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An efficient reduction of azides to amines: synthesis of DNA interactive pyrrolo[2,1-*c*][1,4]benzodiazepines†

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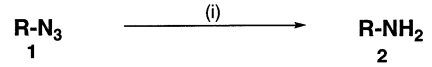
Abstract

Reaction of a variety of azido compounds with $FeSO_4 \cdot 7H_2O/NH_3$ results in quantitative yields of the corresponding amino compounds. This reductive methodology has been extended towards the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine antibiotics. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: azides; amines; reductive cyclization; pyrrolobenzodiazepines.

Azide chemistry has attracted significant attention in view of its application in organic synthesis. Azides can be prepared with good regio-, stereo- and enantioselectivity and their transformation into amino functionality provides a large amount of applications in organic synthesis[1] such as nitrogen containing heterocycles,[2] carbohydrate[3] and nucleoside chemistry. A number of reagents have been reported in the literature[4] for this reductive process including the borohydrides,[5] triphenylphosphine,[6] benzyltriethylammonium tetrathiomolybdate,[7] hexamethyl disilathiane[8] and samarium iodide,[9] etc. Most of these methods have some disadvantages in relation to the general applicability, selectivity, reaction conditions or commercial availability. Therefore, there is considerable interest in exploring more efficient and selective methodologies.[10] In our continuing research programme on the synthesis of natural products, we have been confronted with the challenge of exploring new versatile methods for the reduction of the azido functionality. In this endeavor, we have recently reported a facile reduction of azides to amines employing iodotrimethylsilane.[11] In continuation of these efforts, we wish to report a new and convenient method for the reduction of azides (**1**) to the corresponding amines (**2**) with



Scheme 1. (i) $FeSO_4 \cdot 7H_2O/NH_3$, MeOH, rt.

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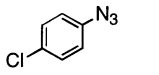
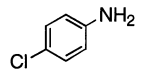
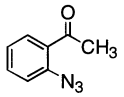
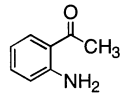
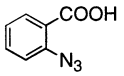
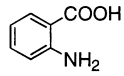
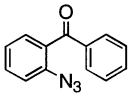
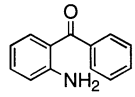
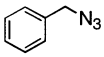
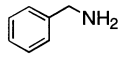
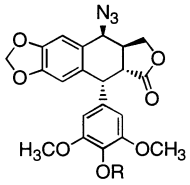
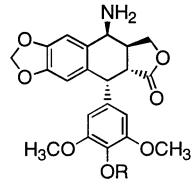
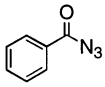
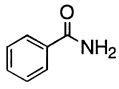
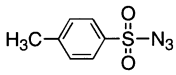
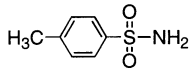
Table 1
Reduction of azides to amines

Entry	Substrate (1)	Time (h)	Product[a] (2)	Yield (%)
a		2.5		98
b		2.5		96
c		2.5		96
d		2.5		94
e		3		90
f[b]		3		60-70
g		1[c]		84
h		3		90

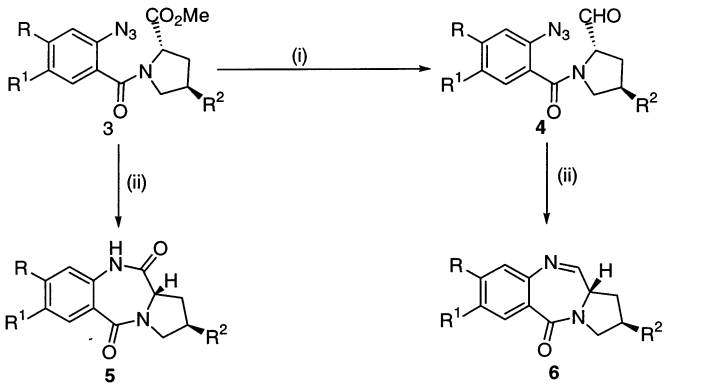
[a]Characterized by spectroscopic data and in comparison with authentic samples [b]R = H, CH_3
[c]Reaction performed under reflux conditions.

$FeSO_4 \cdot 7H_2O/NH_3$ in excellent yields (Scheme 1). Although in the literature $FeSO_4$ in aqueous NH_3 has been reported for the reduction of nitro arenes,[12] this reagent system has not been investigated for the reduction of azido groups.

As seen from the results described in Table 1, this method is applicable for the reduction of 4β-azidopodophyllotoxins to its 4β-amino analogue (**f**). 4β-Amino podophyllotoxins are important building blocks for the DNA-topoisomerase II inhibiting podophyllotoxin congeners. It is interesting to note that these reductions take place in the presence of CH_3NH_2 (40% aqueous solution) instead of aqueous ammonia. This observation eliminates the possibility of a substitution reaction, particularly for the substrates **e**, **g** and **h**, which have been reduced to their

corresponding amines without the formation of *N*-methyl substituted amino/amido compounds. Further, during this reaction process addition of the base (ammonia or methylamine) to the reaction mixture produces a dark brown colour, probably due to the formation of a complex.

A typical procedure: to a stirred solution of **4a** (244 mg, 1 mmol) in dichloromethane (10 ml), $FeSO_4 \cdot 7H_2O$ (1.4 g, 5 mmol) and 25% ammonia solution (1 ml) were added. This reaction mixture was stirred continuously at room temperature for 4 h. On the completion of reaction as indicated by TLC, the mixture was diluted with dichloromethane and filtered through a celite bed. This filtrate was washed with water. The organic layer was dried over $MgSO_4$ 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 70% yield (Scheme 2).



Scheme 2. (i) DIBAL-H, CH_2Cl_2, −78°C, 45 min, 72–75%; (ii) $FeSO_4 \cdot 7H_2O/NH_3$, CH_2Cl_2, 4 h, rt.

The usefulness of this method has also been extended to preparation of the DNA-binding pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) ring system. These compounds interact with DNA in a sequence selective manner and as such have potential as antitumour agents and gene targeting drugs.[13] Many approaches have been investigated for the preparation of these compounds and have met with varying degrees of success having different limitations, particularly for the introduction of imine functionality.[14] Hence, development of this new reductive cyclization method affords an alternate route towards the synthesis of these biologically important PBDs (as illustrated in Scheme 2). The PBD dilactams (**5a**–**d**) have been obtained in 90–95% yields, while PBD imines (**6a**–**d**) have been obtained in 68–72% yields.[15]

In conclusion, we have provided a new practical, cost-effective approach for the reduction of azides to the corresponding amines by employing $FeSO_4 \cdot 7H_2O/NH_3$. This protocol has also been applied to the preparation of 4β-amino podophyllotoxin (precursors of DNA topoisomerase II inhibitors) and DNA interactive pyrrolo[2,1-*c*][1,4]benzodiazepines.

Acknowledgements

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References

1. Scriven, E. F. V.; Turnbull, K. *Chem. Rev*. **1988**, *88*, 297.
2. Smith, S. C.; Heathcock, C. H. *J. Org. Chem*. **1992**, *57*, 6379.
3. McDonald, F. E.; Danishefsky, S. J. *J. Org. Chem*. **1992**, *57*, 7001.
4. Ito, M.; Koyakumaru, K.; Takaya, T. H. *Synthesis* **1995**, 376.
5. (a) Rao, H. S. P.; Siva, P. *Synth. Commun*. **1994**, *24*, 549. (b) Alvarez, S. G.; Fisher, G. B.; Singavam, B. *Tetrahedron Lett*. **1995**, *36*, 2567.
6. Molina, P.; Diaz, I.; Tarraga, A. *Tetrahedron* **1995**, *51*, 5617.
7. Ramesha, A. R.; Bhat, S.; Chandrasekaran, S. *J. Org. Chem*. **1995**, *60*, 7682.
8. (a) Capperucci, A.; Degl Innocenti, A.; Funicello, M.; Mauriello, G.; Scafato, P.; Spagnolo, P. *J. Org. Chem*. **1995**, *60*, 2254. (b) Kamal, A.; Reddy, B. S. P.; Reddy, B. S. N. *Tetrahedron Lett*. **1996**, *37*, 6803.
9. Huang, Y.; Zhang, Y.; Wang, Y. *Tetrahedron Lett*. **1997**, *38*, 1065.
10. Molander, G. A. *Chem. Rev*. **1992**, *92*, 29.
11. Kamal, A.; Rao, N. V.; Laxman, E. *Tetrahedron Lett*. **1997**, *38*, 6945.
12. (a) Foy, B. D.; Smudde, R. A.; Wood, W. F. *J. Chem. Ed*. **1993**, *70*, 322. (b) Malm, J.; Hornfeldt, A.-B.; Gronowitz, S. *Heterocycles* **1993**, *35*, 1.
13. (a) Thurston, D. E. Advances in the Study of Pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) Antitumour Antibiotics. In *Molecular Aspects of Anticancer Drug–DNA Interactions*, Neidle, S.; Waring, M. J., Eds; The Macmillan Press Ltd.: London, 1993, Vol. 1, pp. 54–88. (b) Thurston, D. E.; Bose, D. S.; Howard, P. W.; Jenkins, T. C.; Leoni, A.; Baraldi, P. G.; Guitto, A.; Cacciari, B.; Kelland, L. R.; Foloppe, M. P.; Rault, S. *J. Med. Chem*. **1999**, *42*, 1951. (c) Wilson, S. C.; Howard, P. W.; Forrow, S. M.; Hartley, J. A.; Adams, L. J.; Jenkins, T. C.; Kelland, L. R.; Thurston, D. E. *J. Med. Chem*. **1999**, *42*, 4028.
14. (a) Thurston, D. E.; Bose, D. S. *Chem. Rev*. **1994**, *94*, 433. (b) Kamal, A.; Damayanthi, Y.; Reddy, B. S. N.; Laxminarayana, B.; Reddy, B. S. P. *Chem. Commun*. **1997**, 1050. (c) Kamal, A.; Rao, M. V.; Reddy, B. S. N. *Khim. Geterotsikl. Soedin. (Chem. Het. Compd.)* **1998**, 1588. (d) Kamal, A.; Reddy, B. S. N.; Reddy, G. S. K. *Synlett* **1999**, *8*, 1251.
15. Spectroscopic data of compound **6a**. $[\alpha]_D^{27}$ +318 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.90–2.36 (m, 4H), 3.52–3.92 (m, 3H), 7.28–7.56 (m, 3H), 7.78 (d, 1H, J=4.6 Hz), 8.05 (d, 1H, J=5.2 Hz): IR ($CHCl_3$) 3320, 2970, 2880, 1620, 1575, 1485, 1460, 1255, 1160, 1125, 1030, 875, 830 cm^{-1} MS: m/e 200 (M^+, 100), 171, 160, 144, 120, 103, 83, 70 HRMS: calc. for 200.0950 ($C_{12}H_{12}ON_2$), found 200.0936.