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A new approach for the solid-phase synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines involving reductive cleavage

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Abstract—A methodology based on reductive cleavage followed by cyclization, for the solid-phase synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines employing DIBAL-H, is described.

Solid-phase combinatorial chemistry has presently become a very useful methodology for the generation of libraries of new molecules with biological properties.[1] Natural product derived heterocyclic compounds offer a high degree of structural diversity and thus may lead to useful therapeutic agents. As a consequence, a wide range and increasing number of biologically important heterocyclic compounds have been prepared employing solid-phase procedures.[2] It is well known that such approaches allow the rapid preparation of a large number of individual compounds in a short time and facilitate their assessment in high-throughput screening.[3]

The pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) are a group of potent, naturally occurring, antitumour antibiotics produced by various *Streptomyces* species.[4] These compounds bind selectively in the minor groove of DNA while a covalent aminal bond between the electrophilic C11-position of the PBD and the nucleophilic N2-amino group of a guanine base,[5] possibly result in the biological activity. A number of naturally occurring and synthetic compounds based on this PBD ring system, such as anthramycin, chicamycin, abbeymycin, DC-81 and its dimers[6] (Fig. 1) have shown varying degrees of DNA binding affinity and anticancer activity. For example, a PBD dimer (SJG-136), with an affinity for Pu-GATC-Py sequences is presently under clinical evaluation.[7]

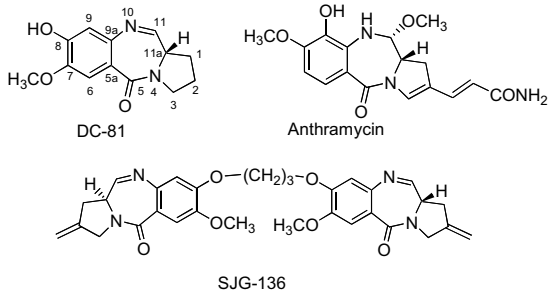

Figure 1.

Recently, Thurston and co-workers reported the solid-phase synthesis of pyrrolobenzodiazepines[8] and we have also developed some new solid-phase methodologies.[9] However, one of the challenges of the solid-phase combinatorial synthesis of heterocyclic compounds is developing chemical routes that provide access to the target compounds without leaving any trace of the linker used for tethering the starting building blocks to the solid support.[10] We report here a new traceless approach for the solid-phase synthesis of pyrrolo[2,1-*c*][1,4]-benzodiazepines.

The imine containing biologically significant pyrrolobenzodiazepine ring system is a reactive moiety and requires extremely mild conditions for the cleavage from the resin during its solid-phase synthesis. There are many methodologies for the preparation of this ring system in solution phase,[11] however, there are very few reports on its solid-phase synthesis.[12] In the present investigation a new traceless methodology based on

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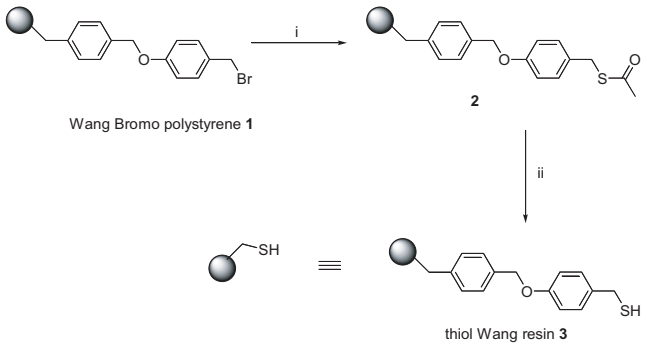
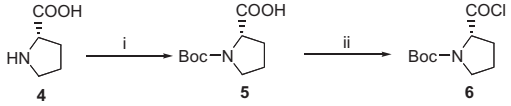


Scheme 1. Reagents and conditions: (i) CH_3COSK, DMF, rt 12 h; (ii) $LiBH_4$, THF, rt, 8 h.

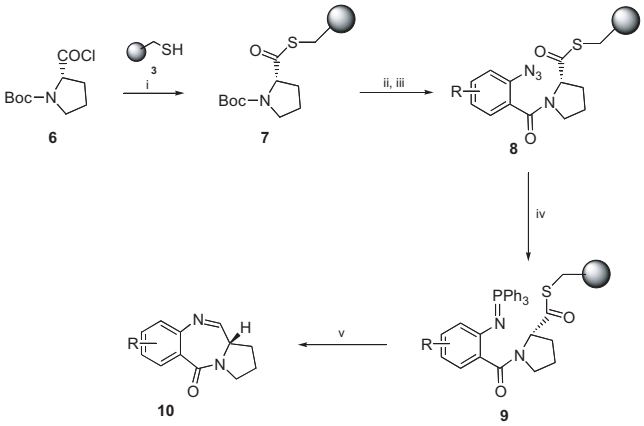


Scheme 2. Reagents and conditions: (i) Boc anhydride, 2 N NaOH, THF, rt, 2 h; (ii) PS-TPP, CCl_4, reflux, 4 h.

reductive cleavage followed by cyclization employing DIBAL-H has been developed.

(4-Bromomethylphenoxy)methyl polystyrene **1** (1.4 mmol/g, 100–200 mesh, 1% DVB) was treated with potassium thioacetate in DMF. The formation of thioester **2** was indicated by a strong carbonyl stretching vibration at 1680 cm^{-1} in the IR spectrum. The reduction of **2** using $LiBH_4$ in THF at room temperature gave the thiol Wang resin **3** (Scheme 1). The precursor Boc protected proline acid chloride **6** was prepared using polystyrene triphenylphosphine in CCl_4 (Scheme 2).[13] The resin **3** was linked to the Boc protected proline acid chloride **6** using triethylamine in dichloromethane to afford Boc protected proline thioester resin **7**. The intermediate, after the deprotection of the Boc group using TFA, was coupled to the corresponding 2-azidobenzoic acid in the presence of TBTU and DIPEA to provide the required resins (**8a**–**h**), as indicated by IR spectra that showed a strong azide stretching vibrations in the range between 2080 and 2170 cm^{-1}. Treatment of **8a**–**h** with excess of PPh_3 in dry toluene at room temperature produced the corresponding resins of iminophosphoranes (**9a**–**h**). Finally, the resins **9a**–**h** were treated with DIBAL-H in dry dichloromethane at −78 °C for 12 h to afford the desired PBD imines (**10a**–**h**)[14] (Scheme 3) in good yields (57–65%) (Table 1). The thiol form of resin **3** was recovered, and could be reused for the preparation of **7**.

In summary, a new traceless solid-phase strategy for imine-containing pyrrolo[2,1-*c*][1,4]benzodiazepine systems has been demonstrated. This is an interesting process involving intramolecular aza-Wittig cyclization through reductive cleavage by employing DIBAL-H. These reaction conditions are readily amenable for generating a PBD combinatorial library with diversity in A and C rings.



Scheme 3. Reagents and conditions: (i) triethylamine, CH_2Cl_2, 0 °C, 6 h; (ii) TFA, CH_2Cl_2, rt, 1 h; (iii) 2-azidobenzoic acid, TBTU, DIPEA, DMF, rt, 6 h; (iv) TPP, anhydrous toluene, rt, 3 h; (v) DIBAL-H, CH_2Cl_2, −78 °C, 12 h.

Table 1. Yields and EIMS for PBD analogues **10a**–**h**

Product	R	Yields (%)[a]	EIMS [M^+]
10a	H	65	200
10b	7-Me	62	214
10c	8-Me	60	214
10d	7-Cl	63	234
10e	8-Cl	60	234
10f	7-OMe	59	230
10g	7-OMe, 8-OMe	61	260
10h	7-OMe, 8-OBn	57	336

[a] From initial loading of Wang bromo polystyrene.

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14. *Preparation of compound* **10a**: To a suspension of resin **8a** (1.4 mmol) in dry toluene, TPP (1.47 g, 5.6 mmol) was added and the mixture allowed to stir for 3 h at room temperature to give the resin **9a**. This was carefully filtered, rinsed with toluene and dichloromethane under dry conditions, and dried in vacuo. To the suspension of resin **9a** in dry dichloromethane (10 mL) was added DIBAL-H (2.8 mL of 1 M solution in hexane, 2.8 mmol) dropwise at −78 °C under nitrogen, and the mixture stirred at the same temperature for 12 h. The reaction was quenched by the addition of 5% HCl. The resin was filtered and washed with dichloromethane (3 × 10 mL). The combined filtrates were evaporated to afford the crude product, which was further purified by column chromatography (silica, ethyl acetate–hexane, 95:5) to get **10a** (182 mg, 65% yield from initial loading of Wang bromo polystyrene). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.02–2.16 (2H, m), 2.26–2.38 (2H, m), 3.36–3.94 (3H, m), 7.28–7.38 (2H, m), 7.53 (1H, t, J = 6.69 Hz), 7.79 (1H, d, J = 4.46 Hz), 8.05 (1H, d, J = 7.43 Hz). MS (EI): m/z 200 [M^+]; $[\alpha]_D^{26}$ +343 (c 0.4, $CHCl_3$).