Notes

Unusual Regioselectivity in the Hydroboration of 5-Methyl-2-hexyne

Suzanne W. Slayden

Department of Chemistry, George Mason University, Fairfax, Virginia 22030

Received November 26, 1979

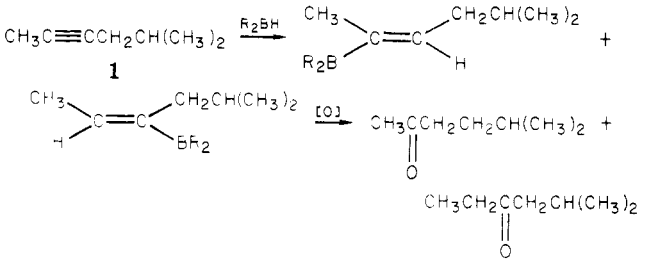
Many systematic investigations have been conducted to provide information on the factors which govern the scope, mechanism, stereochemistry, electronic and structural effects, reactivity, and selectivity of the hydroboration of alkenes and alkynes.[1] Initiation of the present study on the regioselectivity of hydroboration of 5-methyl-2-hexyne (1) (Scheme I) was prompted by the need to compare the steric and electronic effects of alkyl and functional group substituents remote from the triple bond in unsymmetrically disubstituted alkynes.[2]

In order to assure a valid comparison with published results, 2-hexyne was hydroborated with diborane, dicyclohexylborane, disiamylborane, and 9-BBN in both THF and hexane solvents. The boron distribution in the reactions was deduced from GC analysis of the ketone isomers produced after alkaline peroxide oxidation of the corresponding intermediate *B*-vinylboranes. The yields (except from 9-BBN) and ratios of isomeric ketones are the same within experimental error (±3%) as those previously reported.[3]

Identical procedures were used in the hydroborations of **1**. The 5-methyl-2- and -3-hexanone products were each isolated by preparative GC and shown to be pure by NMR analysis. Absence of the products 5-methyl-2- and -3-hexanol demonstrated that no dihydroboration of the alkyne had occurred. The data are summarized in Table I.

The mechanism of borane addition is postulated to occur via a concerted pathway which may be preceded by a π-complex intermediate.[5] Steric and electronic factors in both the unsaturated compound and the hydroborating agent govern the regioselectivity of the reaction. Electronic effects in the hydrocarbon presumably operate by stabilizing the charge distribution on the reacting carbons in the transition state and thus influencing the orientation of the polarized B–H atoms. Nonconjugated, inductively electron-withdrawing groups, whose effects fade with distance from the reaction site, enhance the attachment of boron to the carbon closer to the substituent. The effect of electron-donating alkyl groups, which would direct the boron to the carbon further away, is compounded by a steric effect operating in the same direction. Electronic effects in the hydroborating reagent have not been systematically studied.

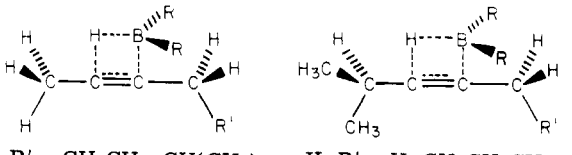
Scheme I



Attachment of boron to the less hindered carbon is enhanced both by α branching in the hydrocarbon and by an increase in the steric requirement of the borane. The steric difference in identically dialkyl-substituted alkenes and alkynes, manifested by an increased regioselectivity with the alkyne, is due to the greater interaction of the hydroborating agent with the atoms substituted on the α carbons of the short, linear acetylene.[4]

As shown in Table I, an increase in selectivity, compared to BH_3, is noted for each alkyne when the more sterically demanding monohydroborating agents are used. Also, as the number of substituents on a carbon α to the triple bond is increased, the regioselectivity becomes more pronounced with all hydroborating agents. The steric requirement of the large *tert*-butyl group is quite effective in directing the boron to the less hindered carbon.

However, an alkyl group which is substituted β to the triple bond should not significantly interfere with groups on boron. On the basis of the model for the most likely alkyne conformation during addition (I), the boron distribution in **1** is expected to be similar to that of the straight-chain alkyne, 2-hexyne. Or, if the sole basis for comparison were apparent steric bulk around the triple bond, then the hydroboration of **1** should be *more* regioselective. In fact, the opposite is true.



I, R' = CH_2CH_3, $CH(CH_3)_2$ II, R' = H, $CH_2CH_2CH_3$

Another example of unexpected regioselectivity in the hydroboration of alkynes can be cited, although these results were not explicitly discussed. Table II summarizes the published data[4] for 4-methyl-2-pentyne (**2**) and 2-methyl-3-octyne (**3**). Replacement of the smaller methyl substituent by the larger *n*-butyl substituent decreases the regioselectivity of the reactions. Thus it could be argued that there is a tendency for the boron distribution to approach 50:50 as the steric bulk on both sides of the triple bond becomes comparable. However, if the point of view is taken that **3** is another case of substitution (ethyl) β to the triple bond, a conformational model (II) may be used again to predict that the hydroborating agent would experience no steric interaction with the substituent. The regioselectivity should be similar to that for **2**.

(1) (a) H. C. Brown, "Organic Synthesis via Boranes", Wiley, New York, 1975; (b) G. M. Cragg, "Organoboranes in Organic Synthesis", Marcel Dekker, New York, 1973.
(2) G. W. Kabalka and S. W. Slayden, *J. Organomet. Chem.*, **93**, 33 (1975).
(3) H. C. Brown, C. G. Scouten, and R. Liotta, *J. Am. Chem. Soc.*, **101**, 96 (1979).
(4) G. Zweifel, G. M. Clark, and N. L. Polston, *J. Am. Chem. Soc.*, **93**, 3395 (1971).
(5) (a) P. R. Jones, *J. Org. Chem.*, **37**, 1886 (1972); (b) M. J. S. Dewar and M. L. McKee, *Inorg. Chem.*, **17**, 1075 (1978).

0022-3263/80/1945-2908$01.00/0

Table I. Directive Effects in the Hydroboration of Methyl-Substituted Alkynes with Several Hydroborating Agents[a]

hydroborating agent	alkyne			
	$CH_3C^2{\equiv}C^3$-$CH_2CH_2CH_3$[b,c]	$CH_3C^2{\equiv}C^3$-$CH_2CH(CH_3)_2$[b] (1)	$CH_3C^2{\equiv}C^3$-$CH(CH_3)_2$	$CH_3C^2{\equiv}C^3$-$C(CH_3)_3$
diborane	60/40	53/47	75/25[d]	79/21[d]
disiamylborane	61/39	54/46	93/7[d]	97/3[d]
dicyclohexylborane	66/34	56/44	92/8[d]	97/3[d]
9-BBN	78/22	72/28	96/4[e]	99/0[e]

[a] The C^2/C^3 distribution ratio of boron was deduced from the isomeric ketones produced after oxidation of the borane intermediates. The data are averages of at least two experiments. The solvent was THF. [b] Yields of ketones were ≥85% in all cases except with 9-BBN (~70%). [c] This study. See also ref 3 and 4. [d] Reference 4. [e] Reference 3.

Table II. Directive Effects in the Hydroboration of Unsymmetrical Disubstituted Alkynes with Thexyl-, Dicyclohexyl-, and Disiamylborane[a]

hydroborating agent	alkyne	
	$(CH_3)_2CH$-$C^3{\equiv}C^2CH_3$[b] 2	$(CH_3)_2CHC^3{\equiv}C^4(CH_2)_3CH_3$[c] 3
thexylborane	19/81	28/72
disiamylborane	7/93	13/87
dicyclohexylborane	8/92	15/85

[a] Reference 4. [b] The C^3/C^2 distribution ratio of boron in the ketone product. [c] The C^3/C^4 distribution ratio of boron in the ketone product.

An interesting paradox is now apparent when the 1/2-hexyne and **2**/**3** studies are compared. In both, the regioselectivity of hydroboration decreases when a smaller group is replaced by a larger group. Only the **2**/**3** case would have been accepted by cursory examination of condensed structural formulas. In neither case would the change in regioselectivity have been predicted with regard to conformational models of the reacting systems (I and II).

If the reacting conformations of the alkynes are as shown, then it seems that steric effects do not greatly control the regioselectivity of the reaction with a given hydroborating agent when the steric bulk is β to the triple bond. If the regioselectivity cannot be assigned to a controlling steric effect, then hydroboration of disubstituted alkynes may exhibit a sensitivity to the differences in alkyl group electronic effects that heretofore has gone unnoticed.

The cause of the observed alkyl effect is not certain. If the β-methyl substituent were acting as an inductive electron-donor, then the regioselectivity, compared to 2-hexyne, would increase. Again, alkyl electronic and steric effects operate in the same direction. However, the methyl group appears to act as an electron-withdrawing group, enhancing attack of boron on the carbon closer to the substituent. The effect, although smaller, resembles that of 5-methoxy-2-hexyne with dicyclohexylborane wherein 61% of the boron is attached to C-3.[2]

A tentative explanation may be offered. The methyl group in the reacting conformation of **1** is in close proximity to C-3 of the triple bond, and it may be exerting a field effect which selectively increases the partial negative charge at that carbon.

This explanation does not account for the difference in regioselectivity for **2**/**3**, however. If **3** were reacting in a coiled structure[6] which places the alkyl group near the triple bond, then the regioselectivity compared to **2** should increase. Until more data is obtained, the paradox is unresolved.

(6) M. S. Newman, "Steric Effects in Organic Chemistry", Wiley, New York, 1956, Chapter 4.

Experimental Section

General Methods. All manipulations were performed in an atmosphere of prepurified nitrogen. Glassware, syringes, and needles were oven-dried and then cooled while being flushed with nitrogen. GC analyses were performed on a Bendix 2300 gas chromatograph. Peak integration was carried out by using a Hewlett-Packard 3380S integrator. NMR analyses were performed on a Hitachi Perkin-Elmer R-24B spectrometer.

Materials. Tetrahydrofuran (Mallincrodt) and cyclohexene (Eastman) were dried with lithium aluminum hydride and distilled under nitrogen. *n*-Hexane (Matheson, Coleman and Bell) was used as received after being checked for purity and dried over molecular sieves. 2-Methyl-2-butene (Aldrich), 2-hexyne (Farchan), and 5-methyl-2-hexyne (Farchan) were used as received after being checked for purity. Borane–methyl sulfide (BMS), 9-BBN/hexane, and 9-BBN/THF (Aldrich) were titrated according to a standard procedure[1a] to determine hydride molarity.

Hydroboration with (A) Dicyclohexylborane and (B) Disiamylborane. The procedure given below for the hydroboration of 2-hexyne is representative.

A dry 50-mL, round-bottomed flask with a septum-covered side arm and a gas inlet adaptor was assembled hot and cooled under a stream of dry nitrogen. The flask was cooled to 0 °C and charged via syringe with 2 mL of solvent (hexane or THF) and 0.5 mL of 10 M BMS.

A. Cyclohexene (10 mmol) was injected slowly into the stirred solution. Dicyclohexylborane precipitated within 15 min and the suspension was stirred at 0 °C for 3 h. The solvent along with any unreacted BMS and alkene was pumped off, and the flask was cooled to 0 °C and then refilled with nitrogen and 5 mL of fresh solvent. A solution of 2-hexyne (5 mmol, 2 mL, 2.5 M) was slowly added to the stirred solution at 0 °C. The solution was kept at 0 °C for 15 min and then at 25 °C for 1.5 h. Oxidation of the hexenylborane was achieved by cooling the solution to 0 °C and then coinjecting 2 mL of 3 N NaOH and 2 mL of 30% H_2O_2. The mixture was warmed to 50 °C for 30 min and was then salted out with NaCl. The organic phase was separated and dried over anhydrous $MgSO_4$.

B. 2-Methyl-2-butene (10 mmol) was injected slowly and the solution stirred at 0 °C for 15 min and then at 25 °C for 2 h. The remainder of the procedure is as in part A.

Hydroboration with 9-BBN. The hydroboration was performed according to a published procedure.[3] A buffer solution of pH 8 was prepared by adding 6 N NaOH to an aqueous 0.5 M solution of NaH_2PO_4. A 5-mL sample of the buffer solution and 2 mL of 30% H_2O_2 were mixed at 0 °C in a glassware assembly identical with that described above. Oxidation was achieved by slowly transferring the *B*-hexenyl-9-borabicyclo[3.3.1]nonane solution via a double-tipped needle to the buffered oxidizing solution. The mixture was stirred for 2 h at 0 °C, warmed to 25 °C, and then salted out with NaCl. The organic phase was separated and dried over anhydrous $MgSO_4$.

Hydroboration with BMS. The procedure given below for the hydroboration of 2-hexyne is representative.

In the glassware assembly described above were injected 5 mL of THF or hexane and 9 mmol of 2-hexyne. The solution was cooled to 0 °C, and 3 mmol of BMS was slowly added. The solution was stirred for 2 h at 0 °C and then oxidized by the

concurrent addition of 1 mL of 3 M NaOH and 1 mL of 30% H_2O_2. The mixture was warmed to 50 °C for 20 min and was then salted out with NaCl. The organic phase was separated and dried over $MgSO_4$.

Registry No. 1, 53566-37-3; BMS, 13292-87-0; cyclohexene, 110-83-8; 2-methyl-2-butene, 513-35-9; 9-borabicyclo[3.3.1]nonane, 280-64-8; diborane, 18099-45-1; disiamylborane, 1069-54-1; dicyclohexylborane, 1568-65-6; 2-hexyne, 764-35-2.

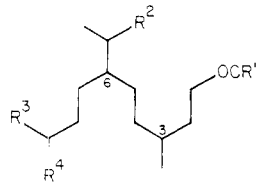
Sex Pheromone of the White Peach Scale: Highly Stereoselective Synthesis of the Stereoisomers of Pentagonol Propionate

R. R. Heath, R. E. Doolittle, P. E. Sonnet,* and J. H. Tumlinson

Insect Attractants, Behavior, and Basic Biology Research Labortory, Agricultural Research, Science and Education Administration, USDA, Gainesville, Florida 32604

Received December 3, 1979

Sex pheromones of scale insects that have recently been identified are those of the white peach scale, *Pseudaulacaspis pentagona* (Targioni-Tozzetti)[1] (**1**), the yellow scale, *Aonidiella citrina* (Coquillett)[2] (**2**), and the California red scale, *A. aurantii* (Maskell)[3] (**3**). Compound **4** has also been isolated from the red scale, but is apparently not biologically active.[3] We report the details of a highly

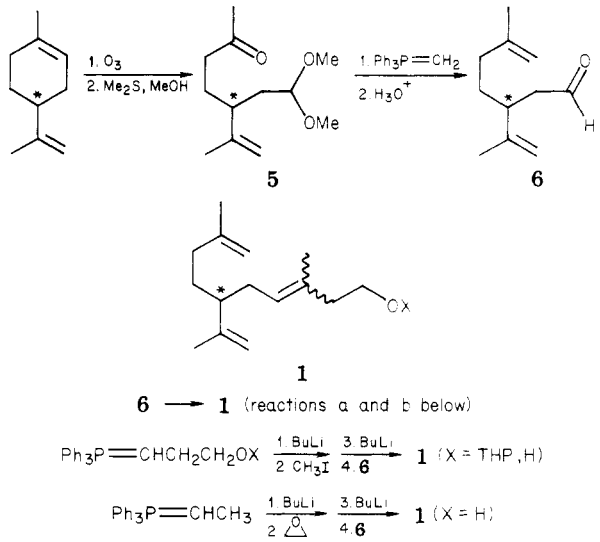


	R^1	R^2	R^3	R^4
1, Δ3(*Z*); 6*(*R*)	C_2H_5	$=CH_2$	CH_3	$=CH_2$
2, 3*(?); Δ5(*Z*); Δ8	CH_3	CH_3	CH_3	CH_3
3, Δ3(*Z*); 6*(*R*)	CH_3	$=CH_2$	H	$=CH_2$
4, 3*(?); 6*(?)	CH_3	$=CH_2$	H	$=CH_2$

stereoselective synthesis of the four stereoisomers of **1** (X = H) (Scheme I), pentagonol propionate [3,9-dimethyl-6-(1-methylethenyl)-3,9-decadien-1-ol propanoate].

A nonselective route was initially established from *dl*-limonene (see Scheme I). The ozonolysis of limonene in methanol was followed by a workup with dimethyl sulfide and *p*-toluenesulfonic acid to provide keto acetal **5** in 73% yield. Reaction of **5** with methylenetriphenylphosphorane followed by acid hydrolysis yielded the dienal **6** (80% yield). The trisubstituted olefinic linkage was then elaborated nonselectively in a multiple, single-pot alkylation in two ways: (1) The triphenylphosphonium salt derived from 3-bromo-1-propanol (hydroxyl either free or protected) was converted to an ylide, which was then alkylated with methyl iodide. The resulting salt was deprotonated and allowed to react with the dienal **6** to give **1** (X = H, 44% yield; or X = OTHP, 52% yield). (2) Alternatively,

Scheme I



ethylidenetriphenylphosphorane was treated with ethylene oxide. The resulting hydroxyethylated betaine was treated with a second equivalent of butyllithium, producing an ylide that reacted with **6** to give **1** (X = H) in 67% yield. The geometrical compositions of the propionates were 54:46 (*Z*:*E*) by the first route and 70:30 by the second. Although we subsequently performed these reactions in a manner that provided **1** (X = H) very stereoselectively, we found that the reactions just described, if performed with readily available (*R*)-(+)-limonene and routed through the sequence using ethylene oxide for generating the trisubstituted olefin, could be coupled with preparative high-performance LC as an efficacious synthesis of gram quantities of very pure (≥99%) (*R*)-(+)-(*Z*)-**1** (X = H). In addition to providing a more favorable *Z*:*E* ratio, the ethylene oxide route generated no byproducts that were difficult to separate. In contrast, the first nonselective route employing methyl iodide and the hydroxypropyltriphenylphosphonium salt invariably provided substantial quantities (~7%) of the demethyl product, which limited the high-performance LC cleanup procedure.

Insect sex pheromones are generally isolated in quantities so limited that assessment of absolute configuration often hinges upon successful synthesis of all enantiomers and the subsequent biological evaluation.[4] The dienal **6** was therefore synthesized from both (*R*)-(+)-limonene and the (*S*)-(−)-isomer as outlined in Scheme I. The convenient method of Bergot et al.[5] was employed to determine enantiomeric purity of **6**. The dienals were oxidized to the acids and, after conversion to their acid halides, were allowed to react with (*R*)-(+)-1-(1-naphthyl)ethylamine. The diastereomer content was then determined by high-performance LC. Although complete analytical details for related compounds employing this useful procedure have been published, synthetic experimental details have not yet been reported. We have therefore incorporated the details of the derivatization in the experimental section. The (*R*)-(+)-dienal **6** was ≥99% *R*, while the enantiomer was ≥96.5% *S* (the limitations, of course, were inherent in the limonene starting material).

Successful completion of a stereoselective route required generation of the homoallylic trisubstituted linkage of **1**. Johnson's extension of the Julia method for homoallylic

(1) R. R. Heath, J. R. McLaughlin, J. H. Tumlinson, T. R. Ashley, and R. E. Doolittle, *J. Chem. Ecol.*, in press.
(2) M. J. Gieselmann, D. S. Moreno, J. Fargerlund, H. Tashiro, and W. L. Roelofs, *J. Chem. Ecol.*, **5**, 27 (1979).
(3) W. L. Roelofs, M. J. Gieselmann, A. M. Carde, H. Tashiro, C. A. Henrick, and R. J. Anderson, *Nature*, **267**, 698 (1977); *J. Chem. Ecol*, **4**, 211 (1978).
(4) The identification of the white peach scale pheromone, for example, was based upon 5 μg of material (ref 1).
(5) B. J. Bergot, R. J. Anderson, D. A. Schooley, and G. A. Henrick, *J. Chromatogr. Sci.*, in press.