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Synthesis of Benzo[5',6']cyclohepta[4,5]pyrrolo[2,3-*b*]pyridin-12-one

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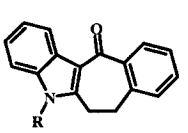
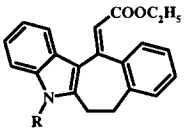
Abstract: The synthesis of a 7-azaindole derivative **8** with potential antitumoral activity is described starting from pyrrolo[2,3-*b*]pyridine; regioselective lithiation/methylation of alkyl 7-azaindole-3-carboxylates **4** afforded the 2-methyl derivatives **5**. Demethylation of ester **6a** using BBr_3 afforded the acid **7**, which is cyclised into the tetracyclic derivative **8**.

Keyword: indole, lithiation, cyclisation, aza compounds

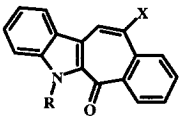
We have recently developed the synthesis of new tetracyclic indolic structures such as **I**,[1,2] **II**,[3] **III**[4] which have been used as synthons for the synthesis of potential antitumoral derivatives. The promising activity of such derivatives led us to investigate the pyrrolo[2,3-*b*]pyridine (7-azaindole) nucleus in order to synthesise the analogue **8** of compound **I**. 7-azaindolic analogues of natural products such as vincamine[5] or ellipticine[6] have already been reported.



I



II



III

The reactivity of pyrrolo[2,3-*b*]pyridine moiety has been poorly investigated[7-11] compared to that of indole, despite the biological potential of 7-azaindoles: NADH models,[12] mimics of adenosine base[13] and dopaminergic ligands[14] illustrated the interest of the 7-azaindole structure. The lower reactivity of carbon C3 towards electrophilic substitution[15,16] in 7-azaindole, precluded an electrophilic ring closure on this carbon atom for generating the cyclohepta ring such as in compound **8**. Thus, we preferred for preparing **8**, an approach based on the cyclohepta ring closure of the 2-substituted-7-azaindole-3-carboxylic acid **7** where the C_3-CO bond is already present.

Thus, compound **7** was prepared from the key intermediate **5**, issued from the 3-formyl-7-azaindole **1**. Compound **1** was prepared from 7-azaindole by treating it with hexamethylenetetramine followed by acetic acid.[15] Benzenesulfonyl chloride was added at 0 °C to the sodium salt of **1** in THF to give **2** in good yield (92%). Esters **4** can be obtained by a tedious procedure *via* the oxime/nitrile route[16] described for the unsubstituted aldehyde **1**. We preferred a straightforward access to the acid **3** by a careful controlled oxidation of **2** with sodium chlorite (95% yield). It was then transformed into the methyl, ethyl or benzyl esters **4a-c** by esterification with the corresponding alcohol in acidic medium or with EDCI/DMAP. Corey oxidation (MnO_2/NaCN/EtOH) of **2** into **4b** did not work despite the reported oxidation of 3-formyl-1-substituted 7-azaindole derivatives.[9] Introduction at the position-2 of **4a** or **4b** of a methyl group by lithiation (LDA/THF/-78 °C then CH_3I) afforded the pivotal intermediate **5a** or **5b** in 77% and 71% yield, respectively. Compounds **5a,b** have a high synthetic potential as referred to the indole analogues.[17,18] A second regioselective lithiation of compounds **5a,b** was performed on the methyl group (LDA/THF/-78 °C, then benzyl bromide) to give the alkylated derivatives **6a,b**.

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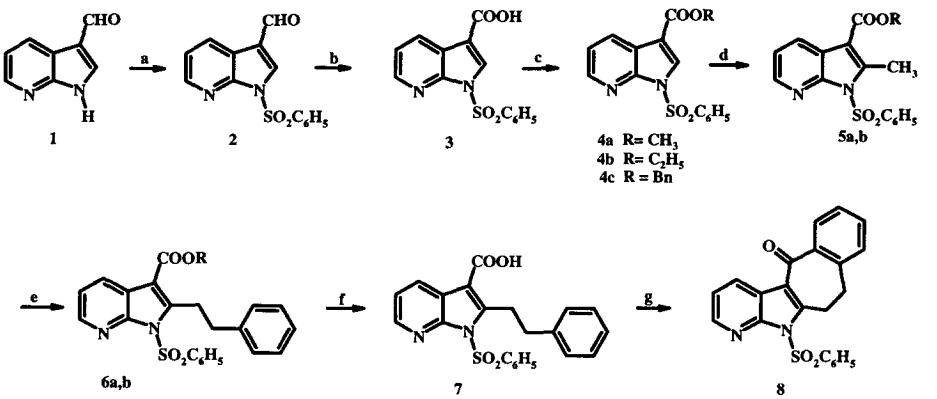

a) $NaH/C_6H_5SO_2Cl/THF/0°C$, 92%; b) $NaClO_2/NH_2SO_3H/Dioxane/H_2O/rt/0.5$ h, 95%; c) ROH/HCl **4a** 91%; **4b** 94%; BnOH/EDCI/DMAP **4c** 98%; d) LDA/THF/-78°C/ICH_3 **5a** 77%, **5b** 71%; e) LDA/THF/-78°C/BnBr **6a** 79%, **6b** 74%; f) BBr_3/CH_2Cl_2/rt, 86%; g) $(CF_3CO)_2O/BF_3$, Et_2O/ $C_2H_4Cl_2$/rt/24h, 62%.

The hydrolysis of the ester group of **6a,b** was not as easy as expected. All attempts, in basic media ($LiOH/MeOH/H_2O$ or K_2CO_3) were unsuccessful due to the weak electrophilic character of the carbonyl group. Nevertheless the use of boron tribromide, at room temperature, with the methyl ester **6a** cleanly afforded the desired acid **7** in 86% yield. Cyclisation of the acid with trifluoroacetic anhydride in the presence of BF_3/Et_2O, at room temperature, in 1,2-dichloroethane gave **8**[19] in 62% yield; the use of PPSE in 1,2-dichloroethane at reflux gave degradation products.

This new azaindolic tricyclic derivative **8** can be used as a scaffold and will help to design potential anticancer candidates.

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19. For **8**: mp 172°C (hexane/CH_2Cl_2); ^{1}H-NMR (250 MHz, $CDCl_3$): δ 3.26 (t, 2H, J = 6.2 Hz, CH_2), 3.76 (t, 2H, J = 6.2 Hz, CH_2), 7.26-7.63 (m, 7H, H_{Ar}), 7.81 (dd, 1H, J = 1.3, 7.6 Hz, H_{Ar}), 8.21 (d, 2H, J = 7.6 Hz, H_{Ar}), 8.43(dd, 1H, J = 1.7, 4.7 Hz, H_{Ar}), 8.80 (dd, 1H, J = 1.7, 7.8 Hz, H_{Ar}); ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 29.4 (CH_2), 33.5 (CH_2), 118.3 (C), 120.7 (CH), 120.9 (C),127.5 (CH), 128.2 (2 CH), 129.0 (CH), 129.3 (3 CH), 131.7 (CH), 132.4 (CH), 134.6 (CH), 138.2 (C), 138.9 (C), 140.0 (C), 145.3 (CH), 148.1 (C), 149.8 (C), 190.2 (CO); MS(ionspray): *m/z* 389 (M^++1).