Sodium Cyanoborohydride in Hexamethylphosphoramide. An Exceptionally Selective Reagent System for the Reduction of Alkyl Iodides, Bromides, and Tosylates

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Summary Sodium cyanoborohydride in hexamethylphosphoramide provides a rapid, convenient and exceedingly selective system for the reductive removal of iodo-bromo-, tosyloxy- and, indirectly, hydroxy-groups.

IN the important area of selective reductions,[1] we report the use of sodium cyanoborohydride in hexamethylphosphoramide (HMPA) as a high-yield, convenient, and remarkably selective system for the reductive removal of primary and secondary iodo- and bromo-groups and of primary tosylates in the presence of practically all other functional groups including such sensitive moieties as epoxides, ketones, and aldehydes.

In the course of another study,[2] we investigated the fate of 1-iodododecane in a sulpholane–dimethylformamide mixture containing $NaBH_3CN$. Surprisingly, a fair amount (60–80%) of n-dodecane was produced, which suggested that cyanoborohydride anion, normally a very mild reducing agent,[3] could serve as a source of nucleophilic hydride for displacements in polar aprotic solvents. Indeed, by merely switching to HMPA as solvent[4] and employing a four-fold molar excess of $NaBH_3CN$, an excellent yield of dodecane (>90%) was obtained at 50° in 1 h. In order to establish optimal conditions, the reduction rates for several representative halides were followed; the results are plotted in the Figure. The rate plots illustrate that primary iodo-groups are removed readily and selectively at 25° (90% in 3 h) while primary bromides, tosylates, and secondary iodides require a higher temperature (70°) to obtain adequate yields in reasonably short times.† These results are best accommodated by an S_N2 process involving direct attack by hydride or cyanoborohydride anion. The following general experimental procedure was developed, and the results are presented in Table 1. The substrate (1 mmol)

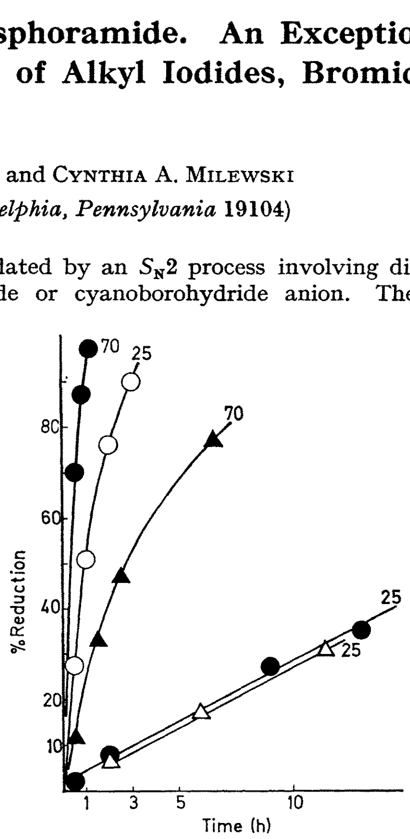

FIGURE. *Reduction of alkyl halides and tosylates with sodium cyanoborohydride in hexamethylphosphoramide. All reaction mixtures were* 0·2 M *in the compound,* 0·8 M *in* $NaBH_3CN$. *The reaction temperature for each compound is indicated on each plot. The % reductions were determined by g.l.c.* ● *1-bromododecane*; ○ *1-iodododecane*; ▲ *1-dodecyl tosylate*; △ *2-iodo-octane.*

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† Primary chlorides were sluggish even at 100° (see Table 1) allowing iodo-, bromo- and tosyloxy-groups to be removed in their presence.

TABLE 1

Selective reduction of alkyl halides and tosylates to hydrocarbons with sodium cyanoborohydride in hexamethylphosphoramide

Entry	Compound[a]	Temp	Time (h)	% Reduction[b] (recovered compd)
1	$CH_3[CH_2]_{11}I$	25°	3 5	91
2		50°	1 0	96
3	$CH_3[CH_2]_{11}Br$	70°	1 1	97
4	$CH_3[CH_2]_{11}OTs$	70°	6 5	78
5	$CH_3[CH_2]_{11}Cl$	25°	92	<2 (>98)
6		100	27	72 (12)
7	$CH_3[CH_2]_9CHBr\ CH_3$	70°	24	97
8	$CH_3[CH_2]_5CHI\ CH_3$	70°	2 0	91
9	$CH_3[CH_2]_3CHBr{\cdot}CO_2Et$	70°	3 0	90
10	Cinnamyl bromide	70°	0 5	76
11	*p*-Nitrobenzyl bromide	70°	1 5	59[c], 85[c d]
12	3-Bromo-1,2-epoxy-1-phenyl-propane	70°	12[e]	63[d]
13	$Br[CH_2]_6CN$	100°	3 0	85[d]
14	3β-(3-Iodopropionoxy)-pregn-5-en-20-one	70°	1 0	89[c,d]
15	Benzophenone	70°	5 0	(92)[d]
16	Undecan-6-one	70°	5 0	(99)[d]
17	$CH_3[CH_2]_{10}CON(C_2H_5)_2$	70°	24	(95)[d]
18	$CH_3[CH_2]_9CHO$	70°	1 0	(91)[d]
19		70°	2 0	(81)[d]

[a] Reaction solutions were 0 2 M in compound, 0·8 M in $NaBH_3CN$ [b] Unless specified otherwise, yields were determined by g l c [c] Isolated yield (purified) [d] Purified $NaBH_3CN$ used [e] Reduction slowed by inductive and steric effects, product was 2% reduced in 4 h when subjected to the reaction conditions, cyclohexene oxide was 19% reduced in 4 h at 70°

was dissolved in HMPA (5 ml), $NaBH_3CN$[5] was added, and the solution stirred at the appropriate temperature (Table 1) When reaction was complete,‡ the mixtures were worked-up by diluting with water or saturated brine, extracting with cyclohexane or ether, and washing the extract with water or brine

Yields of reduction products are generally high (63—97%) in reasonable durations In most cases the reactions are clean with no major side products detected by g l c or n m r § The superior selectivity possible with the reagent system is demonstrated by its inertness toward almost all other functional groups including ester (entry 9), amide (entry 17), nitro (entry 11), chloro (entries 5 and 6), cyano (entry 13), alkene (entries 10 and 14), and even such normally sensitive groups as epoxides (entry 12), ketones (entries 14—16), and, to a lesser extent, aldehydes (entries 18 and 19)

We observed that primary alcohols may be converted directly by a simple two-step-in-one process into the corresponding hydrocarbons The procedure involves conversion of the alcohol (1 mmol) into the iodide with methyltriphenoxyphosphonium iodide[6] (2 mmol) in HMPA (5 ml) at ambient temperature followed by addition of $NaBH_3CN$ (4 mmol), and stirring at 70° for the durations listed in Table 2 Alternatively, the inertness of $NaBH_3CN$ toward methyltriphenoxyphosphonium iodide enables both steps to be combined with no loss in yield (entry 2, Table 2) Noteworthy is the conversion of a neopentyl alcohol into the hydrocarbon in respectable yield (entry 5) considering that the reaction involves two steps[7]

TABLE 2

Direct conversion of alcohols into hydrocarbons with methyltriphenoxyphosphonium iodide and sodium cyanoborohydride

Entry	Alcohol	Time[a] methiodide react (h)	Time[b] reduction (h)	% Yield[c]
1	$CH_3[CH_2]_9OH$	0 5[d]	1 0[e]	100
2		1 5[f]		99
3	Cinnamyl alcohol	0·5[d]	2·0[e]	68
4	$HO[CH_2]_6CN$.	0 5[d]	1 0[e]	66
5	4-Hydroxymethyl-4-methylcyclohexene	3 0[e]	8·0[g]	58

[a] Solutions 0 2 M in alcohol, 0 4 M in methiodide [b] Final solutions 0 8 M in $NaBH_3CN$. [c] Yields determined by g l c [d] At 25° [e] At 70° [f] Solution 0 2 M in alcohol, 0 4 M in the iodide, and 0 8 M in $NaBH_3CN$ at 70° [g] At 100°, sealed tube, 1 2 M in $NaBH_3CN$

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‡ The reductions were conveniently monitored by g l c using internal standards and detector response factors

§ Exceptions noted were the reduction of styrene dibromide to give 13% styrene in addition to an 80% yield of ethylbenzene at 70° and aldehydes which are slowly reduced to alcohols at 70° Also, α-bromo-ketones give substantial amounts of alcohols (20—30% by n m r) even at 25°

[1] H C Brown, "Hydroboration", ch 17, Benjamin, New York, 1962, and references cited therein See also M N Rerick in "Reduction", ed R L Augustine, Marcel Dekker, New York, 1968, ch 1

[2] R O Hutchins, B E Maryanoff, and C A Milewski, *J Amer Chem Soc* , 1971, **93**, 1793.

[3] See ref 2, and R F Borch and H Durst, *J Amer Chem Soc* , 1969, **91**, 3996, R F Borch, M Bernstein, and H Durst *ibid* , 1971, **93**, 2897

[4] H Normant, *Angew Chem Internat Edn* , 1967, **6**, 1046, *Russian Chem Rev* , 1970, **39**, 457 Other polar aprotic solvents including dimethyl sulphoxide were also successful, but the yields were slightly lower

[5] For the reduction of regular alkyl halides, commercial $NaBH_3CN$ from Alfa Inorganics, Beverly, Mass , was satisfactory as received However, when other sensitive groups are present it is advisable to purify the material according to the procedure given by R C Wade, E Sullivan, J Bershied, jun , and K Purcell, *Inorg. Chem* , 1970, **9**, 2146, otherwise somewhat lower yields were obtained (see entry 11, Table 1), presumably because of the presence of some residual $NaBH_4$

[6] S R Landor and H N Rydon, *J. Chem Soc* , 1953, 2224, purification of crude methyltriphenoxyphosphonium iodide is best accomplished as described by J Verheyden and J Moffat, *J Org Chem* , 1970, **35**, 2319

[7] Reductions of neopentyl sulphonates or halides are often unreliable, see for example, J A Marshall and R A Ruden, *J Org Chem* , **1971**, **36**, 594, T. M. Warne, jun , Ph D Thesis, Northwestern University, 1969