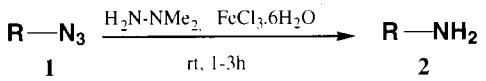
A Mild and Facile Reduction of Azides to Amines by *N,N*-Dimethylhydrazine and Catalytic Ferric Chloride

Ahmed Kamal* and B. S. Narayan Reddy
Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

(Received March 23, 1998; CL-980211)

Reaction of a variety of azido compounds with *N,N*-dimethylhydrazine in the presence of a catalytic amount of ferric chloride hexahydrate in methanol results in excellent yields of the corresponding amino compounds. This reductive system is compatible with a wide assortment of functional groups and has also been extended towards the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine antibiotics.

The chemistry of azides has attracted much attention because of its application in organic synthesis. Reduction of the azide moiety to an amino group constitutes a synthetically important process, since many azides can be prepared with regio and stereo control, subsequent reduction permits a controlled introduction of the amine function.[1,2] In the literature, a wide variety of reagents have been studied including the different borohydrides[3-6], hexamethyldisilathiane,[7,8] Pd/C,[9] H_2S,[10] Ph_3P/H_2O,[11] benzyltriethylammonium tetrathiomolybdate,[12] metallic samarium with catalytic amount of iodine[13-15] etc. Most of them have some disadvantages in relation to their general applicability, selectivity, reaction conditions or commercial availability. As a result, there is always considerable interest in exploring more efficient and selective methods.[16] Herein, we wish to report a new and convenient method for the reduction of azides to the corresponding amines with *N,N*-dimethylhydrazine in presence of catalytic ferric chloride.



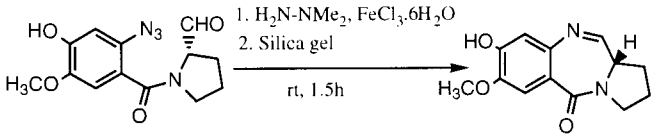
1 2

Azide (**1**)	Amine (**2**) Yield (%)	Reaction time (h)
$C_6H_5N_3$	82	0.5
2-CO_2H, $C_6H_4N_3$	90	1.0
4-NO_2, $C_6H_4N_3$	81	1.5
2-CO_2H, 4-OCH_3, 5-OH, $C_6H_2N_3$	90	1.0
2-CO_2H, 4-OCH_3, 5-OCH_2Ph, $C_6H_2N_3$	81	1.0
$C_6H_5CH_2N_3$	65	2.5
n-$C_8H_{17}N_3$	60	2.5
4-Cl, $C_6H_4N_3$	78	1.0
2-COOMe, $C_6H_4N_3$	80	1.0
2-$COCH_3$, $C_6H_4N_3$	80	1.0
5-CO_2H, $C_6H_{10}N_3$	76	2.0
2-CONHPh, $C_6H_4N_3$	86	1.0

Recently, a wide variety of nitroarenes have been reduced to the corresponding anilines employing *N,N*-dimethylhydrazine/ferric chloride.[17] We have extended this finding for the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine antibiotics via a reductive cyclization process.[18]

During our studies on the total synthesis of natural products, we have been confronted with the problem of exploring better methods for the reduction of aryl as well as alkyl azides.[19] In this connection, we have investigated the above set of reduction conditions for such a process and interestingly *N,N*-dimethylhydrazine/ferric chloride in methanol reduced the aryl azides in exellent yields (81-90%), and alkyl azides in good yields. (60-65%)

Further the usefulness of this procedure has been illustrated by employing it for the DNA-binding pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) ring system.[20] The synthesis of these compounds has received considerable interest recently because of their potential as gene-targeted antitumour antibiotics, mainly by the presence of an imine functionality in the PBD system.[21,22] Many approaches have been investigated for the preparation of these compounds and it is observed that the introduction of an imine or carbinolamine group is generally problematic[20b]. Therefore, development of this new method offers an additional practical approach towards the synthesis of these biologically important PBD compounds. This has been achieved by the azido reductive cyclization[23] of (2S)-*N*-(2-azidobenzoyl)pyrrolidine-2-carboxaldehyde (**3**)[18] by the above set of reduction conditions to obtain the PBD imino methylethers without any racemization. This upon subjecting to column chromatography (silica, chloroform-methanol, 9.8:0.2) affords the imine form of the PBD in excellent yields.



3 4

It is noteworthy to mention that the earlier studies on the reduction of the nitro compounds have been carried out at reflux temperatures in methanol. Whereas, in the present investigation the azido functionality has been reduced at room temperature without affecting the nitro group. Therefore, these conditions do not affect other reducible groups, such as nitro, O-benzyl ether, carboxylic acids, amides, halo, carbonyl and esters. In conclusion, we have provided a novel, chemoselective and efficient protocol for the reduction of alkyl and aryl azides to the corresponding amines employing *N,N*-dimethylhydrazine/ ferric chloride.

One of the author BSNR is thankful to UGC, New Delhi for the award of a research fellowship.

References and notes

1 E. F. V. Seriven and K. Turnbull, *Chem. Rev.*, **88**, 297 (1988).
2 M. Ito, K. Koyakumaru, and T. H. Takaya, *Synthesis*, **1995**, 376.
3 B. C. Ranu, A. Sarkar, and R. Chakraborty, *J. Org. Chem.*, **59**, 4114 (1994).
4 N. M. Yoom, J. Choi, and Y. S. Shon, *Synth. Commun.*, **23**, 3047 (1993).
5 S. G. Alvarez, G. B. Fisher, and B. Singavam, *Tetrahedron Lett.*, **36**, 2567 (1995).
6 H. S. P. Rao and P. Siva, *Synth. Commun.*, **24**, 549 (1994).
7 A. Capperucci, A. Degl'Innocenti, M. Funicello, G.Maurielo, P. Scafato, and P. Sapgnolo, *J. Org. Chem.*, **60**, 2254 (1995).
8 A. Kamal, B. S. P. Reddy, and B. S. N. Reddy, *Tetrahedron Lett.*, **37**, 6803 (1996).
9 a) R. L. Willer, *J. Org. Chem.*, **49**, 5150 (1984). b) T. Gartiser, C. Seve, and J. J. Delpunench, *Tetrahedron Lett.*, **24**, 1609 (1983).
10 M. Saneyoshi, T. Adachi, Y. Yamada, and I. Onoue, *Synthesis*, **1997**, 45.
11 a) K. Baum. P. T. Berkowitz, V. Grakauskas, and T. G. Archibald, *J. Org.Chem.*, **48**, 2953 (1983). b) N. Vaultier, N. Knouzi, and R. Carrie, *Tetrahedron Lett.*, **24**, 763 (1983). c) W. S. Mungall, G. L. Greene, G. A. Heavner, and R. L. 0 Lestsinger, *J. Org. Chem.*, **40**, 1659 (1975).
12 A. R. Ramesha, S. Bhat, and S. Chandrasekaran, *J. Org. Chem.*, **60**, 7682 (1995).
13 D. C. Goulaouic and M. Hesse, *Tetrahedron Lett.*, **36**, 7427 (1995).
14 Y. Huang, Y. Zhang, and Y. Wang, *Tetrahedron Lett.*, **38**, 1065 (1997).
15 L. Benati, P. C. Montevecchi, D. Nanni, P. Spangnolo, and M. Volta, *Tetrahedron Lett.*, **36**, 7313 (1995).
16 G. A. Molander, *Chem. Rev.*, **92**, 29 (1992).
17 S. R. Boothroyd and M. A Kerr, *Tetrahedron Lett.*, **36**, 2411 (1995).
18 A. Kamal, B. S. N. Reddy, and B. S. P. Reddy, *Bioorg. Med. Chem. Lett.*, **7**, 1825 (1997).
19 A. Kamal, B. S. P. Reddy, and B. S. N. Reddy, *Tetrahedron Lett.*, **37**, 6803 (1996).
20 a) D. E. Thurston, "Advances in the Study of Pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) Antitumour Antibiotics," in Molecular Aspects of Anticancer Drug-DNA Interactions, ed by S. Neidle and M. R. Waring, The Macmillan Press Ltd.(1993), Vol. 1, pp 54-88. b) D. E. Thurston and D. S. Bose, *Chem. Rev.*, **94**, 433 (1994). c) A. Kamal, B. S. P. Reddy, and B. S. N. Reddy, *Tetrahedron Lett.*, **37**, 2281 (1996). d) A. Kamal, Y. Damayanthi, B. S. N. Reddy, B. Laxminarayana, and B. S. P. Reddy, *Chem. Commun.*, **1997**, 1015.
21 T. C. Jenkins, L. H. Hurley, S. Neidle, and D. E. Thurston, *J. Med. Chem.*, **37**, 4529 (1994).
22 D. E. Thurston, S. J. Morris, and J. A. Hartley, *Chem. Commun.*, **1996**, 563.
23 A solution of azide (**3**) (0.244 g, 1.0 mmol) in methanol (10ml) was treated with *N,N*-dimethylhydrazine(0.060g, 1.0mmol) (*N,N*-dimethylhydrazine is highly carcinogenic, therefore great care should be taken), $FeCl_3.6H_2O$ (10 mg, 0.04 mmol) and decolourizing charcoal (0.100 g). The reaction mixture was then stirred at rt. for about 1.5 h or until TLC showed the absence of the starting material. The mixture was filtered through celite and the residue was concentrated invacuum and dried over Na_2SO_4. Purification of the crude material by column chromatography on silica gel using chloroform-methanol (9.8:0.2) as eluent gave the pure Imine(**4**) in 72% yield.

IICT Commun. No. 3793.