Selective Reductive Displacement of Alkyl Halides and Sulfonate Esters with Cyanoborohydride Reagents in Hexamethylphosphoramide

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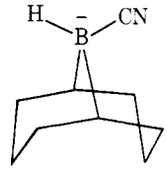
Received July 19, 1976

The combination of sodium or tetrabutylammonium cyanoborohydride, sodium or potassium 9-cyano-9-hydrido-9-borabicyclo[3.3.1]nonane (9-BBNCN), or polymeric cyanoborane in hexamethylphosphoramide furnishes a convenient, efficient, and mild system for the reduction of alkyl halides and sulfonate esters. The reagents are exceptionally selective in that most other functional groups including ester, carboxylic acid, amido, cyano, alkene, nitro, sulfone, ketone, aldehyde, and epoxide are essentially inert under the reaction conditions and thus the reductive procedure is attractive for synthetic schemes where minimum damage to other sensitive portions of the molecule is demanded. The displacement by hydride occurs predominantly with inversion of configuration and, in general, the leaving ability pattern follows the order I > Br ≈ SO_2R > Cl ≫ F, as expected for an S_N2 process. The method is less successful for vinylic, aromatic, and certain tertiary halides.

The reductive removal of organic halides and sulfonate esters is utilized extensively in organic synthesis as an effective tactic for the introduction of methyl and methylene groups. Consequently, considerable effort has been devoted to the development of techniques capable of such transformations.[1,2] Of the successful methods, the most useful generally employ a metal hydride to furnish a hydride anion as a displacement nucleophile. Often, however, such reductions are met with problems which arise because many hydride reagents, such as lithium aluminum hydride, which are powerful enough to displace leaving groups also molest other functionalities or act concomitantly as strong bases. This severely limits the usefulness of such reagents to those molecules devoid of other sensitive moieties and restricts the approaches to synthetic targets.

One relatively recent approach toward tempering the destructiveness of hydride reagents has involved the replacement of a hydrogen on borohydride with a cyanide substituent. This strongly electron-withdrawing group increases the Lewis acidity of the corresponding cyanoborane and thus the cyanoborohydride anion is more reluctant to deliver a hydride. The result is a greatly moderated reducing capability (and an increased stability) which allows a substantially more discriminate selection among functional groups.[3] Furthermore, cyanoborohydride is remarkably stable (among hydrides) toward water and acid (to pH ca. 2–3)[4] and the reducing capabilities of the reagent are exceptionally pH dependent. For instance, at pH >6 the reduction of aldehydes and ketones, normally very sensitive moieties, is essentially negligible.[5] In fact, the only groups which are reduced in neutral media appear to be imminium ions and alkyl halides and sulfonates, these latter only in polar aprotic solvents.[1] Evidently in such S_N2 enhancing media, cyanoborohydride serves very adequately as a source of nucleophilic hydride ion for displacement reactions, but not for attack on unactivated carbonyls and other functional groups. This suggested that exceptionally selective displacements of halides and other good leaving groups with hydrogen might be attainable using cyanoborohydride in hexamethylphosphoramide (HMPA), apparently the most potent polar aprotic solvent available for accelerating S_N2 reactions.[6]

Preliminary investigations revealed that, indeed, such conversions were facile with either sodium or tetrabutylammonium cyanoborohydride[1] and the selectivity, convenience, and gentleness displayed highly recommended the reagents for synthetic applications. This prompted a more thorough and systematic study of the scope and utility of the reagents and, in addition, with two other modified cyanoborohydride derivatives, 9-cyano-9-hydrido-9-borabicyclo[3.3.1]nonane (9-BBNCN$^-$) (1) and polymeric cyanoborane (2). This selection of reagents allowed a range of reduction possibilities to be explored. Thus, tetrabutylammonium cyanoborohydride functions as a phase-transfer reagent[1b,7] which permits reductions in nonpolar solvents. The use of 9-BBNCN$^-$ allows the effect of alkyl groups to be tested while polymeric cyanoborane 2 may conceivably be viewed as a cyanoborohydride ylide which can serve as a source of nucleophilic hydride. The presence of the positive nitrogen attached to boron should render the corresponding boron considerably more electron deficient and consequently further lower the hydride donating (and reducing) ability of the anion compared to cyanoborohydride.



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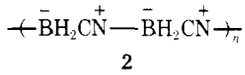

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This article incorporates systematic investigations of the various cyanoborohydride reagents for displacements with particular emphasis given to uncovering the functional group selectivity possible with each. The results are tabulated systematically in Table I. For convenience, these are grouped according to structural types and leaving group and considered separately below.

Results and Discussion

Reagents Sodium cyanoborohydride is available commercially and is satisfactory as obtained.[8] Tetrabutylammonium cyanoborohydride (TBAC) was prepared and purified as previously described.[1a,9] Sodium and potassium 9-borabicyclo[3.3.1]nonane cyanoborohydride (Na and K-9-BBNCN) were secured by the reaction of sodium or potassium cyanide with 9-BBN in THF.[10] Polymeric cyanoborane was prepared as described by Spielvogel[11] from $NaBH_3CN$ and HCl or from Bu_4NBH_3CN and methyl iodide in methylene chloride.[12]

Reductions of Alkyl Monohalides and Sulfonate Esters. Our initial investigation stemmed from the observation that 1-iodododecane suffered considerable reduction to *n*-dodecane (60–80%) when subjected to $NaBH_3CN$ in a sulfolane–dimethylformamide mixture. Considerable experimentation established that hexamethylphosphoramide[6] (HMPA), an exceptional medium for enhancing displacement reactions, provided the most effective solvent[14] and that a 4:1 ratio of

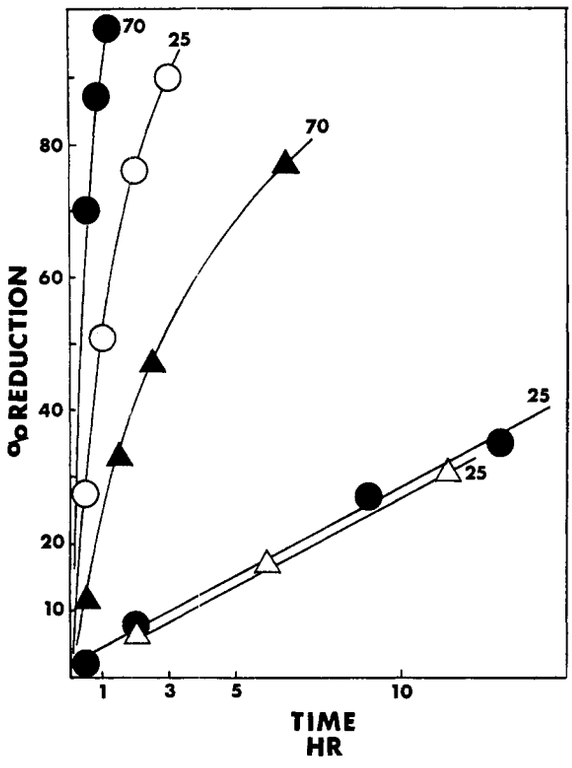


Figure 1. Reduction of alkyl halides and tosylates with sodium cyanoborohydride in hexamethylphosphoramide. All reactions were 0.2 M in the compound, 0.8 M in $NaBH_3CN$. The reaction temperature for each compound is indicated on each plot. The percent reductions were determined by GLC analysis using internal standards and detector response factors: ●, 1-bromododecane; ○, 1-iodododecane; ▲, 1-dodecyl tosylate; △, 2-iodooctane.

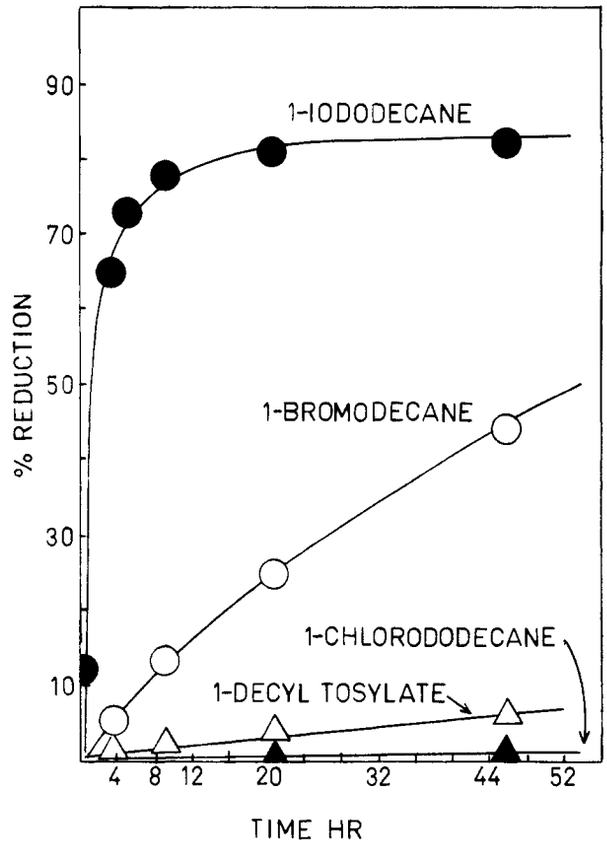


Figure 2. Reduction of primary halides and tosylate with TBAC in HMPA at 25 °C. All solutions were 0.2 M in the compound, 0.8 M in TBAC. The percent reductions were determined by GLC using internal standards.

cyanoborohydride:substrate furnished the most consistently high yields in reasonably short reaction times. In order to establish optimal conditions, the reduction rates for a collection of representative halides were followed with $NaBH_3CN$, Bu_4NBH_3CN, and polymeric cyanoborane; the results are presented in Figures 1–3. Although the rates varied considerably, all demonstrated the same relative patterns for the halides and tosylate leaving groups. Thus, with $NaBH_3CN$ (Figure 1) primary iodo groups are removed readily at 25 °C (90% in 3 h). In fact, at this temperature, the relatively slow reduction of primary bromo, tosyloxy, chloro (i.e., at 25 °C less than 2% reduction of 1-chlorododecane in 92 h), and secondary iodo (all <10% in 3 h) suggests that primary iodo can be selectively displaced in their presence. At higher temperatures (>70 °C) adequate yields of hydrocarbons are obtained from these latter derivatives, except chloro (Table I). Similar results were obtained for Bu_4NBH_3CN and polymeric cyanoborane except that the former (Figure 2) displayed slightly slower rates while the latter (Figure 3) required substantially more vigorous conditions (105 °C) to effect reduction and considerably longer reaction times. With these initial observations, a convenient and simple general experimental procedure was devised. The compound and the cyanoborohydride were dissolved in HMPA (or other solvents with Bu_4NBH_3CN or 9-BBNCN anions; see Table I) so that the concentrations were 0.2 M in the substrate and 0.8 M in cyanoborohydride for analytical reactions or two to three times these concentrations for preparative scale reactions. The solutions were then stirred at the appropriate temperatures for the durations listed in Table I. Upon completion, the mixtures were diluted with water or saturated brine and isolated, generally from cyclohexane or ether. This procedure was followed throughout the investigation except where otherwise noted; in fact, the only

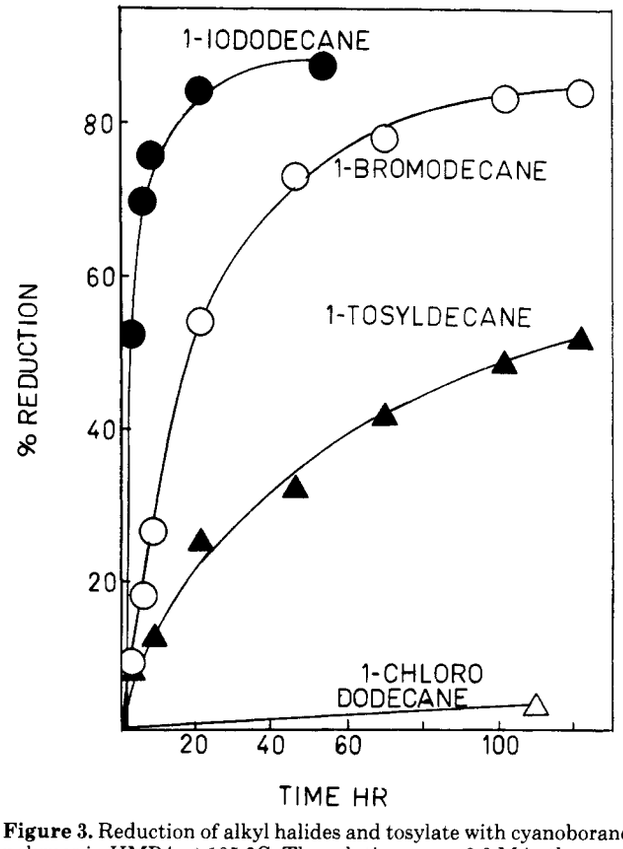


Figure 3. Reduction of alkyl halides and tosylate with cyanoborane polymer in HMPA at 105 °C. The solutions were 0.2 M in the compound and 0.8 M in cyanoborane polymer. The percent reductions were determined by GLC using internal standards and are corrected for detector response.

Table I. Reduction of Halides and Sulfonate Esters with Cyanoborohydrides

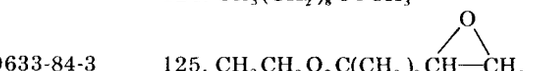
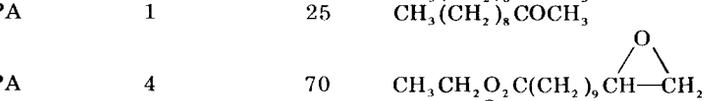
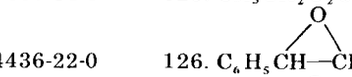
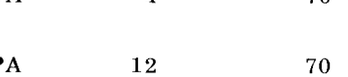
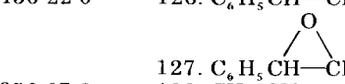
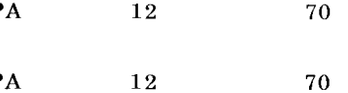
Registry no.	Entry, compd	Reducing agent (mol ratio) (mol redn agent)/ (mol compd)	Solvent[a]	Time, h	Temp, °C	Product	% yield[b] (isolated)
4292-19-7	1. $CH_3(CH_2)_{11}I$	$NaBH_3CN$ (4)	HMPA	0.35	100	$CH_3(CH_2)_{10}CH_3$	100
	2. $CH_3(CH_2)_{11}I$	$NaBH_3CN$ (4)	HMPA	1	50	$CH_3(CH_2)_{10}CH_3$	96
	3. $CH_3(CH_2)_{11}I$	$NaBH_3CN$ (4)	HMPA	3.5	25	$CH_3(CH_2)_{10}CH_3$	91
	4. $CH_3(CH_2)_{11}I$	$NaBH_3CN$ (4)	DMSO	2	100	$CH_3(CH_2)_{10}CH_3$	74
2050-77-3	5. $CH_3(CH_2)_9I$	$NaBH_3CN$ (1.5)	HMPA	2	70	$CH_3(CH_2)_8CH_3$	(88–90)
	6. $CH_3(CH_2)_9I$	TBAC (4)	HMPA	21	25	$CH_3(CH_2)_8CH_3$	81
	7. $CH_3(CH_2)_9I$	TBAC (4)	C_6H_6	7	80	$CH_3(CH_2)_8CH_3$	81
	8. $CH_3(CH_2)_9I$	Na 9-BBNCN (4)	HMPA	1	25	$CH_3(CH_2)_8CH_3$	92
60633-77-4	9. 3β-(3-Iodopropionoxy)pregn-5-en-20-one	$NaBH_3CN$ (4)	HMPA	1	70	3β-Propionoxypregn-5-en-20-one	(89)
60828-67-3	10. **9**	$NaBH_3CN$ (4.6)	HMPA	8	70	**10**	(77)[c]
	11. $CH_3(CH_2)_9I$	Na 9-BBNCN (4)	THF	2	25	$CH_3(CH_2)_8CH_3$	94
	12. $CH_3(CH_2)_9I$	Na 9-BBNCN (4)	HMPA	1	25	$CH_3(CH_2)_8CH_3$	89
	13. $CH_3(CH_2)_9I$	$(BH_2CN)_n$ (4)	HMPA	26	105	$CH_3(CH_2)_8CH_3$	83
143-15-7	14. $CH_3(CH_2)_{11}Br$	$NaBH_3CN$ (4)	HMPA	1.1	70	$CH_3(CH_2)_{10}CH_3$	97
112-29-8	15. $CH_3(CH_2)_9Br$	TBAC (4)	HMPA	137	25	$CH_3(CH_2)_8CH_3$	69
						$CH_3(CH_2)_9Br$	10
	16. $CH_3(CH_2)_9Br$	TBAC (4)	C_6H_6	24	80	$CH_3(CH_2)_8CH_3$	89
112-82-3	17. $CH_3(CH_2)_{15}Br$	Na 9-BBNCN (4)	HMPA	1.5	70	$CH_3(CH_2)_{14}CH_3$	95
	18. $CH_3(CH_2)_9Br$	$(BH_2CN)_n$ (4)	HMPA	70	105	$CH_3(CH_2)_8CH_3$	78
60633-78-5	19. *o*-(2-Bromoethoxy)-benzaldehyde	$NaBH_3CN$ (2)	HMPA	4	70	*o*-Ethoxybenzaldehyde	(56)
60633-79-6	20. **11**	$NaBH_3CN$ (4)	HMPA	12[d]	70	**12**	63
60633-80-9	21. $CH_3CO(CH_2)_3CO_2(CH_2)_3Br$	$NaBH_3CN$ (4)	HMPA	4	70	$CH_3CO(CH_2)_3CO_2(CH_2)_2CH_3$	63
2834-05-1	22. $HO_2C(CH_2)_{10}Br$	$NaBH_3CN$ (3)	HMPA	24	70	$CH_3(CH_2)_9COOH$	(96)[e]
20965-27-9	23. $NC(CH_2)_6Br$	$NaBH_3CN$ (4)	HMPA	3	100	$CH_3(CH_2)_5CN$	85
14660-52-7	24. $C_2H_5O_2C(CH_2)_4Br$	$NaBH_3CN$ (4)	HMPA	25	70	$CH_3(CH_2)_3CO_2C_2H_5$	88
	25. $C_2H_5O_2C(CH_2)_4Br$	TBAC (4)	HMPA	3	70	$CH_3(CH_2)_3CO_2C_2H_5$	78
	26. $C_2H_5O_2C(CH_2)_4Br$	Na 9-BBNCN (4)	HMPA	1	70	$CH_3(CH_2)_3CO_2C_2H_5$	92
112-52-7	27. $CH_3(CH_2)_{11}Cl$	$NaBH_3CN$ (4)	HMPA	92	25	$CH_3(CH_2)_{10}CH_3$	2
						$CH_3(CH_2)_{11}Cl$	98
	28. $CH_3(CH_2)_{11}Cl$	$NaBH_3CN$ (4)	HMPA	27	100	$CH_3(CH_2)_{10}CH_3$	72
						$CH_3(CH_2)_{11}Cl$	12
	29. $CH_3(CH_2)_{11}Cl$	TBAC (4)	HMPA	137	25	$CH_3(CH_2)_{10}Cl$	99
						$CH_3(CH_2)_{10}CH_3$	0
1002-69-3	30. $CH_3(CH_2)_9Cl$	Na 9-BBNCN (4)	HMPA	96	25	$CH_3(CH_2)_9Cl$	78
						$CH_3(CH_2)_8CH_3$	10
	31. $CH_3(CH_2)_9Cl$	$(BH_2CN)_n$ (4)	HMPA	39	105	$CH_3(CH_2)_9Cl$	91
						$CH_3(CH_2)_8CH_3$	0
7205-98-3	32. $C_6H_5SO_2CH_2Cl$	$NaBH_3CN$ (2)	HMPA	7	100	$C_6H_5SO_2CH_3$	0
						$C_6H_5SO_2CH_2Cl$	73
	33. $C_6H_5SO_2CH_2Cl$	$NaBH_3CN$ (4)	HMPA	24	150	$C_6H_5SO_2CH_3$	0
334-56-5	34. $CH_3(CH_2)_9F$	$NaBH_3CN$ (4)	HMPA	120	70	$CH_3(CH_2)_8CH_3$	0
39686-83-4	35. **13**	$NaBH_3CN$ (8)	HMPA	48	110	**14**	(44)
10157-76-3	36. $CH_3(CH_2)_{11}OTs$	$NaBH_3CN$ (4)	HMPA	6.5	70	$CH_3(CH_2)_{10}CH_3$	78
	37. $CH_3(CH_2)_{11}OTs$	$NaBH_3CN$ (4)	HMPA	12	80	$CH_3(CH_2)_{10}CH_3$	(73–78)
	38. $CH_3(CH_2)_{11}OTs$	$NaBH_3CN$ (1.5)	HMPA	8	70	$CH_3(CH_2)_{10}CH_3$	(52)

5509-08-0	39. $CH_3(CH_2)_9OTs$	TBAC (4)	C_6H_6	24	80	$CH_3(CH_2)_8CH_3$	74
	40. $CH_3(CH_2)_9OTs$	Na 9-BBNCN (4)	HMPA	9	25	$CH_3(CH_2)_8CH_3$	11
	41. $CH_3(CH_2)_9OTs$	Na 9-BBNCN (4)	THF	21	25	$CH_3(CH_2)_8CH_3$	39
	42. $CH_3(CH_2)_9OTs$	$-(BH_2CN)-_n$ (4)	HMPA	102	105	$CH_3(CH_2)_8CH_3$	49
			Allylic Halides				
4392-24-9	43. $C_6H_5CH{=}CHCH_2Br$	$NaBH_3CN$ (4)	HMPA	0.5	70	$C_6H_5CH{=}CHCH_3$	76
	44. $C_6H_5CH{=}CHCH_2Br$	$NaBH_3CN$ (4)	HMPA	2.5	25	$C_6H_5CH{=}CHCH_3$	64
	45. $C_6H_5CH{=}CHCH_2Br$	TBAC (4)	HMPA	1.5	70	$C_6H_5CH{=}CHCH_3$	62
	46. $C_6H_5CH{=}CHCH_2Br$	TBAC (4)	HMPA	3	25	$C_6H_5CH{=}CHCH_3$	64
	47. $C_6H_5CH{=}CHCH_2Br$	Na 9-BBNCN (4)	HMPA	0.5	25	$C_6H_5CH{=}CHCH_3$	80
2687-12-9	48. $C_6H_5CH{=}CHCH_2Cl$	$NaBH_3CN$ (4)	HMPA	4	70	$C_6H_5CH{=}CHCH_3$	62
	49. $C_6H_5CH{=}CHCH_2Cl$	TBAC (4)	HMPA	9	70	$C_6H_5CH{=}CHCH_3$	46
	50. $C_6H_5CH{=}CHCH_2Cl$	Na 9-BBNCN (4)	HMPA	2	70	$C_6H_5CH{=}CHCH_3$	72
60633-81-0	51. *E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_2Cl$	$NaBH_3CN$ (4)	HMPA	17	70	*E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_3$	57
	52. *E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_2Cl$	TBAC (4)	HMPA	17	70	*E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_3$	62
	53. *E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_2Cl$	Na 9-BBNCN (4)	HMPA	1.8	70	*E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_3$	92
	54. *E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_2Cl$	$NaBH_3CN$ (4)	HMPA	23	70	*E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_3$	48
	55. *E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_2Cl$	TBAC (4)	HMPA	23	70	*E*-$CH_3(CH_2)_2CH{=}C(C_2H_5)$-$CH_3$	24
3360-52-9	56. 2-Phenyl-3-chloropropene	TBAC (8)	80% aq HMPA	17	70	2-Phenylpropene	55
	57. 2-Phenyl-3-chloropropene	Na 9-BBNCN (4)	HMPA	1	70	2-Phenylpropene	75
3355-31-5	58. $C_6H_5C{\equiv}C{-}CH_2Cl$	$NaBH_3CN$ (4)	HMPA	8	70	$C_6H_5C{\equiv}C{-}CH_3$	34
	59. $C_6H_5C{\equiv}C{-}CH_2Cl$	Na 9-BBNCN (4)	HMPA	1	70	$C_6H_5C{\equiv}C{-}CH_3$	60
			Benzyl Halides				
100-11-8	60. *p*-$NO_2C_6H_4CH_2Br$	$NaBH_3CN$ (4)	HMPA	15	70	*p*-$NO_2C_6H_4CH_3$	(85)
	61. *p*-$NO_2C_6H_4CH_2Br$	TBAC (4)	HMPA	4	70	*p*-$NO_2C_6H_4CH_3$	62
	62. *p*-$NO_2C_6H_4CH_2Br$	Na 9-BBNCN (4)	HMPA	5	25	*p*-$NO_2C_6H_4CH_3$	56
2014-83-7	63. 2,6-di$ClC_6H_3CH_2Cl$	$NaBH_3CN$ (4)	HMPA	17	70	2,6-di$ClC_6H_3CH_3$	94
	64. 2,6-di$ClC_6H_3CH_2Cl$	TBAC (4)	HMPA	17	70	2,6-di$ClC_6H_3CH_3$	91
	65. 2,6-di$ClC_6H_3CH_2Cl$	Na 9-BBNCN (4)	HMPA	1.25	70	2,6-di$ClC_6H_3CH_3$	84
			Secondary Halides				
557-36-8	66. $CH_3(CH_2)_5CHICH_3$	$NaBH_3CN$ (4)	HMPA	2	70	$CH_3(CH_2)_6CH_3$	91
	67. $CH_3(CH_2)_5CHICH_3$	TBAC (4)	HMPA	2.5	70	$CH_3(CH_2)_6CH_3$	85
	68. $CH_3(CH_2)_5CHICH_3$	K 9-BBNCN (4)	HMPA	1	70	$CH_3(CH_2)_6CH_3$	85
60686-40-0	69. 3-Cholesteryl iodide	$NaBH_3CN$ (4)	HMPA	5	70	2,5- and 3,5-cholestadiene	(95)
13187-99-0	70. $CH_3(CH_2)_9CHBrCH_3$	$NaBH_3CN$ (4)	HMPA	24	70	$CH_3(CH_2)_{10}CH_3$	97
	71. $CH_3(CH_2)_9CHBrCH_3$	TBAC (4)	HMPA	36	70	$CH_3(CH_2)_{10}CH_3$	83
	72. $CH_3(CH_2)_9CHBrCH_3$	Na 9-BBNCN (4)	HMPA	18	70	$CH_3(CH_2)_{10}CH_3$	68
615-96-3	73. $CH_3(CH_2)_3CHBrCO_2C_2H_5$	$NaBH_3CN$ (4)	HMPA	3	70	$CH_3(CH_2)_4CO_2C_2H_5$	90
	74. $CH_3(CH_2)_3CHBrCO_2C_2H_5$	TBAC (4)	HMPA	4	70	$CH_3(CH_2)_4CO_2C_2H_5$	86
	75. $CH_3(CH_2)_3CHBrCO_2C_2H_5$	Na 9-BBNCN (4)	HMPA	0.5	70	$CH_3(CH_2)_4CO_2C_2H_5$	86
60633-82-1	76. $CH_3(CH_2)_{10}CHBrCO_2C_2H_5$	$NaBH_3CN$ (4)	HMPA	3	70	$CH_3(CH_2)_{11}CO_2C_2H_5$	(50)
14980-93-9	77. $CH_3(CH_2)_{15}CHBrCOOH$	$NaBH_3CN$ (3)	HMPA	20	70	$CH_3(CH_2)_{16}COOH$	(97)
2534-77-2	78. *exo*-2-Norbornyl bromide	$NaBH_3CN$ (4)	HMPA	15	150	Norbornane	67

Continued

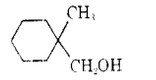
Table I (*Continued*)

Registry no.	Entry, compd	Reducing agent (mol ratio) (mol redn agent)/ (mol compd)	Solvent[a]	Time, h	Temp, °C	Product	% yield[b] (isolated)
		Secondary Benzyl Halides and Sulfonate Esters					
585-71-7	79. $C_6H_5CHBrCH_3$	$NaBH_3CN$ (4)	HMPA	6	70	$C_6H_5CH_2CH_3$	78
	80. $C_6H_5CHBrCH_3$	TBAC (4)	HMPA	5.25	70	$C_6H_5CH_2CH_3$	78
	81. $C_6H_5CHBrCH_3$	Na 9-BBNCN (4)	HMPA	1	70	$C_6H_5CH_2CH_3$	70
672-65-1	82. $C_6H_5CHClCH_3$	$NaBH_3CN$ (4)	HMPA	8	100	$C_6H_5CH_2CH_3$	26
	83. $C_6H_5CHClCH_3$	Na 9-BBNCN (4)	HMPA	57	70	$C_6H_5CH_2CH_3$	51
						$C_6H_5CHClCH_3$	35
776-74-9	84. $(C_6H_5)_2CHBr$	$NaBH_3CN$ (4)	HMPA	3	70	$(C_6H_5)_2CH_2$	91
	85. $(C_6H_5)_2CHBr$	TBAC (4)	HMPA	6	70	$(C_6H_5)_2CH_2$	70
	86. $(C_6H_5)_2CHBr$	Na 9-BBNCN (4)	HMPA	2	70	$(C_6H_5)_2CH_2$	61
90-99-3	87. $(C_6H_5)_2CHCl$	$NaBH_3CN$ (4)	HMPA	45	70	$(C_6H_5)_2CH_2$	30
	88. $(C_6H_5)_2CHCl$	TBAC (4)	HMPA	45	70	$(C_6H_5)_2CH_2$	12
						$(C_6H_5)_2CHCl$	65
60633-83-2	89. (+)-$C_6H_5CH(OMs)CO_2CH_3$	$NaBD_3CN$ (2.2)	HMPA	4	110	(−)-$C_6H_5CHDCO_2CH_3$	(64)[f]
60686-41-1	90. (±)-$C_6H_5CH(OMs)CO_2CH_3$	$NaBH_3CN$ (3)	HMPA	3.5	115	$C_6H_5CH_2CO_2CH_3$	(72)
		Tertiary Halides					
596-43-0	91. $(C_6H_5)_3CBr$	$NaBH_3CN$ (4)	HMPA	2	70	$(C_6H_5)_3CH$	88
	92. $(C_6H_5)_3CBr$	TBAC (4)	HMPA	2	70	$(C_6H_5)_3CH$	87
	93. $(C_6H_5)_3CBr$	Na 9-BBNCN (4)	HMPA	2	70	$(C_6H_5)_3CH$	87
76-83-5	94. $(C_6H_5)_3CCl$	$NaBH_3CN$ (4)	HMPA	4	70	$(C_6H_5)_3CH$	94
	95. $(C_6H_5)_3CCl$	TBAC (4)	HMPA	2	70	$(C_6H_5)_3CH$	88
	96. $(C_6H_5)_3CCl$	Na 9-BBNCN (4)	HMPA	2	70	$(C_6H_5)_3CH$	85
768-90-1	97. 1-Bromoadamantane	$NaBH_3CN$ (8)[g]	HMPA	77	150	Adamantane	36
		Vicinal and Geminal Dihalides					
93-52-7	98. $C_6H_5CHBrCH_2Br$	$NaBH_3CN$ (4)	HMPA	20	70	$C_6H_5CH_2CH_3$	77
						$C_6H_5CH{=}CH_2$	11
	99. $C_6H_5CHBrCH_2Br$	TBAC (4)	HMPA	47	70	$C_6H_5CH_2CH_3$	40
						$C_6H_5CH{=}CH_2$	25
						$C_6H_5CHBrCH_2Br$	20
	100. $C_6H_5CHBrCH_2Br$	Na 9-BBNCN (4)	HMPA	12	70	$C_6H_5CH_2CH_3$	16
						$C_6H_5CH{=}CH_2$	30
						$C_6H_5C(Br){=}CH_2$	31
6269-92-7	101. $CH_3(CH_2)_5CHBrCH_2Br$	$NaBH_3CN$ (4)	HMPA	37	70	$CH_3(CH_2)_6CH_3$	72
						$CH_3(CH_2)_5CHBrCH_3$	7
						$CH_3(CH_2)_5CHBrCH_2Br$	13
	102. $CH_3(CH_2)_5CHBrCH_2Br$	TBAC (4)	HMPA	24	70	$CH_3(CH_2)_6CH_3$	26
						$CH_3(CH_2)_5CHBrCH_3$	18
						$CH_3(CH_2)_5CHBrCH_2Br$	50
	103. $CH_3(CH_2)_5CHBrCH_2Br$	Na 9-BBNCN (4)	HMPA	12	70	$CH_3(CH_2)_8CH_3$	58
						$CH_3(CH_2)_5CH{=}CH_2$	24
2415-79-4	104. **3**	$NaBH_3CN$ (4)	HMPA	18	100	**5**	21
						4	77

31236-94-9	105. 2-Bromocyclododecanone	$NaBH_3CN$ (1.5)	HMPA	1.5	70	Cyclododecanone	(56)
	106. 2-Bromocyclododecanone	$NaBH_3CN$ (1.0)	HMPA	1.5	70	Cyclododecanone	(64)
103-64-0	107. $C_6H_5CH{=}CHBr$	$NaBH_3CN$ (4)	HMPA	40	70	$C_6H_5CH{=}CH_2$	0
						$C_6H_5CH{=}CHBr$	94
	108. $C_6H_5CH{=}CHBr$	TBAC (4)	HMPA	40	70	$C_6H_5CH{=}CH_2$	0
						$C_6H_5CH{=}CHBr$	79
	109. $C_6H_5CH{=}CHBr$	Na 9-BBNCN (4)	HMPA	22	70	$C_6H_5CH{=}CH_2$	0
						$C_6H_5CH{=}CHBr$	65
						$C_6H_5C{\equiv}CH$	7
						$C_6H_5CH_2CH_3$	2
		Aryl Halides					
90-14-2	110. 1-Iodonaphthalene	$NaBH_3CN$ (4)	HMPA	38	100	Naphthalene	88
	111. 1-Iodonaphthalene	TBAC (4)	HMPA	38	100	Naphthalene	85
	112. 1-Iodonaphthalene	Na 9-BBNCN (4)	HMPA	14	100	Naphthalene	15
90-11-9	113. 1-Bromonaphthalene	$NaBH_3CN$ (4)	HMPA	66	100	Naphthalene	93
	114. 1-Bromonaphthalene	TBAC (4)	HMPA	66	100	Naphthalene	99
90-13-1	115. 1-Chloronaphthalene	$NaBH_3CN$ (4)	HMPA	72	100	1-Chloronaphthalene	92
						Naphthalene	3
	116. 1-Chloronaphthalene	TBAC (4)	HMPA	132	100	Naphthalene	46
						1-Chloronaphthalene	55
		Other Functional Groups					
112-44-7	117. $CH_3(CH_2)_9CHO$	$NaBH_3CN$ (4)	HMPA	1	70	$CH_3(CH_2)_9CHO$	91
				2	70	$CH_3(CH_2)_9CHO$	81
	118. $CH_3(CH_2)_9CHO$	TBAC (4)	HMPA	45	25	$CH_3(CH_2)_9CHO$	97
124-19-6	119. $CH_3(CH_2)_7CHO$	TBAC (4)	CH_2Cl_2	10	40	$CH_3(CH_2)_7CHO$	84
	120. $CH_3(CH_2)_7CHO$	TBAC (4)	C_6H_6	24	80	$CH_3(CH_2)_7CHO$	39
	121. $CH_3(CH_2)_9CHO$	Na 9-BBNCN (4)	HMPA	1	25	$CH_3(CH_2)_9CHO$	8
927-49-1	122. $[CH_3(CH_2)_4]_2CO$	$NaBH_3CN$ (4)	HMPA	5	70	$[CH_3(CH_2)_4]_2CO$	99
112-12-9	123. $CH_3(CH_2)_8COCH_3$	TBAC (4)	HMPA	97	25	$CH_3(CH_2)_8COCH_3$	98
	124. $CH_3(CH_2)_8COCH_3$	Na 9-BBNCN (4)	HMPA	1	25	$CH_3(CH_2)_8COCH_3$	65
60633-84-3	125. 	$NaBH_3CN$ (4)	HMPA	4	70		73
4436-22-0	126. 	TBAC (4)	HMPA	12	70		86
	127. 	Na 9-BBNCN (4)	HMPA	12	70		92
3352-87-2	128. $CH_3(CH_2)_{10}CON(C_2H_5)_2$	$NaBH_3CN$ (4)	HMPA	24	70	$CH_3(CH_2)_{10}CON(C_2H_5)_2$	95
	129. $CH_3(CH_2)_{10}CON(C_2H_5)_2$	TBAC (4)	HMPA	69	25	$CH_3(CH_2)_{10}CON(C_2H_5)_2$	100
	130. $CH_3(CH_2)_{10}CON(C_2H_5)_2$	Na 9-BBNCN (4)	HMPA	23	25	$CH_3(CH_2)_{10}CON(C_2H_5)_2$	100
872-05-9	131. $CH_3(CH_2)_7CH{=}CH_2$	Na 9-BBNCN (4)	HMPA	6.5	25	$CH_3(CH_2)_7CH{=}CH_2$	85

[a] Usually the solutions were 0.2 M in the compound and 0.8 M in the reducing agent for analytical runs. Preparative runs were commonly carried out at twice the above concentrations. [b] The yields were determined by GLC using internal standards and detector response factors unless specified otherwise. [c] Reference 13, H. Kuzuhara, K. Sato, and S. Emoto, *Carbohydr. Res.*, **43**, 293 (1975); several carbohydrate derivatives were successfully reduced by these workers. [d] Reduction was slowed by inductive and steric effects; product was 2% reduced in 4 h when subjected to the reaction conditions. [e] Initial product contained B—H and CN, apparently from reaction between the carboxylic acid and cyanoborohydride. Treatment with concentrated HCl; overnight at 70 °C released the carboxylic acid. [f] α_{obsd} +2.9°. [g] Added in two portions, the second one after 53 h.

Table II. Direct Conversion of Alcohols into Hydrocarbons with Methyltriphenoxyphosphonium Iodide and Cyanoborohydride

Registry no.	Entry	Alcohol	Time[a] meth-iodide, h	Time[b] redn, h	% yield[c]
112-30-1	1.	$CH_3(CH_2)_9OH$	0.5[d]	1.0[e]	100
	2.	$CH_3(CH_2)_9OH$		1.5[e]	99
104-54-1	3.	$C_6H_5CH{=}CHCH_2OH$	0.5[d]	2.0[e]	68
17976-80-6	4.	$HO(CH_2)_6CN$	0.5[d]	1.0[e]	66
14064-13-2	5.		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 GLC using internal standards and corrected for detector response. [d] At 25 °C. [e] At 70 °C. [f] Solution 0.2 M in alcohol, 0.4 M in the iodide, and 0.8 M in $NaBH_3CN$ at 70 °C. [g] At 100 °C, sealed tube, 1.2 M in $NaBH_3CN$.

major deviation was noted with molecules containing a carboxylic acid (i.e., entries 22, 77, Table I) which gave uncharacterized B–CN containing products which had to be hydrolyzed with HCl prior to isolation in order to retrieve the acid products.

Reduction of Monoalkyl Halides. The reduction of primary halogen compounds (except chlorides and fluorides) was realized with all cyanoborohydrides in HMPA. The ease of reduction of the primary iodides by three of these reagents at 25 °C (i.e., $NaBH_3CN$, 3.5 h, 91%; TBAC, 21 h, 81%; Na 9-BBNCN, 1 h, 91.5%) recommends such removals for synthetic transformations and, as mentioned, should be successful in the presence of most other functional groups including chlorides, bromides, and sulfonate esters. In addition the reduction of primary iodides could also be accomplished in benzene and THF with TBAC (entry 7) and Na 9-BBNCN (entry 11), respectively. Thus, the reduction of iododecane with TBAC in refluxing benzene gave an 81% yield of decane in 7 h, while a 94% yield of decane was realized with Na 9-BBNCN at 25 °C in 26 h. However, reductions in these solvents were slow compared to the reduction in HMPA. The reduction of tosylates, though much slower at 25 °C, gave fairly good yields at higher temperature (entries 36–42) while chlorides and fluorides are sluggish even at 100 °C. Unlike the situation with $LiAlH_4$,[15] no alkene or alcohol side products were observed. While secondary iodo compounds were reduced with relative ease, the reduction of secondary bromides requires longer reduction times. Thus the reduction of 2-iodooctane occurred readily in 1–2.5 h at 70 °C (entries 66–68) while 2-bromododecane requires at least 24 h under the same conditions (entries 70–72) with all cyanoborohydride reagents. Sulfonate esters also require more vigorous reaction conditions (entries 89, 90) while secondary chlorides are quite unreactive (entries 82–83, 87, 88). Tertiary alkyl halides such as 1-adamantyl bromide are reduced, but very slowly (entry 97). As expected, an S_N2 process is consistent with the observation that only one of the three hydrides of cyanoborohydride is available for replacement of halide. Thus, while a fourfold molar excess of $NaBH_3CN$ gave 96% of dodecane in 1 h at 50 °C (entry 2), the reduction of 1-iododecane with 0.5 M $NaBH_3CN$ gave only 42% of decane after 2 h at 50 °C and no further reaction occurred with longer reaction times.

For synthetic applications, the superior selectivity possible with cyanoborohydride is demonstrated by the inertness toward almost all other functional groups in neutral or basic media. Thus, esters (entries 10, 21, 24–26, 73–76, 89, 90), carboxylic acid (entries 22, 77), amido (entries 128–130), nitro (entries 60–62), cyano (entry 23), alkene (entries 9, 43–59, 107–109, 131), sulfone (entries 32, 33), and even such normally sensitive groups as epoxides (entries 20, 125–127), ketones (entries 9, 21, 105, 106, 122–124), azide (entry 10), and, to a lesser extent, aldehydes (entries 19, 117–121). The exceptional discrimination possible is well illustrated by the selective stripping of the iodo group from the polyfunctional steroid in entry 9 which contains an ester, alkene, and ketone group in addition to the target iodine; the excellent isolated yield (89%) strongly recommends the reagent for such selective removals. The selective displacement of the bromine from 3-bromo-1,2-epoxy-1-phenylpropane is also noteworthy (entry 20). An additional example of the discrimination possible is provided by the selective removal of the primary methanesulfonate group from 3,4,5-trimesyl-1,2-diisopropylidene-D-glucopyranose[16] (entry 35). These latter three examples are illustrated below. The superior selectivity coupled with the ready availability of deuterated (or tritiated) cyanoborodeuteride[3,5] allows the preparation of chiral RCHDR[1] compounds as demonstrated by the conversion of methyl-*O*-mesyl mandelate to optically active methyl-2-*d*-phenyl acetate (entry 89).[17]

Direct Conversion of Primary Alcohols to Hydrocarbons. The facile reduction of primary iodides coupled with the inertness of $NaBH_3CN$ toward most reagents suggested a convenient two-step-in-one process in which primary alcohols may be converted to hydrocarbons. The procedure involves conversion of the alcohol (1 mmol) into the iodide with methyltriphenoxyphosphonium iodide[18] (2 mmol) in HMPA (5 ml) at ambient temperature followed by addition of $NaBH_3CN$ (4 mmol) and stirring at 70 °C for the durations listed in Table II. Alternately, both steps may be combined with no loss in yield (entry 2, Table II). Noteworthy is the conversion of a neopentyl alcohol into the hydrocarbon in respectable yield (entry 5, Table II) considering that the reaction involves two steps.[19]

Attempts to extend the procedure to secondary and tertiary alcohols were unsuccessful. In the former case, the products were invariably either an alkene or a mixture consisting of the corresponding alkane and alkene. In fact, by leaving out the $NaBH_3CN$, excellent yields of alkenes were obtained from most secondary alcohols thus providing an excellent method for the overall selective dehydration of such compounds.[20] This unexpected diversion of secondary systems also prevents the successful reduction of secondary iodides which are especially positioned for facile elimination. Thus, for example, cholesteryl iodide afforded only elimination products upon treatment with $NaBH_3CN$ (entry 69, Table I); apparently axial iodides favor elimination over substitution. Tertiary alcohols, on the other hand, are unreactive with the iodonation reagent in HMPA and may be recovered unchanged.

Reduction of Benzylic and Allylic Halides. Primary benzylic halides are smoothly reduced by all three cyanoborohydrides selectively with no complications (entries 60–65). Likewise, secondary benzylic bromides afford good to excellent yields of the corresponding alkanes with no evidence for double bond production (entries 79–81, 84–86). In all cases, the chloro derivatives were reduced at a much slower rate compared to the bromides (i.e., entries 82, 83, 87, 88) as expected for a displacement mechanism rather than one involving initial ionization and subsequent hydride capture as observed for $NaBH_4$ in aqueous diglyme.[21] We were therefore surprised to observe that the tertiary halides triphenylmethyl bromide and chloride (entries 91–96) afforded excellent yields to triphenylmethane. Apparently, $NaBH_3CN$, as previously observed for $NaBH_4$ (in Me_2SO)[2d,22] and $LiAlH_4$,[2a] attacks halide generating a cation (or radical) which traps a hydrogen. Other tertiary halides which cannot form stable ionic (or radical) intermediates are not reduced as readily. Thus 1-adamantyl bromide was only slowly and incompletely reduced

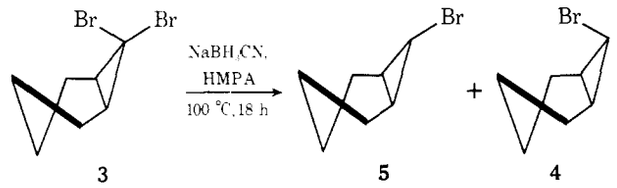
at 100 °C even with a large excess of reducing reagent (entry 97).

The reduction of allylic halides with boron hydride reagents is often complicated by the production of boron intermediates which may subsequently hydroborate alkenes. Thus, $NaBH_4$ in Me_2SO or sulfolane[2g] (or HMPA)[23] successfully removes allylic halides, but the yield of alkene products is lowered by subsequent hydroboration.

A variety of allylic halides were subjected to reduction with $NaBH_3CN$, TBAC, and Na 9-BBNCN. As evident from Table I, all three reagents convert allylic halides to the alkenes (entries 43–59), but the yields varied considerably and depended upon the reagent. With $NaBH_3CN$ and TBAC only fair to moderate yields were obtained (entries 43–46, 48, 49, 51, 52, 54–56, 58). Since no other organic products or starting materials were found, these reagents apparently furnish cyanoborane which cyanohydroborates the alkene products and/or starting materials; in fact, as mentioned previously, cyanoborane is conveniently synthesized by the reaction of $NaBH_3CN$ with organic halides. The most effective reagent was Na 9-BBNCN, which consistantly afforded 60–91% yields of alkenes (entries 47, 50, 53, 57, 59); the advantage is evidently a reflection of the inability of the reagent to furnish a hydroborating species.[24]

Reduction of Vicinal and Geminal Dihalides. The reduction of 1,2-dihalides to the corresponding hydrocarbons is generally complicated by competing elimination to the alkene,[25] although the combination of $NaBH_4$ in Me_2SO is successful.[2d] The cyanoborohydrides appear less applicable for such reductions. Thus, while $NaBH_3CN$ afforded predominantly ethylbenzene (77%) from styrene dibromide along with a minor amount of styrene (11%; entry 98), TBAC reacted only reluctantly and gave primarily styrene and starting material (entry 99) and Na 9-BBNCN produced α-bromostyrene as the principal product (entry 100); apparently the latter, sterically hindered reagent functions well as a base. Likewise, 1,2-dibromooctane reductions were only partly successful and gave mixtures of octane, 2-bromooctane, and unreduced starting material (entries 101–103). Here again, Na 9-BBNCN gave substantial elimination (entry 103).

Geminal dihalides appear to be smoothly reduced by cyanoborohydride initially to the monohalide. Thus, 7,7-dibromobicyclo[4.1.0]heptane (**3**) gave 77% of the cis isomer **4**



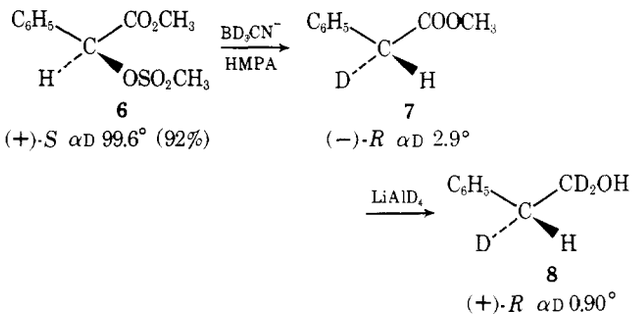
3 5 4

and 21% trans **5** (entry 104) similar to the results with $LiAlH_4$.[2a]

Reduction of Vinylic and Aromatic Halides. Vinylic halides seem quite resistant toward all three cyanoborohydrides (entries 107–109); only Na 9BBNCN gave detectable reaction with β-bromostyrene and then only to the extent of less than 10% in 22 h at 70 °C. The reduction of aryl halides also was of limited utility. The only successful applications found were the removal of iodo and bromo from naphthalene (entries 110–114); benzene derivatives were resistant. The remaining entries further illustrate the inertness of the cyanoborohydrides, especially toward normally sensitive functional groups such as aldehydes, ketones, and epoxides.

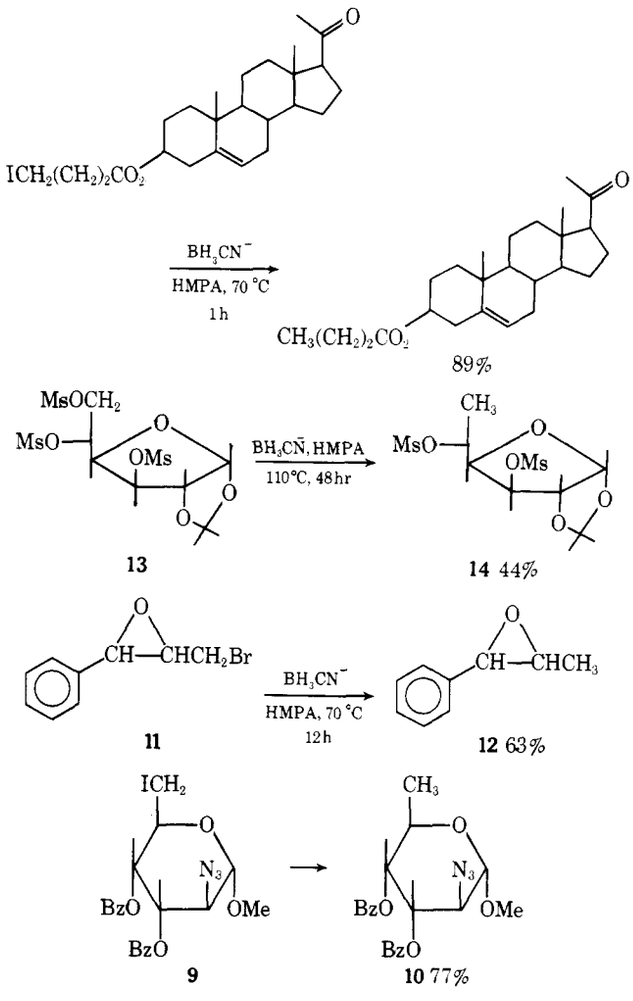
Mechanism of Hydride Displacements. Reduction of Optically Active Systems. Hydride substitutions of primary and secondary halides and sulfonate esters with BH_3CN^- in polar aprotic solvents ostensibly are best accommodated by an S_N2 process as has been implicated in analogous hydride displacements. As previously mentioned, this is evidenced by the expected relative rate order: iodides > bromides ≈ sulfonate esters > chlorides with fluorides unreactive. Since these reductions provide a potentially valuable synthetic procedure for the introduction of deuterium or tritium and for the preparation of optically active $RCHDR^1$ molecules,[26] the stereoselectivity possible in the reduction was of considerable interest and was probed using the sequence outlined in Scheme I. From the known configuration of (+)-(*S*)-methyl-*o*-mesyl mandalate (**6**) and (+)-(*R*)-2-phenyl-1,1,2-ethanol-d_3 (**8**), the displacement of mesyl by D was determined to occur with a minimum of ca. 67% inversion to give optically active **7** which was further reduced with $LiAlD_4$ to **8**.[27] Thus, the high stereoselectivity recommends the procedure for the introduction of deuterium or tritium particularly when both stereo- and functional group selectivity are desired (i.e., **7**).

Scheme I



Conclusions and Summary

The results presented amply suggest that the combination of cyanoborohydride in HMPA provides a mild, effective, and



selective reagent system for the reductive displacement of primary and secondary alkyl halides and sulfonate ester in a wide variety of structural types. Particularly noteworthy synthetic applications include (a) the selective reduction of iodides and bromides in the presence of nearly all other functional groups (in neutral or basic media) including such normally sensitive moieties as aldehydes, ketones, and epoxides; (b) the facile removal of allylic and benzylic halides, particularly with 9-BBNCN$^-$, with a minimum of damage to alkenes; (c) the reduction of tertiary halides which are capable of forming stable carbonium ions (i.e., triphenylmethyl halides); (d) the stereoselective and chemoselective introduction of D (and presumably T) into molecules. The cyanoborohydride reagents described herein all appear effective in these applications and thus the commercially available $NaBH_3CN$ seems sufficient for most applications except when the use of other solvents such as benzene, CH_2Cl_2, etc., is desired. In these cases, TBAC or 9-BBNCN$^-$ are useful; the latter is also apparently the reagent of choice for allylic systems since a hydroborating species is not generated. Polymeric cyanoborane, although capable of halide reductions, is sluggish in its reactions and offers no apparent synthetic advantage.

Experimental Section

All melting points and boiling points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 457 spectrometer either as films or in potassium bromide disks. Proton nuclear magnetic resonance spectra were obtained on a Varian A-60 spectrometer typically as 10–20% solutions using tetramethylsilane as an internal reference. Microanalyses were performed by Chemanalytics Inc., Tempe, Ariz. Gas chromatographic (GLC) analyses were performed on a Hewlett-Packard Model 5250B instrument coupled to an L & N Model W recorder equipped with a disk integrator. Yields of products were determined by GLC using internal standards and corrected for detector response factors. Preparative GLC was also performed on this instrument. All analyses were carried out on either a 6 ft × 0.125 in. or 10 ft × 0.125 in. stainless steel column packed with 10% OV-1 or 20% Carbowax 20M on 80/100 mesh Chromosorb W (DMCS).

Materials. Sodium cyanoborohydride obtained from Alfa Inorganics was purified by decolorizing with alkaline Norit-A in hot tetrahydrofuran (THF) followed by solvent removal at reduced pressure. Samples obtained from Aldrich Chemical Co. were used as received. All the other chemicals used were either commercially available or prepared by standard procedures. Hexamethylphosphoramide (HMPA), obtained from Fisher Scientific Co., was distilled over CaH_2 and stored over 13 A molecular sieves. Tetrahydrofuran was distilled over $LiAlH_4$ and stored over 4 A molecular sieves. Drying of organic solvents was accomplished with anhydrous $MgSO_4$. Tetrabutylammonium cyanoborohydride was prepared as previously described.[1b,9]

Sodium 9-Cyano-9-hydrido-9-borabicyclo[3.3.1]nonane (1). Fisher certified sodium cyanide (13.4 g, 0.27 mol) was dried under vacuum and then added to 250 ml of THF. To this stirred slurry was added 500 ml of 0.5 M 9-BBN solution in THF under nitrogen and the reaction mixture was stirred at 25 °C for 12 h, during which time most of the NaCN dissolved. The solution was then filtered to remove undissolved NaCN and the solvent was removed on a rotary evaporator. The remaining solvent was removed under vacuum to obtain a hygroscopic, white semisolid. This was then redissolved either in THF or HMPA to obtain a ca. 1 M solution of the reducing agent in the corresponding solvent. Attempts to purify the solid were only partly successful; the material was dissolved in anhydrous ether and centrifuged to remove suspended particles. Evaporation of the ether gave a white solid material.

Anal. Calcd for $C_9H_{15}BNNa$: C, 63.2; H, 8.84. Found: C, 61.80; H, 9.09. IR (neat) 2270, 2240 s (BH); 2160 cm^{-1} s (CN). No 1560-cm^{-1} absorption characteristic of B–H–B bridge was observed.

Polymeric Cyanoborane. The general procedure of Spielvogel[11] or a modified method described for diborane[12] was employed to generate the reagent.

Method A.[11] Into a stirred slurry of 6.3 g (0.1 mol) of $NaBH_3CN$ in 100 ml of anhydrous ether was passed HCl gas for 1.5 h. The reaction mixture was filtered and the solvent removed on a rotary evaporator to obtain 2.77 g (71%) of polymeric cyanoborane as a white semisolid: IR (neat) 2469, 2441, and 2429 (B–H); 2295 cm^{-1} (–CN). The product was dissolved in a suitable solvent (HMPA or CH_2Cl_2) and used fresh.[28]

Method B. The preparation of cyanoborane was accomplished analogous to that used for diborane.[12] The cyanoborane was prepared in situ by dissolving the required amount of either $NaBH_3CN$ or TBAC in a suitable solvent (diglyme or CH_2Cl_2) containing 2 mmol of the compound, followed by the dropwise addition of excess (1:2) methyl iodide at 0 °C.

General Reduction Procedure for Halides and Sulfonate Esters. For analytical scale reductions, the compound (2 mmol), reducing agent (8 mmol), and a suitable hydrocarbon internal standard (2 mmol) were dissolved in 10 ml of HMPA. The mixture was stirred at the appropriate temperature (usually 25 or 70 °C) as indicated in Table I. The reactions were conveniently monitored by periodically removing samples, quenching in water, extracting with a small amount of cyclohexane, and analyzing the extracts by GLC. After the appropriate time period (Table I), the products were often isolated in the same manner. For preparative scale reactions the quantity of solvent was usually reduced two- or threefold. Isolation was usually accomplished by dilution with water or brine followed by extraction with cyclohexane or ether, or by filtration in the case of solids. Exceptions included carboxylic acids which required heating the initially formed boron containing product overnight with concentrated HCl to release the free acid. The procedure is illustrated for representative cases below; another detailed description has appeared previously.[1c]

Reduction of 3β-(3-Iodopropionoxy)pregn-5-en-20-one with $NaBH_3CN$. A solution of the iodo steroid[29] (415 mg, 0.85 mmol) and $NaBH_3CN$ (214 mg, 3.4 mmol) in 5 ml of HMPA was heated for 1.0 h at 70 °C and then diluted with 25 ml of water. The resulting white precipitate was filtered and recrystallized from acetone–water to give 280 mg (89%) of shiny, ivory crystals, mp 112–113 °C, identical in all respects with an authentic sample of 3β-propionoxypregn-5-en-20-one.[30]

Reduction of 1-Bromohexadecane with Na 9-BBNCN. A solution of 1-bromohexadecane (3.05 g, 10 mmol) and 40 ml of a 1 M solution of Na 9-BBNCN in HMPA was stirred and heated at 70 °C for 1.5 h. Water was then added and the reaction mixture was extracted with ether (3 × 30 ml). The ether solution was washed with water, dried, and concentrated on a rotary evaporator. Distillation afforded 2.05 g (91%) of hexadecane, bp 114–115 °C (1 mm), identical with an authentic sample.

Reduction of 7-Hydroxyheptanenitrile to Heptanenitrile. A solution of 7-hydroxyheptanenitrile (127 mg, 1.0 mmol) and methyltriphenoxyphosphonium iodide (905 mg, 2.0 mmol) in 5 ml of HMPA was stirred at 25 °C for 30 min. $NaBH_3CN$ (252 mg, 4 mmol) was then added and the solution was heated at 70 °C for 1.0 h, then diluted with water. Cyclohexane (5 ml) and undecane (internal standard) were added and the organic solution analyzed by GLC (10 ft OV-1 column), indicating a 66% yield of heptanenitrile.

Reduction of (+)-(*S*)-Methyl *o*-Mesylmandalate with $NaBD_3CN$ (Table I, Entry 89). A solution of (+)-(*S*)-methyl *o*-mesylmandalate [1.5 g, 6.1 mmol, $[\alpha]^{25}D$ +99.6° (c 18, $CHCl_3$), 89.8% optical purity][31] and $NaBD_3CN$ (0.90 g, 13.7 mmol, 90% deuterium) in 7 ml of dry HMPA was prepared in a flask equipped with a condenser and protected by a drying tube. The solution was heated at 110 °C for 4 h, then cooled and diluted with 10 ml of water. The resulting slurry was extracted with ether, and the ether solution was washed with brine, dried, and concentrated on a rotary evaporator. The residue was distilled in vacuo to obtain 0.60 g (64%) of (−)-(*R*)-methyl-2-*d*-2-phenyl acetate, $\alpha^{25}D$ 2.9° (neat, *l* = 1).

(+)-(*R*)-2-Phenylethanol-*1,1,2-d*$_3$. A solution of (−)-(*R*)-methyl phenylacetate-α-*d* (**7**, 440 mg, 3 mmol, $\alpha^{25}D$ −2.9°, neat) in 5 ml of dry THF was added slowly to a stirred slurry of $LiAlD_4$ (0.20 g, 5 mmol) and 10 ml of dry THF. The mixture was heated at reflux for 3 h and the excess hydride cautiously destroyed by successive addition of 0.2 ml of H_2O, 1 ml of 15% aqueous NaOH, and 0.2 ml of H_2O. The solution was decanted from the precipitated salts, dried, and concentrated. Distillation in a short-path apparatus afforded 0.28 g (76%) of (+)-(*R*)-2-phenylethanol-*1,1,2-d*$_3$ (**8**), bp 47–53 °C (0.03 mm), $\alpha^{25}D$ +0.90° (lit.[27] $\alpha^{26}D$ +1.49°).

Acknowledgments. We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work. C.A.M. thanks the National Science Foundation for an Undergraduate Research Fellowship. We also thank Mr. Frank Cistone for some technical assistance.

Registry No.—**1**, 60645-80-9; **2**, 60633-76-3; **7**, 53546-38-6; **8**, 60633-85-4; sodium cyanide, 143-33-9; 9-borabicyclo[3.3.1]nonane,

280-64-8; $NaBH_3CN$, 25895-60-7; 3β-hydroxypregn-5-en-20-one, 145-13-1; 3-iodopropionyl chloride, 41518-22-3; 3β-propionoxypregn-5-en-20-one, 54552-01-1; propionyl chloride, 79-03-8.

References and Notes

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(8) We noted previously[1a] that $NaBH_3CN$ obtained from past sources gave best results if purified before use for the reduction of halides containing other sensitive groups, presumably because of some residual $NaBH_4$. Recent samples appear satisfactory without purification.

(9) (a) R. O. Hutchins and D. Kandasamy, *J. Org. Chem.*, **40,** 2530 (1975). (b) Several tetraalkylammonium cyanoborohydrides have been prepared in a similar fashion as described in ref 9a; see J. E. Repasky, C. Weidig, and H. C. Kelly, *Synth. React. Inorg. Metal-Org. Chem.*, **5,** 337 (1975).

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(23) Unpublished observations. This problem may be alleviated by the use of $NaBH(OCH_3)_3$ which is incapable of forming a hydroborating reagent.

(24) The combination of $NaBH_3CN$ in acidic methanol is also successful in avoiding hydroboration of alkenes in certain cases; see H. O. House and L. F. Lee, *J. Org. Chem.*, **41,** 863 (1976).

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(27) The α_{max} for **8** has been determined by Morrison and Mosher to be 1.49°. We thank Professor Morrison for communicating their results prior to publication. At least part of the loss of optical activity may be due to racemization induced by the strong base $LiAlD_4$. We hope to alleviate this possible problem via a nonbasic reducing reagent such as AlH_3 or 9-BBN.

(28) A word of caution is in order at this point. Although no problems have been encountered with fresh preparations of the viscous polymeric reagent, on one occasion an old sample which had solidified caught fire when an attempt was made to scrap the sample from flask (in air). Professor Spielvogel has informed us (private communication) of a similar experience with a sample which had been stored for some time in a hydrocarbon solvent in the presence of air. Therefore, to avoid possible hazards, reductions were carried out with freshly prepared material. The polymer was kept in solution in the absence of air whenever possible and otherwise treated with care and respect which *all* borane derivatives deserve. Also, HMPA has been shown to be a carcinogen and thus should be handled with due caution.

(29) Prepared by reaction of 3β-hydroxypregn-5-en-20-one with 3-iodopropionyl chloride in pyridine, mp 129–131 °C (acetone–water). Anal. Calcd for $C_{24}H_{35}O_3I$: C, 57.83; H, 7.09. Found: C, 57.96; H, 7.16.

(30) Prepared from the 3β-alcohol and propionyl chloride in pyridine, mp 112–113 °C (acetone–water). Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.59; H, 9.50. Found: C, 77.70; H, 9.43.

(31) Prepared according to a procedure of J. D. Morrison (private communication); reported $[\alpha]^{20}D$ +111.0° (c 6.6, $CHCl_3$).