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Solid-Phase Synthesis of Pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones†

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Abstract—The solid-phase synthesis of biologically important pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones using Wang resin through amide formation and reductive cyclization procedures is described. Further, N10-substituents have been introduced in the final products and these have been cleaved from the solid support in good yields.

Pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) are a family of antitumour antibiotics derived from various *Streptomyces* species that exert their biological activity interacting with DNA in a sequence selective fashion by forming a covalent bond between the electrophilic C11-position and the exocyclic C2-NH_2 group of a guanine base in the minor groove of DNA.[1] Among the well known methods for the synthesis of these compounds, the iminothioether approach has been extensively employed for the synthesis of naturally occurring PBD imine or their methylether such as tomaymycin, chicamycin[2] and also for the synthesis of structurally modified synthetic PBDs[3] wherein pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones are the intermediates. They are useful precursors for the PBD cyclic secondary amines and have been recently converted by us to PBD imines through a mild oxidative method.[4] It is also described that PBD 5,11-diones are intermediates for the synthesis of compounds with a broad spectrum of biological activity such as antiphage activity,[5a] analgesic antagonist, antiinflammatory, psychomotor depressant activity,[5b] sedative activity,[5c] and even herbicidal properties.[5d] Further, preclinical trials of N10-substituted PBD 5,11-diones possessing anxiolytic activity have been carried out and are found to be invariably more active than the corresponding N10-hydrogen analogues.[6]

There are methods known for the solution-phase synthesis of these tricyclic PBD 5,11-diones.[7,8] However, to the best of our knowledge there is only one report[9a] on the solid-phase synthesis of these biologically important compounds. Nevertheless, there are numerous reports on the solid-supported preparation of bicyclic 1,4-benzodiazepine-2,5-diones.[9] Herein, we report a general and high yielding solid-phase synthesis of N10-substituted PBD 5,11-diones of biological interest (Scheme 1).

Our synthetic strategy is partly based on the solution-phase methodology of Leimgruber and co-workers,[10] which involves the coupling of an aromatic nitro acid with proline methylester. They have carried out this through the acid chloride of the nitro acid, while we have directly coupled the nitro acid with proline methylester using DCC and DMAP.

In the first step 2-nitro 3- or 4-hydroxy methylbenzoate (**1**) is coupled with Wang resin by the Mitsunobu protocol, employing diisopropyl azodicarboxylate (DIAD), triphenyl phosphine (TPP) in *N*-methylpyrrolidine (NMP) to give **2**. Hydrolysis of the methylester afforded the corresponding acid, which has been coupled with proline methylester in the presence of DCC and DMAP to provide the precursor **4**. Reductive cyclization of **4** afforded the desired PBD 5,11-dione (**5**), which upon cleavage from the resin provided 8- or 9-hydroxy substituted PBD 5,11-dione (**7**). Furthermore, reaction of **5** with different alkyl or benzyl or allyl halides, afforded N10-substituted PBD 5,11-diones (**6**) and this upon cleavage from the resin provided N10-substituted PBD 5,11-diones (**7**).

In a typical synthesis, to a solution of methyl-4-hydroxy-5-methoxy-2-nitrobenzoate (**1**, 1.54 g, 6.8 mmol) in NMP (14 mL) is added Wang resin (1 g, 1.7 mmol/g), TPP

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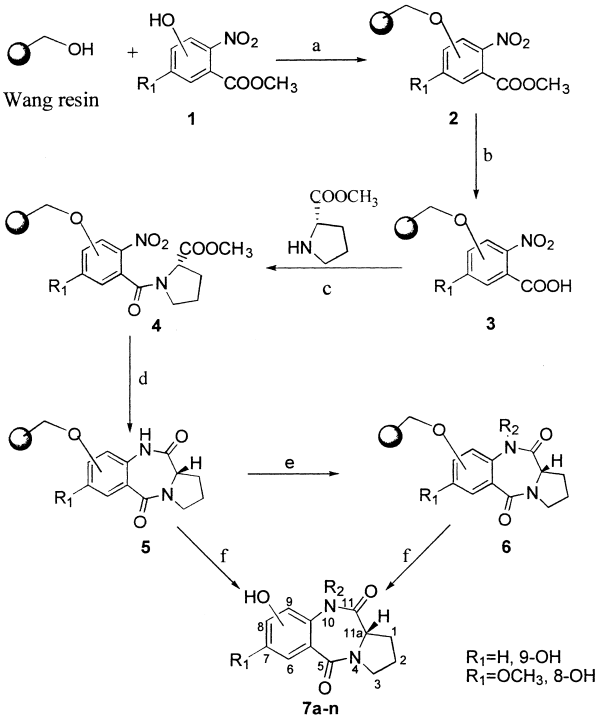
(1.78 g, 6.8 mmol), and DIAD (1.34 mL, 6.8 mmol). The reaction flask is shaken at room temperature for 16 h. The derivatized resin (**2**), is then filtered, rinsed with THF (3×15 mL) and MeOH (3×15 mL), and dried in vacuo. To a suspension of **2** (1.35 g, 1.65 mmol) in dioxane (15 mL) is added 1 N NaOH solution (5 mL) and heated at 100 °C for 12 h. On cooling, the resin (**3**) is filtered and rinsed with water (3×15 mL), water/dioxane (1:9, 3×15 mL), MeOH (3×15 mL), CH_2Cl_2 (3×15 mL) and ether (3×15 mL) and dried in vacuo. To a suspension of resin (**3**, 1.32 g, 1.62 mmol) in CH_2Cl_2 (8 mL) is added DCC (1.34 g, 6.5 mmol), DMAP (10 mg) at 0 °C and shaken at the same temperature for 30 min. Then to this reaction flask is added the solution of proline methylester (0.845 g, 6.5 mmol) in CH_2Cl_2 (5 mL) and allowed to shake at room temperature for 8 h. The product resin (**4**), is filtered and rinsed sequentially using the solvents mentioned above. To a suspension of resin (**4**, 1.50 g, 1.58 mmol) in DMF (12 mL) is added $SnCl_2 \cdot 2H_2O$ (1.40 g, 6.3 mmol) and shaken at 40 °C for 10 h to afford the reductive cyclized lactam resin derivative (**5**). This is filtered and rinsed in a sequential manner with the solvents mentioned earlier and dried in vacuo. The suspension of resin (**5**, 0.2 g, 0.164 mmol) in TFA/CH_2Cl_2 (1:1, 4 mL) is shaken at room temperature for 1 h followed by collection of supernatant. This procedure is repeated once more to ensure the complete cleavage of the product from resin. The combined supernatant is evaporated in vacuo to afford the crude product (**7h**), which is purified by column chromatography (silica gel, ethyl acetate/hexane 4:6). Whereas for the preparation of N10-substituted compounds, the resin **5** (0.2 g, 0.164 mmol) and NaH (0.078 g, 1.6 mmol) are taken in dry DMF (5 mL) and are shaken at room temperature for 2 h, followed by the addition of allyl bromide (0.193 g, 1.6 mmol), which is allowed to shake at the same temperature for 3 h. Later, to the reaction mixture is added saturated aqueous solution of NH_4Cl (10 mL) and the resin rinsed sequentially with the solvents mentioned earlier to give the resin derivative (**6**). Finally, the resin is cleaved by TFA/CH_2Cl_2 to provide the crude product (**7k**),[11] which is further purified by column chromatography.



Scheme 1. (a) TPP, DIAD, NMP. (b) 1 N NaOH, dioxane, 100 °C. (c) DCC, DMAP, CH_2Cl_2, 0 °C–rt. (d) $SnCl_2 \cdot 2H_2O$, DMF, 40 °C. (e) R_2-X, NaH, DMF, 0 °C–rt. (f) TFA/CH_2Cl_2 (1/1).

Table 1. 7,10-Substituted pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones

Compd.	R_1	R_2	Isolated yields (%)
7a	H	H	84
7b	H	CH_3	70
7c	H	$CH_2C_6H_5$	75
7d	H	Allyl	64
7e	H	Prenyl	55
7f	H	$CH_2C_6H_4$-4-OMe	65
7g	H	$CH_2C_6H_2$-3,4,5-$(OMe)_3$	52
7h	OCH_3	H	82
7i	OCH_3	CH_3	71
7j	OCH_3	$CH_2C_6H_5$	76
7k	OCH_3	Allyl	66
7l	OCH_3	Prenyl	53
7m	OCH_3	$CH_2C_6H_4$-4-OMe	62
7n	OCH_3	$CH_2C_6H_2$-3,4,5-$(OMe)_3$	57

Similarly, other N10-substituted PBD 5,11-diones[12a] have been prepared by employing the corresponding halides as illustrated in Table 1. The optical purity of these compounds has been ascertained by comparing the optical rotation of some of the representative examples, such as **7j**[12b] prepared unambiguously by the literature method.[6] The possibility of racemization has been ruled out at C11a position under the reaction conditions employed, as no significant difference has been observed between the optical rotations for the compounds synthesized by both the present and literature methods.

In summary, a straightforward solid-phase synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones is described from commercially available hydroxy substituted 2-nitro benzoic acids and L-proline methylester. This synthetic sequence permits introduction of a diverse array of substituents into both the aromatic portion and N10-position of the PBD 5,11-dione skeleton, thus allowing for the generation of the combinatorial library of this biologically important class of compounds.

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11. Spectral data for **7k**: ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6) δ 1.9–2.18 (m, 3H), 2.68 (m, 1H), 3.54 (m, 1H), 3.7 (m, 1H), 3.9 (s, 3H), 4.12 (m, 1H), 4.3–4.57 (m, 2H), 5.15 (s, 1H), 5.25 (s, 1H), 5.9 (m, 1H), 6.9 (s, 1H), 7.3 (s, 1H), 9.5 (s, 1H), MS (EI) *m*/*z* 302.
12. (a) Selected HRMS data, **7c**: Calcd for $C_{19}H_{18}N_2O_3$ 322.1317, Found 322.1331; **7j**: Calcd for $C_{20}H_{20}N_2O_4$ 352.1423, Found 352.1413; **7n**: Calcd for $C_{23}H_{26}N_2O_7$ 442.1740, Found 442.1761. (b) Optical rotation for **7j** $[\alpha]_D^{30}$ +5 (c = 1.01 $CHCl_3$).