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Selective reduction of aromatic azides in solution/solid-phase and resin cleavage by employing $BF_3{\cdot}OEt_2$/EtSH. Preparation of DC-81

Ahmed Kamal,* N. Shankaraiah, K. Laxma Reddy and V. Devaiah

Biotransformation Laboratory, Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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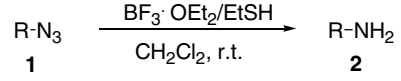
Abstract—An efficient method for the reduction of aromatic azides in both solution and solid-phase has been developed by employing $BF_3{\cdot}OEt_2$/EtSH. This report also describes resin cleavage employing this reagent system. Further, this protocol has been utilized for the solution as well as the solid-phase synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines, including the naturally occurring antibiotic DC-81 and fused [2,1-*b*]quinazolinones.

A variety of reagents have been reported in the literature[1,2] for the reduction of azides including borohydrides,[3] triphenylphospine,[4] benzyltriethylammonium tetrathiomolybdate,[5]hexamethyldisilathiane,[6] SmI_2,[7] etc. However, in terms of their practical applicability, reaction conditions or commercial availability, most of these methods have certain disadvantages and hence considerable effort has been devoted to explore further more efficient and convenient methods.[8]

As part of ongoing research programmes, we have been involved in the synthesis of some important biologically active heterocyclic natural products.[9] In this connection, we have developed solution and solid-phase synthetic methods for the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines[10] and quinazolinones.[11] We herein report a mild, efficient and selective method for the reduction of aromatic azides **1** to their corresponding amines **2** by employing boron trifluoride diethyletherate and ethanethiol, as shown in Scheme 1.

In a typical procedure, to a stirred solution of aromatic azide (**1**, 100 mg, 0.32 mmol) in CH_2Cl_2 (5 mL) was added boron triflouride diethyletherate (0.09 mL, 0.80 mmol), followed by ethanethiol (0.12 mL, 1.60 mmol). The reaction mixture was stirred for 1.5–2 h and then neutralized with saturated aqueous $NaHCO_3$ solution. After separation of the organic phase, it was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product thus obtained was purified by column chromatography through a silica gel (60–120 mesh) pad employing ethyl acetate/hexane (15:85) as eluent to afford the corresponding amine **2**. This procedure has been extended for the reduction of azides **1a–g** to the corresponding amines **2a–g** in excellent yields and the results are given in Table 1.

This methodology has also been applied to the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs). These are naturally occurring antitumour antibiotics that are produced by various *Streptomyces* species, and exert their biological activity by interacting with DNA in a sequence selective manner.[12] PBD-5,11-diones have been employed as intermediates in the synthesis of naturally occurring and synthetically modified PBD imines, such as tomaymycin and chicamycin.[13] They are also precursors of PBD cyclic secondary amines,[14] which



Scheme 1.

Keywords: Pyrrolo[2,1-*c*][1,4]benzodiazepines; Solid-phase synthesis; Boron trifluoride diethyletherate; Resin cleavage; Reductive cyclization.
* Corresponding author. Tel.: +91 40 27193157; fax: +91 40 27193189; e-mail addresses: ahmedkamal@iict.res.in; ahmedkamal@iictnet.org

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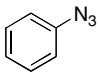
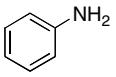
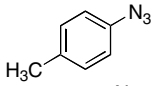
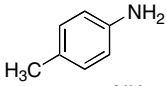
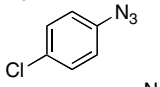
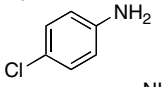
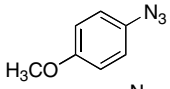
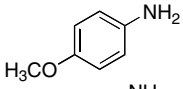
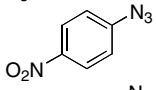
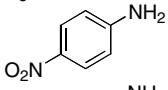
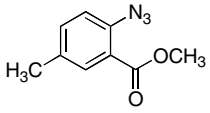
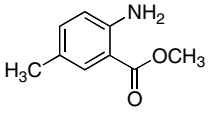
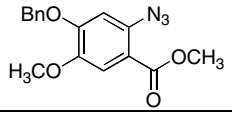
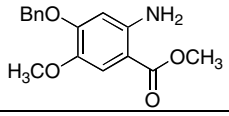
Table 1. Reduction of aromatic azides to amines employing $BF_3{\cdot}OEt_2$/EtSH

Entry	Substrate **1**	Product **2**	Time (h)	Yield (%)
a			1.5	95
b			1.5	98
c			2	90
d			2	92
e			2.5	85
f			2	93
g			1.5	98

can be converted to their PBD imines by a mild oxidation process.[15] Moreover, it is known that PBD-5,11-diones are intermediates for the synthesis of compounds with a wide range of biological activities.[16] With a view to develop new efficient solution and solid-phase procedures,[17] we have employed the $BF_3{\cdot}OEt_2$/EtSH reagent system for the azido reductive process of substrates[18] **3a**–**f** to give the PBD-5,11-diones **4a**–**f** in good yields, as illustrated in Table 2. Similarly, in view of our interest in the synthesis of fused [2,1-*b*]quinazolinones[19] (e.g., deoxyvasacinone), this reagent system has also been employed to extend the azido reductive cyclization protocol for substrates[18] **3g**–**j** to afford fused quinazolinones **4g**–**j** in excellent yields, as shown in Table 2.

This approach has been further applied to the preparation of the naturally occurring PBD antibiotic DC-81 (**7**). This compound exerts its biological activity by covalently binding to the N2 of guanine in the minor groove of DNA. Various approaches towards compounds of this type have been investigated over the past few years,[20] most of these methods have met with varying degrees of success and have different limitations. Herein, we report an efficient and simple method for the synthesis of naturally occurring DC-81 by employing $BF_3{\cdot}OEt_2$/EtSH. By varying the quantities of $BF_3{\cdot}OEt_2$/EtSH, either benzylated DC-81 **9** or debenzylated DC-81 **7** were obtained via ethanethiol protected intermediates **6** and **8**, as shown in Scheme 2.

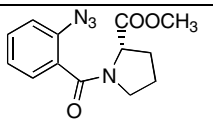
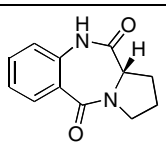
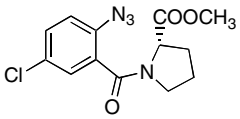
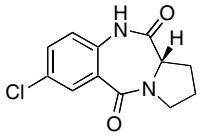
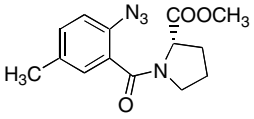
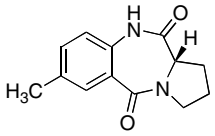
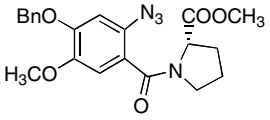
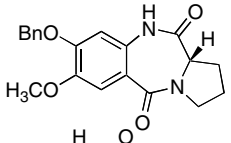
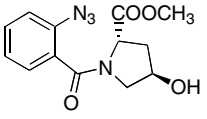
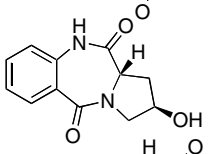
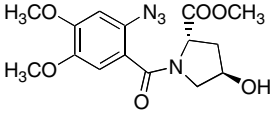
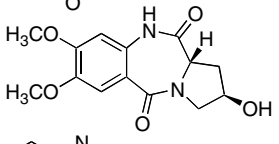
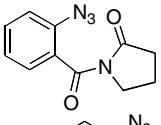
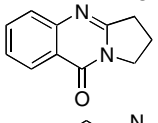
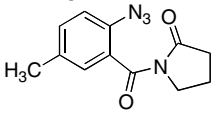
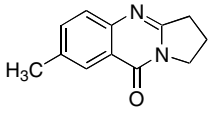
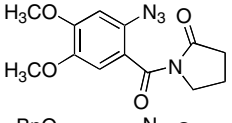
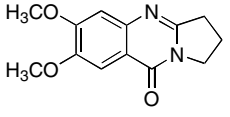
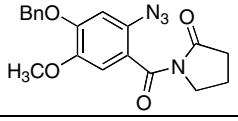
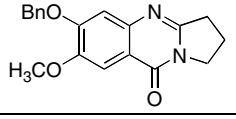
Typical procedure for the preparation of DC-81: To a suspension of **5**[18] (150 mg, 0.39 mmol) in CH_2Cl_2 (5 mL) was added boron trifluoride diethyletherate (0.43 mL, 3.95 mmol) followed by ethanethiol (0.57 mL, 7.90 mmol), and the reaction mixture was stirred for 6 h. The resulting mixture was neutralized with saturated aqueous $NaHCO_3$ solution and the organic layer was separated and dried over Na_2SO_4. The solvent was concentrated under reduced pressure and the crude product thus obtained was purified by column chromatography through a silica gel (60–120 mesh) pad employing ethyl acetate/hexane (40:60) as the eluent. The debenzylated ethanethiol protected amine **6** upon deprotection[21] with $HgCl_2/CaCO_3$ gave the naturally occurring antibiotic DC-81 **7**. Benzylated DC-81 **9** was prepared in a similar manner instead by using boron trifluoride diethyletherate (0.11 mL, 0.99 mmol) and ethanethiol (0.14 mL, 1.98 mmol).

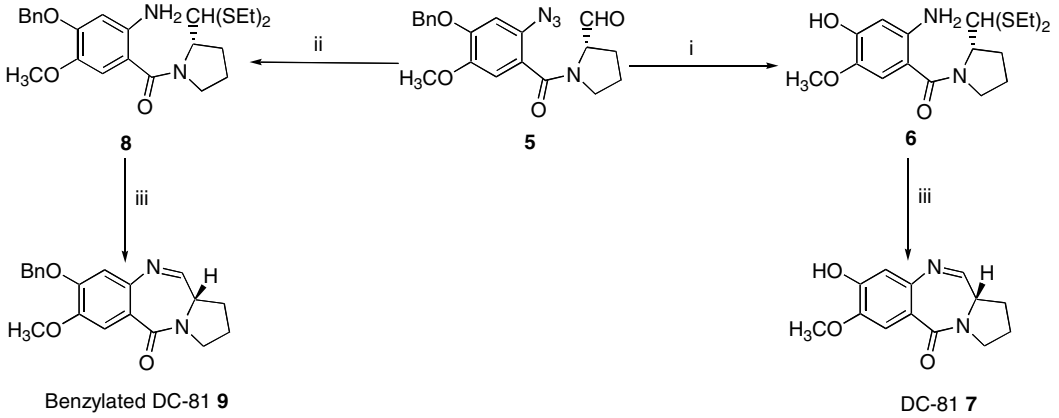
Interestingly, when this procedure was used for the reduction of resin-linked aryl azides the corresponding aminophenols were obtained, and the results are described in Table 3. There are reports in the literature where Lewis acid assisted cleavage of resins[22] is employed, however, to the best of our knowledge this is the first report of the cleavage of a resin by employing $BF_3{\cdot}OEt_2$/EtSH.

During the course of our studies on the development of solid-phase synthetic methods for the PBD ring system, we reported procedures mainly based on reductive cyclization approaches.[10] In this connection, the boron trifluoride diethyletherate reagent system was reacted with resin-linked aryl azido proline esters **12** to afford PBD-5,11-diones **13** by simultaneous reduction of the azide functionality and cleavage of the resin as shown in Scheme 3 and Table 4. This method is advantageous as the reductive cyclization and the resin cleavage take place in the same step, unlike the previous procedures,[10b–d] which employ TFA for cleavage of the resin.

In a typical synthesis, to a suspension of Wang resin **12**[10b] (200 mg, 0.8–1.1 mmol/g, 200–400 mesh and 1%

Table 2. Synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines-5,11-diones and fused [2,1-*b*]quinazolinones through reductive cyclization employing $BF_3{\cdot}OEt_2$/EtSH

Entry	Substrate **3**	Product **4**	Time (h)	Yield (%)
a			1.5	95
b			1.5	95
c			2.5	92
d			2	90
e			2.5	90
f			2.5	90
g			1.5	98
h			1.5	98
i			2	96
j			2	97



Scheme 2. Reagents and conditions: (i) $BF_3{\cdot}OEt_2$/EtSH (10:20 equiv), CH_2Cl_2, rt, 6 h; (ii) $BF_3{\cdot}OEt_2$/EtSH (2.5:5 equiv), CH_2Cl_2, rt, 6 h; (iii) $HgCl_2$–$CaCO_3$, CH_3CN/H_2O (1:1), rt, 12 h.

Table 3. Solid-phase synthesis reduction of aromatic azides to amines employing $BF_3{\cdot}OEt_2$/EtSH

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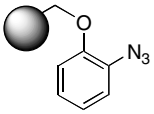
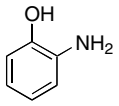
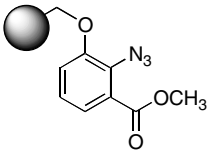
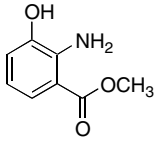
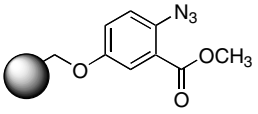
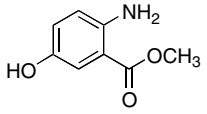
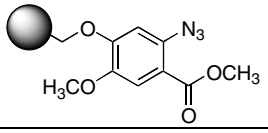
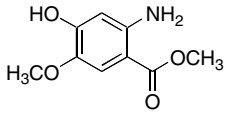
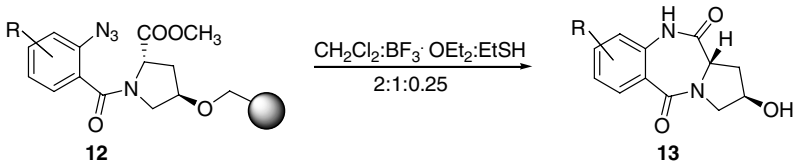
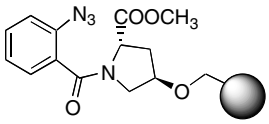
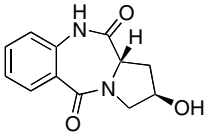
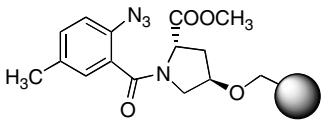
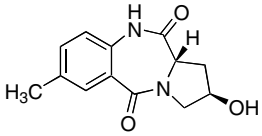
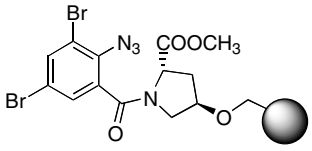
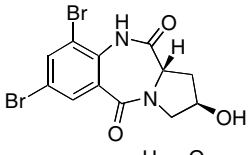
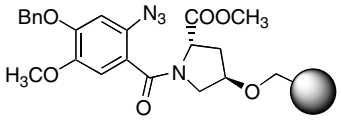
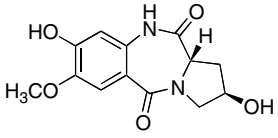
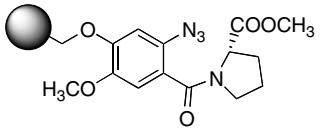
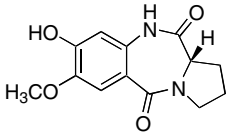
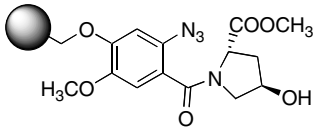
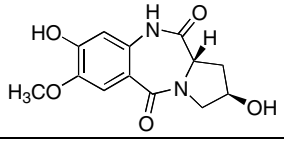
a			2	90
b			2	91
c			2	82
d			2	92



Scheme 3.

Table 4. Solid-phase synthesis reductive cyclization and resin cleavage employing $BF_3{\cdot}OEt_2$/EtSH

Entry	Substrate **12**	Product **13**	Time (h)	Yield (%)
a			3	90
b			3	90
c			3	89
d			6	85
e			2	80
f			2	82

crosslinked) was added boron trifluoride diethyletherate (1 mL) and ethanethiol (0.25 mL) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 2 h then filtered through a glass funnel, and the filtrate was neutralized with saturated aqueous $NaHCO_3$ solution. The organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography through a silica gel (60–120 mesh) pad employing ethyl acetate/hexane (60:40) as eluent to produce pyrrolo[2,1-*c*][1,4]benzodiazepines-5,11-diones **13**.

In summary, a practical approach for the reduction of aryl azides in solution as well as on solid-phase has been described by employing boron trifluoride diethyletherate and ethanethiol. This method has been extended to the synthesis of PBD-5,11-diones and fused quinazolinones via their azido intermediates by employing a reductive cyclization process. This procedure also provides an alternative, simple and short route for the preparation of naturally occurring DC-81, and its analogues. Moreover, this protocol has been utilized for an efficient solid-phase synthesis of PBD-5,11-diones.

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