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Maria Sakarellos-Daitsiotis, Chaim Gilon
Constantinos Sakarellos, Murray Goodman*
Department of Chemistry B-014
University of California, San Diego
La Jolla, California 92093
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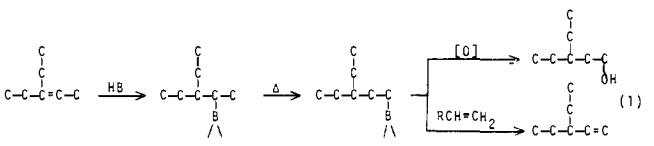
Remarkably Stable Organoboranes Derived from the Hydroboration of Olefins with 9-Borabicyclo[3.3.1]nonane. Utilization to Achieve the Successful Synthesis of Stereospecific Derivatives in 1-Substituted Cyclooctenes and Similar Related Derivatives

Sir:

Trialkylboranes derived from olefins via hydroboration with 9-borabicyclo[3.3.1]nonane are remarkably resistant to thermal isomerization. Thus the *B*-alkyl-9-BBN derived from *cis*-3-hexene requires heating at 150 °C for 168 h to attain the equilibrium distribution of boron along the hexyl chain. At the same temperature, the isomerization of the alkylborane from *cis*-3-hexene and borane is complete in only 1 h.[1c] This unusually sluggish migration of the 9-BBN moiety along the carbon skeleton makes possible the successful stereoselective hydroboration of certain labile systems not readily handled by earlier hydroborating reagents. For example, the hydroboration of 1-methylcyclooctene and 1-phenylcyclooctene with borane:THF produces mixtures of compounds arising from the facile isomerization of the borane intermediates. However, these olefins are readily hydroborated with 9-BBN and the intermediates oxidized to *trans*-2-methylcyclooctanol and *trans*-2-phenylcyclooctanol, isomerically pure.

It has been established that organoboranes undergo thermal isomerization under relatively mild conditions (75–160 °C in the presence of catalytic amounts of hydride).[1] This process apparently involves the migration of the boron atom along the carbon chain to yield products with boron attached predominantly to the least substituted carbon atom. The resulting mixture of organoboranes approaches thermodynamic equilibrium distribution. This isomerization reaction, combined with hydroboration of olefins, has opened up possibilities for useful synthetic transformations, such as the contrathermodynamic equilibration of olefins and the formation of primary alcohols from the corresponding tertiary or secondary isomers (eq 1).[1e] However, in some cases, the facile isomerization of



(1)

organoboranes constitutes an undesirable side reaction.[2] For example, early attempts to convert 1-methylcycloheptene and 1-methylcyclooctene into the corresponding *trans*-2-methylcycloalkanols via hydroboration–oxidation with diborane encountered difficulties because of the facile isomerization of the boron intermediates.[3] The availability of a reagent capable of forming thermally stable organoboranes would be highly desirable.

9-Borabicyclo[3.3.1]nonane (9-BBN)[4] possesses this particular quality. The relative rates of isomerization of borane vs. 9-BBN derived organoboranes (Table I) clearly indicate that the *B*-alkyl-9-BBN derivatives are far more resistant to isomerization than the parent organoboranes.

Table I. The Rates of Thermal Isomerization of the Organoboranes Derived from the Hydroboration of *cis*-3-Hexene Using 9-BBN and BH_3

Reagent	Ratio[a]	Temp, °C	Time, h	Distribution of hexanols,[b] % 3-ol	2-ol	1-ol
9-BBN	1.11	125	0	100	0	0
			1	90	10	Trace
			2	81	19	Trace
			4	69	31	Trace
			8	45	55	Trace
			25	27	70	3
		150	0	100	0	0
			1	51	48	1
			2	33	63	4
			4	25	67	8
			8	21	59	20
			25	15	34	51
			48	10	25	65
			168	4	8	88
BH_3[c]	1.20	125	0	100	0	0
			1	26	30	44
			2	18	25	57
			4	11	15	74
			8	9	9	82
			24	6	6	88
		150	0	100	0	0
			1	4	7	89
			2	3	6	91
			16	4	6	90

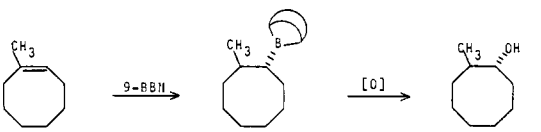
[a] Ratio of equivalent of hydride to 3-hexene. [b] From the alkaline hydrogen peroxide oxidation of the organoborane mixture. [c] H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **88**, 1433 (1966).

The distribution of the boron moiety on the carbons of the hexane chain was determined by gas chromatographic examination of the hexanols following alkaline hydrogen peroxide oxidation of the organoboranes.[5] The change in the isomeric distribution of the product from 3-hexene and 9-BBN (Table I) indicates that the boron moiety moves stepwise down the chain; consequently, it is possible to stop the reaction at an intermediate stage and obtain 2-hexanol in moderate yield.

Analogously, in a sluggish reaction, the *B*-alkyl-9-BBN compounds derived from 1- and 2-hexenes undergo slow isomerization to the same ultimate equilibrium mixture.

Even more striking results were obtained with the organoboranes derived from 1-methyl- and 1-phenylcyclooctene with 9-BBN. Previously, it was observed that the hydroboration of 1-methylcyclooctene with borane, followed by oxidation with alkaline hydrogen peroxide, did not yield the desired pure *trans*-2-methylcyclooctanol.[3,6] It was concluded that the intermediate organoborane must be undergoing a rapid isomerization around the cyclooctane ring, producing isomeric alcohols on oxidation.[6a] Similar results were realized in the present study in the hydroboration–oxidation of 1-phenylcyclooctene by the borane procedure.

However, application of 9-BBN solved the problem completely. Treatment of 1-methylcyclooctene with 9-BBN at 25 °C results in the clean hydroboration of the olefin (eq 2).



(2)

Oxidation of the intermediate with alkaline hydrogen peroxide yielded *trans*-2-methylcyclooctanol in 90% yield.[7] Only insignificant traces of isomeric material were observed in the GC examination of the product.

Similarly, 1-phenylcyclooctene underwent hydroboration–oxidation by this procedure to produce *trans*-2-phenylcyclooctanol[8] free of isomeric material, as revealed by GC and ^{13}C examination.

The reluctance of the 9-BBN moiety to move along the carbon skeleton is probably a reflection of the smaller steric crowding in the *B*-alkyl-9-BBN, as compared with other trialkylboranes. The availability of a hydroborating reagent capable of forming thermally stable organoboranes should prove to be very complementary to the reagents previously shown to yield readily isomerizable organoboranes and should extend application of hydroboration to the solution of problems in synthesis.

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(7) The 9-borabicyclo[3.3.1]nonane skeleton remains intact in all of the isomerization reactions reported, as shown by the quantitative formation of 1,5-cyclooctanediol following oxidation of the organoboranes.
(8) The molecular formula of this compound was obtained by high-resolution mass spectroscopy. The ^1H NMR spectrum displayed absorptions at δ 1.4–2.2 (m, 13 H), 2.75 (m, 1 H), 3.9 (m, 1 H), and 7.23 (s, 5 H).
(9) Visiting Scholar, 1972–1973, on funds provided by the Maruzen Oil Co. Ltd., Osaka, Japan.
(10) Research Associate on leave of absence from Centro de Investigacion IPN, Mexico 14, D.F. Postdoctorate Research Associate on Grant 10937 of the National Institutes of Health.

Hiroaki Taniguchi,[9] Lazaro Brener,[10] Herbert C. Brown*

R. B. Wetherill Research Laboratory, Purdue University
West Lafayette, Indiana 47907

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Aporphines. 22.[1] Electrochemical Synthesis of Aporphines via Cathodic Cyclization of Iodobenzylisoquinolinium Salts

Sir:

The clinical utilization of several aporphine alkaloids for the treatment of Parkinsonism[2a] and in cancer chemotherapy[2b] has focused attention on new methods for the synthesis of such polycyclic ring systems. Nonbiogenetic syntheses of aporphines from benzylisoquinoline precursors have involved principally Pschorr cyclizations or photochemical routes.[3] Biogenetic type syntheses utilizing oxidative coupling reactions of phenols have long been recognized as a mode of carbon–carbon bond formation in the synthesis of aporphines and related compounds.[4,5] Recent studies have demonstrated that electrooxidative cyclization of the benzyltetrahydroisoquinoline alkaloid, (±)-laudanosine, gave a morphinandienone,[6] which in turn could be converted to the aporphine alkaloid (±)-glaucine.[7] We wish to report herewith a novel synthesis of aporphine **3a** and apomorphine dimethyl ether (**3c**) via cathodic cyclization of the 1-(*o*-iodobenzyl)isoquinolinium methiodides **1a** and **1b**, and to propose a mechanism which involves the formation of the intermediate tetradehydroaporphine **2**.

The iodobenzylisoquinolinium salts **1a**[8] and **1b**[9] (mp 230–235 °C) were prepared via Reissert alkylation[10] from 2-benzoyl-1,2-dihydroisoquinaldonitrile and the appropriately substituted benzyl chloride. Cyclic voltammetry of **1a** and **1b** (Figure 1) showed in the cathodic sweep, two one-electron

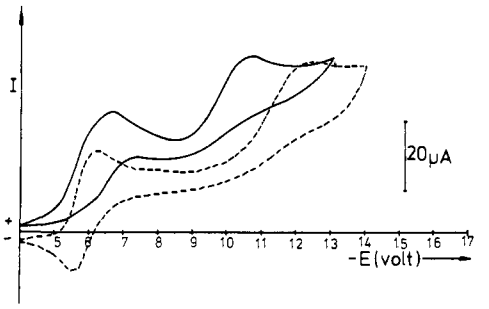
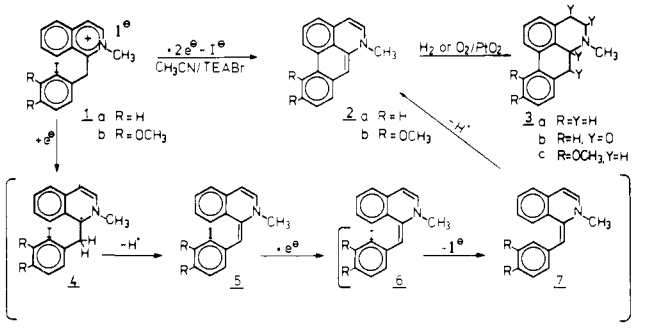


Figure 1. Cyclic voltammogram for the reduction of **1a** (- - -) and **1b** (—) 7×10^{-6} mol in CH_3CN containing 0.1 mol of tetraethylammonium bromide (TEABr). Scan rate 100 mV/s.

Scheme I



reduction waves of which the second was entirely irreversible in the anodic sweep at peak potentials of −660 and −1256 mV for **1a** and −672 and −1072 mV for **1b** (against a silver wire reference electrode).

On the basis of these results, the quantitative electrolysis of **1a** and **1b** was undertaken in a two-compartment cell specially constructed for such reactions.[11] The electrolysis cell consisted of an anodic compartment with a carbon electrode, and a cathodic compartment with a mercury cathode together with a silver wire as a reference electrode. The two-cell compartments containing the electrolyte solution of TEA bromide (0.3 M) in CH_3CN were separated by a Nafion 125 membrane.[12]

One gram (2.05 mmol) of **1a** dispersed in 120 ml of 0.3 N TEA bromide in dry CH_3CN was reduced under a nitrogen atmosphere at room temperature at −1500 mV. The initial current of 120 mA dropped smoothly to 3 mA in approximately 4 h with an uptake of 398 C. (Theoretical uptake for a two-electron reduction process is 396 C.) The solution was then evaporated to dryness, dissolved in 50 ml of CH_2Cl_2 (previously flushed with argon), and chromatographed on a silica gel column (100 g) which had also been preflushed with argon. The yellow eluate was evaporated to dryness to yield 400 mg (86%) of yellow crystals of **2a**: mp 75–77 °C;[13] UV_{max}^{MeOH} (log ϵ) 228 (4.46), 275 (4.20), 300 (3.41), 339 (4.03), 352 (4.09), 404 (3.77), 427 (3.75); NMR ($CDCl_3$) 3.10 (s, 3 H), 5.68 (d, 1 H), 6.11 (s, 1 H), 6.31 (d, 1 H) and seven aromatic protons at 6.82 (d, 1 H), 7.12–7.52 (m, 4 H), 7.96 (d, 1 H), 8.21 (d, 1 H); mass spectrum *m/e* (%) 231 (100, M^+), 216 (91), 189 (23), 135 (72).

Catalytic hydrogenation of **2a** in methanolic HCl with PtO_2 (100 mg) gave aporphine hydrochloride (**3a**·HCl, 88%): mp 258–259 °C dec (lit.[14] 255 °C, 252–254 °C[8]) identical with an authentic sample.[15] When the catalytic reduction of **2a** was carried out with deuterium in CH_3OD with several drops of DCl in D_2O, a product **3b** (mp 258–259 °C dec) was isolated whose mass spectrum indicated that partial aromatic deuteration had also taken place.[16] The mass spectrum exhibited a series of peaks 4–8 mass units higher than the M^+ (235) ion of the hydrogenated compound **3a**. Fragments arising from sequential elimination of hydrogen or deuterium, CH_3, and