Nucleophilic Borohydride: Selective Reductive Displacement of Halides, Sulfonate Esters, Tertiary Amines, and *N,N*-Disulfonimides with Borohydride Reagents in Polar Aprotic Solvents

Robert O. Hutchins,* Duraisamy Kandasamy, Frank Dux III, Cynthia A. Maryanoff, David Rotstein, Barry Goldsmith, William Burgoyne, Frank Cistone, Joseph Dalessandro, and Joseph Puglis

Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104

Received December 30, 1977

Sodium borohydride in polar aprotic solvents (HMPA, Me_2SO, sulfolane) furnishes a convenient and effective source of nucleophilic hydride which may be utilized for the reductive displacement of primary and secondary alkyl halides, sulfonate esters, tertiary amines, and disulfonimides. This latter procedure provides a method for reductive deamination of amines. The mildness of borohydride allows a number of chemoselective transformations without damage to groups normally affected by harsher reagents such as $LiAlH_4$ (i.e., COOR, COOH, CN, NO_2). Sodium trimethoxyborohydride is also an effective hydride source and is particularly valuable with substrates sensitive to borane (i.e., alkenes). A procedure for the two-steps-in-one conversion of alcohols to hydrocarbons is described, along with a convenient synthesis of unsymmetrical tertiary amines. The synthetic utility, scope, and limitations of the reagent system are presented.

Introduction

The eminence of borohydride in the arsenal of reductive weapons available to organic chemists is well established, primarily because of the relative chemoselectiveness, stability, convenience, and inexpense of the reagent in effecting certain important reductive transformations.[1] However, the mildness of the reagent also limits the application of borohydride to a relatively few, easily reduced functional groups such as acid chlorides, aldehydes, and ketones; others, including carboxylic acids, esters, cyano, amido, nitro, most alkenes, halides and sulfonate esters remain untouched under usual conditions.[2]

Some time ago, we envisioned that the utility of borohydride might be augmented by deployment in polar aprotic solvents, such as dimethyl sulfoxide (Me_2SO), sulfolane, and hexamethylphosphoramide (HMPA), which markedly accelerate nucleophilic substitution reactions (S_N2) without greatly enhancing other types of attack such as carbonyl additions.[3] Thus, types of reductions which involve displacement of a σ-bonded functional group by nucleophilic hydride should be enhanced in such solvents. In fact, preliminary investigations by us[4a] and others[4b,c,d] suggested that indeed the reductive removal of halides and sulfonate esters in Me_2SO, sulfolane, HMPA, or DMF were quite effective while other normally resistant groups remained intact. Since the preliminary reports, the reagent system, especially using Me_2SO, has been successfully utilized for a number of mild and selective transformations.[5] This article incorporates a systematic and exploratory investigation of the scope and synthetic utility of such reductions with regard to the chemoselectivity and range of useful leaving groups which may be effectively removed by displacement with borohydride and, to a lesser extent, sodium trimethoxyborohydride. Summarily, the investigations reported here encompass: (a) the selective reduction of alkyl and aryl halides and sulfonate esters;[4a,5v] (b) the direct conversion of alcohols to hydrocarbons;[5v] (c) the reduction of quaternary ammonium salts to tertiary amines including a convenient synthesis of unsymmetrical examples;[5v] and (d) the reductive deaminations of amines via reductive displacement of disulfonimides.[5w]

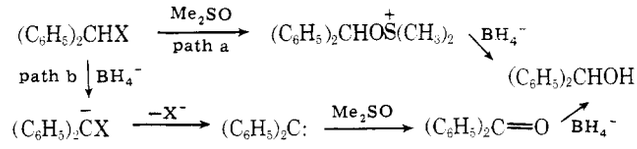
For convenience, the results are tabulated systematically in Tables I–V and considered separately below according to leaving groups.

Results and Discussion

Reductions of Alkyl and Benzyl Halides and Sulfonate Esters.[6] Borohydride anion behaves as an effective source of nucleophilic hydride anion in a variety of polar aprotic solvents including Me_2SO,[4a,b] sulfolane,[4a] HMPA,[4d] DMF,[4c] or diglyme[4b] and may be utilized for the reductive displacement of halides[4] (except fluoride), sulfonate esters,[4] and methyl sulfate anion.[4b] A wide variety of successful conversions are presented in Table I representing the culmination of our efforts during the past several years along with selected examples from the literature. The results illustrate that a variety of experimental conditions are adequate for effective displacements. Thus, primary and secondary iodides, bromides, chlorides, sulfonate esters, and primary benzylic halides are smoothly converted to hydrocarbons at temperatures between 25 and 100 °C using a zero to twofold molar excess of borohydride (entries 1–27, 40–53). Reductions in HMPA are often quite rapid as evidenced by production of dodecane in 87% yield from 1-iodododecane in 90 s at 25 °C (entry 2). Reductions in sulfolane occur less rapidly (entries 2, 6, and 12 vs. 3, 8, and 11), especially with chlorides. If the substrate is devoid of other reducible functional groups, temperatures of 70–100 °C appear to offer maximum yield in minimum reaction time; thus, for example, decane is produced from 1-iododecane in 93% yield in 15 min at 80 °C (Me_2SO, entry 1) while 1-chloropropylbenzene affords propylbenzene in 90% yield in 2 h at 70 °C (HMPA, entry 12). Although secondary examples require longer reaction times, the yields of hydrocarbon products are still good to excellent (entries 18–27).

The reductions of benzhydryl chloride and bromide in Me_2SO afforded substantial quantities of benzhydrol along with the expected diphenylmethane (entries 48 and 52). The corresponding reductions in sulfolane or HMPA gave only the hydrocarbon (entries 49, 52, and 53). The divergent path leading to the alcohol conceivably may arise via either: (a) an initial displacement of halide by Me_2SO to give a sulfonium salt, which is subsequently attacked at oxygen by borohydride[7] to generate benzhydrol (path a, Scheme I); or (b) borohydride induced α elimination of HCl to afford diphenylcarbene which attacks Me_2SO to provide benzophenone[8] followed by borohydride reduction (path b). This latter path was rejected since dimer formation from the carbene (tetra-

Scheme I



0022-3263/78/1943-2259$01.00/0

Table I. Reduction of Halides and Sulfonate Esters in Polar Aprotic Solvents

Entry	Compd	Registry no.	Reducing Agent (mol ratio)[d]	Solvent	Time, h	Temp, °C	Product	% yield[a] (isolated)
			Primary Halides and Sulfonate Esters					
1	1-Iododecane	2050-77-3	$NaBH_4$[e] (2)	Me_2SO	0.25	85	Decane	93
2	1-Iodododecane	4292-19-7	$NaBH_4$ (1)	HMPA	0.025	25	Dodecane	87
3	1-Iododecane		$NaBH_4$ (2)	Sulfolane	0.25	100	Decane	93
4	1-Iodooctane	629-27-6	$NaBH_4$ (5.3)	Diglyme	1.0	45	Octane	91[b]
5	1-Bromodecane	112-29-8	$NaBH_4$ (2)	Me_2SO	1.5	85	Dodecane	94
6	1-Bromododecane	143-15-7	$NaBH_4$ (1)	HMPA	0.022	25	Dodecane	73
7	1-Bromododecane		$NaBH_4$ (2)	Me_2SO	1.5	85	Dodecane	95
8	1-Bromododecane		$NaBH_4$ (2)	Sulfolane	1.5	100	Dodecane	96
9	ω-Bromoundecanoic acid	2834-05-1	$NaBH_4$ (2)	Me_2SO	2.5	25	Undecanoic acid	(98)
10	1-Chlorododecane	112-52-7	$NaBH_4$ (2)	Me_2SO	4	85	Dodecane	91 (80)
11	1-Chlorododecane		$NaBH_4$ (2)	Sulfolane	6	100	Dodecane	85
12	1-Chloropropylbenzene	934-11-2	$NaBH_4$ (4)	HMPA	2	70	Propylbenzene	90
13	Chloromethyl phenyl sulfone	7205-98-3	$NaBH_4$ (3)	HMPA	13	110	Methyl phenyl sulfone	91
14	*n*-Dodecyl tosylate	10157-76-3	$NaBH_4$ (2)	Me_2SO	2	85	Dodecane	87 (85)
15	*n*-Dodecyl tosylate		$NaBH_4$ (2)	Sulfolane	2	100	Dodecane	88
16	Ethyl tosylate	80-40-0	$NaBH_4$ (5.3)	Diglyme	1.0	45	Ethane	35[b]
17	2-Phenyl-1,3-propanediol ditosylate	1570-96-3	$NaBH_4$ (2.2)	Me_2SO	2.75	70	2-Phenylpropane	(54–69)
			Secondary Halides and Sulfonate Esters					
18	2-Iodooctane	557-36-8	$NaBH_4$ (3)	Me_2SO	1	85	Octane	82
19	2-Iodooctane		$NaBH_4$ (3)	Sulfolane	1	100	Octane	81
20	2-Bromododecane	13187-99-0	$NaBH_4$ (3)	Me_2SO	18	85	Dodecane	86
21	2-Bromododecane		$NaBH_4$ (3)	Sulfolane	18	100	Dodecane	69
22	2-Chlorooctane (sealed tube reaction)	628-61-5	$NaBH_4$ (6)	Me_2SO	48	85	Octane	67
23	2-Chlorodecane	1002-56-8	$NaBH_4$ (3)	Me_2SO	18	85	Decane	(68)
24	Ethyl 2-bromohexanoate	615-96-3	$NaBH_4$ (2)	Me_2SO	0.75	15	Ethyl hexanoate	86
25	Ethyl 5-bromovalerate	14660-52-7	$NaBH_4$ (4)	HMPA	0.5	25	Ethyl valerate	85
26	α-Bromo-4-phenylacetophenone	135-73-9	$NaBH_4$ (4)	HMPA	1	25	4-(α-Hydroxyethyl)biphenyl	79
27	Cyclododecyl tosylate	27092-44-0	$NaBH_4$ (3)	Me_2SO	24	85	Cyclododecane	(54)
			Allylic Halides					
28	Cinnamyl bromide	4392-24-9	$NaBH_4$ (4)	HMPA	0.5	25	β-Methylstyrene	47
					2	25	β-Methylstyrene	39
29	Cinnamyl bromide		$NaBH_4$ (8)	80% HMPA[g]	0.5	25	β-Methylstyrene	82
30	Cinnamyl bromide		$NaBH(OCH_3)_3$[f] (3)	HMPA	1	50	β-Methylstyrene	78
31	Cinnamyl chloride	2687-12-9	$NaBH_4$ (4)	HMPA	0.5	70	β-Methylstyrene	0
32	Cinnamyl chloride		$NaBH_4$ (8)	80% HMPA[g]	0.5	70	β-Methylstyrene	81
33	Cinnamyl chloride		$NaBH(OCH_3)_3$ (4)	HMPA	1	50	β-Methylstyrene	60
34	1-Chloro-2-ethyl-2-hexene	65588-46-7	$NaBH_4$ (4)	HMPA	1	70	3-Methyl-3-heptene	0
35	1-Chloro-2-ethyl-2-hexene		$NaBH_4$ (8)	80% HMPA[g]	0.5	70	3-Methyl-3-heptene	71
36	1-Chloro-2-ethyl-2-hexene		$NaBH(OCH_3)_3$ (4)	HMPA	1.75	70	3-Methyl-3-heptene	82
37	3-Chloro-2-phenyl-1-propene	3360-52-9	$NaBH_4$ (8)	80% HMPA[g]	0.5	70	α-Methylstyrene	90
38	3-Chloro-2-phenyl-1-propene		$NaBH(OCH_3)_3$ (4)	HMPA	2	70	α-Methylstyrene	86
39	Phenylpropargyl chloride	3355-31-5	$NaBH_4$ (8)	80% HMPA[g]	0.5	70	1-Phenyl-1-propyne	64
			Benzylic Halides					
40	*p*-Nitrobenzyl bromide	100-11-8	$NaBH_4$ (2)	Me_2SO	1.5	25	*p*-Nitrotoluene	(95)
41	α,2,6-Trichlorotoluene	2014-83-7	$NaBH_4$ (2)	Me_2SO	2.5	25	2,6-Dichlorotoluene	(85)
42	α,2,6-Trichlorotoluene		$NaBH_4$ (6)	Sulfolane	2	100	2,6-Dichlorotoluene	76
43	α-Phenylethyl bromide	585-71-7	$NaBH_4$ (7)	65% Diglyme		45	Ethylbenzene	80[c]
							Styrene	1
							α-Phenylethanol	14
44	α-Phenylethyl bromide		$NaBH_4$ (3)	Me_2SO	1	85	Ethylbenzene	79
45	α-Phenylethyl bromide		$NaBH_4$ (3)	Sulfolane	1	100	Ethylbenzene	82
46	α-Phenylethyl chloride	672-65-1	$NaBH_4$ (4)	HMPA	10	70	Ethylbenzene	98
47	Benzhydryl bromide	776-74-9	$NaBH_4$	80% Diglyme			Diphenylmethane	87[c]
48	Benzhydryl bromide		$NaBH_4$ (3)	Me_2SO	24	25	Diphenylmethane	62
							Benzhydrol	33
49	Benzhydryl bromide		$NaBH_4$ (3)	Sulfolane	1	100	Diphenylmethane	93
50	Benzhydryl chloride	90-99-3	$NaBH_4$	65% Diglyme 1 M NaOH			Diphenylmethane	99[c]
51	Benzhydryl chloride		$NaBH_4$ (6)	Me_2SO	24	35	Diphenylmethane	61
							Benzhydrol	32

Table I (*continued*)

Entry	Compd	Registry no.	Reducing Agent (mol ratio)[d]	Solvent	Time, h	Temp, °C	Product	% yield[a] (isolated)
52	Benzhydryl chloride		$NaBD_4$ (3)	HMPA	11	50	Diphenylmethane-d_1	100
53	Benzhydryl chloride		$NaBH_4$ (3)	Sulfolane	1	100	Diphenylmethane	94
54	Trityl chloride	76-83-5	$NaBH_4$ (4)	HMPA	1	70	Triphenylmethane	85
55	Trityl chloride		$NaBH_4$ (6)	Me_2SO	1.5	85	Triphenylmethane	(90)
			Vinylic Halides					
56	β-Bromostyrene	103-64-0	$NaBH_4$ (8)	80% HMPA[g]	24	70	Ethylbenzene	2
							Phenylacetylene	8
							β-Bromostyrene	52
							Styrene	26
57	β-Bromostyrene		$NaBH(OCH_3)_3$ (4)	HMPA	3.5	70	Phenylacetylene	84
							Styrene	8
			Dihalides					
58	Styrene dibromide	6607-46-1	$NaBH_4$ (4)	Me_2SO	1.5	85	Ethylbenzene	65
59	Styrene dibromide		$NaBH_4$ (4)	Sulfolane	1.5	100	Ethylbenzene	64
60	Styrene dibromide		$NaBH(OCH_3)_3$ (4)	HMPA	1	70	Ethylbenzene	2
							Phenylacetylene	62
							Styrene	24
61	1,2-Dibromooctane	6269-92-7	$NaBH_4$ (4)	HMPA	2	70	Octane	84
62	1,2-Dibromooctane		$NaBH(OCH_3)_3$ (8)	HMPA	2	70	Octane	66
							1-Octene	12
							2-Bromooctane	11

[a] Yields were determined by GLC using internal standards and predetermined detector response factors unless specified otherwise. [b] Reference 4b. [c] Reference 4d. [d] Molarity of reducing agent/molarity of compound. [e] Registry no.: 16940-66-2. [f] Registry no.: 16940-17-3. [g] 20% H_2O.

phenylethene) was not observed and from the absence of deuterium incorporation at the methine position of the alcohol upon reaction with $NaBD_4$ in Me_2SO as required by path b. Similar alcohol side products were not observed for less activated benzyl halides (aryl, alkylaryl, entries 40–46). The highly activated, but hindered, tertiary benzyl halides trityl chloride and bromide also afforded no alcohol product (entries 54 and 55), presumably because of facile ionization of any generated sulfonium ion to give a trityl carbonium ion which is trapped by hydride.[9] Other tertiary halides which contain α hydrogens undergo rapid elimination to alkenes which are subsequently hydroborated; in fact, coupled with treatment with a carboxylic acid, the procedure provides a convenient reductive method for converting tertiary halides to hydrocarbons.[4a,10] Vicinal dihalides are smoothly converted to the corresponding hydrocarbons (entries 58, 59, and 61), in contrast to $LiAlH_4$ reductions which predominately afford olefins[1d,11] or $NaBH_3CN$ which gives mixtures of hydrocarbons and alkenes.[6k,l] Thus, borohydride may be utilized to hydrogenate double bonds in sensitive compounds by way of bromination and reduction. The related derivative $NaBH(OCH_3)_3$ was less successful in that products resulting from incomplete reduction and/or elimination were concomitantly produced (entries 60 and 62). This latter behavior may be due to the presence of methoxy anion formed by disproportionation of the reagent.[12] Likewise, reduction of the vinylic halide β-bromostyrene was not successful with either $NaBH_4$ or $NaBH(OCH_3)_3$, the latter giving elimination to phenylacetylene (entry 57) while the former reluctantly afforded a mixture of reduction and elimination products (entry 56).

The reduction of allylic halides with BH_4^- is complicated by the production of borane, which may further react with alkene products via hydroboration.[10] Thus, attempts to dehalogenate cinnamyl derivatives or 1-chloro-2-ethyl-2-hexene in HMPA gave only a meager amount of the desired alkene product at ambient temperature (entry 28) and virtually none at 70 °C (entries 31 and 34). This problem could be alleviated by conducting the reductions in 4:1 HMPA/H_2O mixture (entries 29, 32, 35, and 27). Apparently, the initially formed borane is hydrolyzed rapidly enough to prevent attack on the product. A propargyl chloride was also successfully reduced in this solvent system (entry 39). Interestingly, a small amount (13%) of propylbenzene was produced with cinnamyl chloride in aqueous HMPA (entry 32), indicating some double bond reduction.[13] Nevertheless, the reagent system appears to offer an attractive method for allylic and propargylic halide removal. Alternatively, $NaBH(OCH_3)_3$ provides good yields of alkenes, since this reagent cannot provide a hydroborating species (entries 30, 33, and 36).

The reductive removal of functional groups is extended by a convenient two-steps-in-one method for conversion of alcohols to hydrocarbons.[14a,b] The process involves the in situ conversion of the alcohol to the iodide with methyltriphenoxyphosphonium iodide[14c] in sulfolane or HMPA and subsequent reduction with BH_4^-. Results for a variety of representative examples along with general reaction conditions are presented in Table II. Thus, primary, secondary, and benzyl alcohols are effectively reduced without concomitant attack of other functional groups such as cyano and nitro. Sodium trimethoxyborohydride is also effective for the reduction and prevents any offending hydroboration of alkene-containing substrates such as cinnamyl alcohol (entry 6).

For synthetic applications, borohydride offers several apparent advantages. First the chemoselectivity available allows the reductive removal of halides and sulfonate esters selectively without affecting a number of other sensitive groups. Thus, esters (entries 24 and 25),[5a,g,h,s] carboxylic acids (entry 9), nitro (entry 40),[5f] cyano (entry 5, Table II),[5h,i] sulfone (entry 13), and, under special conditions as discussed, alkenes (entries 29, 30, 32, 33, 35, 36, 37, and 38);[5b,k,i,r,s] α-halo ketones afford concomitant carbonyl reduction (entry 26). In addition, the products are uncontaminated with alkene side products from elimination, a result which is probably at least partly attributable to the aforementioned hydroboration of any unwanted alkene. When other reducible groups are present, it is usually advisable to conduct the reductions at moderate

Table II. Conversion of Alcohols to Hydrocarbons with Methyltriphenoxyphosphonium Iodide in Sulfolane or Hexamethylphosphoramide

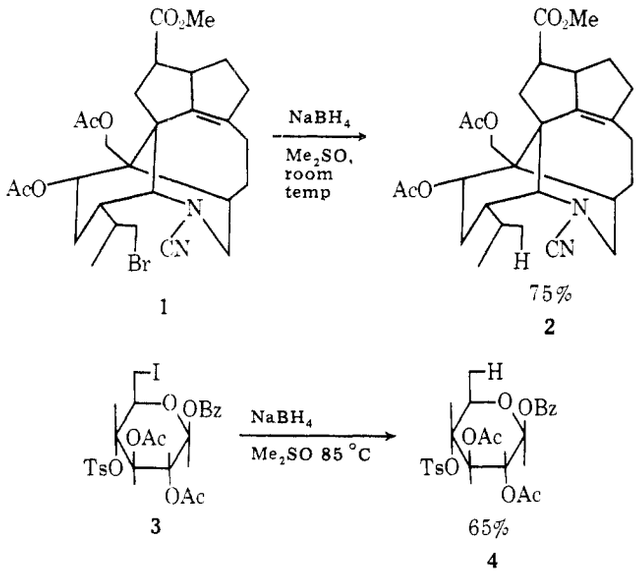
Entry	Compd	Registry no.	Ratio[a] of hydride/ alcohol	Solvent	T, °C	Time, h (Time, reduction)	% yield hydrocarbon[b]
1	1-Decanol	112-30-1	6	Sulfolane	85	0.5 (0.5)	90
2	1-Decanol		6	HMPA	85	0.5 (0.5)	78
3	2-Decanol	1120-06-5	6	Sulfolane	85	0.5 (0.5)	62
4	*m*-Nitrobenzyl alcohol	619-25-0	6	Sulfolane	30	1.0 (2.0)	71
5	7-Hydroxyheptane nitrile	17976-80-6	6	Sulfolane	85	0.5 (1.0, 40 °C)	70
6	Cinnamyl alcohol	104-54-1	9[c]	Sulfolane	40	0.5 (2.5)	73

[a] Solutions were 1.0 in the alcohol and a 0.5 mol excess of methyltriphenoxyphosphonium iodide was employed. [b] Determined by GLC using internal standards and appropriate detector response factors. [c] Sodium trimethoxyborohydride used.

Table III. Dealkylation of Quaternary Ammonium Salts with Hydrides in Polar Aprotic Solvents

Entry	Compd	Registry no.	Hydride (ratio of hydride/ compd)	Solvent	Temp, °C	Time, h	% yield products (Ratio)	
1	Phenyltrimethylammonium iodide	98-04-4	$NaBH_4$ (3)[a]	Me_2SO	85	7.0	89	
2			$NaBH_4$ (3)[a]	Me_2SO	120	1.0	96	
3			$NaBH_4$ (3)[a]	Sulfolane	120	1.0	95	
4			NaH (6)[b]	HMPA	100	2.75	96	
5			$NaBH_4$ (3)	HMPA	85	5.0	96	
6	Phenyldimethylethylammonium iodide	1006-07-1	$NaBH_4$ (3)[a]	Me_2SO	120	1.0	7[c]	82[d]
7			$NaBH_4$ (3)[b]	HMPA	100	1.0	6[c]	85[d]
8	Phenyldimethylisopropylammonium iodide	35616-26-3	$NaBH_4$ (3)[a]	Me_2SO	120	1.5	13[c] (6.4)	84[e]
9			$NaBH_4$ (3)[b]	HMPA	100	1.0	16[c] (4.9)	79[e]
10	Tripropylmethyl ammonium iodide	3531-14-4	$NaBH_4$ (6)[b]	HMPA	175	9.0	54[f]	18[g]
11	Trimethyldodecylammonium bromide	1119-94-4	$NaBH_4$ (6)[b]	HMPA	175	9.0	65[h]	
12	*N,N*-Dimethylaniline + ethyl iodide (1:2 ratio)	121-69-7	$NaBH_4$ (3)	Me_2SO	120	2.0	8[c] (9.9)	79[d]

[a] Solution 0.267 M in compound. [b] Solution 0.40 M in compound. [c] *N,N*-Dimethylaniline. [d] *N*-Methyl-*N*-ethylaniline. [e] *N*-Methyl-*N*-isopropylaniline. [f] Tripropylamine. [g] Dipropylmethylanine. [h] *N,N*-Dimethyldodecylamine. [i] Amine and iodide heated in Me_2SO at 50 °C for 16 h followed by addition of borohydride.

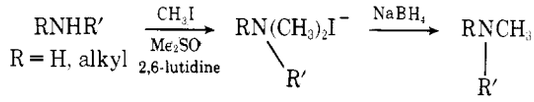


temperatures (i.e., 15–25 °C) to prevent undesirable overreductions. For instance, while nitro groups are inert at 25 °C (entry 40), higher temperatures afford azoxy, azo, and amine derivatives.[2a] Recent examples extracted from the literature of the usefulness and selectivity possible with the reducing system are illustrated by the conversion of 1 to 2 in Me_2SO at room temperature[5h] and the reductive removal of iodo from the carbohydrate derivative 3 (to 4).[5g] Finally, with sensitive alkene-containing substrates, $NaBH(OCH_3)_3$ provides an acceptable alternative (vide infra).

Reduction of Quaternary Ammonium Salts. Synthesis of Tertiary Amines. The reductive removal of alkyl groups from quaternary ammonium salts is an often sought and substantially investigated synthetic technique. Conceptually, the process may often be regarded as an expulsion of a tertiary amine and the most successful techniques have generally employed some nucleophilic reagent usually in combination with S_N2 enhancing solvents.[16] This section describes the utility of $NaBH_4$ in polar aprotic solvents for this transformation coupled with a convenient synthesis of tertiary amines, including unsymmetrical varieties.

Phenyltrimethylammonium iodide was chosen for exploratory investigation and the displacement rate with borohydride in HMPA, Me_2SO, and sulfolane at 75 °C was monitored by GLC as presented in Figure 1. As qualitatively observed for halide displacements and with other systems, HMPA provided the fastest reduction rate, requiring ~5 h for complete conversion. At higher temperatures, (i.e., 100 °C for HMPA, 120 °C for Me_2SO and sulfolane), effective reduction in all three solvents was usually obtained within 1 h (entries 2–3, 6–12).[17] Thus, in the absence of sensitive groups, the higher temperatures are recommended for convenience. The results for a variety of dealkylations are presented in Table III, from which several noteworthy points are evident. First, in cases where a choice is available, a methyl is attacked preferentially to a primary group as expected for a bimolecular substitution reaction (entries 6–9). Thus, the procedure can be used to prepare unsymmetrical amines via alkylation of a

Table IV. Conversion of Primary and Secondary Amines to Tertiary Amines by Alkylation–Demethylation in Me_2SO



Amine (0.01 mol)	Registry no.	CH_3I,[a,b] mol	$NaBH_4$, mol	% yields[b]	
Aniline	62-53-3	0.05	0.07	75	
N-Methylaniline	100-61-8	0.04	0.06	78	
N-Ethylaniline	103-69-5	0.04	0.06	5[c]	71[d]
N-Methyl-*N*-ethylaniline	613-97-8	0.02	0.03	8[c]	79[d]

[a] Amine, methyl iodide, and 0.01 mol of 2,6-lutidine heated at 50 °C for 16 h, followed by addition of $NaBH_4$ and heating at 120 °C for 2 h. [b] Yields determined by GLC using internal standards and corrected for detector response. [c] *N,N*-Dimethylaniline. [d] *N*-Methyl-*N*-ethylaniline.

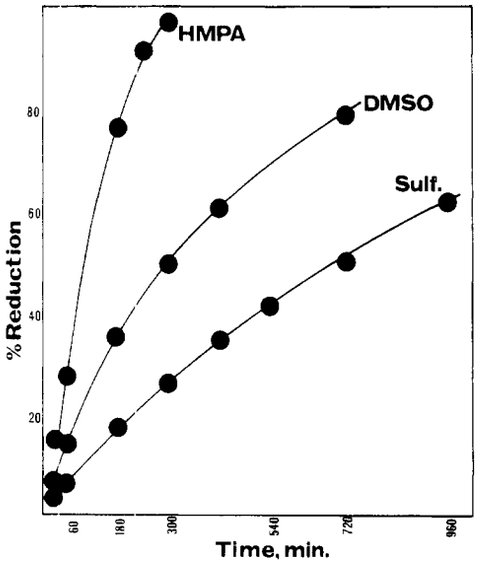


Figure 1. Sodium borohydride reduction of phenyltrimethylammonium iodide at 75 °C: solutions 0.40 M in phenyltrimethylammonium iodide, 1.20 M in $NaBH_4$. The percent reductions were determined by GLC using internal standards and are corrected for detector response.

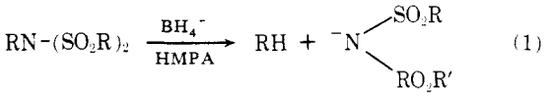
tertiary amine containing an *N*-methyl group followed by demethylation. The higher percentage of isopropyl removal over ethyl (compare entries 6 and 8) suggests that at least part of the dealkylation proceeds by Hofmann elimination in which borohydride or the halide counterion serves as the base. As seen from the table, the reduction of tetraalkyl salts proceeds much less readily than anilinium examples (compare entries 1–9 with 10 and 11), reflecting the increased base strength and, hence, the decreased leaving ability of trialkylamines over aryl derivatives. The relatively strenuous conditions required (i.e., 175 °C, 9 h) tempers the selectivity of the reaction somewhat since several other functional groups (i.e., NO_2, CO_2R, halide) probably could not survive these conditions. An interesting result is shown by entry 4 in which sodium hydride in HMPA functions as an effective nucleophile toward the methyl salt, affording a 96% yield of the tertiary amine. This represents one of the few cases where an alkali metal hydride apparently functions as a displacing nucleophile.[6s] Since NaH is a poor reducing agent toward most functional groups, this suggests that very selective displacements may be attainable with alkali metal hydrides under the proper conditions, a topic which is being explored.

Noting that both alkylation of amines to produce quaternary salts (Menschutkin reaction) and subsequent reductive dealkylation both involve S_N2 type processes, a convenient two-steps-in-one synthetic procedure was suggested for direct alkylation–demethylation to generate tertiary amines as demonstrated in Table IV. The method involves treatment of a primary, secondary, or tertiary amine with excess methyl iodide in Me_2SO using 2,6-lutidine to remove HI[18] followed by reduction with BH_4^- without prior isolation of the intermediate quaternary salt. The results in Table IV indicate the procedure to be effective for producing tertiary amines in good yields (considering that two steps are involved) with a high predominance of the demethylated product.

Reductive Deamination of Primary Amines via *N,N′*-Disulfonamides. The activation of hydroxyl groups for displacement or elimination via conversion to suitable leaving groups (i.e., sulfonate esters, halides) has enjoyed considerable success and has led, at least partially, to the great importance of alcohols as synthetic intermediates. Unfortunately, the analogous functionalization and utilization of amines is primitive in comparison, primarily because most nitrogen derivatives are relatively strong bases, and, consequently, poor leaving groups. Apparently, the incorporation of even a strong electron-withdrawing group on a nitrogen is not normally sufficient to stabilize the departing amine derivative anion.

One successful recent approach to this problem has involved stabilization of the developing leaving anion by the incorporation of two powerful withdrawing groups, principally sulfonyl[19] or carbonyl moieties.[20] In fact, use of the former (as disulfonimides) has generated several synthetic applications for substitution and elimination reactions;[19] evidently, the disulfonimide anion is sufficiently stable and nonbasic to allow facile ejection.

Along the above lines, we envisioned that BH_4^- in S_N2 enhancing solvents should provide sufficiently potent nucleophilic hydride to displace disulfonamides (i.e., eq 1) and thus

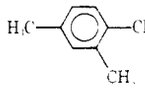
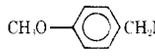
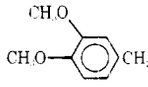
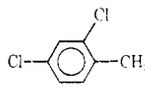
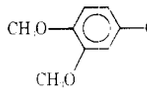
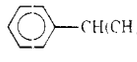


(1)

introduce a convenient approach to the reductive deamination of primary amines. This section describes our successful efforts in this area along with the scope and limitations encountered. A preliminary account of this investigation has previously appeared.[5w]

Any general and useful synthetic approach requires that essential intermediates, in this case disulfonimides, be conveniently available via reliable and high yielding methods. Fortunately, Baumgarten and DeChristopher have described a generally excellent procedure to disulfonimides by way of readily obtainable sulfonamides.[19c] In our hands, this method was quite sufficient for unhindered amines located on primary carbons, but less successful when the amino group is flanked by alkyl groups. Thus, while the disulfonimides of 2-amino-

Table V. Reduction of Disulfonimides with Borohydride in HMPA

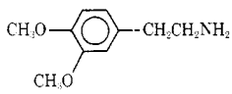
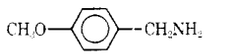
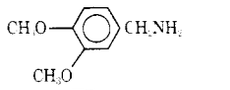
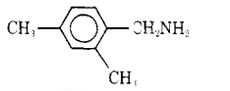
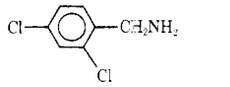
Entry	Compd[a]	Registry no.	Ratio of MBH_4^-/M compd	Temp, °C	Time, h	% yield of hydrocarbon[b] (Isolated)
1	$CH_3(CH_2)_9N(Ts)_2$	56079-36-8	2	25	48	30
2			2	110	46	43
3			2	150	4.0	80
4			2	175	4.0	84
5			2	175	8.0	88
6			4	175	8.0	91
7			4 ($NaBH_3CN$)	175	26.5	23
8			3 ($LiBHEt_3$)[c]	reflux	8.0	0[d]
9	$CH_3(CH_2)_9N(Bs)_2$	56079-37-9	2	150	4.0	73
10	$CH_3(CH_2)_{11}N(Ts)_2$	56079-38-0	2	175	4.0	68
11		65588-47-8	2	150	4.0	(78)
12		56079-40-4	2	175	4.0	(78)
13		65588-48-9	2	175	4.0	(32)
14		65588-49-0	2	175	12	22[f]
15		65588-50-3	2	150	6.0	(64)
16	$C_6H_5(CH_2)_4N(Ts)_2$	65588-51-4	2	175	4.0	88
17	$CH_3(CH_2)_9N(SO_2CF_3)_2$	65588-52-5	2	25	120	36
18			2	100	5.0	33
19			2 (18-crown-6)	100	5.0	33
20			2	175	4.0	36
21	$CH_3(CH_2)_9N(Ns)_2$	65588-53-6	2	150	4.0	0
22			2 (18-crown-6)	Reflux	22.0	0
23	$CH_3(CH_2)_6CH(CH_3)N(Bs)_2$	65588-54-7	4	175	8.0	66
					19.0	73
24	Cyclododecyl-$N(Ts)_2$	56079-41-5	4	175	20	Trace[e]
25	Cyclooctyl-$N(Ts)_2$	65588-55-8	4	175	18	23
26	$CH_3CH(CH_3)(CH_2)_3CH(CH_3)$-$N(Ts)_2$	65588-56-9	2	175	4.0	54
27		65588-57-0	3	175	4.0	77

[a] Solutions were 0.2 M. [b] Yields were determined by GLC using internal standards and corrected for detector response. [c] Solvent was a 1:1 mixture of THF and HMPA. [d] A 96% yield of *n*-decyl-*p*-toluenesulfonamide was isolated. [e] A 71% yield of cyclododecyl-*p*-toluenesulfonamide was isolated. [f] A 51% yield of *N*-(2,4-dichlorobenzyl)-*p*-toluenesulfonamide was also isolated.

nonane, cyclooctylamine and cyclododecylamine were procured the yields were modest, while all attempts to prepare sulfonimides of other, more severely hindered amines (i.e., 1-adamantyl, *exo*-2-aminonorborane, aminodiphenylmethane) were singularly unsuccessful although the intermediate sulfonamides were readily obtained. Since these results potentially restrict the utilization of disulfonamides, we explored a variety of approaches in hopes of finding a viable synthetic alternative. Since the problem involved the introduction of the second sulfonyl group, the general sulfonation procedure (DMF, NaH as base)[19c] was modified in several minor ways (solvents, times, and temperatures), but unfortunately with no success. Likewise, the use of the thallium salt of the sulfonamide, reported to improve displacement of the second sulfonyl halide,[22] also led to no improvement in our hands. As a last resort, the very potent electrophilic reagent *p*-toluenesulfonyl perchlorate was employed,[23] but again to no avail. Evidently, sulfonamide anions severely resist addition of a second sulfonyl moiety in even moderately hindered environments, which suggests an unusually inflated steric requirement for sulfonimides. Indeed, Bartsch and co-workers[19k] have recently noted an extreme regioselectivity in the elimination of disulfonimides to afford almost exclusively the Hofmann alkene, a result attributed to an abnormally great bulkiness of the disulfonimide leaving group.[19k,24] Apparently the steric requirement of the $-N(SO_2)_2$ portion equals or even surpasses that of the trimethylammonium ion! In any case, with this final synthetic frustration, our efforts to find an acceptable procedure for hindered sulfonimides were abandoned.

Initial reductive investigations with *N*-(*n*-decyl)-*N*,*N*-di(*p*-toluene)sulfonimide established that replacement of the disulfonimide anion by hydride (to give decane) was obtainable in reasonable reaction times (4–8 h) at 150–175 °C in HMPA using a twofold molar excess of BH_4^-. The progress of the reductions was conveniently monitored by GLC and the products were readily obtained by dilution with water and extraction with an organic solvent (i.e., cyclohexane). In this fashion, a number of successful conversions to hydrocarbons were accomplished as presented in Table V.

Table VI. Sulfonamides and Disulfonimides

Amine	Registry no.	Sulfonamide[a] Mp, °C	Sulfonamide[a] Registry no.	Disulfonimide[a] mp, °C
$CH_3(CH_2)_9NH_2$	2016-57-1	62–63[b]	1228-64-4	51–53
$CH_3(CH_2)_9NH_2$		75–77[c]	65588-58-1	75–77
$CH_3(CH_2)_9NH_2$		86–87[d]	65588-59-2	122–123
$CH_3(CH_2)_{11}NH_2$	124-22-1	172–174[b]	1635-09-2	36–37
$C_6H_5(CH_2)_4NH_2$	13214-66-9	50–53[b]	5435-06-3	71–73
	120-20-7	129–131[b]	14165-67-4	119–121
	2393-23-9	122–124[b]	54879-64-0	148–150
	5763-61-1	127–129[b]	65588-60-5	156–158
	94-98-4	88–89[b]	54879-65-1	146–147.5
	95-00-1	111–113[b]	65588-61-6	187–188
$CH_3(CH_2)_6CH(CH_3)NH_2$	13205-58-5	liq[c,e]	65588-62-7	79–80
$(CH_3)_2CH(CH_2)_3CH(CH_3)NH_2$	543-82-8	50–52[b,e]	65588-63-8	72–74
$C_6H_5CH(CH_3)NH_2$	98-84-0	77–80[b]	4809-56-7	153–155
Cyclododecylamine	1502-03-0	152.5–154[b]	65588-64-9	202–204 dec
Cyclooctylamine	5452-37-9	64–66[b]	16801-74-4	197–198

[a] Satisfactory combustion analytical data for C and H (±0.3%) were reported for these compounds. [b] *p*-Toluenesulfonyl derivative. [c] *p*-Bromobenzenesulfonyl derivative. [d] *p*-Nitrobenzenesulfonyl derivative. [e] Product obtained as a mixture of the sulfonamide and disulfonimide.

Several alternatives were pursued in attempts to discover less vigorous experimental conditions, but with only limited success. In hopes of further enhancing the leaving ability of the disulfonimide anion, the strongly electron-withdrawing trifluoromethylsulfonyl[19i] and *p*-nitrophenylsulfonyl groups were incorporated into the disulfonimide derivatives. However, with the former, the yield of hydrocarbon product was consistently low under a variety of conditions (including the use of the phase transfer reagent 18-crown-6,[25] entries 19 and 22), although room temperature (25 °C) could be employed. The invariance of yield conceivably reflects a competition between displacement and elimination to give an alkene; the absence of the latter in the product mixture probably stems from the aforementioned hydroboration by generated borane (vide infra). Utilization of the *p*-nitrobenzene derivative resulted in no detectable yield of hydrocarbon (entries 21 and 22). Furthermore, an attempt at improvement by employing the more potent hydride delivering reagent $LiBH(C_2H_5)_3$ ("Super Hydride")[6g,h,i,16q,26] was surprisingly unsuccessful, affording only *N*-decyl-*p*-toluenesulfonamide (entry 8) resulting either by attack at nitrogen (or sulfur) or initial halide induced elimination of *p*-toluenesulfinic acid and subsequent reduction of the resulting *N*-tosylimine **5**. This latter path was discarded, since the corresponding reduction with $LiBD(C_2H_5)_3$ gave the sulfonamide without concomitant incorporation of deuterium at the carbon adjacent to nitrogen. Apparently, the coupled steric requirements of the bulky triethylborohydride and sulfonimide groups preclude approach even to an adjacent primary carbon.[27] Predictably, BH_3CN^- was considerably less successful than BH_4^- as a hydride source, affording only a mediocre yield of hydrocarbon product under strenuous conditions (entry 7).

$CH_3(CH_2)_8CH{=}NTs$

5

At this stage our attempts to temper the reaction conditions were abandoned. Nevertheless, the general procedure is effective for deamination of unhindered primary, benzylic, and certain secondary disulfonimides in good to excellent yields (entries 1–6, 9–13, 15, 16, 23, 24, 26, and 27). The relatively congested cyclododecyldisulfonimide gave exclusive S–N bond cleavage (entry 24), again reflecting the steric requirement of the leaving group coupled with the reluctance of the system to undergo S_N2 displacements.[28] The corresponding cyclooctyl derivative (entry 25) afforded cyclooctane, albeit in low yield (23%).

Summary

Sodium borohydride in polar aprotic solvents (Me_2SO, HMPA, and sulfolane) provides a convenient and effective source of nucleophilic hydride which may be utilized for the reductive displacement of a number of functional leaving groups. Successful, selective conversions to hydrocarbons are accomplished for primary, secondary, and triaryl tertiary halides and sulfonates esters, quaternary ammonium salts, and unhindered primary and secondary disulfonimides.[29] Alcohols are conveniently transformed to hydrocarbons via initial in situ conversion to iodides followed by reduction. Likewise, unsymmetrical tertiary amines result from exhaustive alkylation of amines to quaternary salts and subsequent demethylation with BH_4^-. With substrates susceptible to hydroboration (i.e., allylic and other alkene containing molecules), aqueous HMPA or use of $NaBH(OCH_3)_3$ provides viable alternatives.

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 using

tetramethylsilane as an internal standard. Microanalyses were performed by Chemanalytics Inc., Tempe, Ariz. Gas chromatography (GLC) was performed on a Hewlett-Packard Model 5250B instrument. Yields of products were determined by GLC using internal standards and were corrected for detector response.

Materials. Sodium borohydride from Alfa Inorganics was used as obtained. Hexamethylphosphoramide, (HMPA), dimethyl sulfoxide (Me_2SO), and sulfolane were distilled from BaO (HMPA) or CaH_2 and stored over molecular sieves. Alkyl halides, alcohols, amines, and other reagents were obtained commercially and usually distilled or recrystallized before use. Sulfonate esters and quaternary salts were prepared by standard procedures. Disulfonimides were prepared via the sulfonamides from the corresponding amines. In all cases, IR and NMR data were consistent with assigned structures.

Reductions with Sodium Borohydride: General Procedure. The reductive methods used for halides, sulfonate esters, quaternary ammonium salts, and disulfonimides are similar and straightforward. The appropriate quantities of reagents, as provided in the tables, were reacted at the indicated temperatures for the required times as determined by GLC. Workup involved simply dilution with water and extraction with an organic solvent, usually cyclohexane, $CHCl_3$, or ether. For reductions in HMPA, $CHCl_3$ should be avoided since this solvent preferentially complexes with HMPA. An internal standard was then added to the organic solution for analysis by GLC. For preparative isolations, the organic phase was washed with water or brine to remove residual reduction solvent, dried ($MgSO_4$), and concentrated at reduced pressure.

The reductions of alcohols to alkanes listed in Table II were conducted in a similar manner. A solution of the alcohol and methyltriphenoxyphosphonium iodide[14c] in the proper solvent was reacted under the conditions presented in Table II. The $NaBH_4$ was then cautiously added (the reaction is initially very vigorous) and stirring continued for the appropriate time. Water was then slowly added, followed by cyclohexane and an internal standard. The cyclohexane solution was analyzed by GLC. For preparative isolations, the organic solution was washed with dilute aqueous NaOH (to remove small amounts of phenol) and twice with water, dried ($MgSO_4$), and concentrated at reduced pressure.

The following reduction is presented as a representative example of the general procedure used for all leaving groups. A solution of *N*-(2,5-dimethylbenzyl)-*N*,*N*-di(*p*-toluene)sulfonimide (3.55 g, 8 mmol) and $NaBH_4$ (605 mg, 16 mmol) in 40 mL of HMPA was heated for 4 h at 150 °C, diluted with water, and extracted three times with cyclohexane. The cyclohexane solution was washed three times with water, dried, and concentrated on a rotary evaporator to give 852 mg of colorless oil. Flash distillation at reduced pressure (Kugelrohr apparatus) afforded 747 mg (78%) of 1,2,5-trimethylbenzene product, identified by comparison with an authentic sample.

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. Michael Pacanna for some technical assistance.

References and Notes

(1) For excellent reviews of borohydride as well as other metal hydride reductions see: (a) H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, New York, N.Y., 1972, Chapter 2; (b) E. R. H. Walker, *Chem. Soc. Rev.*, **5**, 23 (1976); (c) H. C. Brown, "Boranes in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1972; (d) N. G. Gaylord, "Reductions with Complex Metal Hydrides", Interscience, New York, N.Y., 1956; (e) for a comprehensive and excellent review of the use of BH_4^- in conjunction with metal catalysts, including industrial applications, see R. C. Wade, D. G. Holak, A. H. Hughes, and B. C. Hui, *Catal. Rev., Sci. Eng.*, **14**, 211 (1976).

(2) Exceptions include the following. (a) The reduction of aromatic nitro groups in Me_2SO or pyridine to amines, azoxy, or azo compounds [see R. O. Hutchins, D. W. Lamson, L. Rua, C. Milewski, and B. Maryanoff, *J. Org. Chem.*, **36**, 803 (1971); H. J. Shine and E. Mallory, *ibid.*, **27**, 2390 (1962); G. Otani, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.*, **16**, 1840 (1968); (with metal complexes) Y. Arai, A. Mijin, and Y. Takahashi, *Chem. Lett.*, 743 (1972); K. Hanaya and T. Ono, *J. Chem. Soc. Jpn.*, **92**, 1225 (1971); K. Hanaya, N. Fujita, and H. Kudo *Chem. Ind. (London)*, 794 (1973); B. Loubinoux, J. J. Chanof, and P. Caubere, *J. Organomet. Chem.*, **88**, C4 (1975)], or using Pd/C catalysis to give amines [T. Neilson, H. Wood, and A. Wylie, *J. Chem. Soc.*, 371 (1962)] or various heterocycles [cf., R. T. Coutts and M. Wohlebe, *Can. J. Chem.*, **52**, 3432 (1974)]. (b) Alkenes activated by electron-withdrawing substituents are often smoothly reduced to the saturated derivatives: see J. H. Schaulle, G. J. Walter, and J. G. Moxin, *J. Org. Chem.*, **39**, 755 (1974); S. B. Kadin, *ibid.*, **31**, 620 (1966); J. A. Meschino and C. H. Bond, *ibid.*, **28**, 3129 (1963); J. A. Marshall and R. D. Carroll, *ibid.*, **30**, 2748 (1965); H. LeMoal, R. Carrie, and M. Bargain, *C. R. Held. Seances Acad. Sci.*, **255**, 2541 (1960); L. Berlinquet, *Can. J. Chem.*, **33**, 1119 (1955); G. W. K. Cavill and F. B. Whitfield, *Proc. Chem. Soc., London*, 380 (1962); H. Shechter, D. E. Ley, and E. B. Roberson, Jr., *J. Am. Chem. Soc.*, **78**, 4984 (1956); A. I. Meyers and J. S. Sircan, *J. Org. Chem.*, **32**, 4134 (1967); A. Hassner and C. Heathercock, *ibid.*, **29**, 1350 (1964). (c) Borohydride anion in carboxylic acid solvents reductively alkylates certain heterocyclic amines [see G. W. Gribble, P. D. Lord, J. Skotnicki, S. E. Dietz, J. T. Eaton, and J. L. Johnson, *J. Am. Chem. Soc.*, **96**, 7812 (1974); G. W. Gribble and P. W. Heald, *Synthesis*, 650 (1975); P. Marchini, G. Liso, A. Reho, F. Liberatore, and F. M. Moracci, *J. Org. Chem.*, **40**, 3453 (1975)]; the reagent system also reduces amides to the corresponding amines [see, N. Umino, T. Iwakuma, and N. Itoh, *Tetrahedron Lett.*, 763 (1976)], selectively reduces aldehydes in the presence of ketones [G. W. Gribble and D. C. Ferguson, *J. Chem. Soc., Chem. Commun.*, 535 (1975)], reduces nitrimines to nitramines [M. J. Haire, *J. Org. Chem.*, **42**, 3446 (1977)], converts certain arylmethanols to hydrocarbons [G. W. Gribble, R. M. Leese, and B. E. Evans, *Synthesis*, 172 (1977)], and transforms tosylhydrazones to hydrocarbons [R. O. Hutchins and N. R. Natale, *J. Org. Chem.*, in press (1978). (d) The reduction of certain esters has also been noted: see, for example, S. Takahashi and S. A. Cohen, *ibid.*, **35**, 1505 (1970); M. S. Brown and R. Rapoport, *ibid.*, **28**, 3261 (1963). (e) Borohydride also has been used sparingly for the reduction of imines to amines: see, for instance, K. A. Schellenberg, *ibid.*, **28**, 3259 (1963); P. R. Farina, L. J. Farina, and S. J. Benkovic, *J. Am. Chem. Soc.*, **95**, 5409 (1973); A. I. Meyers, H. W. Adickes, I. R. Politzer, and W. N. Beverung, *ibid.*, **91**, 965 (1969); A. I. Meyers, G. R. Malone, and H. W. Adickes, *Tetrahedron Lett.*, 3715 (1970). (f) Infrequent reduction of amides has also been reported: see, for example, Y. Kikugawa, S. Ikegame, and S. Yawada, *Chem. Pharm. Bull. Jpn.*, **17**, 98 (1969).

(3) Reviews of the utility of polar aprotic solvents in organic chemistry are available; see: (a) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969); (b) H. Normant, *Angew Chem., Int. Ed. Engl.*, **6**, 1046 (1968); *Russ. Chem. Rev.* (*Engl. Transl.*), **39**, 457 (1970); (c) for a recent general review of solvent concepts as applied to reaction type, see V. Gutmann, *Chem., Tech.*, 255 (1977), and references cited therein.

(4) (a) R. O. Hutchins, D. Hoke, J. Keogh, and D. Koharski, *Tetrahedron Lett.*, 3495 (1969); (b) H. M. Bell, C. W. Vanderslice, and A. Spehar, *J. Org. Chem.*, **34**, 3923 (1969); (c) M. Volpin, M. Dvolaitzky, and I. Levitin, *Bull. Soc. Chim. Fr.*, 1526 (1970); (d) sodium borohydride in aqueous diglyme also effectively reduces halides in systems capable of forming stable carbonium ions: see H. C. Brown and H. M. Bell, *J. Am. Chem. Soc.*, **88**, 1743 (1966).

(5) (a) K. Kato and Y. Hirata, *J. Chem. Soc., Chem. Commun.*, 1324 (1970); K. Kato, Y. Hirata, and S. Yamamura, *Tetrahedron*, **27**, 5897 (1971); (b) E. J. Corey, R. A. Kirst, and J. A. Katzenellenbogen, *J. Am. Chem. Soc.*, **92**, 6314 (1970); (c) W. Kreiser, *Justus Liebigs Ann. Chem.*, **745**, 164 (1971); (d) H. Weidman, W. Timpe, and N. Wolf, *Carbohydr. Res.*, **25**, 67 (1972); (e) T. Hijama, S. Fujita, and H. Nozaki, *Bull. Chem. Soc. Jpn.*, **45**, 2797 (1972); (f) A. Mannschreck and L. Ernt, *Chem. Ber.*, **104**, 228 (1971); (g) H. Weidman, N. Wolf, and W. Timpe, *Carbohydr. Res.*, **24**, 184 (1972); (h) H. Irikawa, S. Yamamura, and Y. Hirata, *Tetrahedron*, **28**, 3727 (1972); (i) H. Niwa, M. Toda, S. Ishimaru, Y. Hirata, and S. Yamamura, *ibid.*, **30**, 3031 (1974); (j) Y. Houminer, *J. Org. Chem.*, **40**, 1361 (1975); (k) W. Timpe, K. Dax, N. Wolf, and H. Weidman, *Carbohydr. Res.*, **39**, 53 (1975); K. Dax and H. Weidmann, *Adv. Carbohydr. Chem.*, **33**, 189 (1976); (l) M. Ramah and B. Laude, *Bull. Soc. Chim. Fr.*, 2651 (1975); (m) G. M. Blackburn, A. J. Flavell, P. T. Taussig, and J. P. Will, *J. Chem. Soc., Chem. Commun.*, 358 (1975); (n) J. N. Labows, Jr., and N. Landmesser, *J. Org. Chem.*, **40**, 3798 (1975); (o) D. Cook, *ibid.*, **41**, 2173 (1976); (p) F. Bellesia, M. M. Pagnoni, and R. Trave, *J. Chem. Soc., Chem. Commun.*, 34 (1976); (q) $NaBH_4$ reduces α-haloalkylcobaloximes ($RCHXCo^{III}(DMG)_2py$), but apparently not by a direct displacement mechanism, see M.-N. Ricroch, C. Bied-Charreton, and A. Gaudemer, *Tetrahedron Lett.*, 2859 (1971); (r) F. Bellesia, U. M. Pagnoni, and R. Trave, *Gaz. Chim. Ital.*, **106**, 895 (1976); (s) N. Murofushi, I. Yamaguchi, H. Ishigooka, and N. Takahashi, *Agric. Biol. Chem.*, **40**, 2471 (1976); (t) P. R. Jefferies, J. R. Knox, and B. Scaf, *Aust. J. Chem.*, **27**, 1097 (1974); (u) M. Sliwa, H. Sliwa, and P. Maitte, *Recl. Trav. Chem. Pays-Bas*, 958 (1974); (v) R. O. Hutchins, L. Rua, C. A. Milewski, and F. Dux, III, presented at the 160th National Meeting of the American Chemical Society, Chicago, Ill., September, 1970, Abstract No. ORGN-140; (w) R. O. Hutchins, F. Cistone, B. Goldsmith, and P. Heuman, *J. Org. Chem.*, **40**, 2018 (1975); R. O. Hutchins, F. Cistone, B. Goldsmith, W. Burgoyne, and D. Rotstein presented at the 170th National Meeting of the American Chemical Society, Chicago, Ill., August 1975, Abstract No. ORGN-82.

(6) Other procedures available for converting halides and sulfonate esters include the following. Lithium aluminum hydride: (a) Cf. C. W. Jefford, D. Kirkpatrick, and F. Dalay, *J. Am., Chem. Soc.*, **94**, 8905 (1972); (b) C. W. Jefford, U. Berger, M. Laffer, and N. Kabengile, *Tetrahedron Lett.* 2493 (1973); (c) J. Hatem and B. Waegell, *ibid.*, 2023 (1973); (d) G. J. Karobatsos, R. L. Shone, and S. E. Schepple, *ibid.*, 2113 (1964); (e) H. C. Brown and S. Krishnamurthy, *J. Org., Chem.*, **34**, 3918 (1969) (these latter two references are for aromatic halides). Sodium bis(2-methoxyethoxy)aluminum hydride: (f) M. Capka and V. Chvalovsky, *Collect. Czech. Chem. Commun.*, **34**, 2783, 3110 (1969). Trialkylborohydrides: (g) H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **95**, 1669 (1973); (h) S. Krishnamurthy and H. C. Brown, *J. Org. Chem.*, **41**, 3064 (1976); (i) R. W. Holder and M. G. Matturro, *ibid.*, **42**, 2166 (1977); 9-BBN-ate complexes: (j) Y. Yamamoto, H. Toi., S. Murahashi, and I. Moritani, *J. Am. Chem. Soc.*, **97**, 2558 (1975). Sodium and tetrabutylammonium cyanoborohydride, sodium 9-BBNCN: (k) R. O. Hutchins, B. E. Maryanoff, and C. A. Milewski, *Chem. Commun.*, 1097 (1971); R. O. Hutchins, D. Kandasamy, C. A. Maryanoff, D. Masilamani, and B. E. Maryanoff, *J. Org. Chem.*, **42**, 82 (1977); R. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *Org. Synth.*, **53**, 107 (1973); (l) R. O. Hutchins and D. Kandasamy, *J. Am. Chem. Soc.*, **95**, 6131 (1973). $TiCl_3Mg$: (m) S. Tyrlik and I. Wolochowicz, *J. Chem. Soc., Chem. Commun.*, 781 (1975).

(π-Cp)$_2$TiCl$_2$Mg: (n) T. R. Nelson and J. J. Tufariello, *J. Org. Chem.*, **40**, 3159 (1975). Cu hydride complexes, cf.: (o) S. Masamune, N. A. Rossy, and G. S. Bates, *J. Am. Chem. Soc.*, **95**, 6452 (1973); S. Masamune, G/ S. Bates, and P. G. Georgiou, *ibid.*, **96**, 3686 (1974); T. Yoshida and E. Negishi, *J. Chem. Soc., Chem. Commun.*, 762 (1974). Li–amine reductions of diethyl phosphates or tetramethylphosphorodiamides of alcohols: (p) R. E. Ireland, D. C. Muchmore, and M. Hengartner, *J. Am. Chem. Soc.*, **94**, 5098 (1972). Trialkyltin hydrides: (q) H. G. Kuivila, *Synthesis*, **2**, 499 (1970); E. J. Corey and J. W. Suggs, *J. Org. Chem.* **40**, 2554 (1975). Hydridotetracarbonylferrate anion: (r) H. Alper, *Tetrahedron Lett.*, 2257 (1975). NaH–THF (aromatic halides): (s) R. B. Nelson and G. W. Gribble, *J. Org. Chem.*, **39**, 1425 (1974). NaH–*t*-AmONaNi, -Co, or -Cu salts (aromatic halides): (t) G. Guillaumet, L. Mordenti, and P. Caubere, *J. Organomet. Chem.*, **92**, 43 (1975). Pyridinium salts: (u) T. Ho and C. M. Wong, *J. Org. Chem.*, **39**, 562 (1974). Zn–HOAc: (v) C. DeSelms, *Org. Prep. Proced. Int.*, **5**, 303 (1973). Zn(Ag)–CH_3OH: (w) R. D. Clark and C. H. Heathcock, *J. Org. Chem.*, **38**, 3658 (1973). Zn/aprotic solvent: (x) Y. Fujimoto and T. Tatsuno, *Tetrahedron Lett.*, 3325 (1976). Raney Ni/base: (y) W. A. Szarek, A. Zamojski, A. R. Gibson, D. M. Vyas, and J. K. N. Jones, *Can. J. Chem.*, **54**, 3783 (1976). $R_3SiH/AlCl_3$: (z) M. P. Doyle, C. C. McOsker, and C. T. West, *J. Org. Chem.*, **41**, 1393 (1976). $CrCl_3/LiAlH_4$, Y. Okude, T. Hiyama, and H. Nozaki, *Tetrahedron Lett.*, 3829 (1977). $LiAlH_4$/trans metals: E. C. Ashby and J. J. Lin, *J. Org. Chem.*, **43**, 1263 (1978).

(7) C. R. Johnson and W. G. Phillips, *J. Org. Chem.*, **32**, 3233 (1967).

(8) R. Oda, M. Mieno, and Y. Hayashi, *Tetrahedron Lett.*, 2363 (1968); F. Dost and J. Gosselck, *Chem., Ber.*, **105**, 948 (1972).

(9) Similar reductions have been observed with diborane or diisocamphyborane in nitromethane: cf. S. Matsumura and N. Tokuro, *Tetrahedron Lett.*, 363 (1969).

(10) R. O. Hutchins, R. J. Bertsch, and D. Hoke, *J. Org. Chem.*, **36**, 1568 (1971); see also, S. Matsumuro and N. Tokura, *Tetrahedron Lett.*, 4703 (1968); J. Jacobus, *Chem. Commun.*, 338 (1970).

(11) L. W. Trevoy and W. G. Brown, *J. Am. Chem. Soc.*, **71**, 1675 (1949); J. F. King and R. G. Pews, *Can. J. Chem.*, **42**, 1294 (1964).

(12) H. C. Brown, H. I. Schlesinger, H. R. Hoekstra, and L. R. Rapp, *J. Am. Chem. Soc.*, **75**, 199 (1953).

(13) The formation of this product is apparently complicated and does not result from simple double bond reduction of the starting material or product by BH_4^- or BH_3. Investigations of the mechanistic aspects of this reaction will be reported separately (unpublished work with D. Kandasamy).

(14) Other one-step procedures for the reductive removal of alcohols include the following. (a) Reduction of initially formed sulfate monoesters with $LiAlH_4$ (for allylic and benzylic alcohols): E. J. Corey and K. Achiwa, *J. Org. Chem.*, **34**, 3667 (1969). (b) $NaBH_3CN$ reduction of preformed iodides, see ref 6k. (c) S. R. Landor and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953). Purification of the reagent is best accomplished as described by J. Verheyden and J. Moffat, *J. Org. Chem.*, **35**, 2319 (1970).

(15) In addition, BH_4^- does not affect positions adjacent to the reductive site. Thus, $C_6H_5CHBrCD_2CH_3$ is reduced cleanly to $C_6H_5CH_2CD_2CH_3$ (Me_2SO, 75% yield) without removal of deuterium; we thank Professor J. Jacobus (Clemson University) for communicating his unpublished results.

(16) Successful systems include the following. $LiALH_4$: (a) A. C. Cope, E. Ciganek, L. J. Fleckenstein, and M. Meisinger, *J. Am. Chem. Soc.*, **82**, 4651 (1960). Ethanolamine: (b) S. Hunig and W. Baron, *Chem. Ber.*, **90**, 395 (1957). LiI: (c) H. O. House, M. Muller, C. Pitt, and P. Wickham, *J. Org. Chem.*, **28**, 2407 (1963). Acetate anion: (d) N. D. V. Wilson and J. A. Joule, *Tetrahedron*, **24**, 5493 (1968). Thiophenoxide anion: (e) M. Shamma, N. C. Deno, and J. F. Remar, *Tetrahedron Lett.*, 1375 (1966); (f) T. Kametani, K. Kignsawa, M. Hiiragi, N. Wagatsuma, and K. Wakisada, *ibid.*, 639 (1969); (g) D. J. Jenden, I. Hanin, and S. I. Lamb, *Anal. Chem.*, **40**, 125 (1968); D. J. Jensen, B. Campbell, and M. Roch, *Anal. Biochem.*, **35**, 209 (1970). Lithium *N*-propylmercaptide/HMPA: (h) R. O. Hutchins and F. J. Dux, III, *J. Org. Chem.*, **38**, 1961 (1973); (i) J. P. Kutney, G. B. Fuller, R. Greenhouse, and I. Itoh, *Synth. Commun.*, **4**, 133 (1974). Copper (I) thiophenoxide/pyridine: (j) G. H. Posner and J.-S. Ting, *ibid.*, **4**, 355 (1974). 1,4-Diazabicyclo[2.2.2]octane/DMF, HMPA: (k) T. L. Ho, *Synthesis*, 702 (1972). Lithium 2-methylpropane-2-thiolate/HMPA: (l) S. M. Hecht and J. W. Kozarich, *J. Chem. Soc., Chem. Commun.*, 387 (1973). $(C_6H_5)_3P$/HMPA, CH_3CN (for *N*-alkylpyridinium salts): (m) J. P. Kutney and R. Greenhouse, *Synth. Commun.*, **5**, 119 (1975). $(C_6H_5)_3P$/DMF; (n) T. L. Ho, *ibid.*, **3**, 99 (1973). (o) U. Berg, R. Galli, and J. Metzger, *J. Org. Chem.*, **41**, 2621 (1976). (for *N*-alkylpyridinium salts); refluxing DMF alone: (p) D. Aumann and L. W. Deady, *J. Chem. Soc., Chem. Commun.*, 32 (1973). Lithium triethylborohydride: (q) M. P. Cooke, Jr., and R. P. Parlman, *J. Org. Chem.*, **40**, 531 (1975). Lithium naphthalimide/THF: (r) I. Angres and H. E. Zieger, *ibid.*, **39**, 1013 (1974). Pt/O_2: (s) R. D. Birkenmeyer and L. A. Dolak, *Tetrahedron Lett.*, 5049 (1970). Na/NH_3: (t) E. Grovenstein, Jr., S. Chandra, C. Collum, and W. Davis, *J. Am. Chem. Soc.*, **88**, 1275 (1966). Salt pyrolysis: (u) J. H. Brewster and E. L. Eliel, *Org. React.*, **7**, 142 (1953).

(17) A note of caution is in order at this point. HMPA has been shown to be a carcinogen and, in addition, is relatively expensive. For small-scale reactions and using adequate and careful precautions, handling this material, in our opinion, does not offer severe problems. With large-scale reactions however, Me_2SO might be preferred considering safety and expense.

(18) (a) This alkylation procedure is a modified version of that described by H. Sommer and L. Jackson, *J. Org. Chem.*, **35**, 1558 (1970); (b) for a recent alternative method for quaternary salt formation, see F. C. M. Chen and N. L. Benoiton, *Can. J. Chem.*, **54**, 3310 (1976).

(19) (a) R. J. Baumgarten, *J. Chem. Educ.*, **43**, 598 (1966); (b) P. J. DeChristopher, J. P. Adamek, G. D. Lyon, J. J. Galante, H. E. Haffuer, R. J. Baggio, and R. J. Baumgarten, *J. Am. Chem. Soc.*, **91**, 2384 (1969); (c) P. J. DeChristopher, J. P. Adamek, G. D. Lyon, S. A. Klein, and R. J. Baumgarten, *J. Org. Chem.*, **39**, 3525 (1974); (d) V. A. Curtis, A. Raheja, J. E. Rejowski, R. W. Majewski, and R. J. Baumgarten, *Tetrahedron Lett.*, 3107 (1975); (e) P. J. DeChristopher, J. P. Ademek, S. A. Kelin, G. D. Lyon, and R. J. Baumgarten, *J. Org. Chem.*, **40**, 3288 (1975); (f) V. A. Curtis, H. S. Schwartz, A. F. Hartmen, R. M. Pick, L. W. Kolar, and R. J. Baumgarten, *Tetrahedron Lett.*, 1969 (1977); (g) R. S. Galls, *Chem. Commun.*, 1546 (1971); (h) R. S. Glass and R. C. Hoy, *ibid.*, 1777 (1976); (i) J. B. Hendrickson, R. Bergeron, A. Giga, and D. Steinbach, *J. Am. Chem. Soc.*, **95**, 3412 (1973); (j) N. H. Anderson and H. Uh, *Synth. Commun.*, **2**, 297 (1972); (k) R. A. Barsch, J. A. Allaway, D. D. Ingram, and J.-G. Lee, *J. Am. Chem. Soc.*, **97**, 6873 (1975).

(20) S. B. Kadin, *J. Org. Chem.*, **38**, 1348 (1973).

(21) The reluctance of hindered systems to add a second sulfonyl moiety has been noted previously (ref 19c and communications with Professors Baumgarten and Glass), and apparently stems from an unusually severe steric requirement of sulfonimides, see ref 19k.

(22) H.-L. Pan and T. L. Fletcher, *Synthesis*, 39 (1975).

(23) F. Klages and F. E. Malecki, *Justus Liebigs Ann. Chem.*, **691**, 15 (1966).

(24) The related phthalimido and succinimido groups also present relatively large steric environments as evidenced by their reluctance to occupy axial positions in cyclohexane; see H. Booth and G. C. Gidley, *Tetrahedron Lett.*, 1449 (1964).

(25) For a review of the utility of crown ethers as phase transfer reagents see, a) G. W. Gokel and H. D. Durst, *Synthesis*, 168 (1975); D. J. Cram and J. M. Cram, *Science*, **183**, 803 (1974).

(26) S. Krishnamurthy, R. M. Schubert, and H. C. Brown, *J. Am. Chem. Soc.*, **95**, 8486 (1973).

(27) The preference for S–N over C–N cleavage has been noted by others even with small nucleophiles such as hydroxide, cyanide, or mercaptide; see, for example, ref 19e, and 19f and references cited therein.

(28) This sluggish behavior of 12-membered rings toward S_N2 reactions has been previously noted: see P. J. C. Fierens and P. Verschelden, *Bull. Soc. Chim. Belg.*, **61**, 427, 609 (1952); L. Schotsmans, P. J. C. Fierens, and T. Verlie, *ibid.*, **68**, 580 (1959).

(29) Other deamination procedures include: (a) NHF_2; C. Baumgardner, K. J. Martin, and J. P. Freeman, *J. Am. Chem. Soc.*, **85**, 97 (1963); (b) NH_2O-SO_3H–base; A. Nickon and A. S. Hill, *ibid.*, **86**, 1452 (1964); G. A. Doldouras and J. Kollonitsch, *ibid.*, **100**, 341 (1978).