J. Org. Chem. **1994**, 59, 4687−4688

Selective Reduction of Alkyl Halides with Borohydride Exchange Resin−Nickel Acetate in Methanol

Nung Min Yoon,* Hyun Ju Lee, Jin Hee Ahn, and Jaesung Choi

Department of Chemistry, Sogang University, Seoul 121-742, Korea

Received January 3, 1994

Although the reduction of alkyl halides is easily carried out by lithium aluminum hydride[1,2] and lithium triethylborohydride,[3] sodium borohydride and sodium cyanoborohydride in aprotic solvents such as dimethyl sulfoxide, diglyme, or hexamethylphosphoric triamide have an advantage over these strong hydrides in that they display greater selectivity toward other reducible groups in the same molecule.[4−6] Sodium borohydride in the presence of a phase-transfer catalyst such as hexadecyltributylphosphonium bromide,[7] lithium borohydride in THF,[8] and a nickel complex reducing agent (Ni CRA)[9] also have been reported to be useful for the selective reduction of alkyl halides. On the other hand, the combination of Ni_2B with $NaBH_4$ in alcohol was reported to be effective for dechlorination of polychlorinated hydrocarbon pesticides.[10] However, alkyl chlorides are inert to Ni_2B itself while bromides and iodides are reduced in poor yields, although this boride is excellent for dehalogenation of α-halo ketones and *vic*-dibromides.[11] Recently, we have studied the reducing characteristics of borohydride exchange resin (BER)−$Ni(OAc)_2$ in methanol[12] and found this is also a convenient reducing system for halides. In this paper, we wish to report the selective reduction of alkyl halides with this system.

Scheme 1

$$\mathrm{RX} \xrightarrow[\mathrm{rt/1\text{-}3\ h}]{\mathrm{BER/Ni(OAc)_2/MeOH}} \mathrm{RH}$$

X = Cl, Br, I, OTs

As shown in Table 1, primary bromides and iodides were quantitatively reduced in 3 h under our standard conditions: BER (5.0 equiv)−$Ni(OAc)_2$ (0.1 equiv), 25 °C (entries 2−4). However, it is surprising that cyclohexyl bromide and cyclohexyl iodide were reduced at almost the same rate as the corresponding primary halides (entries 7 and 8). In a typical S_N2 reduction with $LiAlH_4$, only 17% of cyclohexyl bromide was reduced in 24 h whereas butyl bromide was completely reduced in 3 h at room temperature.[2] We also confirmed that this reduction did not proceed by catalytic hydrogenation over nickel boride. Therefore, this reaction is likely a nickel boride catalyzed borohydride reduction. Tertiary bromide, 3-bromo-3-methylpentane, was reduced slowly, yielding only 40% of the alkane after 3 h under our standard conditions. However, a quantitative yield could be obtained in 3 h using 0.5 mol equiv of $Ni(OAc)_2$ and 10.0 mol equiv of BER. The above results suggest that this reducing system is better than Ni CRA[9] which readily reduces primary and secondary bromides but requires 40 h at 65 °C to reduce 2-bromo-2-methyldodecane in 60% yield. Chlorides were inert to this reducing system (entries 1, 6, and 9), contrary to earlier reports.[10] However, benzyl chloride and β-phenethyl chloride were reduced in 3 h using 0.1 and 0.3 equiv of $Ni(OAc)_2$, respectively (entries 11 and 12), and *p*-methoxybenzyl chloride was reduced quantitatively to *p*-methylanisole (entry 14). α-Phenethyl bromide gave only 69% of the expected reduced product, ethylbenzene, accompanied by a substantial amount of a product arising from coupling 2,3-diphenylbutane (entry 15). This formation of the coupled product and the quantitative reduction of secondary and tertiary bromides strongly suggest involvement of radical intermediates. Halogens as α-substituents in esters and amides were reduced readily (entries 16−19, 21, and 22) . This is similar to what has been observed with other hydride systems.[4−7] Benzyl acetate was obtained in 98% isolated yield from benzyl α-bromoacetate, and no hydrogenolysis occurred during the reduction (entry 18). It is also interesting to note the ready reduction of β-phenethyl chloride and ethyl β-chlorobutyrate (entires 12 and 20) since chlorides are normally inert to this system, and the reduction of γ-chloropropylbenzene (entry 13) was also sluggish. Selective reduction of a bromide in the presence of a nitrile and chloride is demonstrated in entries 23 and 24. Finally, 1-octyl tosylate was inert to this system; however, *in situ* formation of octyl iodide by treating the tosylate with 3.0 mol equiv of sodum iodide in methanol at 65 °C for 2.0 h followed by subsequent reduction for 1 h afforded octane in 95% yield (entry 25). The formation of 2-octyl iodide from 2-octyl tosylate was not successful in methanol; however, the transformation could be carried out in acetone, and reduction after removal of acetone gave an equally excellent yield (93%) (entry 26).

In summary, BER−$Ni(OAc)_2$ in methanol is a good alternative to the other selective reagents for the reduction of aliphatic halides, and this system possess two more advantages: (1) methanol is a more convenient solvent than other aprotic solvents such as DMSO or HMPA and (2) since easy removal of BER−Ni_2B by filtration gives a methanol solution of the pure product, the workup procedure is very simple.

Experimental Section

General. $NaBH_4$ (98% Nisso Bentron) was used without further purification. Anion exchange resin (Amberite IRA-400) was used supporting the polymer of BER. All organic materials were obtained from commercial suppliers and used without further purification. Commercial grade 99.5% methanol was

---

[1] (a) Imamoto, T. Reduction of Saturated Alkyl Halides to Alkanes. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon Press: Oxford, 1991; Vol. 8, pp 793−809. (b) Entwistle, I. D.; Wood, W. W. Hydrogenolysis of Allyl and Benzyl Halides and Related Compounds. *Ibid.* pp 955−982.

[2] Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1982**, *47*, 276.

[3] Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1983**, *48*, 3089.

[4] Hutchins, R. O.; Kandasamy, D.; Dux, F.; Maryanoff, C. A.; Rotstein D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* **1978**, *43*, 2259.

[5] Bell, H. M.; Vanderslice, C. W.; Spehar, A. *J. Org. Chem.* **1969**, *34*, 3923.

[6] Hutchins, R. O.; Kandasamy, D.; Maryanoff, C. A.; Masilamani, D.; Maryanoff, B. E. *J. Org. Chem.* **1977**, *42*, 82.

[7] Rolla, F. *J. Org. Chem.* **1981**, *46*, 3909.

[8] Cho, B. T.; Yoon, N. M. *J. Korean Chem. Soc.* **1983**, *27*, 46.

[9] Vanderesse, R.; Brunet, J.-J.; Caubere, P. *J. Org. Chem.* **1981**, *46*, 1270.

[10] Dennis, W. H., Jr.; Cooper, W. J. *Bull. Environ. Contam. Toxicol.* **1975**, *14*, 738, as cited in: Ganem, B.; Osby, J. O. *Chem. Rev.* **1986**, *86*, 763.

[11] Sarma, J. C.; Borbaruah, M.; Sharma, R. P. *Tetrahedron Lett.* **1985**, *26*, 4657.

[12] Yoon, N. M.; Choi, J. *Synlett* **1993**, 135.

0022-3263/94/1959-4687$04.50/0

Table 1. Selective Reduction of Alkyl Halides with BER−$Ni(OAc)_2$ in Methanol at Room Temperature

entry	substrate	product	$Ni(OAc)_2$ (equiv)	reaction time (h)	yield[a] (%)
1	octyl chloride	octane	0.5	3.0	tr.[b]
2	octyl bromide	octane	0.1	3.0	100
3	hexadecyl bromide	hexadecane	0.1	3.0	(98)
4	octyl iodide	octane	0.1	1.0	97
5	2-bromohexane	hexane	0.3	3.0	98
6	cyclohexyl chloride	cyclohexane	0.5	3.0	tr.[b]
7	cyclohexyl bromide	cyclohexane	0.1	3.0	98
8	cyclohexyl iodide	cyclohexane	0.1	1.0	96
9	3-chloro-3-methylpentane	3-methylpentane	0.5	3.0	tr.[b]
10	3-bromo-3-methylpentane	3-methylpentane	0.5	3.0	96[b]
11	benzyl chloride	toluene	0.1	3.0	96
12	*β*-phenethyl chloride	ethylbenzene	0.3	3.0	98
13	*γ*-chloropropylbenzene	propylbenzene	0.3	3.0	7
14	*p*-methoxybenzyl chloride	*p*-methylanisole	0.1	1.0	(94)
15	α-phenethyl bromide	ethylbenzene	0.1	1.0	69[c]
16	ethyl α-chloroacetate	ethyl acetate	0.1	1.0	99
17	ethyl α-bromoacetate	ethyl acetate	0.1	1.0	98
18	benzyl α-bromoacetate	benzyl acetate	0.1	1.0	(98)
19	ethyl α-chlorobutyrate	ethyl butyrate	0.1	3.0	96
20	ethyl *β*-chlorobutyrate	ethyl butyrate	0.5	3.0	97[b]
21	octyl α-bromopropionate	octyl propionate	0.1	1.0	(95)
22	α-chloroacetamide	acetamide	0.1	1.0	(97)
23	octyl bromide	octane	0.1	3.0	98
	capronitrile	hexylamine			0
24	1-bromo-4-chlorobutane	1-chlorobutane	0.1	3.0	95
25	1-octyl tosylate	octane	0.1	3.0	0
			0.1	3.0	95[d]
26	2-octyl tosylate	octane	0.1	4.0	93[d]

[a] Yields by GLPC. Isolated yields are in parentheses. [b] 10.0 mmol equiv of BER was used. [c] Remainder was 2,3-diphenylbutane. [d] *Via* 1- or 2-octyl iodide.

used as solvent. The ^1H NMR spectra were obtained with tetramethylsilane as an internal standard.

Preparation of Borohydride Exchange Resin.[13,14] An aqueous solution of sodium borohydride (1 M, 1 L) was stirred with wet chloride-form anion exchange resin (Amberlite IRA-400 (20−50 mesh), 200 g) for 1 h. The resulting resin was washed thoroughly with distilled water until free from excess $NaBH_4$. The borohydride form anion exchange resin was then dried *in vacuo* at 60 °C for 5 h. The dried resin was analyzed for borohydride content by hydrogen evolution on acidification with 2 N HCl, and the average hydride content of BER was found to be 3.3 mmol of BH_4^- per gram. The dried resin was stored under nitrogen in refrigerator (~4 °C). The hydride content was constant over 6 weeks.

Typical Procedure for Reduction of Alkyl Halides. The reduction of hexadecyl bromide is representative. BER (15.2 g, 50 mmol) was added to the methanol solution (150 mL) of $Ni(OAc)_2{\cdot}4H_2O$ (0.25 g, 1 mmol) and hexadecyl bromide (3.05 g, 10 mmol), and the mixture was stirred at room temperature for 3 h. Complete reduction was confirmed by GLPC, and the resin was removed by filtration. Methanol was evaporated under reduced pressure to give pure hexadecane (2.22 g, 98%): n^{22}_{D} 1.4340 (lit.[15] n^{20}_{D} 1.4345); ^1H NMR ($CDCl_3$) δ 0.90 (t, 6 H, J = 12 Hz), δ 1.29 (br s, 28H).

***p*-Methylanisole**: n^{22}_{D} 1.5121 (lit.[15] n^{19}_{D} 1.5124); ^1H NMR ($CDCl_3$) δ 2.32 (s, 3 H), δ 3.81 (s, 3 H), δ 6.83 (dd, 2 H, J = 8.4, 2.1), δ 7.12 (d, 2 H, J = 8.4).

Benzyl acetate: n^{22}_{D} 1.5229 (lit.[15] n^{20}_{D} 1.5232); ^1H NMR ($CDCl_3$) δ 2.12 (s, 3 H), δ 5.13 (s, 2 H), δ 7.37 (s, 5 H).

Octyl propionate: n^{22}_{D} 1.4220 (lit.[15] n^{15}_{D} 1.4221); ^1H NMR ($CDCl_3$) δ 0.89 (t, 3 H, J = 6.8), δ 1.15 (t, 3 H, J = 7.7), δ 1.41 (m, 10 H), δ 1.62 (m, 2 H), δ 2.33 (q, 2 H, J = 7.7), δ 4.08 (t, 2 H, J = 6.8).

Acetamide: mp 81−82 °C (lit.[15] 82−83 °C); ^1H NMR ($CDCl_3$) δ 1.99 (s, 3 H), δ 6.00−7.41 (br d, 2 H).

Attempted Reduction of Octyl Bromide by Catalytic Hydrogenation over Nickel Boride. In the hydrogenation flask of a Brown automatic hydrogenator[16] were mixed $Ni(OAc)_2{\cdot}4H_2O$ (0.03 g, 0.1 mmol) and BER (0.09 g, 0.3 mmol) in methanol (10 mL), and borohydride was destroyed by keeping the mixture at 40 °C for 3.0 h. A methanol solution (2 mL) of octyl bromide (0.19 g, 1.0 mmol) was added, and the mixture was stirred for 3.0 h under static hydrogen pressure. No hydrogen uptake was observed, and octyl bromide was intact as checked by GLPC analysis.

Competitive Reduction of Octyl Bromide in the Presence of Capronitrile. BER (5.0 mmol) was added to the methanol solution (20 mL) of $Ni(OAc)_2{\cdot}4H_2O$ (0.03 g, 0.1 mmol), octyl bromide (0.19 g, 1 mmol), and capronitrile (0.10 g, 1 mmol), and the mixture was stirred at room temperature. GLPC analysis after 1.0 h showed 98% octane and no reduction of capronitrile.

One-Pot Reduction of Octyl Tosylates *via* Octyl Iodides. 1-Octyl tosylate (0.27 g, 1.0 mmol) was mixed with sodium iodide (0.45 g, 3.0 mmol) in methanol (20 mL) and refluxed for 2.0 h. GLPC analysis showed that no 1-octyl tosylated was present. $Ni(OAc)_2{\cdot}4H_2O$ (0.03 g, 0.1 mmol) and BER (1.52 g, 5.0 mmol) were added, and the mixture was stirred at room temperature for 1.0 h. GLPC analysis showed 95% yield of octane. In the case of 2-octyl tosylate, the tosylate (0.27 g, 1.0 mmol) was mixed with sodium iodide (0.45 g, 3.0 mmol) in acetone (20 mL) and refluxed for 2.0 h (40% of 2-iodidooctane and 60% of 2-methoxyoctane was formed in methanol). After acetone was removed by a rotary evaporator, BER (1.52 g, 5.0 mmol) and methanol (20 mL) containing $Ni(OAc)_2{\cdot}4H_2O$ (0.03 g, 0.1 mmol) were added, and the mixture was stirred at room temperature for 1.0 h. GLPC analysis showed 93% yield of octane.

Acknowledgment. This work was supported by the Organic Chemistry Research Center sponsored by the Korea Science and Engineering Foundation.

---

(13) Yoon, N. M.; Park, K. B.; Gyoung, Y. S. *Tetrahedron Lett.* **1983**, *24*, 5367.

(14) Kabalka, G. W. Wadgaonkar, P. P.; Chatla, N. *Synth. Commun.* **1990**, *20*, 293 and references cited therein.

(15) *Handbook of Chemistry and Physics*, 70th ed.; CRC Press: Boca Raton, 1989.

(16) Brown, C. A.; Brown, H. C. *J. Org. Chem.* **1966**, *31*, 3989.