November 1997 SYNLETT 1253

The Efficient Chemoselective Reduction of Azides to Primary Amines

Anima Boruah, Mukulesh Baruah, Dipak Prajapati and Jagir S. Sandhu* Regional Research Laboratory, Jorhat 785 006, Assam, India Received 5 June 1997

Abstract : Reduction of azides to amines or amides occurs in excellent yields upon treatment with a novel reduction system consisting of Zn-NiC1₂•6H₂O-THF.

The transformation of azides to amines is a synthetically important process and its value has been well established, particularly in the field of carbohydrate and nucleoside chemistry. Since various azides are readily available by the SN2 azidolysis of alkyl halides and tosylates, the reaction has been widely exploited for the regio and stereospecific introduction of an amino function¹. A wide variety of reagents including zinc borohydride², samarium iodide³, (BER)-nickel acetate⁴, lithium aminoborohydrides⁵, sodium borohydride,⁶ benzyltriethylammonium tetrathiomolybdate⁷, etc. for this purpose have been reported recently. But most of them have some disadvantages in relation to their general applicability, selectivity, ready availability, operational convenience or toxicity. For instance, LiAlH₄ is not tolerable to many functionalities such as CO₂R, NO₂ etc., and now on the other hand, catalytic hydrogenation and diborane reduction have limitations for being applied to unsaturated compounds containing a double or a triple bond. As a result, there is always considerable interest in finding more selective methods. Herein we report a novel reduction system consisting of zincnickel chloride hexahydrate in tetrahydrofuran for the chemoselective reduction of various azidoarenes and aroylazides. The reductions generally proceeded with high yields at room temperature and showed selectivity over other labile substituents.

$$\begin{array}{ccc}
R-N_3 & \xrightarrow{Zn-NiCl_2.6H_2O-THF} & R-NH_2 \\
1 & 2 & 2
\end{array}$$

R = Aryl, Aroyl, Arylsulfonyl and Alkyl

In a typical procedure, to a mixture of zinc powder (10 mmol) and nickel chloride hexahydrate⁸ (15 mmol) was added a solution of the azido benzene (2 mmol) in freshly distilled tetrahydrofuran. A vigorous exothermic reaction takes place immediately which is controlled by keeping the reaction in an ice bath. After about 2 hours when TLC of the reaction mixture showed disappearance of the starting material the reaction mixture is diluted with THF (100 ml) and filtered. Evaporation of the filtrate gave the corresponding aniline which is further purified by chromatography. Similar treatment of other aryl or aroyl azides gave the corresponding amines or amides respectively in 78-92% yields (Table 1).

The high yields of the reduction products demonstrate the efficiency of this new method. Table 1 summarizes our results on the reduction of a number of aryl, aroyl and arylsulfonyl azides. In all the reactions, the cleavage takes place between the N-N bond, rather than the C-N or S-N bond. At the same time, azides are selectively reduced in the presence of a double bond (entry 12) or an aromatic methoxy group (entry 3). In case of nitro substituted aromatic azides, the corresponding nitroaniline was selectively obtained without any further reduction of nitro group (entry 2). Furthermore, haloaromatic azides showed remarkable selectivity to give the amine without any dehalogenation (entry 5,6&7). Also the amides are not reduced further to the corresponding amines. In addition it was worth commenting that 4-acetyl-1-azidobenzene was converted to the 4-aminoacetophenone and the sensitive carbonyl group

Table 1: Reduction of RN₃ to R-NH₂ with Zn-NiCl₂.6H₂O-THF System.

Entry	Azides ^a	Reaction time (hr.)	Yield ^b %
1	C ₆ H ₅ N ₃	2	90
2	$4-NO_2-C_6H_4N_3$	2.5	80
3	4-CH ₃ O-C ₆ H ₄ N ₃	2	85
4	4-MeCOC ₆ H ₄ N ₃	2	80
5	4-ClC ₆ H ₄ N ₃	2.5	85
6	3-ClC ₆ H ₄ N ₃	2.5	78
7	4-BrC ₆ H ₄ N ₃	2.5	92
8	4-MeC ₆ H ₄ CON ₃	2	85
9	C ₆ H ₅ CON ₃	2.5	82
10	$C_6H_5SO_2N_3$	2	85
11	$4-\text{MeC}_6\text{H}_4\text{SO}_2\text{N}_3$	2	90
12	C ₆ H ₅ CH=CHCON ₃	2.5	80
13	CH ₃ (CH ₂) ₅ N ₃ N ₃	2	72
14		2.5	70
15	HO NO	3.5¢	65 ¹⁰

^aAll products are known compounds and gave satisfactory m.p., IR and ¹H NMR spectra. ^bAll the yields refer to isolated chromatographically pure compounds. ^cThe reduction was performed under nitrogen in THF for 3.5 hr. Further increasing the reaction time gave no significant improvement in yields but rather decomposition occurred.

remains intact. However, the reduction of 4-nitrophenol did not proceed successfully with this reduction system. To include an example of nucleoside azide we have carried out the reduction of 2'-azido-2'-deoxyuridine under the same conditions and the corresponding 2'-amino-2'-deoxyuridine was obtained in 65% yield. The use of other new reduction systems consisting of zinc-cerium chloride or zinc-indium chloride did not give any encouraging results and the corresponding primary amines or amides were obtained in fair to moderate yields.

In conclusion, the present results demonstrate the novelty of zinc-nickel chloride hexahydrate combination system which shows unique selectivity and constitutes a useful alternative to the commonly accepted procedure⁹ for the synthesis of various primary amines or amides. Moreover, this simple and easily reproducible technique affords various adducts in excellent yields without involvement of toxic or expensive material and without the formation of any undesirable side products of the classical methods.

Acknowledgement: We thank the Department of Science and Technology (DST), New Delhi, for financial support to this project.

1254 LETTERS SYNLETT

References and notes:

- (1) Grundmann, C.; in: Houben-Weyl, Methoden der Organischen Chemie, 4th ed., Muller, E. (ed), Vol. 10/3, Georg Thieme Verlag. Stuttgart, 1965, p. 822; Sheradsky, T., The Chemistry of the Azido Group ed. by Patai, S., Interscience Publishers, London, 1971. p-333.
 - A recent review has updated the rich scope of azide chemistry and provided exhaustive coverage of methods for the reduction of azides to amines see: Sriven, E.; Turnbull, K., *Chem. Rev.*, **1988**, 88, 297.
- Ranu, B. C.; Sarkar, A.; Chakraborty, R., J. Org. Chem., 1994, 59, 4114.
- (3) For most recent reports using expensive samarium or samarium iodide see: Huang, Y.; Zhang, Y.; Wang, Y., *Tetrahedron Lett.*, **1997**, *38*, 1065.
 - Salunkhe, A. M.; Brown, H. C., *Tetrahedron Lett.*, **1995**, *36*, 7987.
 - Afonso, C. A. M., Tetrahedron Lett., 1995, 36, 8857.
 - Benati, L.; Montevecchi, P. C.; Nanni, D.; Spagnolo, P.; Volta, M., *Tetrahedron Lett.*, **1995**, *36*, 7313. Using Bakers' yeast see: Baruah, M.; Boruah, A.; Prajapati, D.; Sandhu, J. S., *Synlett*, **1996**, 1193.
- (4) Yoom, N. M.; Choi, J.; Shon, Y. S., Synth. Commun., 1993, 23, 3047.

- (5) Alverez, S. G.; Fisher, G. B.; Singavam B., Tetrahedron Lett., 1995, 36, 2567.
- (6) Smith, P. A. S.; Hall, J. H.; Kan, R O., J. Am. Chem. Soc., 1962, 84, 485.
 Gastiser, T.; Selve, C.; Delpucch, J. J., Tetrahedron Lett., 1983, 24, 1609.
- (7) Ramesha, A. R; Bhat, S.; Chandrasekan, S., J. Org. Chem., 1995, 60, 7682.
- (8) Zinc powder and nickel chloride used were of commercial grade and procured from Central Drug House (Pvt.) Ltd., New Delhi -110002.
- For other methods using Lindlar Catalyst see: Corey, E. J.;
 Nicolaou, K. C.; Balanson, R. D.; Machida, Y., Synthesis, 1975,
 590
 - Using Cr(ll)/H⁺ see: Kirk, D. N.; Wilson, M. A., *J. Chem. Soc.*, *Chem. Commun.*, **1970**, 590.
 - Using Bu₃SnH/AlBN see: Samano, M. C.; Robins, M., Tetrahedron Lett., 1991, 32, 6293.
 - Using Mg or Ca/MeOH see: Maiti, S. N.; Spevak, P.; Reddy, A. V. N., Synth. Commun., 1988, 18, 1201.
 - Using LiAlH₄ see: Boyer, J.H., J. Am. Chem. Soc., 1951, 73, 5865
- (10) Verheyden, J. P. H.; Wagner, D.; Moffatt, J. G., J. Org. Chem., 1971, 36, 250.