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SYNTHESIS OF NOVEL C7-ARYL SUBSTITUTED PYRROLO[2,1-*c*][1,4]BENZODIAZEPINES (PBDs) *VIA* PRO-N10-TROC PROTECTION AND SUZUKI COUPLING

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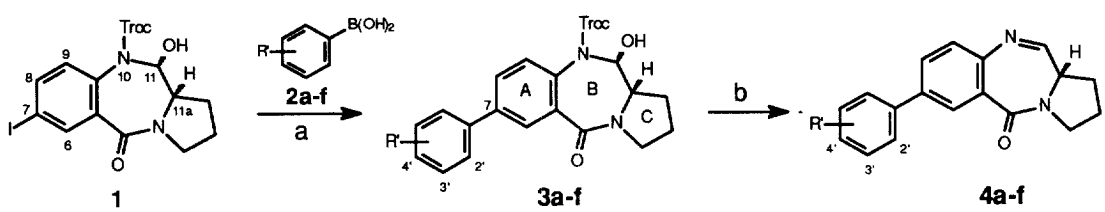
Abstract: Novel C7-aryl pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) have been synthesized via Suzuki coupling between a 7-Iodo N10-Troc-protected PBD carbinolamine and commercially available boronic acids.

The pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) antitumour antibiotics bond covalently to the N2 of guanines in the minor groove of DNA[1], inhibiting the interaction of enzymes with DNA[2] including the process of transcription[3]. There is interest in developing this group of compounds as gene targeting vectors and as antitumour and diagnostic agents[4]. We have recently applied a novel and concise synthetic approach to the PBD ring system based on the use of a pro-N10-2,2,2-trichloroethyl carbamate (Troc) protecting group[5,6] which can be removed easily under mild conditions. The ability to synthesize the 7-iodo N10-Troc-protected intermediate (**1**, Scheme 1) prompted us to investigate methods of C-C bond formation at the C7-position. PBDs of this type are of interest because of the *para* relationship of the C7-substituent to the N10 nitrogen atom of the DNA-interactive N10-C11 imine moiety. Molecular modeling studies have suggested[4] that although C7-substituents point out of the minor groove and do not appear to have a significant steric effect on DNA interaction, they can influence the electronic characteristics of the imine, thus affecting its electrophilicity and ability to interact with DNA.

Suzuki coupling[7] is based on the palladium-catalyzed reaction of organoboron compounds with aryl iodides and appeared to be an attractive means to generate biphenyls in the PBD system due to the mild conditions involved (Palladium catalyst, Na_2CO_3, refluxing benzene/water) and the relative stability of organoboron compounds. Using the previously synthesized 7-iodo N10-Troc-protected PBD (**1**) and commercially available boronic acids as starting materials, the 7-aryl PBDs **4a-f** have been synthesized in yields of up to 93% (Scheme 1 and Table 1).



Scheme 1: a: $Pd(Ph_3P)_4$, Na_2CO_3, benzene, H_2O; **b:** 10% Cd/Pb couple, 1N NH_4OAc aq.

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Compounds	R'	% Yield (2 Steps)	IC_{50} (μM): A2780	IC_{50} (μM): CH1
4a	H	93	1.15	1.5
4b	4' -CH_3	35	0.58	1.5
4c	4' -F	40	0.66	4.7
4d	3' -NO_2	56	34.5	22.5
4e	2' -OCH_3	77	1.18	4.8
4f	4' -OCH_3	55	0.56	1.35

Table 1: Substituent Patterns, Corresponding Yields and Cytotoxicity Values (96 hour exposure).

In a typical procedure, a solution of 7-iodo-10-(2',2',2'-trichloroethoxycarbonyl)-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (**1**, 0.5 g, 0.96 mmol) in benzene (20 ml) was heated at reflux with benzeneboronic acid (**2a**, 0.15 g, 1.22 mmol), $Pd(Ph_3P)_4$ (15 mg), Na_2CO_3 (0.16 g, 1.48 mmol), H_2O (2 ml) and ethanol (2 ml) for 12 h. After cooling to room temperature, the mixture was diluted with ethyl acetate (20 ml) and extracted with water (2 x 20 ml). The organic phase was dried ($MgSO_4$) and evaporated *in vacuo* to afford a yellow oil which was purified by flash chromatography to afford 7-phenyl-10-(2',2',2'-trichloroethoxycarbonyl)-1,2,3,10,11,11a-hexahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (**3a**) as a pale yellow oil (0.43 g, 95%). The Troc protecting group was then removed by the method of Dong[6] to afford the C7-phenyl-PBD **4a** in excellent yield (0.19 g, 98%)[8].

This new class of PBD exhibits μM IC_{50} values in a number of cell lines, two examples of which are shown in Table 1. Cytotoxicity appears to be influenced by the type and position of functional group in the C7-phenyl ring. This is more likely to be an electronic rather than a steric effect, as substituents at the C7-position of the PBD nucleus are known to point out of the minor groove[1,4]. The electron withdrawing 3'-nitro group reduces activity by approximately 30- and 15-fold in the A2780 and CH1 cell lines, respectively. Conversely, there is evidence that a 4'-methoxy group raises the activity (e.g. 2-fold in A2780).

In conclusion, a Pd(0) catalyzed C-C bond formation reaction (the Suzuki coupling) has been used to produce a novel family of C7-aryl-substituted PBDs in excellent yield *via* a cyclisation procedure involving a pro-N10-Troc protecting group. These compounds can be used to study the electronic influence of C7-substituents on the electrophilicity of the N10-C11 imine functionality.

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8. ^1H NMR (Chemical Shift in ppm; Coupling Constants in Hertz; Internal Standard, TMS; $CDCl_3$): δ 1.90-2.1 (m, 2H); 2.30-2.40 (m, 2H); 3.50-3.64 (m, 1H); 3.80-4.0 (m, 2H); 7.36-7.80 (m, 8H); 8.29 (d, 1H, J = 2.2 Hz); ^{13}C NMR ($CDCl_3$): δ 24.4, 29.6, 46.9, 53.9, 126.9, 127.3, 127.7, 127.9, 128.2, 128.8, 130.5, 139.5, 139.7, 145.0, 164.5, 165.1; $[\alpha]^{D}_{25}$ = +131.4 (c = 0.19, $CHCl_3$).