G. H. Williams, *Intra-Sci. Chem. Rep.*, **3**, 229 (1969); P. H. Oldham, G. H. Williams, and B. A. Wilson, *J. Chem. Soc. B*, 1346 (1970).
(6) A. Weissberger, Ed., "Technique of Organic Chemistry", Vol. VII, Interscience, New York, N.Y., 1955.

Registry No.—**2**, 10304-79-7; **3**, 65915-27-7; hexafluorobenzene, 392-56-3; cyclohexane, 110-82-7.

Sodium Borohydride in Acetic Acid. A Convenient System for the Reductive Deoxygenation of Carbonyl Tosylhydrazones

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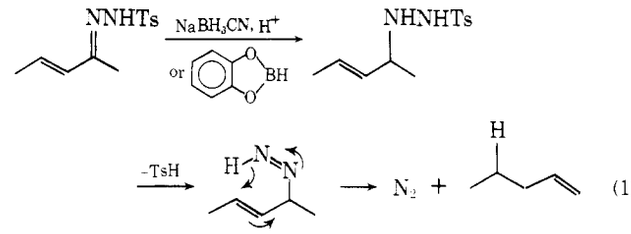
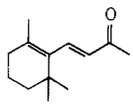
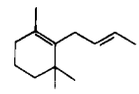
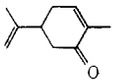
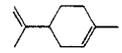
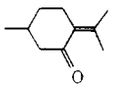
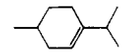
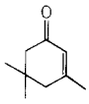
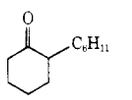
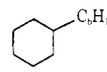
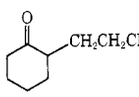
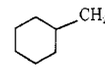
The reductions of carbonyl tosylhydrazones to hydrocarbons with sodium cyanoborohydride in acidic media[1] or with catecholborane[2] provide mild and selective alternatives to standard Wolf–Kishner deoxygenation.[1,2] With α,β-unsaturated derivatives, alkenes are usually furnished in which the double bond migrates to the position formerly occupied by the carbonyl (eq 1) even when such movement produces less thermodynamically stable positional isomers. Thus, alkene linkages may be moved from conjugation with aromatic rings or other π systems and the procedures offer a convenient pathway to exocyclic olefins.[1,2] The mechanism for this intriguing "alkene walk" reaction apparently proceeds through a diazene intermediate which deposits a hydride via a 1,5 migration as illustrated in eq 1.



(1)

The full synthetic potential of the methods are, however, hampered by the relative expense of both hydride reagents,

Table I. Reductive Deoxygenation of Tosylhydrazones with Sodium Borohydride–Acetic Acid

Tosylhydrazone	Registry no.	Method[a]	Time at 70 °C, h	Product	Registry no.	% yield isolated
	21195-61-9	A B C B[b]	2.5 1.0 2.5 3.0		13066-63-2	87 89 52 81
	41780-85-2	A B	2.0 1.0		1003-64-1	72 61
	21195-60-8	A B	2.0 1.5		138-86-3	10 70
	21195-64-2	B	1.5		500-00-5	51
	65226-90-6	B	4.0		1712-47-6	67
	65226-92-8	B	3.0		65226-94-0	57
	21195-62-0	B	5.0		503-44-6	18
$C_6H_5CH{=}CHCHO$	7318-33-4	A B	1.5 1.5	$C_6H_5CH_2CH{=}CH_2$	300-57-2	42 56
$C_6H_5CH{=}CHCOCH_3$	17336-65-1	B	3.0	$C_6H_5CH_2CH{=}CHCH_3$	1560-06-1	54
$CH_3(CH_2)_4CO(CH_2)_4CH_3$	65930-66-7	A B	1.5 1.5	$CH_3(CH_2)_9CH_3$	1120-21-4	81 84
	41780-66-9	A B	2.0 2.0		92-51-3	61 61
	13992-91-1	A B	2.0 2.0		41010-09-7	68 70
$o\text{-}OC_2H_5C_6H_4CHO$	65609-76-9	A B	2.0 3.0	$o\text{-}OC_2H_5C_6H_4CH_3$	614-71-1	44 80
$C_6H_5CO(CH_2)_2CH_3$	41780-81-8	B	4.0	$C_6H_5(CH_2)_3CH_3$	104-51-8	68

[a] Method C involved preparation and utilization of $NaBH(OAc)_3$ in benzene as described in ref 7f; this procedure appears inferior for the present application. [b] The tosylhydrazone prepared in situ in acetic acid from the ketone and tosylhydrazone followed by addition of $NaBH_4$.

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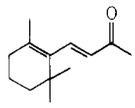
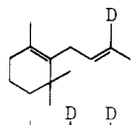
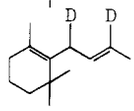
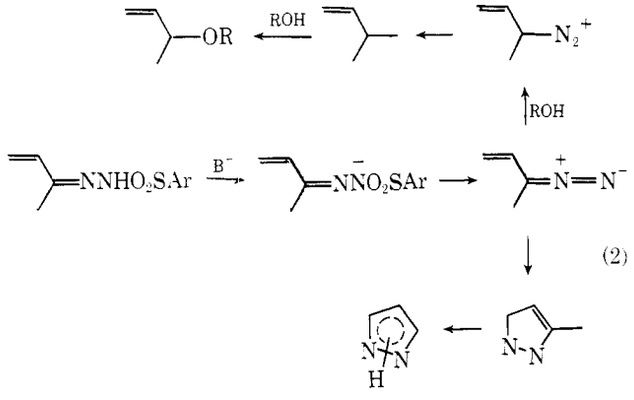
Table II. Deuterium Incorporation in the Reductive Deoxygenation of Tosylhydrazones

Tosylhydrazone	Method	Time at 70 °C, h	Product	Registry no.	% yield isolated
	A: $NaBD_4$, HOAc	1.5		16940-66-2	75
	D:[a] $NaBD_4$, DOAc	1.5		64-19-7	81
$C_6H_5CO(CH_2)_2CH_3$	A:[b] $NaBD_4$, HOAc	4.0	$C_6H_5CHD(CH_2)_2CH_3$	15681-89-7	60
	E:[c] $NaBD_4$, DOAc	4.0	$C_6H_5CD_2(CH_2)_2CH_3$	758-12-3	72

[a] Method D: the deuteride reagent (12.5 mmol) was dissolved in 10 mL of HOAc or DOAc and added to a slurry of 5 mmol of the tosylhydrazone in 10 mL of HOAc or DOAc. The solution was stirred at room temperature for 1 h and at 70 °C for 1.5 h and worked up as in method A. [b] A fivefold excess of $NaBD_4$ was used. [c] Method E: same as method D, fivefold excess of $NaBD_4$.

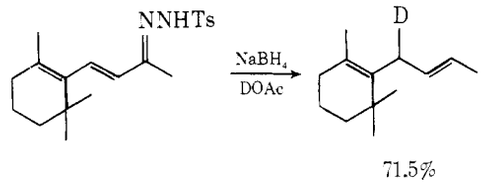
the relative inconvenience of handling moisture-sensitive catecholborane, at least for large scale and/or industrial applications, and the reluctance of $NaBH_3CN$ to attack aryl[3] and cyclic enone derivatives. Unfortunately, although $NaBH_4$ in the usual solvents (CH_3OH, C_2H_5OH, THF) reduces saturated tosylhydrazones to hydrocarbons,[4] the application to α,β-unsaturated cases fails, leading instead to allylic ethers and/or pyrazoles in alcohol solvents.[5] These divergent pathways have been attributed by Pagnoni and co-workers[5] to a decreased electrophilicity of conjugated imine π bonds which allows initial abstraction of the acidic N–H proton by the basic BH_4^- followed by elimination to a diazo ketone and subsequent conversion to ethers or pyrazoles as presented in eq 2.



(2)

The recent disclosures and exploitation of the utility of $NaBH_4$ in carboxylic acid solvents[7] suggested the possible advantage of this reagent system to circumvent the problems associated with conjugated (and aryl) tosylhydrazones. Thus, protonation of the imine nitrogen should increase the rate of nucleophilic attack while, concomitantly, preventing production of the offending tosylhydrazone anion.

This report presents the successful realization of the use of $NaBH_4$ in acetic acid as a convenient and relatively inexpensive alternative method for the reductive deoxygenation of most types of tosylhydrazones, including α,β-unsaturated and aryl cases. General experimental procedures have been developed for successful conversion of structural varieties, dependent upon the ease or reluctance of reduction. For unhindered aliphatic and several unsaturated systems, the procedure (method A) involves dissolving a 2.5 mol excess of $NaBH_4$ (conveniently handled in the pellet form) in glacial acetic acid (ca. 1.4 mL/mmol $NaBH_4$) while keeping the temperature between ca. 15 and 20 °C with an ice bath. To this solution (probably $NaBH(OAc)_3$)[7] is added the tosylhydrazone and the mixture is stirred at ambient temperature for 1 h and then at 70 °C for 1–4 h to complete the reduction. Workup is accomplished by pouring the solution into crushed ice, adjustment of the pH to ca. 9 with aqueous NaOH, and extraction with pentane or hexane. Evaporation and distillation (or recrystallization) provide the product hydrocarbon. For less electrophilic tosylhydrazones (aromatic and certain conjugated derivatives), a more vigorous procedure was required for adequate conversions (method B). Thus, the tosylhydrazone is slurried in glacial acetic acid (ca. 3.5 mL/mmol tosylhydrazone) and a 10 mol excess of $NaBH_4$ pellets is added at such a rate that foaming does not become an inconvenience. After addition, the solution is stirred at ambient temperature for 1 h and then at 70 °C for 1–4 h; workup is accomplished as in method A. Although the above procedures have not been completely optimized, we have found no need for an inert atmosphere, only adequate ventilation for hydrogen generated in the reaction. The results for a variety of structural types are presented in Table I and illustrate the versatility of the systems. The convenience and relative inexpense of the reagent suggest considerable utility for such transformations, especially on large scale. Furthermore, use of $NaBD_4$ in CH_3COOH or CH_3COOD allows the regioselective introduction of one or two deuterium atoms, respectively (i.e., eq 3 and Table II),



(3)

71.5%

thus augmenting applications of the procedure. With CH_3COOD, exchange of the tosylhydrazone N–H proton evidently is faster than reduction and hydride transfer to carbon.

A limitation was encountered involving isophorone tosylhydrazone which furnished only 18% of the desired rearranged alkene. Apparently, steric encumbrance to situating the required pseudoaxial diazene link over the ring (containing a pseudoaxial methyl) for hydride deliverance interupts the mechanism and allows other, unknown reactions to compete. Furthermore, nitro groups do not always survive the reaction conditions. Thus, *p*-nitrobenzaldehyde tosylhydrazone afforded a complex mixture of unidentified products and essentially no *p*-nitrotoluene.[8]

Experimental Section

Materials. $NaBH_4$ in pellet form was supplied by Alfa Inorganics (Ventron Corp.) and used as received. $NaBD_4$ (98% D) was obtained from Merck & Co., Inc. The carbonyl tosylhydrazones were prepared as previously described.[1a,b,2d] Drying of organic solvents was accomplished with anhydrous Na_2SO_4.

Tosylhydrazone Reductions. The general reduction procedures are described in the text and Table II. The following representative

descriptions are provided for each method.

Method A. A solution of $NaBH(OAc)_3$ was prepared by dissolving $NaBH_4$ pellets (25 mmol, 945 mg, 4 pellets) in glacial acetic acid (35 mL) with ice-bath cooling such that the temperature was maintained between 15 and 20 °C. To this was added β-ionone tosylhydrazone[1b] (3.60 g, 10 mmol) and the mixture was stirred at ambient temperature for 1 h followed by 2.5 h at 70 °C. The solution was then poured into crushed ice, made basic with aqueous NaOH, and extracted with three portions of pentane. The pentane solution was dried and concentrated on a rotary evaporator and the residue was carefully distilled at reduced pressure (Kugelrohr apparatus) to obtain 1.66 g (87%) of diene product, identical in all respects with an authentic sample.[1b]

Method B. To a stirred slurry of 6-undecanone tosylhydrazone (5.08 g, 15 mmol) in 50 mL of glacial acetic acid was added $NaBH_4$ pellets (ca. 5.67 g, 150 mmol, 24 pellets) at such a rate that foaming was not a problem (ca. 1 h). The solution was stirred at room temperature for 1 h and then at 70 °C for 1.5 h and worked up as in method A. Distillation at reduced pressure (Kugelrohr apparatus) yielded 1.96 g of undecane, identical with an authentic sample.

Method C. See Table I, footnote *a*.

Method D. A partial solution of β-ionone tosylhydrazone (1.80 g, 5 mmol) in 10 mL of CH_3COOD was prepared by warming for a few minutes under an N_2 atmosphere. To this was added a solution of $NaBD(OAc)_3$ prepared by carefully adding $NaBD_4$ (523 mg, 12.5 mmol) to CH_3COOD (10 mL). The solution was stirred at room temperature for 1 h followed by 1.5 h at 70 °C. Workup as before afforded 0.77 g (81%) of 4-(2-methylcyclohexenyl)-2-butene-*2,4-d*, which showed 95 ± 5% d_2 incorporation by NMR.

Method E. Similar to method D; solutions of $NaBD_4$ (1.046 g, 25 mmol) and propyl phenyl ketone tosylhydrazone (1.58 g, 5 mmol) were each prepared in 10 mL of CH_3COOD. The combined solution was stirred at room temperature for 1 h and at 70 °C for 4 h and worked up as before to give 0.48 g (72%) of 1-phenylbutane-*1,1-d*$_2$. Analysis by NMR indicated 95 ± 5% d_2.

Acknowledgments. The authors thank the donors of the Petroleum Research Fund, administered by The American Chemical Society, for support of this work. We also thank Ventron Corp. for a generous supply of $NaBH_4$ (pellet form).

Registry No.—$NaBH_4$, 16940-66-2; HOAc, 64-19-7; $NaBD_4$, 15681-89-7; CH_3COOD, 758-12-3.

References and Notes

(1) (a) R. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *J. Am. Chem. Soc.*, **95,** 3662 (1973); (b) R. O. Hutchins, M. Kacher, and L. Rua, *J. Org. Chem.*, **40,** 923 (1975); (c) E. J. Taylor and C. Djerassi, *J. Am. Chem. Soc.*, **98,** 2275 (1976).
(2) (a) G. W. Kabalka and J. D. Baker, Jr., *J. Org. Chem.*, **40,** 1834 (1975); (b) G. W. Kabalka, D. T. C. Yang, J. H. Chandler, and J. D. Baker, Jr., *Synthesis*, 124 (1977); (c) G. W. Kabalka, D. T. C. Yang, and J. D. Baker, Jr., *J. Org. Chem.*, **41,** 574 (1976); (d) N. R. Natale and R. O. Hutchins, *Org. Prep. Proced. Int.*, **9,** 103 (1977); (e) review: G. W. Kabalka, *ibid.*, **9,** 133 (1977).
(3) Recently, the successful reductive deoxygenation of aryl tosylhydrazones with $NaBH_3CN$ has been accomplished via the mercuric complexes; see, G. Rosini and A. Medici, *Synthesis*, 530 (1976).
(4) (a) L. Caglioti, *Tetrahedron*, **22,** 487 (1966); (b) L. Caglioti and P. Grasselli, *Chem. Ind. (London)*, 153 (1964); (c) G. Rosini, G. Baccolini, and S. Cacchi, *Synthesis*, 44 (1975).
(5) (a) R. Grandi, A. Marchesini, U. M. Pagnoni, and R. Trave, *J. Org. Chem.*, **41,** 1755 (1976); (b) R. Grandi, W. Messerotti, U. M. Pagnoni, and R. Trave, *ibid.*, **42,** 1352 (1977).
(6) Similar divergent pathways leading to solvolytic products have been sporadically noted for tosylhydrazones under typical Bamford–Stevens conditions (strong base, protic or aprotic solvents, heat); see, for example, J. W. Wilt, C. A. Schneider, H. F. Dabek, Jr., J. F. Kraemer, and W. J. Wagner, *ibid.*, **31,** 1543 (1966); for an excellent general discussion of the Bamford–Stevens and related reactions, including mechanistic interpretations, see, R. H. Shipiro, *Org. React.*, **23,** 405 (1976).
(7) (a) 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); (b) G. W. Gribble and D. C. Ferguson, *J. Chem. Soc., Chem. Commun.*, 535 (1975); (c) G. W. Gribble and P. W. Heald, *Synthesis*, 650 (1975); (d) G. W. Gribble and R. M. Leese, *ibid.*, 172 (1977); (e) P. Marchini, G. Liso, and A. Reho, *J. Org. Chem.*, **40,** 3453 (1975); (f) N. Umino, T. Iwakuma, and N. Itoh, *Tetrahedron Lett.*, 763 (1976); (g) M. J. Haire, *J. Org. Chem.*, **42,** 3446 (1977).
(8) The reduction of nitro groups by borohydride has been previously noted; R. O. Hutchins, D. W. Lamson, L. Rua, C. Milewski, and B. Maryanoff, *ibid.*, **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).

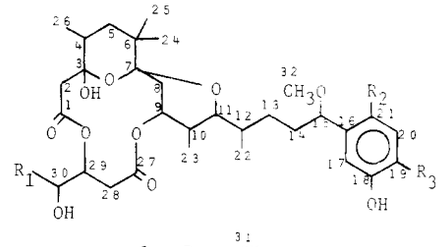
Communications

Toxins from Blue–Green Algae:[1] Structures of Oscillatoxin A and Three Related Bromine-Containing Toxins

Summary: Oscillatoxin A, a major toxic metabolite of a mixture of *Oscillatoria nigroviridis* and *Schizothrix calcicola* from Enewetak, has been identified from high-frequency ^1H and ^{13}C NMR studies as 31-nordebromoaplysiatoxin. Three minor bromine-containing toxic compounds from this algal mixture, viz., 21-bromooscillatoxin A, 19,21-dibromooscillatoxin A, and 19-bromoaplysiatoxin, have also been identified.

Sir: At one time a cyanophyte was suspected to be the primary causative organism of ciguatera, a disease associated with outbreaks of fish poisoning in the tropical and subtropical Pacific. While examining possible sources of the toxin in ciguateric fish of the Gilbert Islands, Banner found that two lipid-soluble toxins were present in *Schizothrix calcicola* from the atoll of Marakei, but neither toxin was characterized and both proved to be nonciguateric.[2]

In a previous communication[3] we reported the isolation of debromoaplysiatoxin (DAT, **1**) from a mixture of predominately two cyanophytes belonging to the Oscillatoriaceae tentatively identified as *Oscillatoria nigroviridis* and *Schizothrix calcicola*. We have now isolated from this algal mixture a second major toxic[4] component which we have named oscillatoxin A (OT-A, **2**) along with small amounts of 21-



1 $R_1 = CH_3$, $R_2 = R_3 = H$

2 $R_1 = R_2 = R_3 = H$

3 $R_1 = R_3 = H$, $R_2 = Br$

4 $R_1 = H$, $R_2 = R_3 = Br$

5 $R_1 = CH_3$, $R_2 = R_3 = Br$

bromo- and 19,21-dibromooscillatoxin A (**3** and **4**) and 19-bromoaplysiatoxin (**5**). DAT and OT-A may be identical with or related to the two lipid-soluble toxins that Banner had detected in *S. calcicola* from Marakei.

Frozen *O. nigroviridis-S. calcicola* (8 kg wet weight) collected from the seaward reef flat of Enewetak Island was homogenized and extracted with a mixture of methylene chloride and methanol (1:2 by volume). Water was added to the filtrate and the methylene chloride layer was washed repeatedly with water, dried over anhydrous sodium sulfate, and evaporated

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