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A New Convenient Procedure for the Synthesis of Pyrrolo[2,1-*c*][1,4]benzodiazepines

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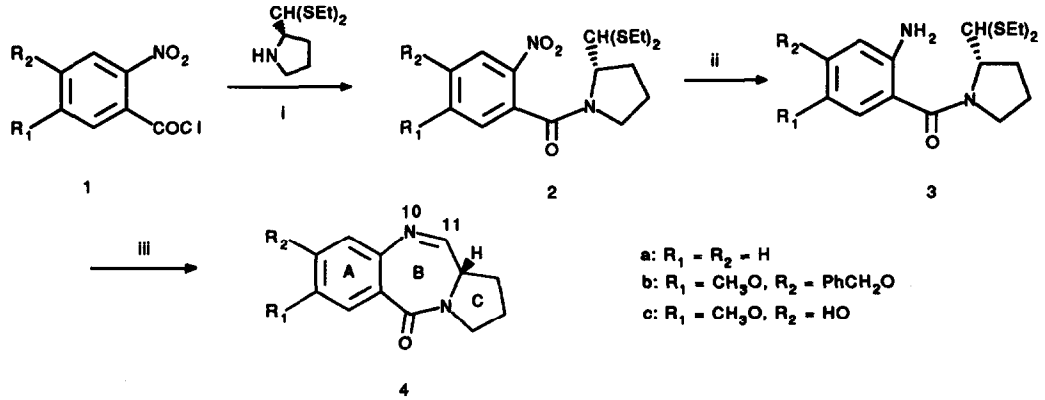
Abstract: An efficient synthesis of the pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) ring system based on a new cyclisation procedure is reported. The parent unsubstituted PBD (**4a**) and the benzyl derivative (**4b**) of the natural product DC-81 (**4c**) have been synthesized to illustrate the utility of this procedure.

The pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) family of antitumour antibiotics[1] are produced by various *Streptomyces* species; well known members include anthramycin, tomaymycin and DC-81[2a,b] (**4c**). Much interest has centred around both the antitumour activity[1] of these compounds which is associated with their DNA-binding ability, as well as synthesis of the problematic, unstable N10-C11 carbinolamine-imine functionality[2]. Various approaches to the synthesis of these compounds have been investigated over the past few years[3], the most successful to date involving the cyclisation of amino dithioacetals of type **3** using aqueous mercuric chloride to afford the desired imine products[2]. However, separation of the final products from excess mercuric salts is always difficult and can reduce yields significantly. The new approach described here centres around the use of sulfuryl chloride[4] as the cyclisation reagent. This allows cyclisation of the B-ring to take place with no by-products and involves a simple and rapid work-up procedure.



1 2 3 4

Reagents: (i) Et_3N, H_2O, THF (ii) $SnCl_2 \cdot 2H_2O$, MeOH (iii) SO_2Cl_2, SiO_2, H_2O-CH_2Cl_2

The appropriate 2-nitrobenzoyl chlorides (**1a,b**) were coupled to (2S)-pyrrolidine-2-carbaldehyde diethyl thioacetal[2c] in quantitative yield to give the amides (**2a,b**). After reduction of the nitro groups with stannous chloride, the corresponding amines (**3a,b**) were cyclized using sulfuryl chloride in wet silica to give the desired imines (**4a,b**) in almost quantitative crude yield. Even after purification by column chromatography, with this new procedure we were able to obtain 20% and 60% yields of **4a**[2c,5] and **4b**[2a] respectively, at a purity level suitable for biochemical and pharmacological evaluation. Full NMR assignments for **4a** are reported here[6].

In a typical procedure, sulfuryl chloride (2.4 equiv; 1M solution in dichloromethane) was added dropwise at room temperature to a stirred mixture of wet silica (0.2g silica gel and 0.2g water) and the amino dithioacetal (0.3g) in dichloromethane. After stirring for 0.5-2 h (until TLC indicated complete reaction), potassium carbonate (anhydrous; 0.3g) was added and stirring continued for a further 0.5 h. The reaction mixture was filtered and the filtrate evaporated *in vacuo* to give the crude product which was further purified by flash chromatography.

In summary, this new cyclisation procedure is capable of producing good yields of DNA-interactive PBDs (e.g. 60% for **4b**, after purification) in their imine form using a simple work up procedure.

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6. **4a:** ^{1}H-NMR (270 MHz, $CDCl_3$): δ 2.01-2.17 (2H, m, $-CH_2-$), 2.23-2.37 (2H, m, $-CH_2-$), 3.48-3.65 (1H, m, -NCHβ), 3.72-3.77 (1H, m, -CH-), 3.82-3.91 (1H, m, -NCHα), 7.31-7.37 (2H, m, ArH, H7 or H8), 7.53-7.55 (1H, m, ArH), 7.78 (1H, d, N=CH, J= 4.4Hz), 8.05 (1H, dd, ArH, J_1= 8.2Hz, J_2=1.5Hz). ^{13}C-NMR ($CDCl_3$): δ 24.2, 29.6, 46.6, 53.5, 116.7, 126.5, 126.8, 130.3, 131.4, 145.7, 164.4, 164.9. MS (EI) m/z (rel. int.): 200 (M^+, 79), 186 (26), 171 (20), 144 (11), 119 (8), 103 (13), 97 (8), 91 (18), 84 (100), 86 (69), 70 (38), 56 (24), 51. HRMS: Calc. for $C_{12}H_{12}N_2O$ (200.0949), found 200.0953.

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