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Simple and facile reduction of azides to amines: synthesis of DNA interactive pyrrolo[2,1-*c*][1,4]benzodiazepines

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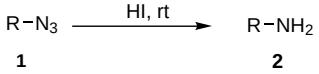
Abstract—The reduction of aromatic azido compounds to the corresponding amines with hydriodic acid has been investigated and found to result in high yields. This reductive methodology which proceeds under non refluxing condition has been extended for the synthesis of DNA-interactive pyrrolo[2,1-*c*][1,4] benzodiazepine antibiotics. © 2002 Elsevier Science Ltd. All rights reserved.

The reduction of aromatic azido compounds to the corresponding amines is an important chemical transformation in synthetic organic chemistry. Azides can be prepared with good regio-, stereo- and enantioselectivity, and their transformation into amines provides a large amount of applications in organic synthesis,[1] such as in the preparation of nitrogen containing heterocycles[2] and carbohydrates[3] and in nucleoside chemistry. A number of reagents have been described in the literature[4] for this reductive process includes borohydrides,[5] triphenylphosphine,[6] benzyltriethylammonium tetrathiomolymbdate,[7] hexamethyl-disilathiane[8] and samarium iodide,[9] etc. In terms of practical applicability, reaction conditions or commercial availability, most of these methods have some disadvantages. Hence there is a continuing need to explore more efficient and convenient methodologies.[10] We have been involved in the development of new versatile methods for the reduction of azides which were required for the synthesis of natural products and recently we reported such a reduction employing iodotrimethylsilane.[11] In continuation of these efforts, we wish to report a simple and efficient method for the reduction of azido compounds **1** to the corresponding amines **2** with hydriodic acid (HI) in excellent yields (Scheme 1).



Scheme 1.

Hydrogen iodide mediated reduction of aromatic nitro compounds to aromatic amines has been extensively studied[12] and recently reinvestigated.[13] However, the reduction of aromatic azido compounds by employing HI has not been examined. In continuation of our efforts in the development of new synthetic methodologies for the preparation of biologically important heterocyclic natural products, we have investigated HI for the reduction azide functionality, particularly in view of its ready availability. It can be observed from the results described in Table 1, that this method is applicable for the reduction of azides in a wide variety of substrates ranging from aryl to sulphonyl azides.

It is interesting to observe that in the case of entry **f**, the *O*-benzyl groups are intact after this reduction in contrast to the conventional methods for azide reduction employing Pd/C. There are some selective reagents for such azido reductions but most of these reagents are expensive.

Furthermore, this method has been extended for the preparation of the DNA-binding pyrrolo[2-1-*c*][1,4]-benzodiazepine (PBD) ring system. PBDs have been known to interact with DNA in a sequence selective manner and as such have potential as antitumor agents and gene targeting drugs.[14] A large number of methods have been examined for the preparation of PBDs but most of these have met with varying degrees of success having different limitations.[15]

This has necessitated the exploration and development of the new azido reductive cyclization method as an alternative route for the synthesis of these biologically important PBDs. As described in Scheme 2, the PBD

Keywords: amines; reductive cyclization; hydriodic acid; pyrrolobenzodiazepines.

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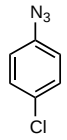
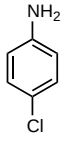
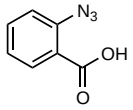
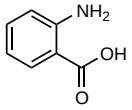
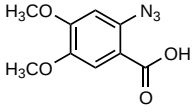
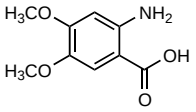
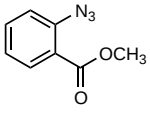
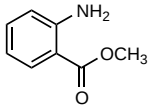
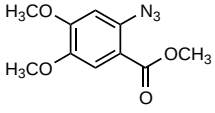
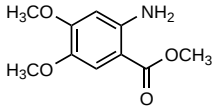
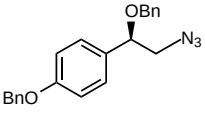
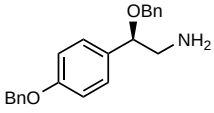
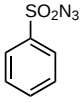
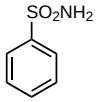
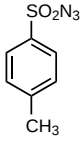
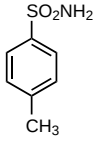
Table 1. Reduction of azides to amines using aq. HI (57% w/w)

Entry	Substrate	Time(h)	Product[a]	Yield(%)
a		1.5		90
b		1.5		95
c		2		95
d		1.5		95
e		2		90
f		2.5		80
g		1.5		90
h		1.5		93

[a]Characterized by spectroscopic data and in comparison with authentic samples.

dilactams **5a**–**d** have been obtained in 90–95% yields, while the PBD imines **6a**–**b** were obtained in 70–75% yields.[16]

Typical procedure: A suspension of **4a** (244 mg, 1 mmol) in an aqueous solution of HI (57% w/w, 6 ml) was stirred continuously at room temperature for 3.5 h. On completion of reaction as indicated by TLC, the reaction mixture was diluted with EtOAc and washed with saturated aq. $Na_2S_2O_3$. The colorless organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane 9:1) to afford the imine **6a** in 73% yield (Scheme 2).

In summary, a simple, practical and cost-effective method has been developed for the reduction of azides to corresponding amines by employing HI. This approach has been applied for the synthesis of the DNA interactive pyrrolo[2-1-*c*][1,4]benzodiazepine.

Acknowledgements

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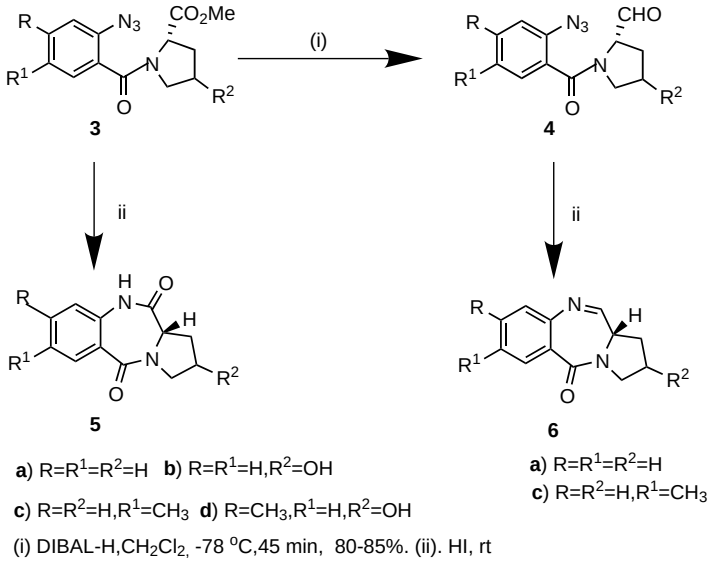

Scheme 2.

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16. Spectroscopic data of compound **6a**. ^{1}H NMR ($CDCl_3$): δ 1.92–2.35 (m, 4H), 3.50–3.92 (m, 3H), 7.26–7.56 (m, 3H), 7.78 (d, 1H, $J=4.5$ Hz), 8.05 (d, 1H, $J=5.3$ Hz); MS: m/e 200 (M^+, 100), 171, 144, 103, 70, 43.