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Efficient reduction of aromatic nitro/azido groups on solid support employing indium: synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones

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Abstract—An efficient method for the reduction of aromatic nitro and azido compounds on solid support using indium/NH_4Cl is described. This solid-phase reduction technique has been applied to the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones.

Recently, the generation of compound libraries through combinatorial methods has received tremendous attention mainly as a means of accelerating the drug discovery process.[1] In this connection the development of new solid-phase methodologies is a significant and essential part of increasing the range of compounds which are accessible by this approach. In solution-phase chemistry, aromatic nitro and azido groups have been reduced by a variety of reagents.[2] However, a large number of these methods are not suitable for application in solid-phase organic chemistry. The most common method presently in use for the reduction of solid-phase bound nitro and azido groups utilizies tin(II) chloride.[3] In spite of the advantages of tin reduction there are instances in the literature where substantial quantities of tin by-products remain bound within the resin matrix and are liberated upon acidic cleavage of the desired product. Furthermore, most of the cell lines biologically screened have proven intolerant to tin at these levels. Attempts to wash any residual tin remaining within the resin by employing different methods have only been partly successful.[4]

Pyrrolo[2,1-*c*][1,4]benzodiazepine (PBDs) antitumour antibiotics have been derived biosynthetically from different *Streptomyces* species and exert their biological activity by interacting with DNA in a sequence selective manner.[5] Pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones have been employed as intermediates in the synthesis of naturally occurring and synthetically modified PBD imines such as tomaymycin and chicamycin.[6] They are also useful precursors for the PBD cyclic secondary amines[7] which can be converted to PBD imines by mild oxidation.[8] Their importance as intermediates for a wide range of biologically active compounds, such as psychomotor depressant activity[9a] and sedative activity[9b] has been extensively investigated.

During the course of our studies on the development of solid-phase synthetic methodologies for the pyrrolo[2,1-*c*][1,4]benzodiazepine ring system,[10] we herein report a practical procedure which works in neutral conditions and is specific to the reduction of nitro and azido groups in the presence of other functionalities by employing indium/NH_4Cl. The present method describes a useful and high yielding solid-phase synthesis of PBD-5,11-diones of biological interest, and is also a general procedure for the solid-phase reduction of aromatic nitro and azido functionalities as illustrated in Table 1 (entries **d**, **e, h** and **i**). Moreover, the solid-phase reduction of nitro and azido groups is the key step in the synthesis of a variety of biologically important small organic molecules,[11] and this method has potential in the preparation of such compounds. Our synthetic strategy is mainly based on the solution phase nitro and azido reductive cyclization process employing other types of reagents[12] (Scheme 1).

In a typical synthesis, trichloroacetonitrile (1.5 ml) was added to a suspension of Wang resin (**1**, 0.5 g, 0.85 mmol) in dry CH_2Cl_2 (10 ml), and the mixture was cooled to 0°C. DBU (0.1 ml) was then added dropwise to the suspension over a period of 5 min and the resin was allowed to stir at 0°C for 40 min. The derivatized

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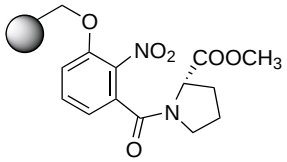
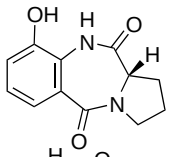
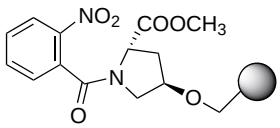
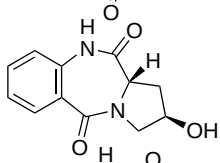
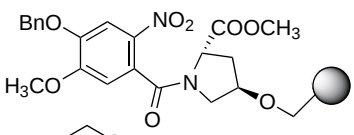
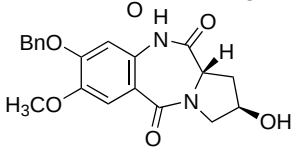
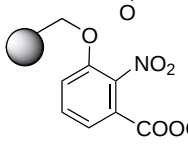
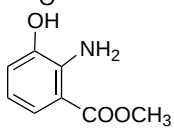
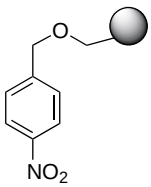
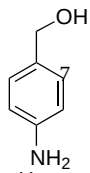
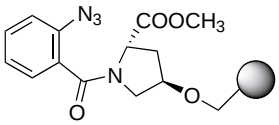
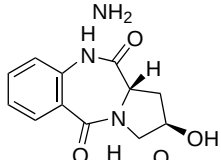
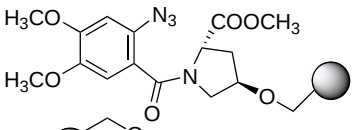
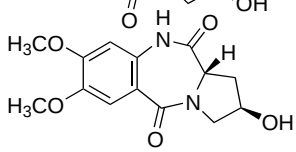
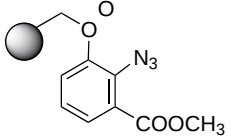
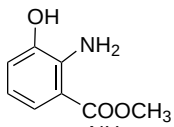
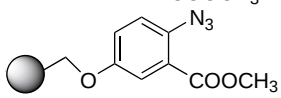
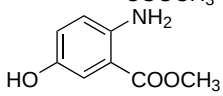
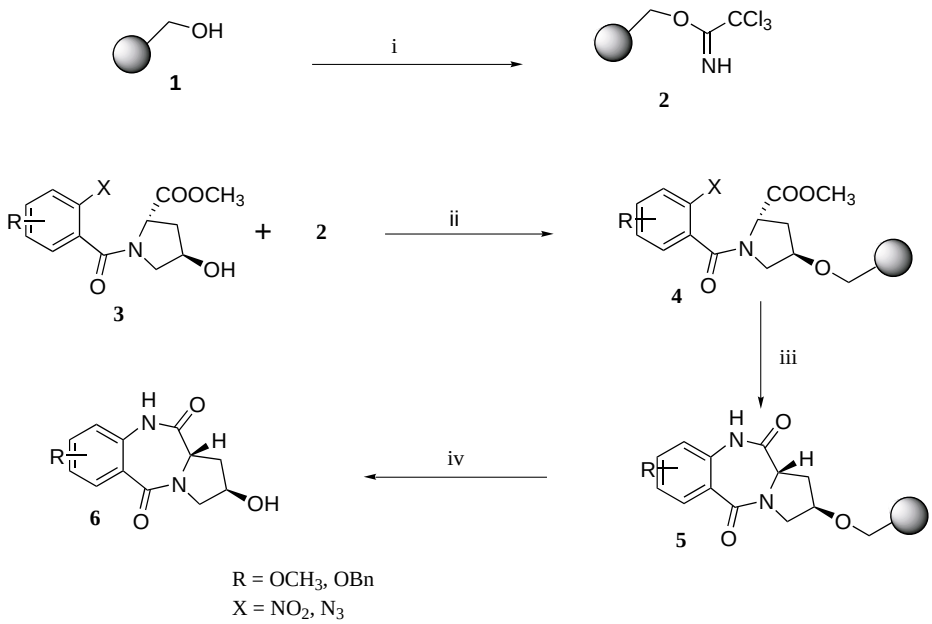
Table 1. Reduction of nitro/azido compounds using indium followed by TFA cleavage

Entry	Substrate (**4**)	Time (h)	Product (**6**)	Yield (%)[a]
a		4		80
b		4		85
c		4		82
d		3		80
e		5		5
f		3		92
g		3		90
h		4		88
i		4		86

[a] Isolated yields.

resin (**2**) was filtered and rinsed with CH_2Cl_2, DMSO, THF and CH_2Cl_2 and dried in vacuo. To a suspension of **2** (0.622 g, 0.85 mmol) in dry CH_2Cl_2 (10 ml) was added azido ester (**3**, 1.186 g, 3.4 mmol) and trifluoromethanesulphonic acid (10 μl), and the resulting mixture stirred for 10–15 min. The resin derivative (**4**) was filtered and rinsed with CH_2Cl_2, DMSO and THF. To a suspension of resin (**4**, 0.782 g, 0.73 mmol) in ethanol or DMF (10 ml) was added indium powder (0.420 g, 3.65 mmol) and saturated ammonium chloride solution (3 ml) and the mixture was refluxed for 3 h to afford the reductively cyclized lactam resin derivative (**5**). This was filtered and rinsed with water, ethanol, DMF and CH_2Cl_2. Finally, the resin was cleaved by TFA/CH_2Cl_2 (1:3, 4 ml) to provide the crude product (**6g**),[13] which was further purified by column chromatography ($CHCl_3$: MeOH, 9.8:0.2).

In summary, we have demonstrated that indium/NH_4Cl is a practical alternative method to tin(II) chloride and other reducing agents in solid-phase synthesis. The reduction occurs under mild conditions resulting in high yields and compares favorably with known methods and may be superior in some cases. The use of this reagent system in the preparation of combinatorial chemical libraries will be reported in due course.



Scheme 1. (i) Trichloroacetonitrile, DBU, CH_2Cl_2, 40 min, 0°C; (ii) Trifluoromethanesulphonic acid, CH_2Cl_2, 10 min; (iii) Indium/NH_4Cl, DMF or EtOH, reflux for 3 h; (iv) TFA/CH_2Cl_2 (1:3).

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13. Spectral data for **6g**: ^1H NMR (200 MHz, $CDCl_3$): δ 2.0–2.1 (m, 1H), 2.7–2.9 (m, 1H), 3.5–3.6 (m, 1H), 3.8–3.9 (m, 1H), 3.9 (s, 6H), 4.1–4.2 (t, 1H), 4.4–4.5 (m, 1H), 6.6 (s, 1H), 7.5 (s, 1H), 10.0 (brs, 1H), MS (EI) m/z 292.