

5. Hauteville, M., *J. Heterocyclic Chem.*, **1988**, *25*, 715
6. Johnson, J. L., Pattison, I., *J. Heterocyclic Chem.*, **1986**, *23*, 249
7. Steiger, R. E., *J. Org. Chem.*, **1944**, *9*, 396
8. Zentmyer, D. T., Wagner, E. C., *J. Org. Chem.*, **1949**, *14*, 967
9. Bain, D. I., Smalley, R. K., *J. Chem. Soc. (C)*, **1968**, 1593
10. Woodland, E. D., Ph.D thesis, Nottingham Polytechnic, U.K., **1992**
11. Bogert, M. T., Gotherf, A. H., *J. Am. Chem. Soc.*, **1900**, *22*, 534
12. Williams, A., Salvadori, G., *J. Chem. Soc. (B)*, **1971**, 1105
13. Koelsch, C. F., *J. Am. Chem. Soc.*, **1944**, *66*, 2019
14. Archer, J. G., Barker, A. J., Smalley, R. K., *J. Chem. Soc. Perkin Trans. I*, **1973**, 1169
15. Ferlux, Fr. Demande **2,121,341**, 29 Sep 1972.; *Chem. Abbs.* 136312w, **1973**, 78, 389

(Received in the UK 08 July 1993)

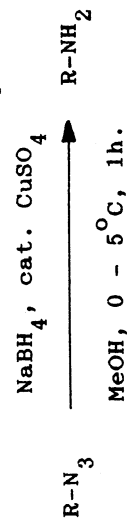
FACILE REDUCTION OF AZIDES WITH SODIUM BOROHYDRIDE / COPPER (II) SULPHATE SYSTEM

H. Surya Prakash Rao* and P. Siva

Department of Chemistry,
Pondicherry University,
Pondicherry - 605 014, INDIA

ABSTRACT: Sodium borohydride / copper (II) sulphate reduces alkyl and aryl azides to primary amines and aryl azides to amides under mild conditions.

Reduction of an azido group to an amine is an important reaction in synthetic organic chemistry¹. This reaction has been used extensively in the synthesis of nitrogen containing heterocycles² and carbohydrate molecules³. Reagents commonly employed for this purpose include catalytic hydrogenation using hydrogen gas⁴ or transfer hydrogenation⁵, lithium aluminium hydride⁶, triphenylphosphine / water⁷, triethylphosphite / p-toluenesulphonic acid⁸, hydrogen sulphide / pyridine / water⁹, propane-1,3-dithiol¹⁰, acetylacetone / triethylamine¹¹, stannous chloride¹², titanium (III) chloride / water¹³, tri n-butyltin hydride¹⁴, magnesium or calcium in methanol¹⁵ and

Table. Reduction of azides with NaBH_4 / Cu (II) SO_4 

No.	R	Yield [%] ^a	No.	R	Yield [%] ^a
1.	$\text{CH}_3(\text{CH}_2)_2\text{CH}_2^-$ ^b	95	7.	$4\text{-NO}_2\text{-C}_6\text{H}_4^-$	95
2.	$\text{CH}_3(\text{CH}_2)_4\text{CH}_2^-$	80	8.	$\text{C}_6\text{H}_5\text{CO}-$	90
3.	$\text{CH}_3(\text{CH}_2)_6\text{CH}_2^-$	82	9.	$4\text{-OMe-C}_6\text{H}_4\text{CO}-$	92
4.	C_6H_5^-	80	10.	$4\text{-Cl-C}_6\text{H}_4\text{CO}-$	90
5.	$4\text{-Cl-C}_6\text{H}_4^-$	95	11.	$4\text{-NO}_2\text{-C}_6\text{H}_5\text{CO}-$	95
6.	$4\text{-OMe-C}_6\text{H}_4^-$	95			

^a Yields are of isolated and purified products.

^b Isolated as a hydrochloride salt.

electrochemical methods¹⁶. Sodium borohydride, a mild hydride reducing agent does not reduce azides to amines satisfactorily¹⁷ but modified sodium borohydride reducing agents such as sodium borohydride with stoichiometric amounts of methanol in boiling THF¹⁸ and complex reducing agents¹⁹ such as sodium borohydride / nickel (II) chloride²⁰ have been used for this purpose. We now report that aryl and alkyl azides can be reduced to primary amines and aroyl azides to the corresponding amides with the sodium borohydride / copper (II) sulphate system²¹ under mild conditions.

Table summarises our results on the reduction of a number of aryl, alkyl and aroyl azides. Results from the reduction of several aryl and aroyl azides with electron-donating group (4-OMe, entry 5, 9) or electron-withdrawing groups (4-Cl, entry 6, 10 and entry 7, 11) indicate that substitution of groups with +I or -I effects in the para position of the aryl ring does not have much effect upon the rate of reduction. Thus, the reduction of azides with sodium borohydride / copper (II) sulphate, similar to other complex reducing agents¹⁹, is more like catalytic hydrogenation involving radical intermediates. Reduction of p-nitrophenyl azide to p-nitroaniline (entry 7) and p-nitrobenzoyl azide to p-nitrobenzamide (entry 11) show that reduction of the azido group can be carried out without nitro group reduction. This result is in contrast to our earlier observation that sodium borohydride / nickel (II) chloride does not selectively reduce an acyl azido group in the presence of a nitro group^{20b}. We have modified the reduction conditions to assess their effect on the rate and course of the reaction. Thus, when the reduction of benzoyl azide was carried out under a. sonication, b. phase transfer conditions (dichloromethane, tetra n-butylammonium bromide), c. elevated temperatures (methanol reflux), d. excess sodium borohydride (10 molar equivalents) and e. copper (II) sulphate adsorbed over silica gel (60 - 120 mesh), there was no change in the product formed or increase in the yield.

We have thus shown that alkyl and aryl azides can be reduced to the corresponding primary amines and aryl azides to the corresponding benzamides with sodium borohydride / copper (II) sulphate under mild, convenient and high yielding conditions.

EXPERIMENTAL SECTION

General Methods: Starting azides were prepared by known procedures²² and products were characterised on comparison with authentic samples (co-TLC) and spectral data (IR and NMR).

Reduction of Aryl azides; Representative procedure:

To a cooled (0° - 5° C), stirred solution of copper (II) sulphate pentahydrate (0.085g, 0.034 mmol) in methanol (10ml) was added sodium borohydride (0.037g, 1 mmol). To the resulting black suspension was added benzoyl azide (0.5g, 3.40 mmol) in methanol (5ml). Reaction was continued by the addition of sodium borohydride (0.092g, 2.4 mmol) in four portions during one hour. During this time reaction progress was monitored by TLC. The reaction mixture was then filtered through celite and most of the methanol (80%) was removed under reduced pressure. The resulting concentrated solution was diluted with dichloromethane (50ml), washed with water (10ml), brine (10ml), dried (Na_2SO_4) and concentrated to give benzamide (0.312g, 80%) identical to an authentic sample.

Reduction of aryl and alkyl azides:

Essentially the above procedure was followed for the reduction of aryl and alkyl azides to the corresponding primary amines except that the methanolic solution obtained after completion of the reaction was made sufficiently alkaline (pH = 12) with 1N sodium hydroxide before workup.

Acknowledgment: H. Surya Prakash Rao thanks C.S.I.R. India for financial support. He also thanks Professor K. Turnbull for helpful suggestions.

REFERENCES:

1. a. Sheradsky, T. in "Chemistry of the Azido Group", Patai, S. ed., Interscience, New York, 331 - 395, 1971.
- b. Scherer, H. and Regitz, M. in "Methodicum Chemicum", Korte, F. ed. Vol 6, Academic Press, Orlando, 301 - 327 and 747 - 752, 1975.
- c. Patai, S. and Rapaport, Z., eds. "The Chemistry of Functional Groups, Supplement D. The Chemistry of Halides and Pseudohalides and Azides", Wiley, New York, 1982.
- d. Scriven, E. F. V., ed. "Azides and Nitrenes", Academic Press, Orlando, 1984.
- e. Rolla, F., J. Org. Chem., 47, 4327 (1982).
- f. Scriven, E. F. V. and Turnbull, K., Chem. Revs., 88, 297 (1988).
2. E.g. see, Smith, S. C. and Heathcock, C. H., J. Org. Chem., 57, 6379 (1992).

3. E. g. see, McDonald, F. E. and Danishefsky, S. J., J. Org. Chem., **57**, 7001 (1992).
4. Bretschneider, H. and Hormann, H. H., Monatsh. **84**, 1021 (1953).
5. Gartsner, T., Selve, C. and Delpuech, J.-T., Tetrahedron Lett., **24**, 1609 (1983).
6. Boyer, J. H., J. Am. Chem. Soc., **73**, 5865 (1951).
7. a. Staudinger, H. and Meyer, J., Helv. Chim. Acta., **2**, 635 (1919).
 b. Mungall, W. S., Greene, G. A., Heavner, G. A. and Letsinger, R. L., J. Org. Chem., **40**, 1659 (1975).
 c. Vaultier, M., Knouzi, N. and Carrie, R., Tetrahedron Lett., **24**, 763 (1983).
8. Koziara, A. and Zwierzak, A., Tetrahedron Lett., **28**, 6513 (1987).
9. a. Adachi, T., Yamada, Y., Inoue, I. and M. Saneyoshi, Synthesis, **45** (1977).
 b. Surya Prakash Rao, H. and Doss, D., Sulfur Lett., **14**, 61 (1992).
10. Bayley, H., Standring, D. N. and Knowles, J. R., Tetrahedron Lett., **3633** (1978).
11. Stanovnik, B., Tisler, M., Polanc, S. and Zitnik, J., Synthesis, **491** (1977).
12. a. Maiti, S. N., Singh, M. P. and Micetich, R. G., Tetrahedron Lett., **27**, 1423 (1986).
 b. Bartra, M., Urpi, F. and Villarrasa, J., Tetrahedron Lett., **28**, 5941 (1987).
13. Stanovnik, B., Tisler, M., Polanc, S. and Gracner, M., Synthesis, **65** (1978).

14. a. Otvos, L., Beres, J., Sagi, Gy., Tomoskozi, I. and Gruber, L., Tetrahedron Lett., **28**, 6381 (1987).
 b. Frankel, M., Wagner, D., Gertner, D. and Zilkha, A., J. Org. Met. Chem., **7**, 518 (1967).
15. Maiti, S. N. Spevak, P. and Reddy, A. V. N., Synthetic Commun., **18**, 1201 (1988).
16. Arai, T., Shingaki, T. and Inagaki, M., Chem. Lett., **765** (1981).
17. a. Boyer, J. H. and Ellzey, Jr., S. E., J. Org. Chem., **23**, 127 (1958).
 b. Surya Prakash Rao, H., Synthetic Commun., **20**, 45 (1990).
18. Soai, K., Yokoyama, S. and Ookawa, A., Synthesis, **48** (1987).
19. Ganem, B. and Osby, J. O., Chem. Rev., **86**, 763 (1986).
20. a. Sarma, J. C. and Sharma, R. P. Chem. Ind., **764** (1987).
 b. Surya Prakash Rao, H. Reddy, K. S., Turnbull, K. and Borchers, V., Synthetic Commun., **22**, 1339 (1992).
21. Yoo, S-e. and Lee, S-h, Syn. Lett., **419** (1990).
22. Sandler, S. R. and Karo, W., "Organic Functional Group Preparations", Vol II, Academic Press, London, **268 - 284**, 1971.

(Received in the UK 15 July 1993)