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SELECTIVE REDUCTION OF TERTIARY, ALLYL, AND BENZYL HALIDES BY ZINC-MODIFIED CYANOBOROHYDRIDE IN DIETHYL ETHER[1]

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Abstract : Zinc-modified cyanoborohydride in diethyl ether reduces tertiary, allyl, and benzyl halides to the corresponding hydrocarbons but the reagent is inert toward primary alkyl, secondary alkyl, vinyl, and aryl halides.

Sodium cyanoborohydride is well-known as being useful for imine reduction, carbonyl amination, deoxygenation of aldehydes and ketones, and reductive displacement of halides and tosylates.[2] Although in the past decade considerable efforts have been devoted to modify the usual reduction ability of sodium borohydride by the combination of sodium borohydride and metal salts,[3] there is only one report in the literature on the use of sodium cyanoborohydride and metal salts.[4]

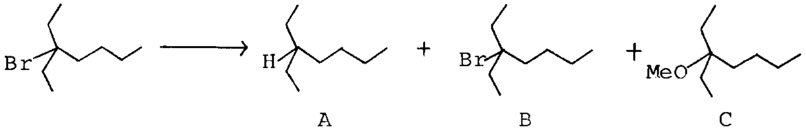
We wish to report an efficient method for the selective reduction of tertiary, allyl, and benzyl halides to the corresponding hydrocarbons without attacking primary alkyl, secondary alkyl, vinyl, and aryl halides by using zinc-modified cyanoborohydride in ether (eq. 2). Zinc-modified cyanoborohydride was prepared by mixing sodium cyanoborohydride and zinc chloride in a 2:1 molar ratio in various solvents such as ether, tetrahydrofuran, dimethoxyethane, and methanol (eq. 1). When the reagent was prepared in ether, a white precipitate appeared. However, the precipitate was a mixture of sodium chloride and the hydroborate species and contained approximately 85% of the reducing power,[5] indicating that the reagent is partially soluble in ether.[6] Unlike rapid decomposition of zinc borohydride in water or alcoholic solvents, the decomposition of the reagent in water was less than 2 mol % at room temperature after 24 h.[7] Thus, the utility of the reagent may be greatly enhanced by its stability in aqueous media.

$$2\ NaBH_3CN + ZnCl_2 \xrightarrow{\qquad} \text{Zn-modified Cyanoborohydride (Reagent I)} \qquad (1)$$

$$RX + \text{Reagent I} \xrightarrow[Et_2O]{} RH \qquad (2)$$

R = tertiary, allyl, benzyl X = I, Br, Cl

Table I. Solvent Effect on the Reduction of Tertiary Alkyl Bromide at Room Temperature in 2 h



Solvent	Product Ratio, %[a] A	B	C
Diethyl Ether	99	<1	
Tetrahydrofuran	47	53	
Dimethoxyethane	15	85	
Methanol	10	35	55

[a] The ratio was determined by GLC analysis.

The nature of solvent was found to be an important factor for the reduction of organic halides as being illustrated in Table I. Among the solvents employed, ether gave the best results and is generally recommended. For instance, 3-bromo-3-ethylheptane was cleanly reduced to the 3-ethylheptane in ether in 2 h, whereas the reduction proceeded rather slowly either in tetrahydrofuran or in dimethoxyethane. Furthermore, the reaction in methanol afforded the solvolysis product as a major product along with a mixture of the reduction product and the unreacted halide. Solvolytic displacement of tertiary halides by zinc oxide has been reported recently.[8] Thus, remaining reductions were carried out in ether by using a 2:2:1 mixture of organic halides, sodium cyanoborohydride, and zinc chloride at room temperature.

The following procedure is representative for the reduction of organic halides. To a stirred solution of freshly dried zinc chloride (137 mg, 1 mmol) in ether (10 ml) at room temperature was added sodium cyanoborohydride (125 mg, 2 mmol). After the reaction mixture was stirred for 20 min, triphenylmethyl bromide (645 mg, 2 mmol) was added. The resulting mixture was stirred for 30 min at room temperature and quenched with saturated $NaHCO_3$. After addition of ether the reaction mixture was washed with water and saturated NaCl, and dried over $MgSO_4$. Triphenylmethane was obtained in 95% yield on solvent removal in vacuo.

Table II summarizes the results obtained in the reduction of various organic halides with zinc-modified cyanoborohydride in ether. Tertiary alkyl (entries 1 and 2) and tertiary aryl (entry 3) halides were cleanly reduced to the corresponding hydrocarbons in excellent yields without elimination products. Allyl halides (entries 4 and 5) were rapidly reduced to the desired alkenes. Secondary benzyl halides (entries 6 and 7) were reduced to the corresponding hydrocarbons within 3 h, while primary benzyl halides (entries 8 and 9) were rather slowly reduced. Zinc-modified cyanoborohydride in ether was inert toward primary alkyl (entries 10 and 11), secondary alkyl (entry 12), vinyl (entry 13), and aryl halides (entry 14).

Table II. Reduction of Halides with Zinc-modified Cyanoborohydride in Diethyl Ether at Room Temperature

Entry	Substrate	Time, h	Product	Yield, %[a]
1	3-Bromo-3-ethylheptane	2.5	3-Ethylheptane	(92)
2	3-Chloro-3-ethylheptane	2.5	3-Ethylheptane	96
3	Triphenylmethyl bromide	0.5	Triphenylmethane	(95)
4	Cinnamyl bromide	0.5	β-Methylstyrene	60
			Allylbenzene	30
5	1-Bromo-2-cyclohexene	0.5	Cyclohexene	90
6	Benzhydryl bromide	0.5	Diphenylmethane	(99)
7	α-Methylbenzyl bromide	3	Ethylbenzene	(91)
8	Benzyl bromide	24	Toluene	74, 17[b]
9	Benzyl chloride	24	Toluene	47, 40[b]
10	n-Nonyl bromide	24	n-Nonane	0[c]
11	n-Nonyl iodide	24	n-Nonane	0[c]
12	Cyclohexyl bromide	24	Cyclohexane	0[c]
13	β-Bromostyrene	24	Styrene	0[c]
14	P-Bromotoluene	24	Toluene	0[c]

[a] The yields were determined by GLC. The isolated yields are indicated in the parentheses. [b] The unreacted halides were detected. [c] The halides were quantitatively recovered.

The results obtained here are in marked contrast with earlier findings that sodium cyanoborohydride in hexamethylphosphoramide reduces effectively primary alkyl and secondary alkyl halides via a S_N2 process, whereas it does not readily reduce tertiary alkyl halides.[9] Furthermore, it seems that the affinity of zinc to the halogen atom and the coordinating ability of etheral solvents for zinc play important roles in the selective reduction of organic halides.

In conclusion, zinc-modified cyanoborohydride in ether should be valuable for selective reduction of tertiary, allyl, and benzyl halides without simultaneous attack of primary alkyl, secondary alkyl, vinyl, and aryl halides in the system and offers advantages of the simplicity, the excellent selectivity, the mildness of the reaction condition, the readily available reagent, and high yields over other hydride reducing agents.[10]

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References and Notes

1. Part of this work was presented at the 185th National Meeting of American Chemical Society, Seattle, WA, March 1983.
2. For an excellent review, see: C. F. Lane, *Synthesis* 135 (1975) and references therein.
3. For recent studies on this subject, see: (a) $NaBH_4/Sn(IV)$: Y. Tsuda, T. Sano, and H. Watanabe, *Synthesis* 652 (1977); S. Kano, Y. Yuasa, and S. Shibuya, *J. C. S. Chem. Commun.*, 796 (1979). (b) $NaBH_4/Ce(III)$; J-L. Luche, *J. Am. Chem. Soc.*, *100*, 2226 (1978); J-L. Luche and A. L. Gemal, *Ibid*, *101*, 5848 (1979). (c) $[(C_6H_5)_3P]_2CuBH_4$; G. W. J. Fleet, C. J. Fuller, and P. J. C. Harding, *Tetrahedron Lett.*, 1437 (1978); T. N. Sorrell and R. J. Spillane, *Ibid*, 2473 (1978); G. W. J. Fleet and P. J. C. Harding, *Ibid*, 975 (1979). (d) $NaBH_4/Ni(0)$; S-T. Lin and J. A. Roth, *J. Org. Chem.*, *44*, 309 (1979). (e) $NaBH_4/CO(II)$; S-K. Chung, *Ibid*, *44*, 1014 (1979). (f) $NaBH_4/Cd(II)/DMF$; I. D. Entwistle, P. Boehm, R. A. W. Jonstone, and R. P. Telford, *J. C. S. Perkin* I, 27 (1980). (g) $NaBH_4/Rh(III)$; M. Nishiki, H. Miyataka, Y. Niino, N. Mitsuo, and T. Satoh, *Tetrahedron Lett.*, 193 (1982).
4. R. O. Hutchins and M. Markowitz, *Tetrahedron Lett.*, 813 (1980).
5. The hydride concentration was determined by iodometric titration.
6. The reagent was soluble in tetrahydrofuran but the amount of precipitated sodium chloride was approximately 40% of the calculated value and we were unable to isolate zinc cyanoborohydride upon numerous attempts. Thus, we designate this reagent as zinc-modified cyanoborohydride rather than zinc cyanoborohydride.
7. The decomposition of the hydride in 0.01N aqueous acetic acid and pure acetic acid at room temperature in 24 h was 9% and 64%, respectively.
8. K. N. Grudutt, B. Rabindranath, and S. Srinivas, *Tetrahedron*, *38*, 1843 (1982).
9. R. O. Hutchins, D. Kandasamy, C. A. Maryanoff, D. Masilamani, and B. E. Maryanoff, *J. Org. Chem.*, *42*, 82 (1977).
10. For selective reduction of tertiary, allyl, and benzyl halides, see: H. Toi, Y. Yamamoto, A. Sonoda, and S-I, Murahashi, *Tetrahedron*, *37*, 2261 (1981) and references therein.

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