Reduction of Azides with Zinc Borohydride

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Zinc borohydride in 1,2-dimethoxyethane provides an efficient procedure for the reduction of organic azides. Aroyl, acyl, and arylsulfonyl azides readily undergo reduction at room temperature to produce amides and sulfonamides in excellent yields; however, substitution with electron-withdrawing groups in the aroyl azides leads to the corresponding benzyl alcohols. Reduction of aryl and alkyl azides has also been achieved in high yields, under some modified conditions.

The reduction of azides to amines constitutes a synthetically useful process,[1] and since many excellent methods are now available for the preparation of azides with regio-, stereo-, and enantiocontrol,[2] subsequent reduction permits a controlled introduction of an amine function. A wide variety of reagents including lithium aluminum hydride, catalytic hydrogenation, triphenylphosphine, hydrogen sulfide, diborane, tributyltin hydride, zinc–hydrochloric acid, etc. have been reported[3] for this conversion. But these reagents have one or more limitations with regard to general applicability, selectivity, ready availability, operational convenience, and toxicity. For instance, $LiAlH_4$ is not tolerable to many functionalities such as $-CO_2R$, $-NO_2$, etc., and on the other hand, catalytic hydrogenation and diborane reduction have limitations for being applied to unsaturated compounds containing a double or triple bond. Borohydrides, in general, are milder reducing agent and more selective and, hence, could be the better choice. But, unfortunately, sodium borohydride does not usually convert azides to amines in good yield at ambient conditions in homogeneous systems, except in the case of arylsulfonyl azides.[4] Recently, a number of reports describing reduction of azides by sodium borohydride with different modifications appeared in the literature. But these observations are also capricious. For instance, reaction of benzoyl azide with sodium borohydride in dioxane produced only 29% of benzamide,[5a] whereas reduction in methanol yielded a 9:1 mixture of benzyl alcohol and benzamide.[5b] On the other hand, sodium borohydride under phase-transfer conditions[5c] and on an ion-exchange resin support[5d] readily reduced aryl and arylsulfonyl azides to the corresponding amines. And, alkyl and aroyl azides were reduced to the corresponding amines[5e] and amides,[5f] respectively, with a sodium borohydride–nickel (II) chloride system, although this reagent has serious restrictions for use in the presence of a nitro group.[6] Thus, a simple and efficient reducing agent of general applicability to all types of azides with tolerance to other sensitive functionalities will be well appreciated. Our recent endeavor of selective reduction of various important functionalities with zinc borohydride[7] prompted us to initiate a systematic investigation of reduction of organic azides including aroyl, acyl, arylsulfonyl, aryl, and alkyl.

Scheme 1

$$RN_3 \xrightarrow{Zn(BH_4)_2} RNH_2$$

R = aroyl, acyl, arylsulfonyl, aryl, alkyl

We have observed that zinc borohydride in 1,2-dimethoxyethane (DME) reduces aroyl, acyl, and arylsulfonyl azides efficiently to the corresponding products in excellent yields. The reaction is carried out by simply stirring the azide with a solution of zinc borohydride in DME at room temperature for a certain period of time as required for completion (monitored by TLC and IR). Several structurally varied azides are subjected to reduction by this procedure, and the results are summarized in Table 1. As is evident from the results, the substitution pattern in the aromatic ring of the aroyl azides has a great influence on the course of reduction. Thus, unsubstituted benzoyl azide and those having electron-donating substituents like $-CH_3$ and $-OCH_3$ at the para-position are cleanly reduced to the corresponding amides (entries 1–3, Table 1), whereas substitution of groups with a −I effect such as $-NO_2$ and −Cl in the meta- or para-position of the benzoyl azide ring leads to the formation of the corresponding benzyl alcohols (entries 4–6, Table 1). This is quite obvious because substitution of groups with a −I effect in the aromatic ring renders the carbonyl carbon of the aroyl azide more electron deficient and thus invites hydride attack at this position to produce the corresponding aldehyde which then undergoes reduction to give alcohol (path a, Scheme 2). In unsubstituted and +I group-substituted aroyl azides, hydride attack occurs at the relatively electron-deficient nitrogen of the azide moiety leading to amides (path b, Scheme 2).

Acyl azides, in general, are reduced more rapidly to produce the corresponding amides (entries 7–9, Table 1); but interestingly, phenylacetyl azide (entry 10), under the same conditions, undergoes Curtius-type rearrangement followed by hydride attack to yield *N*-benzylforma-

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(1) (a) Sheradsky, T. *The Chemistry of the Azido Group*; Patai, S., Ed.; Interscience Publishers: New York, 1971; Chapter 6. (b) Scriven, E. F. V., Ed. *Azides and Nitrenes, Reactivity and Utility*; Academic Press, Inc.: New York, 1984.

(2) (a) Blandy, C.; Choukroun, R.; Gervais, D. *Tetrahedron Lett.* **1983**, *24*, 4189. (b) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557. (c) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1650. (d) Onaka, M.; Sugita, K.; Izumi, Y. *Chem. Lett.* **1986**, 1327. (e) Sinou, D.; Emziane, M. *Tetrahedron Lett.* **1986**, *27*, 4423. (f) Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886.

(3) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 298.

(4) Hedayatullah, M.; Guy, A. *Synthesis* **1978**, 357.

(5) (a) Boyer, J. H.; Ellzey, S. E., Jr. *J. Org. Chem.* **1958**, *23*, 127. (b) Rao, H. S. P. *Synth. Commun.* **1990**, *20*, 45. (c) Rolla, F. *J. Org. Chem.* **1982**, *47*, 4327. (d) Kabalka, G. W.; Wadgaonkar, P. P.; Chatla, N. *Synth. Commun.* **1990**, *20*, 293. (e) Sarma, J. C.; Sharma, R. P. *Chem. Ind. (London)* **1987**, 764. (f) Rao, H. S. P.; Reddy, K. S.; Turnbull, K.; Borchers, V. *Synth. Commun.* **1992**, *22*, 1339.

(6) Osby, J. O.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 6413.

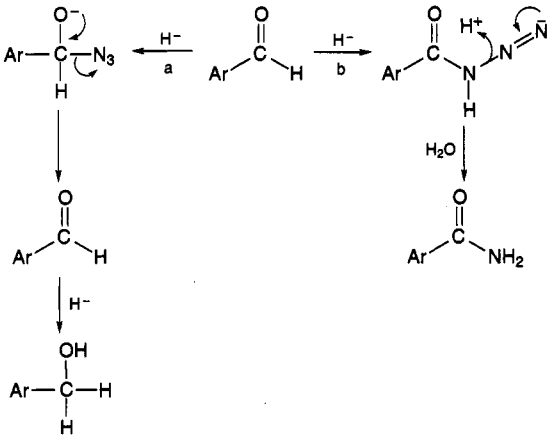
0022-3263/94/1959-4114$04.50/0

Table 1. Reduction of Aroyl, Acyl, and Arylsulfonyl Azides with Zinc Borohydride in DME

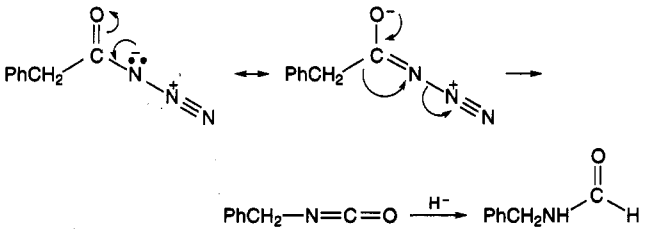
entry	azide	time (h)	product	yield[a] (%)	mp (°C)
1	benzoyl azide	3	benzamide	90	127–128[12]
2	*p*-methylbenzoyl azide	3.5	*p*-methylbenzamide	95	159–161[13]
3	*p*-methoxybenzoyl azide	6	*p*-methoxybenzamide	92	166–168[12]
4	*p*-nitrobenzoyl azide	4	*p*-nitrobenzyl alcohol	96	92–93[12]
5	*p*-chlorobenzoyl azide	5.5	*p*-chlorobenzyl alcohol	94	70–71[12]
6	*m*-chlorobenzoyl azide	5.5	*m*-chlorobenzyl alcohol	92	oil
7	cyclohexanoyl azide	2.5	cyclohexanecarboxamide	88	186[13]
8	lauroyl azide	0.5	lauramide	92	99–100[13]
9	stearoyl azide	0.5	stearamide	95	107–109[13]
10	oleoyl azide	1.5[b]	oleamide	84	75–76[13]
11	phenylacetyl azide	3	*N*-benzylformamide	85	60–62[12]
12	*p*-toluenesulfonyl azide	3.5	*p*-toluenesulfonamide	95	139[12]
13	2-naphthalenesulfonyl azide	4	2-naphthalenesulfonamide	90	215–217[14]

[a] All yields refer to pure isolated products, fully characterized by IR, ^{1}H NMR, and mp. [b] The reaction is run at 0–5 °C.

Scheme 2



Scheme 3



mide (Scheme 3). Reduction of arylsulfonyl azides to the corresponding sulfonamides is also effected smoothly with this reagent (entries 11 and 12, Table 1).

The reduction of aryl azides with zinc borohydride in DME at room temperature is relatively sluggish. However, efficient reduction in a much shorter time has been achieved when the reaction is carried out under sonication. A variety of substituted aryl azides have been found to undergo reduction by this process to produce the corresponding amines in high yields. The results are presented in Table 2. The pattern of substitution in the aromatic ring has practically no effect on the rate or course of reduction.

Although alkyl azides undergo reduction to amine with zinc borohydride in DME at room temperature, in some cases (entries 11 and 12, Table 2) the best results in terms of yield and time are obtained when the reactions are done under sonication in the presence of silica gel. Although the exact role of silica gel in this process is not clear, its presence definitely activates the system toward reduction as observed previously for a number of substrates.[7c,j]

The present procedure of reduction of azides has several practical advantages. Zinc borohydride has unique and uniform reducing properties toward all types of azides. The reduction is carried out in an aprotic solvent (DME). This avoids the disadvantages of using a protic solvent like methanol[5d] or water[5c] during reduction using sodium borohydride, which often causes problems for molecules containing easily solvolyzable functionalities. Moreover, zinc borohydride is neutral, mild, and compatible with a variety of normally reducable functional groups such as chloro (entries 5 and 6, Table 1), methoxy (entries 2 and 3; Table 1), nitro (entry 4, Table 1), carboxylic ester (entry 10, Table 2), and double bond (entry 10, Table 1) and thus superior to many commonly used reagents like $LiAlH_4$, B_2H_6, and H_2-(Pd–C). The reactions are also reasonably fast and high yielding.

In conclusion, zinc borohydride thus appears to be a mild and efficient reagent for the reduction of a broad spectrum of azides to the corresponding amines in high yields. Moreover, the easy availability of the reagent, operational simplicity, and superior selectivity make this procedure extremely attractive and a practical alternative to the existing methods,[3,5] and we believe this will find general acceptance in organic synthesis.

Experimental Section

IR spectra were recorded on a Perkin-Elmer Model 298 spectrometer, and ^{1}H NMR spectra were recorded on an EM 360 spectrometer from Varian Associates in CCl_4 and $CDCl_3$ solutions with Me_4Si as internal standard. Thin-layer chromatography was done on precoated silica gel plates (E. Merck, Germany). Silica gel (60-120 mesh, SRL, India) was used for column chromatography. 1,2-Dimethoxyethane was distilled from benzophenone–sodium under N_2 immediately before use. Acetone was distilled over calcium carbonate. DMF was dried by distillation over CaH_2. Ether refers to diethyl ether.

Zinc borohydride in DME was prepared from zinc chloride and sodium borohydride according to the reported procedure[8] and kept in the refrigerator as a standard stock solution for subsequent uses.

Preparation of Aroyl, Acyl, and Arylsulfonyl Azides. Representative Procedure.[9] A suspension of benzoic acid (1.2 g, 10 mmol) in freshly distilled thionyl chloride (8 mL)

(7) (a) Ranu, B. C.; Das, A. R.; Sarkar, D. C. *J. Org. Chem.* **1990**, *55*, 5799. (b) Ranu, B. C.; Chakraborty, R. *Tetrahedron Lett.* **1990**, *31*, 7663. (c) Ranu, B. C.; Das, A. R. *J. Chem. Soc., Chem. Commun.* **1990**, 1334. (d) Ranu, B. C.; Basu, M. K. *Tetrahedron Lett.* **1991**, *32*, 3243. (e) Ranu, B. C.; Chakraborty, R. *Tetrahedron Lett.* **1991**, *32*, 3579. (f) Ranu, B. C.; Das, A. R. *J. Org. Chem.* **1991**, *56*, 4796. (g) Ranu, B. C.; Das, A. R. *Tetrahedron Lett.* **1992**, *33*, 2361. (h) Ranu, B. C.; Chakraborty, R. *Tetrahedron* **1992**, *48*, 5317. (i) Ranu, B. C.; Das, A. R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1561. (j) Ranu, B. C.; Das, A. R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1881. (k) Ranu, B. C.; Chakraborty, R.; Saha, M. *Tetrahedron Lett.* **1993**, *34*, 4659. (l) Ranu, B. C. *Synlett* **1993**, 885.

(8) Crabbe, P.; Garcia, G. A.; Rius, C. *J. Chem. Soc., Perkin Trans. 1* **1973**, 810.

Table 2. Reduction of Aryl and Alkyl Azides with Zinc Borohydride in DME

entry	azide	time (h)	amine	yield[a] (%)	mp (°C)
1	phenyl azide	1.5[b]	aniline	70	113–114[d]
2	*p*-nitrophenyl azide	1.5[b]	*p*-nitroaniline	90	146–147[13]
3	*m*-nitrophenyl azide	1.5[b]	*m*-nitroaniline	92	114–115[13]
4	*o*-methoxyphenyl azide	3[b]	*o*-anisidine	89	88–89[d]
5	*p*-methoxyphenyl azide	3.5[b]	*p*-anisidine	88	130[d]
6	*o*-methylphenyl azide	3[b]	*o*-toluidine	90	110–111[d]
7	*m*-chlorophenyl azide	3.5[b]	*m*-chloroaniline	89	79–80[d]
8	*p*-chlorophenyl azide	3[b]	*p*-chloroaniline	92	69–70[13]
9	α-naphthyl azide	1.5[b]	α-naphthylamine	94	158–160[d]
10	ethyl 3-azidopropionate	6	ethyl 3-aminopropionate	85	oil[e]
11	benzyl azide	8[c]	benzylamine	65	103–104[f]
12	undecyl azide	6[c]	undecylamine	92	60–61[f]
13	(*S*)-(−)-1-phenylethyl azide[15]	8[c]	(*S*)-(−)-1-phenylethylamine	62	oil[g]

[a] All yields refer to pure isolated products, fully characterized by IR and ^{1}H NMR. [b] The reaction was carried out under sonication (method B). [c] The reaction was performed in the presence of silica gel (method C). [d] The melting point refers to that of the corresponding acetamide.[13] [e] Anal. Calcd for $C_5H_{11}O_2N$: c, 51.28; H, 9.40. Found: C, 51.12; H, 9.49. [f] The melting point reported is that of the corresponding benzamide.[13,14b] [g] $[\alpha]^{25}_D$ −36.4 (MeOH), mp of acetamide 104–105 °C.[14c]

was heated under reflux with stirring until all the solid dissolved. Excess thionyl chloride was removed under vacuum, and the residual acid chloride was dissolved in dry acetone (20 mL). The solution was cooled in an ice–water bath (5–10 °C), and a solution of sodium azide (2.6 g, 40 mmol) in acetone (10 mL) was added to it dropwise under stirring. This mixture was stirred for another 30 min and evaporated under vacuum to distill out the maximum amount of acetone. The residue was taken up in ether (50 mL). The ether solution was washed with brine, aqueous sodium bicarbonate, and brine and dried over Na_2SO_4. Evaporation of ether furnished the crude azide which was purified by quick column chromatography over silica gel to give benzoyl azide (1.3 g, 90%), sufficiently pure (IR, ^{1}H NMR, TLC) to be used for subsequent reduction.

All aroyl, acyl, and arylsulfonic azides were prepared following the same procedure.

Preparation of Aryl Azides. Representative Procedure. An aqueous solution of sodium nitrite (1.0 g, 15 mmol, dissolved in 25 mL of H_2O) was added dropwise to a cooled (0–5 °C) solution of aniline (930 mg, 10 mmol) in hydrochloric acid (6 N, 10 mL) under stirring. The reaction mixture was stirred at 0–5 °C for an additional 0.5 h, and to it was added dropwise an aqueous solution of sodium azide (2.6 g, 40 mmol, dissolved in 50 mL of H_2O). After being stirred for 1 h the reaction mixture was extracted with ether (3 × 50 mL), and the ether extract was washed with brine, aqueous sodium bicarbonate, and brine and dried (Na_2SO_4). Evaporation of solvent furnished the crude azide which was filtered through a short column of silica gel to produce pure phenyl azide (1 g, 85%).

Preparation of Undecyl Azide.[10] Solid sodium azide (780 mg, 17 mmol) was added to a solution of undecyl bromide (2.35 g, 10 mmol) in dry DMF (25 mL), and the resulting mixture was heated at 80 °C for 12 h. The solvent was evaporated under vacuum, and the residual oil was taken up in ether (50 mL). The ether solution was washed with water and brine and dried (Na_2SO_4). Evaporation of solvent afforded the crude azide which was purified by slow bulb to bulb distillation (1.48 g, 75%).

Benzyl azide and ethyl 3-azidopropionate were prepared from benzyl bromide and ethyl 3-bromopropionate, respectively, following the procedure of Priebe.[11]

All azides are known compounds[5] and are easily characterized by IR and ^{1}H NMR.

General Procedure for Reduction. (A) For Aroyl, Acyl, and Arylsulfonyl Azides. A solution of zinc borohydride (950 mg, 10 mmol) in DME (10 mL) was added to benzoyl azide (735 mg, 5 mmol) at room temperature with stirring. The reaction mixture was stirred for a certain period of time (Table 1) as required for completion (monitored by IR and TLC) and then quenched with careful dropwise addition of H_2O at 0–5 °C. The organic phase was separated, and the aqueous layer was extracted with chloroform (3 × 20 mL). The combined organic phase was dried over Na_2SO_4 and evaporated to provide the crude product which was purified by filtration through a short column of silica gel to give pure benzamide (545 mg, 90%). In some cases amides were also purified by recrystallization.

The amides are known compounds[5] and were characterized easily by comparison with authentic samples (IR, ^{1}H NMR, mp).[12–14]

(B) Reduction of Aryl Azides. After addition of a solution of zinc borohydride (950 mg, 10 mmol) in DME (10 mL) to phenyl azide (605 mg, 5 mmol), the resulting mixture was immersed in an ultrasonic bath and sonicated for a certain period of time (Table 2). The reaction mixture was then quenched with H_2O at 0–5 °C and acidified with 1:1 HCl. The organic phase was separated and discarded. The aqueous part was basified with cold aqueous NaOH solution, and the liberated amine was extracted with ether (3 × 25 mL). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of solvent left the crude product which was purified by column chromatography over silica gel to provide pure aniline (325 mg, 70%).

(C) Reduction of Alkyl Azides. The reaction was carried out in the same way as described in method B but in the presence of silica gel (HF 254, 2 g per 5 mmol of azide). After the reaction was over (IR and TLC), the reaction mixture was filtered and the filtrate was worked up as in method B. Benzyl amine, undecyl amine, and (*S*)-(−)-1-phenylethylamine were obtained from benzyl azide, undecyl azide, and (*S*)-(−)-1-phenylethyl azide,[2b] respectively, following this procedure, whereas reduction of ethyl 3-azidopropionate was carried out according to method A.

The amines obtained by methods B and C were identified by comparison with authentic samples (IR, ^{1}H NMR, and mp).[12–14]

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(9) With modification of a reported procedure: Rewcastle, G. W.; Denny, W. A. *Synthesis* **1985**, 220.

(10) Following a related reported procedure: Schultz, A. G.; Dittami, J. P.; Myong, S. O.; Sha, C. K. *J. Am. Chem. Soc.* **1983**, *105*, 3273.

(11) Priebe, H. *Acta Chem. Scand.* **1984**, *B38*, 895.

(12) Pouchert, C. J. *The Aldrich Library of NMR Spectra*, 2nd ed.; Aldrich Chemical Company, Inc.: Milwaukee, 1983; Vols. 1 and 2.

(13) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Volgel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman: U.K., 1989.

(14) (a) Pollock, J. R. A.; Stevens, R. Ed. *Dictionary of Organic Compounds*; Eyre and Spottiswoode: London, 1965; Vol. 4, p 2372. (b) Heilbron, I., Bunbury, H. M., Eds. *Dictionary of Organic Compounds*; Eyre and Spottiswoode: London, 1953; Vol 4, p 650. (c) Pollock, J. R. A., Stevens, R. Eds. *Dictionary of Organic Compounds*; Eyre and Spottiswoode: London, 1965; Vol. 1, p 131.