solvent evaporated at reduced pressure. Trimethyl borate, 12.8 ml (11.8 g, 113 mmol), and 2.5 ml of 2.42 *M* borane in THF (catalyst) were added to the crude organoborane and the mixture was heated to 120–130° (bath temperature) for 3 hr. Distillation of the resultant products (10-in. concentric tube column) gave, after a forerun (3.05 g), 10.4 g (74%) of *B*-methoxyborepane (**5**), bp 74–78° (32 mm), in *ca.* 95% purity. The only contaminant was *B*-OCH_3-9-BN (*ca.* 5%) as determined by glpc.[18] No *B*-methoxy-2-methylborinane (**10**) was detected.

Reactivity of 9-BBN (13) and Borepane (2) toward Ring Opening by Borane. (a) **9-BBN.** To 32.8 ml (20 mmol) of 0.611 *M* 9-BBN in THF at *ca.* 25° was added 1.64 ml (10 mmol) of *n*-octane (glpc standard) followed by 8.3 ml (20 mmol) of 2.40 *M* borane in THF. At periodic intervals 10-ml samples of the solution were treated with 1.1 ml (28 mmol) of methanol and analyzed by glpc for *B*-OCH_3-9-BBN.[18] After 48 hr only a 0.7-mmol (3.5%) loss of 9-BBN was observed. Infrared spectral analysis after addition of borane revealed bands at 2400 cm^{-1} (s) (BH_3 in THF), 1550 cm^{-1} (s) (BH_2B bridge), and weak bands in the 2500–2600 cm^{-1} region (terminal B–H of $R_3BH \cdot BH_3$ complex). No change in the spectrum was observed in 48 hr.

(b) **Borepane (2).** A THF solution of borepane (theory 25 mmol), 9-BBN (theory 50 mmol), and *n*-octane (15 mmol) was prepared in the manner previously described for the exchange reaction of **14** at reflux. The final volume of the solution was adjusted to 110 ml with dry THF. Glpc analysis[18] of a 10-ml methanolyzed sample indicated a 22.2 mmol (89%) yield of borepane and 45.7-mmol (91%) yield of 9-BBN. The remaining reaction mixture was divided into two 50-ml portions. To one was added 4.7 ml (11.3 mmol, equal to theoretical quantity of borepane) and the other 9.4 ml (22.6 mmol, twice the theoretical quantity of borepane) of 2.4 *M* borane in THF at *ca.* 25°. At scheduled intervals 5-ml samples were methanolyzed and analyzed by glpc for *B*-methoxyborepane (**5**) and *B*-OCH_3-9-BBN.[18] The quantity of **5** present after 48 hr was 19.1 mmol in the former experiment and 14.2 mmol in the latter experiment. This represents a 14 and 36% loss of borepane, respectively, based on the experimentally determined initial quantity. Small amounts of tetramethyl 1,6-hexanediboronate (**15**) were observed in the 48-hr glpc analysis in the latter experiment (identified by comparison of retention time with authentic sample). No significant changes in the amount of 9-BBN present were observed in either experiment.

Acknowledgments. The authors gratefully acknowledge the assistance of Dr. R. E. Cook and staff for assistance in obtaining mass spectral data, and the financial support of this research by the U. S. Army Research Office (Durham) and the National Institutes of Health.

Selective Deoxygenation of Ketones and Aldehydes Including Hindered Systems with Sodium Cyanoborohydride[1]

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Abstract: The reduction of aliphatic ketone and aldehyde tosylhydrazones with sodium cyanoborohydride in acidic 1:1 DMF–sulfolane provides a mild, convenient, and high-yield method for deoxygenation without the production of side products. Noteworthy features and advantages of the procedure include: (a) superior selectivity in that most other functional groups (*i.e.*, ester, amide, cyano, nitro, chloro) are not affected under the reaction conditions allowing carbonyls to be removed in their presence; (b) most hindered carbonyls are reliably reduced to hydrocarbons without side reactions; (c) α,β-unsaturated carbonyls are reduced in good yields specifically to alkenes with migration of the double bond; (d) a limitation of the method involves aryl carbonyls which are resistant to reduction unless the ring is substituted with an electron donating group.

A key functional group transformation which often presents itself in organic synthesis is the conversion of carbonyl derivatives to methyl or methylene groups after such intermediates have served their synthetic purpose of activating molecules for the host of reactions essential for building complex structures. Consequently, a voluminous amount of literature exists concerning direct[3] or indirect[3,4] deoxygenation methods, but the standard procedures are often afflicted with problems. In particular, the rather vigorous conditions and harsh reagents required for most methods preclude the presence of many other susceptible

(1) A preliminary account of portions of this work has been previously reported: R. O. Hutchins, B. E. Maryanoff, and C. A. Milewski, *J. Amer. Chem. Soc.*, **93**, 1793 (1971).

(2) National Science Foundation undergraduate research participant, 1971.

(3) Excellent recent critical reviews of deoxygenation methods are available; see W. Reusch in "Reduction," R. L. Augustine, Ed., Marcel Dekker, New York, N. Y., 1968, pp 171–211; (b) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, Chapter 4.

(4) A common and often effective indirect method involves the reduction of carbonyl derivatives to alcohols, which are converted to a suitable leaving group and subsequently displaced by a hydride source, usually lithium aluminum hydride (ref 3a and 3b, Chapter 2; and C. W. Jefford, D. Kirkpatrick, and F. Delay, *J. Amer. Chem. Soc.*, **94**, 8905 (1972)) or a trialkyltin hydride (ref 5). (b) Sodium borohydride or cyanoborohydride in polar aprotic solvents also serve as effective displacing agents for aliphatic halides and tosylates; see R. O. Hutchins, D. Hoke, J. Keogh, and D. Koharski, *Tetrahedron Lett.*, 3495 (1969); H. M. Bell, C. W. Vanderslice, and A. Spehar, *J. Org. Chem.*, **34**, 3923 (1969); M. Vol'pin, M. Dvolaitzky, and H. Levitin, *Bull. Soc. Chim. Fr.*, 1526 (1970); E. J. Corey, H. A. Kirst, and J. A. Katzenellenbogen, *J. Amer. Chem. Soc.*, **92**, 6314 (1970); R. O. Hutchins, R. Bertsch, and D. Hoke, *J. Org. Chem.*, **36**, 1568 (1971); J. Jacobus, *Chem. Commun.*, 338 (1970). (c) For use of cyanoborohydride, see R. O. Hutchins, B. E. Maryanoff, and C. A. Milewski, *ibid.*, 1097 (1971). (d) Aromatic acids may be converted directly to hydrocarbons with trichlorosilane and a trialkylamine, see R. A. Benkeser, K. M. Foley, J. M. Gaul, and G. S. Li, *J. Amer. Chem. Soc.*, **92**, 3232 (1970); other methods for the conversion of carbonyls to hydrocarbons are also available; see for examples, ref 6 and 7.

(5) H. G. Kuivila, *Accounts Chem. Res.*, 1, 299 (1968); H. G. Kuivila, *Synthesis*, 2, 499 (1970).

(6) (a) R. G. Melton, E. J. Eisenbraun, P. Flanagan, and M. Hamming, *Org. Prep. Proced.*, 2, 37 (1970); (b) J. W. Burnham and E. J. Eisenbraun, *J. Org. Chem.*, **36**, 737 (1971).

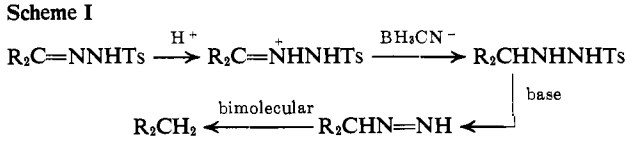
(7) S. S. Hall, A. P. Bartels, and A. M. Engman, *ibid.*, **37**, 760 (1972); (b) R. M. Coates and J. E. Shaw, *ibid.*, **35**, 2601 (1970); (c) R. E. Ireland, D. C. Muchmore, and J. Hengartner, *J. Amer. Chem. Soc.*, **94**, 5098 (1972).

functional groups.[8] This often limits the approaches to a particular structure or necessitates the use of such techniques as blocking a sensitive site or reconversion of a transformed moiety to the original; both methods require extra, often costly, synthetic steps. In addition, traditional procedures often fail or give low yields with sterically hindered systems, even under forcing conditions.[13]

Recently, cyanoborohydride anion has been found to be a remarkably mild, acid stable,[14] reducing agent, with a propensity for selectively attacking imminium ions.[15] These features suggested the attractive possibility of using cyanoborohydride to reduce protonated tosylhydrazones to hydrocarbons with a minimum of damage to other portions of susceptible molecules. Scheme I illustrates the envisioned reaction path in line with the postulated mechanism for borohydride reduction of tosylhydrazones[9,11] and the known decomposition pathway of diazenes.[16]

Preliminary investigations[1] revealed that such reductions were indeed successful and prompted a thorough exploratory investigation as to the utility of the procedure for organic synthesis, the scope and limitations of the reduction with respect to steric hindrance and other structural features, and the selectivity possible in the presence of other functional groups.

Scheme I



Results and Discussion

In order to establish optimum reaction conditions for reduction, a variety of solvents and solvent combinations were tested, and the concentrations of $NaBH_3CN$ and acid were varied. The yields of hydrocarbon product varied considerably with solvent; the most favorable media employed was a 1:1 mixture of DMF and sulfolane. Several others such as sulfolane, DMF, HMPA, DMSO, dioxane, methanol, and 2-propanol gave less satisfactory results. The most successful mole ratio of $NaBH_3CN$ to tosylhydrazone was found to be 4:1; less than this gave slightly lower yields while a higher ratio did not improve the reaction. The rate plots for 2-undecanone tosylhydrazone (Figure 1) illustrate that increasing the acid concentration markedly accelerates the reduction rate. However, at pH lower than *ca.* 1, destruction of cyanoborohydride apparently competes with reduction,[14] resulting in lower final yields of hydrocarbon products. Finally, the relatively slow rate of reduction of carbonyls compared with imminium ions[15] permitted the generation of the tosylhydrazones to be conducted *in situ*. This provided the advantage of enabling the preparation of these intermediates and the subsequent reduction to be carried out in one step.

With the above results in hand, a general and convenient synthetic procedure was developed for the reduction of *aliphatic, unhindered* aldehydes and ketones as follows (method A). The carbonyl compound (1 mmol) and *p*-toluenesulfonylhydrazine (1.25 mmol) were dissolved in 5 ml of 1:1 DMF–sulfolane containing 25 mg of *p*-toluenesulfonic acid monohydrate. The solution was heated to 100–105° and $NaBH_3CN$ (4 mmol) added. Progress of the reductions was conveniently followed by adding an internal standard and 5 ml of cyclohexane to the reactions.[17a] At appropriate intervals the cyclohexane solution was analyzed by glpc. Under the above conditions, most compounds required only 1–4 hr for complete reduction. Work-up of the completed reactions involved simply diluting with water or brine and extracting with cyclohexane or ether (see Experimental Section).

The results for several reductions conducted in the outlined manner are presented in Table I. Especially noteworthy features include: (1) good to excellent yields of deoxygenated products (62–98%) are obtained

(8) For example, the use of strong base and high temperatures in standard Wolff–Kishner reductions is detrimental to such groups as ester, amide, halogen, cyano, and nitro, to name a few; see ref 3a and Huang-Minlon, *J. Amer. Chem. Soc.*, 70, 2802 (1948). The Wolff–Kishner modification introduced by Caglioti (ref 9a) which involves sodium borohydride reduction of ketone and aldehyde tosylhydrazones is a much milder procedure. However, the selectivity of borohydride is not high at the reduction temperatures (refluxing methanol or dioxane). For instance, concomitant reduction of acetoxy groups was observed by Caglioti (ref 9a) and reduction of esters by borohydride has been observed by others [*cf.* M. S. Brown and H. Rapport, *J. Org. Chem.*, 28, 3261 (1963); S. Takahashi and L. A. Cohen, *ibid.*, 35, 1505 (1970)]. Aromatic nitro groups are also reduced by borohydride (ref 10) and alkene side products are sometimes observed in the reduction of tosylhydrazones with borohydride (ref 11) and at least one instance of a cleavage reaction has been noted (ref 12).

(9) (a) L. Caglioti, *Tetrahedron*, 22, 487 (1966); (b) L. Caglioti and P. Grasselli, *Chem. Ind. (London)*, 153 (1964).

(10) H. J. Shine and H. E. Mallory, *J. Org. Chem.*, 27, 2390 (1962); R. O. Hutchins, D. Lamson, L. Rua, C. Milewski, and B. Maryanoff, *ibid.*, 36, 803 (1971).

(11) M. Fischer, Z. Pelah, D. Williams, and C. Djerassi, *Chem. Ber.*, 98, 3236 (1965).

(12) H. O. House and J. K. Larson, *J. Org. Chem.*, 33, 61 (1968).

(13) Sterically hindered ketones are often resistant to Wolff–Kishner reductions and several more vigorous modifications have been developed; see, for example, W. Nagata and H. Itazaki, *Chem. Ind. (London)*, 1194 (1964); D. H. R. Barton, D. Ives, and B. Thomas, *J. Chem. Soc.*, 2056 (1955). However, these also are sometimes unreliable; see, for example, R. M, Schisla and W. C. Hammann, *J. Org. Chem.*, 35, 3224 (1970); E. J. Corey, M. Ohno, R. Mitra, and R. Vatakencherry, *J. Amer. Chem. Soc.*, 86, 478 (1964). Clemmensen reductions are also inhibited by steric interference [*cf.* J. Brewster, J. Patterson, and D. Fidler, *ibid.*, 76, 6368 (1954)], or lead to rearranged products. Both thioketal formation and subsequent desulfurization with Raney nickel often fail with hindered ketones. For instance, see J. W. Wilt, J. F. Zawadzki, and D. G, Schultenover, S. J., *J. Org. Chem.*, 31, 876 (1966). Reductions of hindered alkyl halides or tosylates to hydrocarbons, particularly neopentyl systems, with lithium aluminum hydride are often very sluggish [*cf.* J. A. Marshall and R. A. Ruden, *ibid.*, 36, 594 (1971); see, however, ref 4c and H. C. Brown and S. Krishnamurthy, *J. Amer. Chem. Soc.*, 95, 1669 (1973)] or, in the case of tosylates, the attack occurs at sulfur which regenerates an alcohol [see J. L. Dolby and D. R. Rosencrantz, *J. Org. Chem.*, 28, 1888 (1963)].

(14) M. M. Kreevoy and J. E. C. Hutchins, *J. Amer. Chem. Soc.*, 91, 4330 (1969).

(15) (a) R. F. Borch and H. D. Durst, *ibid.*, 91, 3996 (1969); R. F. Borch, M. D. Bernstein, and H. D. Durst, *ibid.*, 93, 2897 (1971); R. F. Borch and A. I. Hassid, *J. Org. Chem.*, 37, 1673 (1972). (b) The inertness of cyanoborohydride toward most other functional groups including cyano, amido, ester, carboxylic acid, and even such a normally sensitive group as epoxide has also been demonstrated (ref 4c); see also, A. Padwa, P. Cimiluca, and D. Eastman, *ibid.*, 37, 805 (1972).

(16) (a) T. Tsuji and E. M. Kosower, *J. Amer. Chem. Soc.*, 93, 1992 (1971); (b) T. Tsuji and E. M. Kosower, *ibid.*, 93, 1999 (1971); (c) C. E. McKenna and T. G. Traylor, *ibid.*, 93, 2313 (1971).

(17) (a) In addition to aiding in monitoring the progress of the reactions, the cyclohexane solution serves two other purposes. First, the immiscibility with DMF and sulfolane allows the hydrocarbon product to be removed from the solvents as it is formed; this minimizes contact of other functional groups with the reducing system. Furthermore, the blanket of cyclohexane vapor prevents the destruction of the intermediate diazenes by oxygen (ref 16a); in fact, if the reactions are run in the presence of oxygen, the yields of products are greatly reduced. (b) Wolff–Kishner conditions also often lead to competing elimination reactions with carbonyl compounds containing α substituents which are good leaving groups; see ref 3a and N. J. Leonard and S. Gelford, *J. Amer. Chem. Soc.*, 77, 3269, 3272 (1955).

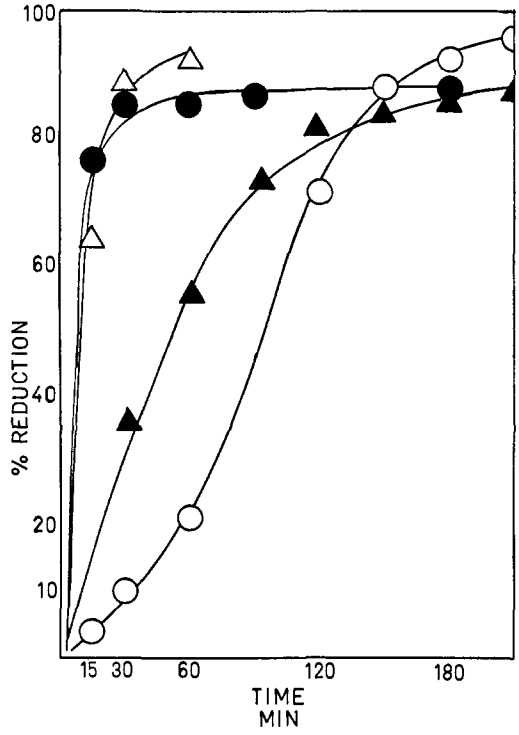


Figure 1. Reduction of 2-undecanone and cholestan-3-one tosylhydrazones with $NaBH_3CN$ in 1:1 dimethylformamide–sulfolane at 100°. All solutions were 0.2 *M* in tosylhydrazone and 0.8 *M* in $NaBH_3CN$. The per cent reduction was determined by glpc analysis using internal standards: (○) 2-undercanone tosylhydrazone, solvent contained 500 mg of *p*-TsOH·H_2O/100 ml; (▲) 2-undecanone tosylhydrazone, solvent contained 600 mg of *p*-TsOH·H_2O/100 ml; (●) 2-undecanone tosylhydrazone, solvent contained 1000 mg of *p*-toluenesulfonic acid monohydrate/100 ml; (△) cholestan-3-one tosylhydrazone, solvent contained 500 mg of *p*-toluenesulfonic acid monohydrate/100 ml. Using 1:1 DMF–sulfolane containing 250 mg of *p*-TsOH·H_2O/100 ml of solvent, the reduction was very slow (*i.e.*, 2.5% reduction in 2 hr.).

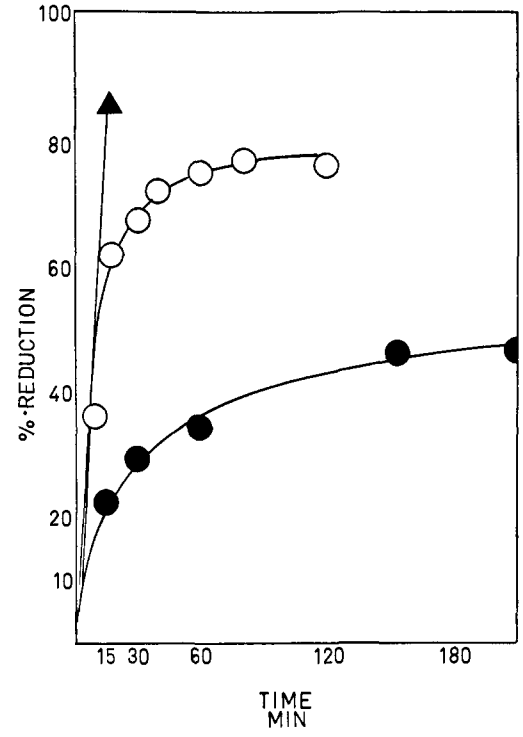


Figure 2. Reduction of 4-*tert*-butylcyclohexanone (▲), 2-*tert*-butylcyclohexanone (●), and 3,3,5-trimethylcyclohexanone (○) tosylhydrazones. Solutions were 0.2 *M* in tosylhydrazone and 0.8 *M* in $NaBH_3CN$. The solvent contained 1000 mg of *p*-TsOH·H_2O/100 ml. The per cent reactions were determined by glpc analysis using internal standards.

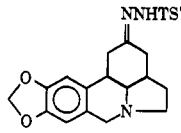
in relatively short reaction times; (2) the reactions were clean in that no alkene or other side products were detected by glpc or, in some cases, nmr; (3) a variety of other, normally sensitive functional groups are inert under the reaction conditions. Thus, esters (entries 14–18), amides (entry 19), cyano (entry 18), nitro (entry 21), chloro (entry 22), and an acetal (entry 20) survived treatment. The superior selectivity provided by the reagent system is demonstrated by the deoxygenation of keto esters (entries 14–17) and a cyano keto ester (entry 18) to the corresponding esters and cyano ester, respectively. In fact, of the functional groups tested, only primary bromo, iodo, and a thiophenoxy group α to a carbonyl[17b] did not survive (entries 23–25); evidently, cyanoborohydride serves as an efficient source of nucleophilic hydride in the polar aprotic solvents DMF and sulfolane.[4c]

Hindered Ketones. As previously mentioned, a severe problem often encountered is that classical deoxygenation procedures work poorly and unpredictably when applied to hindered carbonyl compounds. Consequently, we investigated the fate of ketones with varying degrees of blockage around the carbonyl under the experimental conditions above. We observed that with more than one substituent adjacent to the carbonyl two major problems arose. First, tosylhydrazone formation in DMF–sulfolane was extremely slow and varying amounts of ketones were recovered unchanged even after several hours at 100–105°. Fortunately, for all but severely hindered systems, superior yields of tosylhydrazones in high purity could be obtained simply by refluxing the ketone with *p*-toluenesulfonylhydrazine in absolute ethanol for varying lengths of time (see Table V and Experimental Section). For exceptionally blocked ketones flanked with four alkyl substituents (*i.e.*, di-*tert*-butyl ketone, fenchone) even this procedure failed and indirect methods were required for tosylhydrazone formation.

As expected, reductions of the more hindered tosylhydrazones in acidic DMF–sulfolane were also slowed. This is illustrated in Figure 2 in which the reduction rates of 2- and 4-*tert*-butyl- and 3,3,5-trimethylcyclohexanone tosylhydrazones were monitored by glpc. The axial methyl group in the latter case decreased the rate, presumably by interfering with top-side attack[18] by BH_3CN anion. With a 2-*tert*-butyl group, the steric interference was much more severe and the reaction essentially stopped at about 45% completion; apparently, the destruction rate of cyanoborohydride competes favorably to deplete the reducing species. This problem was alleviated by employing excess amounts of reagents added in portions and by conducting the reactions at 110° (method B); under these conditions most examples afforded good to excellent yields (54–95%) of hydrocarbons. The results for a variety of examples and structural types are presented in Table II. For convenience, formation of

(18) (a) J. C. Richer, *J. Org. Chem.*, **30**, 324 (1965); (b) H. Haubenstock and E. L. Eliel, *J. Amer. Chem. Soc.*, **84**, 2363, 2368 (1962); (c) E. L. Eliel and Y. Senda, *Tetrahedron*, **26**, 2411 (1970).

Table I. Selective Reduction of Aliphatic Ketones and Aldehydes to Hydrocarbons with Sodium Cyanoborohydride

Entry	Carbonyl compd[a]	Time, hr	Product	% yield[b] (isolated)
1	$CH_3(CH_2)_8C{=}NNHTs(CH_3)$	3.5	$CH_3(CH_2)_9CH_3$	95
2	Cholestan-3-one tosylhydrazone	1.0	Cholestane	93
3	*N*-Benzylpiperidone 4-tosylhydrazone	4.0	*N*-Benzylpiperidine	79
4	4-*tert*-Butylcyclohexanone[c] tosylhydrazone	0.25	4-*tert*-Butylcyclohexane	86
5	$CH_3(CH_2)_9CH{=}NNHTS$	4.0	$CH_3(CH_2)_9CH_3$	66
6	$CH_3(CH_2)_8COCH_3$	4.0	$CH_3(CH_2)_9CH_3$	91 (86)
7	$CH_3(CH_2)_7COCH_2CH_3$	3.0	$CH_3(CH_2)_9CH_3$	86
8	$CH_3(CH_2)_6CO(CH_2)_2CH_3$	3.0	$CH_3(CH_2)_9CH_3$	87
9	$CH_3(CH_2)_5CO(CH_2)_3CH_3$	3.0	$CH_3(CH_2)_9CH_3$	90
10	$CH_3(CH_2)_4CO(CH_2)_4CH_3$	3.0	$CH_3(CH_2)_9CH_3$	89
11	Cholestan-3-one	2.0	Cholestane	98 (88)
12	*N*-Benzylpiperidone	2.0	*N*-Benzylpiperidine	56
13	4-*tert*-Butylcyclohexanone	3.0	4-*tert*-Butylcyclohexane	77
14	$CH_3CO(CH_2)_3CO_2(CH_2)_7CH_3$	2.0	$CH_3(CH_2)_4CO_2(CH_2)_7CH_3$	87 (80)
15	$CH_3CO(CH_2)_2CO_2(CH_2)_7CH_3$[c,d]	2.0	$CH_3(CH_2)_3CO_2(CH_2)_7CH_3$	80
16	$CH_3(CH_2)_2COCH_2CO_2(CH_2)_7CH_3$	2.0	$CH_3(CH_2)_4CO_2(CH_2)_7CH_3$	62
17	$CH_3COCH_2CO_2(CH_2)_9CH_3$	4.0	$CH_3(CH_2)_2CO_2CH_2CH_3$	65
18	$CH_3CO(CH_2)_3CO_2(CH_2)_6CN$	2.0	$CH_3(CH_2)_4CO_2(CH_2)_6CN$	75
19	$CH_3(CH_2)_{10}CON(C_2H_5)_2$	8.0		0 (100% rec)
20			α-Lycorane	(80)
21	4-Nitrobiphenyl	10.0		0 (79% rec)
22	$CH_3(CH_2)_{11}Cl$	24.0	$CH_3(CH_2)_{10}CH_3$	0 (100% rec)
23	$CH_3(CH_2)_{11}Br$	8.0	$CH_3(CH_2)_{10}CH_3$	59
24	$CH_3(CH_2)_{11}I$	2.0	$CH_3(CH_2)_{10}CH_3$	76
25	$C_6H_5SCH_2C(CH_3){=}NNHTs$	2.0	$C_6H_5SCH_2CH_2CH_3$	0[f]

[a] Reaction mixtures were 0.2 *M* in the carbonyl compound, 0.8 *M* in $NaBH_3CN$ in a 1:1 mixture of DMF and sulfolane acidified with 500 mg of *p*-toluenesulfonic acid monohydrate/100 ml of solvent unless specified otherwise (method A). For reductions of ketones directly, the solutions also contained *p*-toluenesulfonylhydrazine (0.25 *M*). [b] Yields of products were determined by glpc using internal standards and detector response factors. Isolated yields represent purified products. [c] 1.0 g of *p*-toluenesulfonic acid/100 ml of solvent. [d] 1.6 *M* in $NaBH_3CN$. [e] B. Ganem, *Tetrahedron Lett.*, 4105 (1971); no experimental details for the reaction were given. [f] Thiophenol was detected by glpc.

the tosylhydrazone intermediates and reductions may be combined by removing the ethanol solvent at reduced pressure after tosylhydrazone formation, adding DMF–sulfolane, and completing the reduction as above (see entries 3, 5, 12, and 15, Table II).

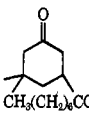
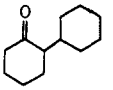
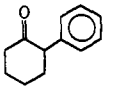
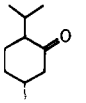
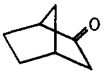
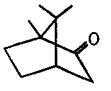
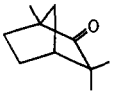
Difficulty was encountered in attempting to apply the above modified procedure to *d*-camphor and fenchone. In the former case, although the tosylhydrazone was produced in excellent yield (98%), the subsequent reduction was extremely slow. Apparently, attack on the imminium ion by hydride from the less hindered endo side with concomitant formation of tetrahedral geometry at carbon 2 is impeded considerably by steric interaction between the developing tosylhydrazine and the proximate 7-methyl group. Similar marked rate decreases caused by 7,7-dimethyl substitution have been observed in the reductions of bicyclic ketones with sodium borohydride.[19] The problem was at least partly alleviated by employing even more strenuous conditions (method C). Thus, by using a tenfold excess of $NaBH_3CN$ and keeping the pH below 3.8 throughout the reduction (by adding concentrated HCl and bromcresol green indicator), a 40% yield of camphane was realized in a total of 36 hr reaction time (entry 17). The rate of reduction of di-*tert*-butyl ketone tosylhydrazone was also increased using these forcing conditions (entry 20). With fenchone tosylhydrazone (entry 21), no identifiable organic product could be detected. Probably, rearrangement and/or polymerization occurred with this sensitive ring system under the acidic reaction conditions. The reduction of *l*-menthone tosylhydrazone was noteworthy. The product consisted of a mixture of *trans*- and *cis*-1-methyl-4-isopropylcyclohexanes indicating that acid-catalyzed equilibration of the substituent adjacent to the tosylhydrazone group occurred, probably during its formation. The trans/cis ratio steadily decreased as the reaction proceeded (from 1.38 at 3 hr to 0.66 at 22.5 hr; see Table II, entry 10); ostensibly, the trans isomer of the tosylhydrazone was reduced at the faster rate, but the cis isomer was predominant.[20]

Aryl Ketones and Aldehydes. Aryl carbonyl deriva-

(19) H. C. Brown and J. Muzzio, *J. Amer. Chem. Soc.*, **88**, 2811 (1966).

(20) The predominance of the cis stereoisomer of menthone tosylhydrazone probably arises from the favored axial deposition of substituents adjacent to exocyclic C=N ("Allylic Strain;" see, F. Johnson and D. T. Dix, *J. Amer. Chem. Soc.*, **93**, 5931 (1971)). The observation that the trans/cis ratio substantially changed over the course of the reaction suggests that acid-catalyzed equilibration during the reduction was slow; otherwise, reestablishment of equilibrium would have kept the ratio nearly constant. It is noteworthy that the *less* stable isomer of the product hydrocarbon is produced in the greater amount by this procedure and, thus, a combination of equilibrium and reduction of such tosylhydrazones may be synthetically useful for generation of the less favored isomers of disubstituted cyclohexanes. We are currently exploring this possibility.

Table II. Reduction of Hindered Ketone Tosylhydrazones

Entry	Entry tosylhydrazone	Reduction method[a]	Time red, hr	Portions of rgts (hr per portion)	% yield[b]
1		B	3	1	76
2	$CH_3(CH_2)_6COCH(CH_3)_3$	B	6	1	90
3	*c*	B	6	1	83
4		B	5.5	1	95
5	*c*	B	5.5	1	74
6		B	6.0	2 (3)	91
7		B	6.0	2 (3)	71
8	Adamantanone	B	6.0	2 (3)	82
9		B	6.0	3 (2)	84[d]
10		B	3.0	1	29[e] (1.38)[f]
			26.0	2 (3)	49[e] (0.98)[f]
			9.0	3 (3)	57[e] (0.84)[f]
			22.5	3 (3)[g]	72[e] (0.66)[f]
11	$[CH_3CH_2CH(CH_3)_2]CO$	B	12.0	4 (3)	74
12	*c*	B	6.0	3 (2)	54
13	$(CH_3(CH_2)_6COC(CH_3)_3$	B	6.0	2 (3)	81
14		B	6.0	3 (2)	92
15	*c*	B	6.0	3 (2)	56
16		B	6.0	3 (2)	94
17		C	36.0	3 (12)	40
18		B	36.0	3 (12)	12 (60% rec)
19	$(CH_3)_3CCOC(CH_3)_3$	B	10.0	5 (2)	96
20		C	3	1	89
21		C	12	1	0 (57% rec)

[a] Method B; solutions 0.2 *M* in the tosylhydrazone, 0.8 *M* in $NaBH_3CN$ in a 1:1 mixture of DMF and sulfolane acidified with 1.0 g of *p*-toluenesulfonic acid monohydrate/100 ml of solvent; reaction temperature 110°. Method C; solutions 0.2 *M* in the tosylhydrazone, 2.0 *M* in $NaBH_3CN$ in a 1:1 mixture of DMF and sulfolane acidified with concentrated HCl to pH < 3.8; reaction temperature was 110°. [b] Yields of products determined by glpc using internal standards and detector response factors. [c] Tosylhydrazone not isolated. [d] Isolated yield (purified). [e] Product consisted of a mixture of *trans*- and *cis*-1-methyl-4-isopropylcyclohexanes. [f] Ratio trans/cis. [g] Last portion of reagents added after 6.0 hr.

tives proved to be quite resistant to reduction by cyanoborohydride using any method, although tosylhydrazone formation occurred readily. Evidently, the decrease in electrophilicity of the imminium carbon rendered attack very slow. Table III summarizes the results for reduction of several examples of aryl derivatives. The only case which gave a respectable yield of hydrocarbon was *p*-methoxyacetophenone and even here vigorous conditions were required. Rings substituted with strongly electron-withdrawing groups such as nitro or cyano were effectively inert toward reduction. The results indicate that deoxygenation of aryl carbonyl systems with cyanoborohydride is probably not of synthetic value, and, in fact, that aliphatic ketones and aldehydes may be selectively removed in their presence.

Conjugated Ketones and Aldehydes. Complications are often encountered in applications of the standard deoxygenation methods to α,β-unsaturated substrates resulting in isomerization[3,6,21] or reduction[3a,22] of the double bond or cyclization to pyrazolines.[3,23] It was hoped that the mildness of the cyanoborohydride method coupled with the selectivity for imminium ion reduction would allow the selective conversion of

(21) See, for example, (a) P. Wharton, S. Dunny, and L. S. Krebs, *J. Org. Chem.*, **29**, 958 (1964); (b) R. A. Sneen and N. P. Matheny, *J. Amer. Chem. Soc.*, **86**, 5503 (1964); (c) H. Hamptmann, *ibid.*, **69**, 562 (1947); (d) P. Plattner, A. Furst, and H. Els, *Helv. Chim. Acta*, 37, 1399 (1954).

(22) S. Hunig, H. Muller, and W. Thier, *Tetrahedron Lett.*, 353 (1961).

(23) The pyrazoline intermediates offer a synthetic route to cyclopropanes, see (a) H. G. Heller and R. Morris, *J. Chem. Soc. C*, 1004 (1966); (b) R. J. Peterson and P. S. Skell, *Org. Syn.*, **47**, 98 (1967).

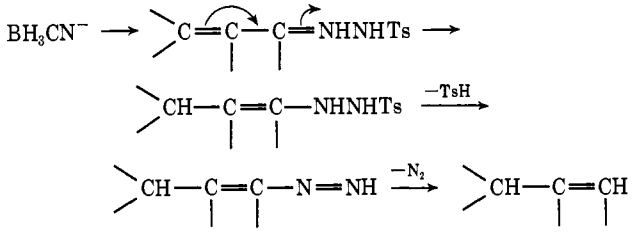
Table III. Reduction of Aryl Ketones and Aldehydes with $NaBH_3CN$

Entry	Aryl carbonyl tosylhydrazone	Red method	Time, hr	Portions rgts (hr/ portion)	% yield[a]
1	C_6H_5CHO	B[b]	3.5	1	7
2	p-CNC_6H_5CHO	A[c] or B[b]	8.0	1	<5
3	m-$NO_2C_6H_5CHO$	A[c]	18	1	~4
4	$C_6H_5CO(CH_2)_2CH_3$	D[d]	2.0	1	39
5		D[d]	17.5	2 (2)	48
6	p-$NO_2C_6H_5COCH_3$	C[b]	6.0	1	Trace
7	p-$CH_3OC_6H_5COCH_3$	D[d]	2.0	1	54
8		D[d]	4.0	2 (2)	66
9	C_6H_5CO-c-C_3H_5	D[d]	4.0	2 (2)	23

[a] Yields determined by glpc using internal standards and detector response factors. [b] See footnote *a*, Table II. [c] See footnote *a*, Table I. [d] Method D; solutions 0.2 *M* in tosylhydrazone, 0.8 *M* in $NaBH_3CN$ in a 1:1 mixture of DMF and sulfolane acidified with concentrated HCl to pH <3.8.

α,β-unsaturated carbonyls to the alkenes cleanly without any of the above mentioned side reactions. We found, however, that while such reductions were indeed clean and free of side products, in all examples studied the product was the alkene resulting from migration of the double bond with only a trace, if any, of the unrearranged alkene detectable by glpc. A variety of examples are presented in Table IV. The selectivity displayed suggests that the initial attack by BH_3CN^- occurs in a Michael fashion to give the rearranged tosylhydrazine intermediate which subsequently decomposes as illustrated in Scheme II. The propensity for BH_3CN^- and BH_4^- to add to conjugated systems in this fashion has been previously noted[24] and $LiAlH_4$ reduction of carvone tosylhydrazone affords principally the alkene resulting from double bond migration.[25] The specific formation of the *less* stable alkenes in several examples (entries 1–6, Table IV) militates against a mechanism which involves protonation of an initially formed carbanion. Thus, the reduction appears to offer a synthetically useful method for the preparation of less stable alkene isomers, especially exocyclic alkenes (entry 1), and for bringing double bonds out of conjugation with aromatic rings (entries 4–6) or polyenes.

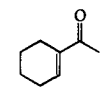
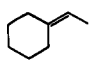
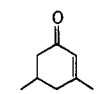
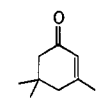
Scheme II



Experimental Section

Materials. $NaBH_3CN$ was obtained from Alfa Inorganics and was used without purification. Sulfolane and DMF were distilled from CaH_2 and stored over 4A molecular sieves. The ketones and aldehydes were either commercial materials (purified) or prepared by standard procedures. Glpc analyses were performed on Hewlett-Packard Model 5250B instrument equipped with a Disc Integrator using either a 6-ft or 10-ft 10% OV-1 on 80–100 Chromosorb W (AW-DMCS) column. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Elemental analyses were determined by A. Bernhardt, West Germany, or Chemalytics, Tempe, Ariz. Drying of organic solvents was accomplished with anhydrous $MgSO_4$. Nmr and ir spectra for the compounds described are available upon request.

Table IV. Reduction of α,β-Unsaturated Carbonyl Compounds with $NaBH_3CN$

Entry	Carbonyl tosylhydrazone	Time,[a] hr	Product	% yield[b] (isolated)
1		2.0		79
2		2.0 2.0		48
3				36
4	$C_6H_5CH{=}CHCHO$	3.0	$C_6H_5CH_2CH{=}CH_2$	98
5	$C_6H_5CH{=}CHCOCH_3$	2.0	$C_6H_5CH_2CH{=}CHCH_3$	71
6	p-$CH_3OC_6H_4CH{=}CHCOCH_3$	3.0	p-$CH_3OC_6H_4CH_2CH{=}CHCH_3$	67 (57)
7	$C_6H_5CH{=}CHCOC_6H_5$	4.0	$C_6H_5CH_2CH{=}CHC_6H_5$	60

[a] Reduction conducted using method D (see Table III, footnote *d*). [b] Yields were determined by glpc using internal standards and detector response factors. Isolated yield is for purified product.

Tosylhydrazone Formation. General Procedure for Hindered Carbonyls. After substantial experimentation, the most successful procedure for hindered ketones was as follows. The ketone and a 10–20% mol excess of p-toluenesulfonylhydrazine in a minimum amount of absolute ethanol (*ca.* 2 ml of ethanol/0.01 mol of p-tosylhydrazine) were refluxed for 1–24 hr depending upon the degree of hindrance (see Table V). Acid was not added in order to minimize rearrangement of branched ketones prior to tosylhydrazone formation. Cooling the solutions afforded crystalline products in good to excellent yields. The products were usually quite pure and further recrystallization was not necessary for the reduction step. Satisfactory ir and nmr data were obtained for the derivatives, and melting point data are presented in Table V.

Di-*tert*-butyl Ketone Tosylhydrazone was prepared according to the procedure of Hartzler[26] and had mp 177–179 dec (lit.[26] 177–179°).

***d*-Fenchone Tosylhydrazone.** A mixture of 17.7 g (0.116 mol) of *d*-fenchone, 14.0 g of hydrazine sulfate, and 42 ml of hydrazine

(24) Borch and coworkers (ref 15a) obtained cyclopentanol upon reduction of 2-cyclopentanone with $NaBH_3CN$ in acidic media and similar results have been observed with $NaBH_4$ [*cf.* H. C. Brown and H. M. Hess, *J. Org. Chem.*, **34**, 2206 (1969)].

(25) I. Elphimoff-Felkin and M. Verrier, *Tetrahedron Lett.*, 1515 (1968).

(26) H. D. Hartzler, *J. Amer. Chem. Soc.*, **93**, 4527 (1971).

Table V. Ketone and Aldehyde *p*-Toluenesulfonylhydrazones

Tosylhydrazone[a]	% yield (hr reflux)	Mp, °C
2-Undecanone	98 (1)	85–86
3-Cholestanone	93 (0.2)	168–170[b]
N-Benzyl-4-piperidone	~50	160–161 dec
4-*tert*-Butylcyclohexanone	78 (0.05)	143–145
2-*tert*-Butylcyclohexanone	93 (12)	144–145
2-Cyclohexylcyclohexanone	94 (1)	154–155
2-Phenylcyclohexanone	80 (1)	145.5–146
3,3,5-Trimethylcyclohexanone	91 (1)	129–130
2,2,6-Trimethylcyclohexanone	50 (24)	125–125.5
l-Menthone	72 (1.5)	114.5–116
Adamantanone	98 (24)	174–175.5 dec
Norboranone	94 (4)	205–207[c]
d-Camphor	98 (24)	161–161.5[d]
Fenchone	60[e]	116.5–118
2-Methyl-3-decanone	92 (8)	67.5–68
2,2-Dimethyl-3-heptanone	81 (12)	104–105
3,5-Dimethyl-4-heptanone	55 (16)	94–96
Di-*tert*-butyl ketone	48[e]	177–179 dec[f]
1-Acetylcyclohexene	70 (0.5)	120–121.5
3,5-Dimethyl-2-cyclohexenone	94 (0.25)	153–154
Isophorone	84 (0.25)	143.5–145
Cinnamaldehyde	88 (1)	160–162 dec
1-Phenylbuten-3-one	88 (0.5)	183–185[g]
1-(*p*-Methoxyphenyl)buten-3-one	84 (0.5)	149–152 dec
Benzalacetophenone	65	164–166
1-Phenylbutanone	97	121–122
4-Methoxyacetophenone	88 (0.5)	169–171
4-Nitroacetophenone	98 (0.02)	197–198
Phenylcyclopropyl ketone	80 (12)	134.5–136
4-Cyanobenzaldehyde	94 (0.25)	161.5–163.5
3-Nitrobenzaldehyde	91 (0.25)	162.5–163
Benzaldehyde	94 (0.25)	128.5–130[h]
Thiophenoxyacetone	96 (0.25)	144.5–146

[a] Results of elemental analysis, which were made available to the Editor, were well within the limits of acceptable error. [b] Lit. 173–174°: L. Caglioti and M. Magi, *Tetrahedron*, **19**, 1127 (1963). [c] D. G. Farnum, *J. Org. Chem.*, **28**, 870 (1963). [d] Lit. 163–164°: W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952). [e] From the hydrazone, see Experimental Section. [f] Lit. 177–179°; ref 26. [g] Lit. 185–187°: T. Sato and I. Hamma, *Bull. Chem. Soc. Jap.*, **44**, 1885 (1971). [h] Lit. 128°, ref *c* above.

hydrate was refluxed for 40 hr and then extracted with three portions of ether. The ether solution was dried, evaporated at reduced pressure, and distilled *in vacuo* to obtain 17.3 g (89%) of fenchone hydrazone, bp *ca.* 80° (2–5 mm). A solution of 550 mg (3.3 mmol) of the hydrazone in 5 ml of dry pyridine was cooled in a Dry Ice–acetone bath and a solution of 1 g (5.5 mmol) of *p*-toluenesulfonyl chloride in 5 ml of pyridine added slowly over a 5-min period. The solution was allowed to warm to room temperature and diluted with 1:1 methanol–water. The resulting pale yellow crystals (505 mg, 60%) had mp 115–116°. Recrystallization from aqueous ethanol afforded the analytical sample (Table V, footnote *a*).

Reduction of Ketones and Aldehydes to Hydrocarbons. General Procedures. Method A. The reduction method is presented in the text. For preparative applications the deoxygenation of *n*-octyl-5-keto hexanoate to *n*-octyl hexanoate is typical. To a solution of the keto ester (1.45 g, 6.0 mmol) and *p*-toluenesulfonylhydrazine (1.42 g, 7.5 mmol) in 30 ml of a 1:1 mixture of DMF–sulfolane containing 150 mg of *p*-toluenesulfonic acid at 100° was added $NaBH_3CN$ (1.51 g, 24 mmol) and 10 ml of cyclohexane, and the solution was heated at 100–105° for 2 hr. The reaction was then diluted with 70 ml of water and extracted three times with cyclohexane. The cyclohexane solution was washed twice with water, dried, and concentrated on a rotary evaporator. Distillation of the residue *in vacuo* afforded 1:1 g (80%) of product, bp 98–99° (0.8 mm), identical in all respects with an authentic sample.

Method B. A solution of the tosylhydrazone (1 mmol), $NaBH_3CN$ (4 mmol), and 50 mg of *p*-toluenesulfonic acid in 5 ml of a 1:1 mixture of DMF–sulfolane[27] was heated at 110°. In order to monitor the reactions, an appropriate inert internal standard and 5 ml of cyclohexane were added and, at intervals, the cyclohexane solution was analyzed by glpc. At appropriate times (Tables II and III), additional identical portions of the reagents were added and the heating was continued. Upon completion, the reactions were diluted with water or brine, the layers were separated, and the cyclohexane solution was analyzed by glpc. Alternately, the ketone and a 10–25% excess of *p*-toluenesulfonylhydrazine in 2–5 ml of ethanol/mmol of ketone were refluxed for 1–24 hr (Table V) to produce the *p*-tosylhydrazone. The ethanol solvent was then removed at reduced pressure, replaced with 1:1 DMF–sulfolane, and the reduction conducted as above. Preparative applications of the method are illustrated for the reduction of adamantanone to adamantane. A solution of adamantanone tosylhydrazone (1.91 g, 6 mmol), $NaBH_3CN$ (1.51 g, 24 mmol), and 300 mg of *p*-toluenesulfonic acid in 20 ml of 1:1 DMF–sulfolane and 10 ml of cyclohexane contained in a one-neck flask equipped with condenser and drying tube was heated with stirring at 110°. After 2 hr, additional equal portions of $NaBH_3CN$ and tosylic acid were added and the process was repeated after 4 hr. After 6 hr total, the reaction was diluted with 40 ml of water and extracted several times with benzene. The benzene solution was dried and *carefully* evaporated on a rotary evaporator. Sublimation of the residue at 50° (1 atm) afforded 689 mg (84%) of adamantane, identical in all respects with an authentic sample.

Method C. The procedure was similar as above except the 1:1 DMF–sulfolane solution was 0.2 *M* in the tosylhydrazone and 2.0 *M* in $NaBH_3CN$. Acidification was carried out by adding a small amount of Bromcresol Green and then cautiously adding concentrated HCl dropwise through the top of the condenser until the blue-green color changed to tan. The reactions were heated at 110° and the pH was kept below 3.8 by adding concentrated HCl as indicated by the Bromcresol Green. Additional portions of the reagents (including Bromcresol Green) were added for severely hindered systems. Work-up was identical as above.

Method D. The procedure was identical with method C, except the solution was 0.8 *M* in $NaBH_3CN$.

Acknowledgments. We wish to express our thanks to the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and the National Science Foundation for an Undergraduate Fellowship to C. A. M.

(27) For larger scale reactions the relative amount of solvent may be reduced.