Sodium Borohydride Reactions under Phase-Transfer Conditions: Reduction of Azides to Amines

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Under phase-transfer catalysis (PTC) conditions organic azides are reduced to amines in high yields by aqueous sodium borohydride: aryl and arylsulfonyl azides give the corresponding amino derivatives at room temperature, while alkyl azides require more drastic conditions (80 °C). *tert*-Butyl 2-azido-2-phenylacetate, after reduction at room temperature and acidic workup, gives phenylglycine in a 72% overall yield. The PTC technique allows the conversion of alkyl chlorides, bromides, and methanesulfonates into pure primary amines via a one-pot procedure by reacting a mixture of the substrate and a PTC agent first with aqueous NaN_3 and then with aqueous $NaBH_4$.

The reduction of azides to amines by lithium aluminium hydride[1-5] or by catalytic hydrogenation[1-4,6] represents an important tool in organic chemistry. Recently a number of new reagents have been introduced for the reduction of particular azides.[7-15] Sodium borohydride normally gives poor yields in the conversion of azides to amines in homogeneous systems,[4,16,17] the reduction of arylsulfonyl azides representing, however, an interesting exception.[18]

We have found that under phase-transfer-catalysis (PTC) conditions $NaBH_4$ efficiently performs the reaction

$$RN_3 \xrightarrow[\text{I (catalyst), toluene}]{NaBH_4,\ H_2O} RNH_2$$

R = alkyl, aryl, arylsulfonyl

The process is carried on by adding at the appropriate temperature an aqueous solution of sodium borohydride (1.1–10 mol)[19] to a toluene solution of the azide (1 mol) and of hexadecyltributylphosphonium bromide (I) as a PTC agent (0.1 mol, Table I); the reaction is followed either by IR or GC analysis. Under PTC conditions aryl and arylsulfonyl azides are rapidly and quantitatively reduced to the corresponding amino derivatives at room temperature. Alkyl azides require more drastic conditions (80 °C, 16 h), affording however pure products in high yields (79-92%). *tert*-Butyl 2-azido-2-phenyl-2-acetate,[21] after an acidic workup, gives phenylglycine in a 72% overall yield (Table I). It should be noted that, under homogeneous conditions, both alkyl azides and 2-azido-2-phenylacetates are not reduced by sodium borohydride.[16]

This PTC procedure allows the conversion of alkyl chlorides, bromides, and methanesulfonates into primary amines by a one-pot reaction: the halide or sulfonate ester is first reacted with aqueous sodium azide in the presence of catalytic amounts of a PTC agent according to a reported procedure[23] (Table II), the aqueous phase is then replaced by an aqueous solution of sodium borohydride (Table I). Overall yields of this one-pot procedure are similar to those found in the conversion of azides to amines. This system thus avoids dangerous separation and purification of high-boiling azides.

With respect to the literature methods,[1-17] the PTC technique shows the novelty of using sodium borohydride as an efficient reducing agent for a broad spectrum of compounds. It affords pure products in high yields and offers the advantages of permitting a one-pot conversion of halides and methanesulfonates into pure primary amines with very simple operative conditions.

Experimental Section

NMR spectra were recorded on a Varian EM-390 90 MHz spectrometer with Me_4Si as an internal standard. IR spectra were measured as films or Nujol mulls on a Perkin-Elmer 377 grating spectrophotometer by using NaCl cells. GC data were obtained on a Hewlett-Packard Model 5850 A gas chromatograph by using a 2-m, 3% SE-30 on Chromosorb column; conversions were corrected for detector response.

Materials. Sodium borohydride, sodium azide, and toluene, commercially available reagents, were used as purchased. Catalysts, halides, and sulfonate esters were prepared by standard procedures or were commercially available products.

Azides. Phenyl,[26] naphthyl,[26] and *p*-toluenesulfonyl[27] azides were prepared according to the literature; their physical properties were in agreement with those reported. The other azides were prepared according to a previously described PTC procedure;[23]

(1) Boyer, J. H.; Canter, F. C. *Chem. Rev.* **1954**, *54*, 1.
(2) Schröter, R. "Methoden der Organischen Chemie (Houben-Weyl)", 4th ed.; Müller,E., Ed.; Georg Thieme Verlag: Stuttgart, 1957; Vol. 11, Part 1, p 539.
(3) Grundmann, C. "Methoden der Organischen Chemie (Houben-Weyl)", 4th ed.; Müller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1965; Vol. 10, Part 3, p 822.
(4) Sheradsky, T. "The Chemistry of the Azido Group"; Patai, S.; Ed.; Interscience: New York, 1971; Chapter 6.
(5) Boyer, J. H. *J. Am. Chem. Soc.* **1951**, *73*, 5865.
(6) Corey, E. J.; Nicolaou, K. C.; Balanson, R. D.; Machida, Y. *Synthesis* **1975**, 590 and references therein.
(7) Stanovnik, B.; Tišler, M. *Tetrahedron* **1967**, *23*, 387 and references therein.
(8) Adaki, T.; Yamada, Y.; Inoue, I. *Synthesis* **1976**, 815.
(9) Stanovnik, B.; Tišler, M.; Polanc, S.; Zitnik, J. *Synthesis* **1977**, 491.
(10) Stanovnik, B.; Tišler, M.; Polanc, S.; Gracner, M. *Synthesis* **1978**, 65.
(11) Polanc, S.; Stanovnik, B.; Tišler, M. *Synthesis* **1980**, 830.
(12) Ho, T.-L.; Henninger, M.; Olah, G. A. *Synthesis* **1976**, 815.
(13) Hedayatullah, M.; Guy, A. *Tetrahedron Lett.* **1975**, 2455.
(14) Bayley, H.; Standring, D. N.; Knowles, J. R. *Tetrahedron Lett.* **1978**, 3633.
(15) Atkinson, J. G.; Girard, Y.; Rokach, J.; Rooney, C. S.; McFarlane, C. S.; Rackham, A.; Share, N. N. *J. Med. Chem.* **1979**, *22*, 99.
(16) Boyer, J. H.; Ellzey, S. E. *J. Org. Chem.* **1958**, *23*, 127.
(17) Smith, P. A.; Hall, J. H.; Kan, R. O. *J. Am. Chem. Soc.* **1962**, *84*, 485.
(18) Hedayatullah, M.; Guy, A. *Synthesis* **1978**, 357.
(19) The hydride excess is necessary since $NaBH_4$ is not completely stable in aqueous solution, the decomposition rate depending on the pH of the medium.[20]
(20) Gardiner, J. A.: Collat, J. W. *J. Am. Chem. Soc.* **1965**, *87*, 1692, and references therein.
(21) Under PTC conditions carboxylic esters of simple primary alcohols are rapidly hydrolyzed in the presence of an aqueous basic phase.[22]
(22) Dehmlow, E. V.; Dehmlow, S. S. "Phase-Transfer Catalysis"; Verlag Chemie: Weinheim/Bergstr., Germany, 1980; p 155.
(23) Reeve, W. P.; Nahr, M. L. *Synthesis* **1976**, 823.
(24) Levene, P. A.; Rothen, A.; Kuna, M. *J. Biol. Chem.* **1936**, *115*, 415.
(25) Curtius, T.; Ehrhart, G. *Ber. Dtsch. Chem. Ges.* **1922**, *55*, 1559.
(26) Philips, J. C. *J. Chem. Soc.* **1908**, *93*, 918.
(27) Curtius, T.; Klavehn, W. *J. Prakt. Chem.* **1926**, *112*, 65.

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Table I. Reduction of Azides to Amines with Aqueous Sodium Borohydride under PTC Conditions

substrate (1 mol)	product	I, mol	$NaBH_4$,[a] mol	toluene[b]	temp, °C	time,[c] h	yield,[d] %
n-octyl azide	*n*-octylamine	0.1	3	1	80	16	92
		0	3	1	80	16	10[e]
n-hexadecyl azide	*n*-hexadecylamine	0.1	3	1	80	16	88
sec-octyl azide	*sec*-octylamine	0.1	10	1	80	48	79
benzyl azide	benzylamine	0.1	3	2	70	3	89
phenyl azide	aniline	0.1	1.1	2	20	1	92
		0	1.1	2	20	5	15[e]
1-naphthyl azide	1-naphthylamine	0.1	1.1	2	20	6	89
toluenesulfonyl azide	toluenesulfonamide	0.1	1.1	8	20	0.5	94
		0	3	8	20	20	25
tert-butyl 2-azido-2-phenylacetate	phenylglycine	0.1	3	3	20	6	72
		0	3	3	20	24	15

[a] An aqueous saturated solution was used. [b] Milliliters per gram of substrate. [c] After the end of the addition of the aqueous phase. [d] Isolated product. [e] By GC analysis.

Table II. Azides Prepared under PTC Conditions[23]

azide	starting material	reaction conditions[a] time, h	reaction conditions[a] temp, °C	yield,[b] %	bp, °C (mm)	n^{22}_D	formula or ref	IR,[c] cm^{-1}	NMR,[d] δ
n-octyl azide	*n*-octyl methanesulfonate	8	40	89	73-75 (3)	1.4345	23	2100	3.2 (t)
n-octyl azide	*n*-octyl bromide	8	80	85	73-75 (3)	1.4348	23	2100	3.2 (t)
n-hexadecyl azide	*n*-hexadecyl bromide	8	80	89	*e*	1.4548	$C_{16}H_{33}N_3$[f]	2100	3.2 (t)
sec-octyl azide	*sec*-octyl bromide	16	80	79	56-58 (3)	1.4357	24	2100	2.6-3.2 (m)
benzyl azide	benzyl chloride	16	20	84	*e*	1.5356	25	2085	4.3 (s)
tert-butyl 2-azido-2-phenylacetate	*tert*-butyl 2-chloro-2-phenylacetate	24	20	94	*e*	1.5010	$C_{12}H_{15}N_3O_2$[g]	2100	4.65 (s)

[a] Reactions were performed by stirring the heterogeneous mixture of the halide (1 mol), trioctylmethylammonium chloride chloride (0.05 mol), and 25% aqueous sodium azide (2.5 mol).[23] [b] Yield of isolated pure product. [c] ν_{N_3}, (film). [d] For CH_2N_3 or CHN_3 (CCl_4); multiplicity given in parentheses. [e] The azide was purified by column chromatography (silica gel, eluent ether). [f] Anal. Calcd for $C_{16}H_{33}N_3$: C, 71.85; H, 12.44; N, 15.71. Found: C, 71.97; H, 12.53; N, 15.54. [g] Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.78; H, 6.48; N, 18.02. Found: C, 61.98; H, 6.57; N, 17.87.

reaction conditions, yields, and physical data of these azides are reported in Table II.

***tert*-Butyl 2-Chloro-2-phenylacetate.** To a solution of 2-chloro-2-phenylacetic chloride (37.8 g, 0.2 mol) and *tert*-butyl alcohol (51.8 g, 0.7 mol) in benzene (200 mL) was added triethylamine (22 g, 0.22 mol) in 1 h at room temperature, and the resulting solution was refluxed 6 h with stirring. After addition of water (100 mL), the organic layer was separated and washed successively with water, 5% sodium hydrogen carbonate, and water. Elimination of the solvent afforded pure *tert*-butyl 2-chloro-2-phenylacetate which was used as such: 36 g (80% yield); n^{21}_D 1.5020; IR (film) 1795 cm^{-1}; NMR (CCl_4) δ 7.5–7.1 (m, 5 H), 5.1 (s, 1 H), 1.4 (s, 9 H). Anal. Calcd for $C_{12}H_{15}ClO_2$: C, 63.57; H, 6.65. Found: C, 64.03; H, 6.87.

Synthesis of Amines. Typical Procedures. (A) Reduction of Alkyl and Aryl Azides. Synthesis of *n*-Octylamine. To a stirred solution of *n*-octyl azide (15.5 g, 0.1 mol) and I (5.1 g, 0.01 mol) in toluene (15.5 mL) was added a solution of $NaBH_4$ (11.7 g, 0.3 mol) in water (30 mL) in 30 min at 80 °C. The mixture was stirred at this temperature for 16 h; the layers were separated and the organic phase was extracted with 10% HCl. The catalyst, recovered as a viscous oil (95% yield) from the organic phase by elimination of the solvent, may be reused as such. Basification of the acid phase and extraction (ether) afforded pure *n*-octylamine: 11.9 g (92% yield); bp 172–174 °C (760 mm); n^{22}_D 1.4285 [lit.[28] bp 176.5 °C (763 mm)]; IR (film) 3350 cm^{-1}; NMR (CCl_4) δ 2.7 (t, 2 H), 2.1–1.0 (br s and m, 14 H), 0.9 (t, 3 H).

(B) Reduction of *p*-Toluenesulfonyl Azide. To a stirred solution of *p*-toluenesulfonyl azide (19.7 g, 0.1 mol) and I (5.1 g, 0.1 mol) in toluene (155 mL), a solution of $NaBH_4$ (4.2 g, 0.11 mol) in water (11 mL) was added in 30 min with stirring while the inner temperature was maintained under 30 °C (exothermic reaction). The reaction mixture was kept at room temperature for 30 min, and then the product was extracted with dichloromethane and purified by crystallization from aqueous ethanol: 16.1 g (94% yield); mp 136–138 °C (lit.[16] 137–138 °C); IR (Nujol) 3350, 3250, 1380, 1170 cm^{-1}; NMR (Me_2SO-d_6) δ 7.6 (q, 4 H), 7.3 (br s, 2 H), 3.4 (s, 3 H).

(C) Reduction *tert*-Butyl 2-Azido-2-phenylacetate. To a stirred solution of *tert*-butyl (2-azido-2-phenylacetate (23.2 g, 0.1 mol) and I (5.1 g, 0.01 mol) in toluene (70 mL) was added a solution of $NaBH_4$ (11.7 g, 0.3 mol) in water (30 mL) in 30 min at room temperature. The mixture was stirred 6 h at this temperature, the layers were separated, and the organic phase was washed with water. The hydrolysis of the crude ester was effected according to the following two-phase procedure:[29] 37% HCl (100 mL) was added to the toluene solution, the mixture was stirred 3 h at room temperature, the organic layer was removed, the aqueous phase was concentrated to a volume of about 70 mL, the pH was adjusted to 6–7 with aqueous ammonia, and the solution was stored 16 h at 5 °C. The precipitate was filtered and washed successively with cold water, ethanol, and ether to afford pure phenylglycine: 10.9 g (72% yield); mp 279–281 °C (lit.[30] mp 279–281 °C).

(D) One-Pot Procedure for the Conversion of Alkyl Halides and Methanesulfonates into Primary Amines. Synthesis of *n*-Octylamine from *n*-Octyl Bromide. A mixture of *n*-octylbromide (19.3 g, 0.1 mol), I (5.1 g, 0.01 mol), NaN_3 (16.2 g, 0.25 mol), and water (50 mL) was stirred at 80 °C for 8 h. The aqueous phase was then carefully removed, the organic phase was diluted with toluene (15.5 mL), and then a solution of $NaBH_4$ (11.7 g, 0.3 mol) in water (30 mL) was added in 30 min. The mixture was stirred at 80 °C for 16 h. The workup, effected

(28) Vogel, A. I. *J. Chem. Soc.* **1948**, 1825.

(29) Landini, D.; Rolla, F. *J. Org. Chem.* **1982**, *47*, 154.

(30) Landini, D.; Montanari, F.; Rolla, F. *Synthesis* **1979**, 26.

according to procedure A, afforded pure *n*-octylamine, 11.4 g (88% yield).

Registry No. I, 14937-45-2; *n*-octyl azide, 7438-05-3; *tert*-butyl 2-chloro-2-phenylacetate, 40058-90-0; *sec*-octyl azide, 22513-48-0; benzyl azide, 622-79-7; phenyl azide, 622-37-7; 1-naphthyl azide, 6921-40-0; toluenesulfonyl azide, 941-55-9; *tert*-butyl 2-azido-2-phenylacetate, 82430-95-3; *n*-octylamine, 111-86-4; *n*-hexadecylamine, 143-27-1; *sec*-octylamine, 693-16-3; benzylamine, 100-46-9; aniline, 62-53-3; 1-naphthylamine, 134-32-7; toluenesulfonamide, 70-55-3; phenylglycine, 69-91-0; *n*-octyl methanesulfonate, 16156-52-8; *n*-octyl bromide, 111-83-1; *n*-hexadecyl bromide, 112-82-3; *sec*-octyl bromide, 557-35-7; benzyl chloride, 100-44-7; *n*-hexadecyl azide, 66143-67-7; sodium borohydride, 16940-66-2; trioctylmethylammonium chloride, 5137-55-3; 2-chloro-2-phenylacetic chloride, 2912-62-1; *tert*-butyl alcohol, 75-65-0; sodium azide, 26628-22-8.

Synthesis and Stereochemistry of 11-Substituted 5,6,7,8,9,10-Hexahydro-6,9-methanobenzocyclooctenes

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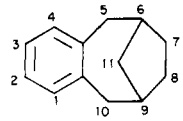
5,6,7,8,9,10-Hexahydro-6,9-methanobenzocyclooctene is a ring system where the cyclooctene ring could exist either in a boat or in a chair conformation. Molecular modeling calculations indicated that the boat conformation is the favored conformation when position 11 is substituted by a ketone group, an amino group, or a hydroxy group. NMR shift reagent studies have shown that these same derivatives exist in this boat conformation. The same studies have also demonstrated that chemical modifications of carbon-11 transforming it from a sp^2 to sp^3 (i.e., reduction of carbonyl to alcohol) give rise to endo derivatives exclusively. Attempts to obtain the exo derivatives by displacement reactions of sulfonates or Ritter reactions were unsuccessful. The only exo derivative obtainable was the 11-*exo*-amino-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene, isolated in low yields from the base-catalyzed equilibration of its *N*-benzylidene derivative.

Introduction

The 5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene ring system 1 is a somewhat poorly studied system



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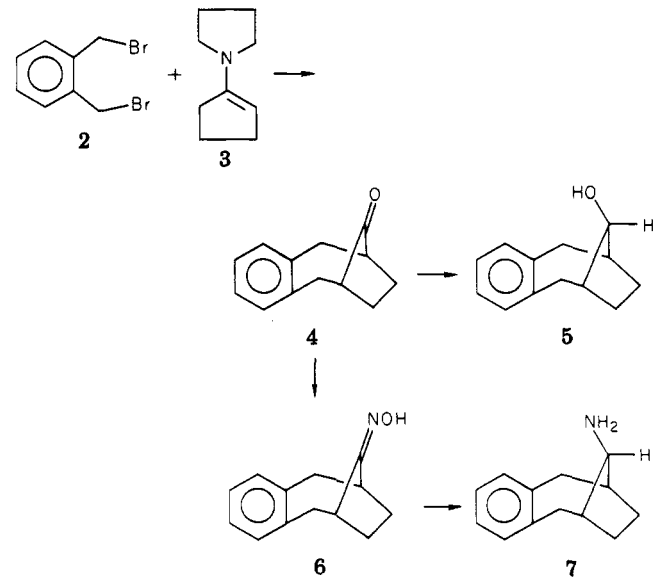
as compared to the other isomeric systems, such as the 5,6,7,8,9,10-hexahydro-5,9-methanobenzocyclooctene (which is the backbone of the benzomorphan analgesics). In our laboratories, we decided to investigate this system for the development of novel analgesics. For this purpose, the stereochemistry of the substituent on the methano part (carbon-11) was of great importance, and great care was taken to ensure the endo orientation of this group. Also, it was imperative that the ring system should adopt a boat conformation, since the distance between substituents at carbon-2 and -11 was critical to our requirements. Should the preferred conformation be a chair, the distance would be completely different, and it is well known that the relative positions of the basic nitrogen and phenol are very critical in potent analgesics.[1,2]

Therefore, we present here the data we have obtained on this system, which extends the observations Hahn and Jatczak[3] have obtained recently on this ring system.

Scheme I



Results and Discussion

A. Preparation of Derivatives of 5,6,7,8,9,10-Hexahydro-6,9-methanobenzocyclooctene. We carried out the preparation of 11-oxo-5,6,7,8,9,10-hexahydro-6,9-methanobenzocyclooctene (4) according to Opitz and Mildenberger[4] by reacting *o*-xylidene dibromide **2** with the pyrrolidine enamine of cyclopentanone **3** in acetonitrile,

(1) B. Belleau, T. Conway, F. R. Ahmed (*London*) and A. D. Hardy, *J. Med. Chem.*, **17**, 908 (1974).
(2) A. S. Horn and J. R. Rodgers, *Nature* (*London*) **260**, 797 (1976).
(3) W. E. Hahn and M. Jatczak, *Pol. J. Chem.*, **53**, 1221 (1979).
(4) G. Opitz and H. Mildenberger, *Justus Liebigs Ann. Chem.*, **650**, 115 (1961).

0022-3263/82/1947-4329$01.25/0