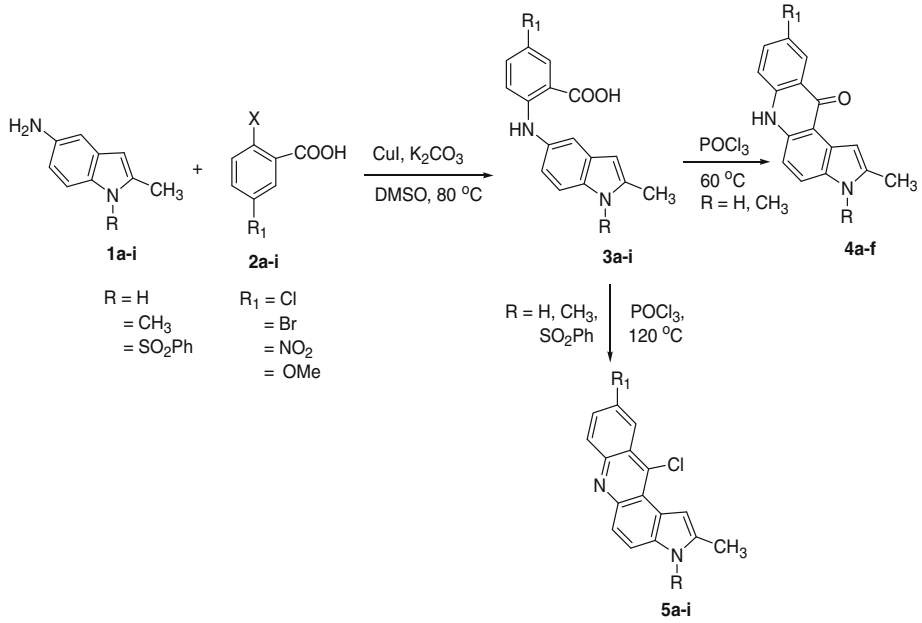

Scheme 1. Synthesis of pyrroloacridones and pyrroloacridines.

Table 1
Synthesis of pyrroloacridones and pyrroloacridines

S.No.	R	R_1	X	Condensed product	Time (h)	Yield (%)	Cyclized product	Time (h)	Yield (%)
1	H	H	I	**3a**	0.5	86	**4a**	0.5	75
							5a	3.0	76
2	H	H	Br	**3a**	2.0	80	**4a**	0.5	75
							5a	3.0	76
3	H	OMe	Br	**3b**	2.0	81	**4b**	0.5	74
							5b	3.0	71
3	CH_3	H	I	**3c**	0.5	91	**4c**	0.5	72
							5c	3.0	75
4	CH_3	H	Br	**3c**	2.0	82	**4c**	0.5	72
							5c	3.0	75
5	CH_3	Cl	I	**3d**	0.5	87	**4d**	0.5	77
							5d	3.0	77
6	CH_3	Br	I	**3e**	0.5	79	**4e**	0.5	76
							5e	3.0	73
7	CH_3	NO_2	I	**3f**	0.25	84	**4f**	0.5	79
							5f	3.0	82
8	SO_2Ph	H	I	**3g**	0.5	71	**5g**	3.0	73
9	SO_2Ph	H	Br	**3g**	2.0	68	**5g**	3.0	73
10	SO_2Ph	H	Cl	**3g**	3.0	65	**5g**	3.0	73
11	SO_2Ph	Cl	I	**3h**	0.5	75	**5h**	3.0	72
12	SO_2Ph	Br	I	**3i**	0.5	77	**5i**	3.0	75

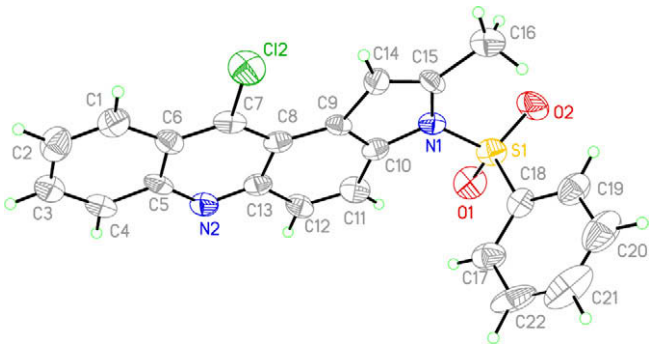

Figure 2. ORTEP diagram of **5g**.

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Supplementary data

Characterization data for all compounds, ^1H and ^{13}C NMR spectra of all compounds. LC–MS and elemental analysis of **3d**, **4c**, **4e**, **5d,** and **5i** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.044.

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14. *Typical procedure for the* preparation *of 5-chloro-2-(1,2-dimethyl-1H-5-indolylamino)benzoic acid* (**3d**): A mixture of 5-amino-1,2-dimethylindole (1.0 mmol), 5-chloro-2-iodobenzoic acid (1.0 mmol), CuI (0.1 mmol), and K_2CO_3 (1.0 mmol) in DMSO was heated at 80 °C for 0.5 h. Then the reaction mixture was poured into water and extracted with ethylacetate (3 × 20 mL). Then the solvent was evaporated under reduced pressure and the crude material was purified by column chromatography (15% ethylacetate/hexane). Mp: 223–224 °C; IR (KBr): 3350, 2916, 2550, 1657, 1502, 1440, 1332, 1280, 1161, 812, 738, 657 cm^{-1}; ^1H NMR (400 MHz, TMS, $CDCl_3$): δ 9.5 (1H, s, NH), 7.76 (1H, s), 7.37 (1H, d, J = 7.6 Hz), 7.26 (2H, s), 6.91 (2H, d, J = 6.4 Hz), 6.16 (1H, s), 3.64 (3H, s, CH_3), 2.37 (3H, s, CH_3); ^{13}C NMR (100 MHz, TMS, $CDCl_3$): δ 175.2, 142.8, 140.0, 138.4, 136.5, 133.2, 130.6, 129.3, 123.2, 120.3, 119.8, 116.3, 115.1, 114.4, 104.3, 34.3, 17.5; LC–MS: m/z = 314.5 (M), 316.5 (M+2); Anal. Calcd for molecular formula $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.8; N, 8.9. Found: C, 64.81; H, 4.85; N, 8.98.
15. *Typical procedure for the preparation of 9-chloro-2,3-dimethyl-6,11-dihydro-3H-pyrrolo[3,2-a]acridin-11-one* (**4d**) *and 9,11-dichloro-2,3-dimethyl-3H-pyrrolo[3,2-a]acridine* (**5d**): 5-Chloro-2-(1,2-dimethyl-1*H*-5-indolylamino)benzoic acid (1.0 mmol) in excess of $POCl_3$ (5 mL) was heated for 0.5 h at 60 °C. Then the reaction mixture was poured onto the crushed ice and then neutralized with 10% aq NaOH solution. Then it was extracted with dichloromethane (3 × 10 mL) and the solvent was evaporated and the crude material was purified by column chromatography (30% ethylacetate/hexane) to obtain the pure product **4d**. When the reaction was performed at 120 °C for 3 h, **5d** was obtained. The crude material was purified by column chromatography (5% ethylacetate/hexane). *Compound* **4d**: mp: 147–148 °C; IR (KBr): 3477, 1635, 1560, 1475, 1415, 1016, 655 cm^{-1}: ^1H NMR (400 MHz, TMS, $CDCl_3$): δ 11.4 (1H, s, NH), 8.37 (1H, d, J = 4.0 Hz), 7.61 (1H, t, J = 8.0 Hz), 7.53–7.45 (3H, m), 7.22 (1H, d, J = 8.0 Hz), 3.76 (3H, s), 2.50 (3H, s); ^{13}C NMR (100 MHz, TMS, $CDCl_3$): δ 181.9, 143.2, 143.0, 142.3, 136.7, 136.4, 130.3, 129.9, 128.7, 127.0, 123.7, 121.3, 117.8, 114.5, 108.0, 34.5, 17.9; LC–MS: m/z = 296.5 (M), 298.5 (M+2). *Compound* **5d**: mp 202–203 °C; IR (KBr): 2924, 1628, 1520, 1415, 1261, 1080, 866, 802, 767, 663, 601 cm^{-1}; ^1H NMR (400 MHz, TMS, $CDCl_3$): δ 8.45 (1H, s), 8.31 (1H, d, J = 8.4 Hz), 7.96 (1H, d, J = 8.8 Hz), 7.83 (1H, d, J = 9.2 Hz), 7.69 (1H, d, J = 8.8 Hz), 7.50 (1H, s), 3.8 (3H, s), 2.54 (3H, s); ^{13}C NMR (100 MHz, TMS, $CDCl_3$): δ 138.5, 136.1, 134.0, 133.6, 132.1, 132.0, 127.4, 126.6, 123.7, 121.79, 121.75, 120.2, 119.3, 116.2, 107.5, 31.2, 14.0; LC–MS: m/z = 315 (M), 317 (M+2); Anal. Calcd for molecular formula $C_{17}H_{12}N_2Cl_2$: C, 64.78; H, 3.84; N, 8.89. Found: C, 64.81; H, 3.88; N, 8.93.
16. CCDC number of **5g** is 737672.