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Facile reduction of aromatic nitro/azido functionality on solid support employing Al/$NiCl_2 \cdot 6H_2O$ and Al/NH_4Cl: synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines

Ahmed Kamal,* K. Laxma Reddy, V. Devaiah and G. Suresh Kumar Reddy

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

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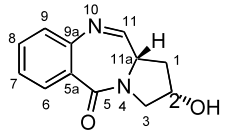
Abstract—An efficient and mild method for the reduction of aromatic nitro and azido groups on solid support using Al/$NiCl_2 \cdot 6H_2O$ and Al/NH_4Cl is described. This solid phase reduction technique has been applied towards the synthesis of DNA binding pyrrolo[2,1-*c*][1,4]benzodiazepine antitumour antibiotics. © 2003 Published by Elsevier Science Ltd.

The preparation of small molecules on solid phase is emerging as an expedient method and is being utilized towards generating compounds for screening against biological systems, and enhance the drug discovery effort.[1] In this connection, the development of new solid-phase methodologies is an essential component for increasing the range of compounds that could be accessible by this approach. The reduction of nitro compounds to amines[2] is a very useful synthetic transformation, for which a vast array of reagents is known in solution phase. However, relatively few reagents are known for this synthetically and industrially important reaction on a solid support. Moreover, a large number of solution phase methods are not suitable for application to solid phase organic chemistry. The most common methods presently in use for the reduction of solid phase bound nitro and azido groups utilizes tin(II) chloride,[3] phosphines for azido groups[4] and borohydride/copper salts for nitro groups.[5] 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 away any residual tin remaining within the resin have only been partly successful.[6]

Pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) are a group of potent,[7] naturally occurring antitumour antibiotics produced by various *Streptomyces* species. The cytotoxic and antitumour effects of these compounds are believed to arise from modification of DNA, which leads to inhibition of nucleic acid synthesis and production of excision-dependent single and double strand breaks in cellular DNA. These antibiotics bind selectively in the minor groove of DNA via a covalent aminal bond between the electrophilic C11-position of the PBD and the nucleophilic C2-amino group of the guanine base, resulting in the observed biological activity. Anthramycin, tomaymycin, neothramycin, chicamycin, abbeymycin, DC-81 and its dimers are well-known examples of PBDs. Recently, PBD imines have been used in the development of gene-targeting agents with the potential to down-regulate genes of therapeutic interest. Among the well known methods for the synthesis of these compounds[8] the imino-thioether approach has been extensively employed for



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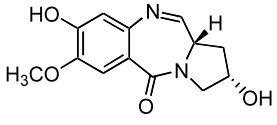
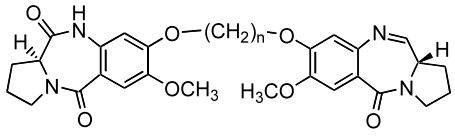


Chicamycin A



imine-amide PBD dimers

* Corresponding author. Tel.: +91-40-27193157; fax: +91-40-27193189; e-mail: ahmedkamal@iict.ap.nic.in

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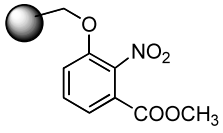
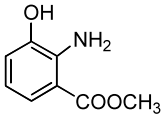
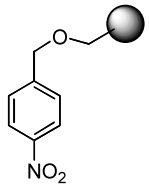
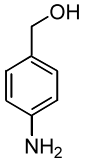
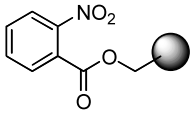
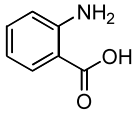
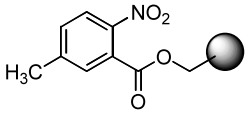
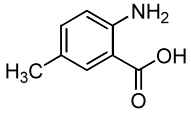
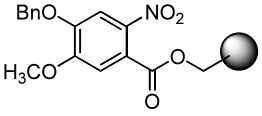
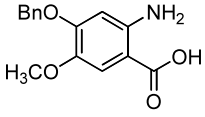
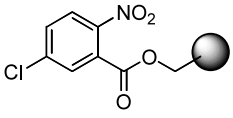
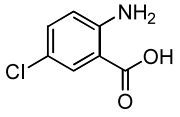
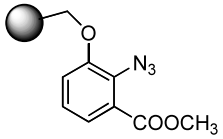
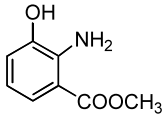
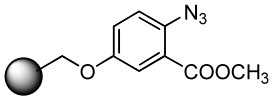
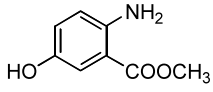
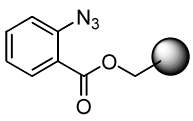
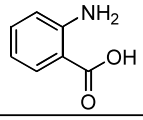
the synthesis of naturally occurring PBD imines or their methyl ethers such as tomamycin, chicamycin and also for the synthesis of structurally modified synthetic PBDs[9] wherein pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones are the intermediates. PBD-5,11-diones are also useful precursors for the PBD cyclic secondary amines which have recently been converted in our laboratory to PBD imines through a mild oxidative method.[10] Moreover, it is well known that PBD-5,11-diones are intermediates for the synthesis of compounds with a broad spectrum of biological activity such as antiphase activity, analgesic antagonist, anti-inflammatory, psychomotor depressant activity and even herbicidal properties.[11]

Furthermore, the C2-hydroxy substituent in the PBD ring system plays an important role in non-covalent interactions with the DNA and therefore generation of compounds with hydroxyl group at the C2-position is helpful in investigating the SARs.

Table 1. Reduction of nitro/azido groups followed by TFA cleavage

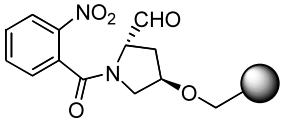
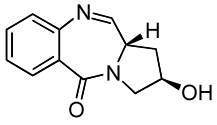
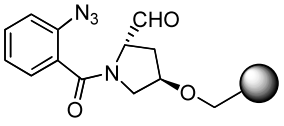
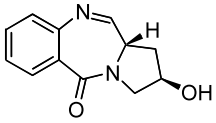
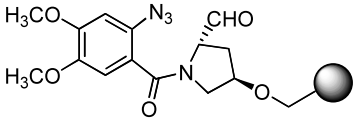
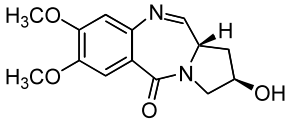
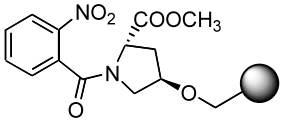
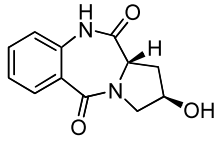
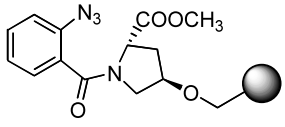
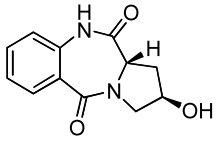
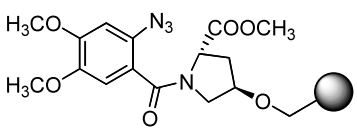
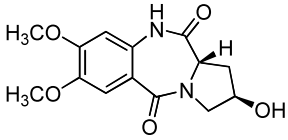
Entry	Substrate	$Al/NiCl_2.6H_2O$ Time (min) and Yields (%)[a]	Al/NH_4Cl Time (min) and Yields (%)[a]	Product
a		60 / 80	180 / 70	
b		60 / 85	175 / 75	
c		70 / 80	175 / 70	
d		60 / 85	170 / 75	
e		65 / 80	180 / 70	
f		70 / 80	175 / 70	
g		30 / 90	120 / 80	
h		25 / 95	125 / 85	
i		30 / 90	120 / 80	

[a]Isolated yields

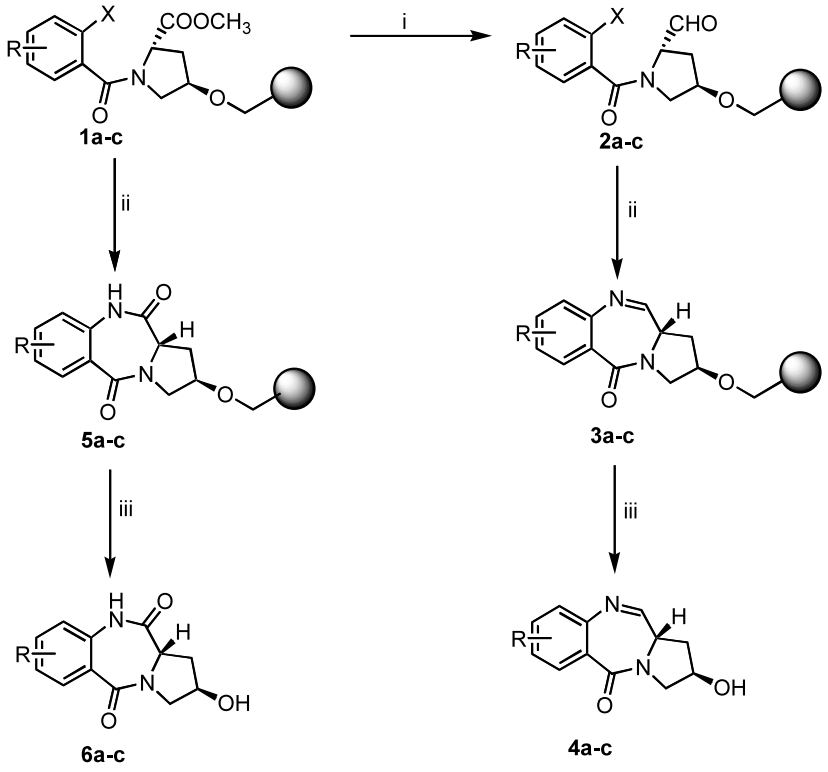
During the course of our studies on the development of solid phase synthetic methodologies for PBD ring systems,[12] we have earlier reported a procedure employing indium for nitro and azido reductive cyclization. In continuation of these efforts, we have been interested in the development of a cost-effective and efficient method for such a process by employing $Al/NiCl_2{\cdot}6H_2O$ and Al/NH_4Cl reagent systems. This method provides a useful and high yielding solid phase procedure for a variety of substituted aryl amines from their nitro and azido precursors as shown in Table 1. Interestingly, this solid phase reduction of nitro and azido groups is a key step in the synthesis of a large number of biologically important heterocyclic compounds.[13] Moreover, in this investigation the solid phase procedure has been applied for the synthesis of imine-containing PBD ring systems and their 5,11-diones as illustrated in Table 2. The present synthetic strategy for the PBD ring system (Scheme 1) is based partially on the solution phase approach of Lown and Joshua,[14] which involves the reductive cyclization of *N*-2-(nitrobenzoyl)pyrrolidine-2-carboxaldehyde with H_2/catalyst. It was observed that $Al/NiCl_2{\cdot}6H_2O$ offers several advantages over Al/NH_4Cl. The solid phase reductive process with the former reagent system takes place at room temperature in comparison to the latter which requires reflux conditions. Further, not only the yields are higher, the reaction rates are faster using $Al/NiCl_2{\cdot}6H_2O$.

Preparation of **4a**:[15] To the suspension of resin **1a**[12c] (0.60 g, 0.83 mequiv./g) in CH_2Cl_2 (10 mL) was added DIBAL-H (1 mL of a 1 M solution in hexane, 1 mmol) dropwise at −78°C under dry nitrogen, and the mixture stirred at the same temperature for 2 h. The reaction was quenched by the addition of 10 mL of 0.5% HCl. The resin **2a** was filtered off and rinsed with hexane, water, THF, CH_2Cl_2 and dried in vacuo. To the suspension of resin **2a** (0.60 g, 0.83 meq./g), in freshly distilled THF, a freshly mixed solid mixture of aluminium powder (0.22 g, 8.3 mmol) and nickel chloride hexahydrate (2.95 g, 12.45 mmol) was added then the mixture was stirred for 75 min at rt. The imine resin **3a** was filtered off and rinsed with 5% HCl (after stirring or sonicating for about 10 min) and this process was repeated thrice, followed by water, THF,

Table 2. Synthesis of PBD imines and dilactams by nitro/azido reductive cyclization followed by TFA cleavage

Entry	Substrate	Al-$NiCl_2.6H_2O$ Time(min) and Yield(%)[a]	Al/NH_4Cl Time(min) and Yield(%)[a]	Product
2a		75 / 80	180 / 70	
2b		30 / 85	120 / 80	
2c		30 / 85	120 / 80	
1a		70 / 85	180 / 75	
1b		30 / 90	120 / 85	
1c		30 / 90	120/ 85	

[a]Isolated yields



Scheme 1. *Reagents and conditions*: (i) DIBAL-H, CH_2Cl_2, −78°C, 2 h; (ii) Al/$NiCl_2{\cdot}6H_2O$, THF, rt or Al/NH_4Cl, DMF or EtOH, reflux, 3 h; (iii) TFA/CH_2Cl_2 (1:3).

MeOH and CH_2Cl_2. Alternatively, to the suspension of resin **2a** (0.60 g, 0.83 meq./g), in EtOH or DMF (10 mL) was added aluminium powder (0.11 g, 4.15 mmol) and saturated ammonium chloride solution (3 mL) and the mixture was refluxed for 3 h. The imine resin **3a** was filtered and rinsed with 5% HCl (after stirring or sonicating for about 10 min) and this process was repeated thrice, followed by water, EtOH, DMF, MeOH and CH_2Cl_2 and dried in vacuo. Finally, **3a** was cleaved from the solid support using TFA/CH_2Cl_2 (1:3) to yield the crude product **4a**, which was further purified by column chromatography.

Synthesis of **6a**: To the suspension of resin **1a** (0.60 g, 0.83 meq./g), in distilled THF, a freshly mixed solid mixture of aluminium powder (0.22 g, 8.3 mmol) and nickel chloride hexahydrate (2.95 g, 12.45 mmol) was added and the mixture stirred for 70 min at rt to afford the lactam resin derivative **5a** by reductive cyclization. This was filtered off and rinsed with 5% HCl (after stirring or sonicating for about 10 min) and this process was repeated thrice, followed by water, THF, MeOH and CH_2Cl_2 and dried in vacuo. Alternately, to the suspension of resin **5a** (0.60 g, 0.83 meq./g), in EtOH or DMF (10 mL) was added aluminium powder (0.11 g, 4.15 mmol) and saturated ammonium chloride solution (3 mL) and the mixture was refluxed for 3 h to afford the reductively cyclized lactam resin derivative **5a**. This was filtered off and rinsed with 5% HCl (after stirring or sonicating for about 10 min) and this process was repeated thrice, followed by water, EtOH, DMF, MeOH and CH_2Cl_2 and dried in vacuo. The resin was filtered and rinsed with toluene and CH_2Cl_2. The suspension of **5a** in TFA/CH_2Cl_2 (1:3, 10 mL) was allowed to stir at 25°C for 2 h. The resin was filtered and washed with CH_2Cl_2 (3×10 mL). The combined filtrates were evaporated to afford the crude product **6a**, which was further purified by column chromatography.

In summary an efficient and cost effective solid phase synthesis of substituted arylamines from their corresponding nitro and azido substrates has been demonstrated. This procedure has been further extended towards the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines and their dilactams in good yields. This method is expected to generate combinatorial libraries for pyrrolo[2,1-*c*][1,4]benzodiazepines based compounds particularly those having a 2-hydroxy substituent on the C-ring.

Acknowledgements

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15. Spectral data for **4a**: ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.70–1.80 (m, 1H, C1), 1.95–2.10 (m, 1H, C1), 3.50–3.75 (m, 2H, C3), 4.02 (m, 1H, C11a), 4.17–4.26 (m, 1H, C2), 4.92 (d, 1H, $J=4.8$ Hz, C2-OH), 6.70–6.80 (m, 2H, C6, C7), 6.95 (d, 1H, $J=5$ Hz, C9), 7.12–7.26 (m, 1H, C8), 7.84 (d, 1H, $J=7.3$ Hz, C11 imine); ^{13}C NMR (50 MHz, DMSO-d_6): δ 39.5 (C11a), 52.0 (C3), 56.6 (C1), 71.0 (C2), 125.2 (C5a), 128.6 (C6), 131.4 (C7), 131.7 (C8), 133.5 (C9), 144.6 (C9a), 150.2 (C11 imine), 166.5 (C5); EIMS: m/z 216.