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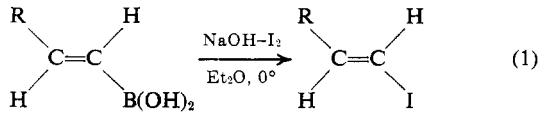
A Stereospecific Conversion of Alkenylboronic Acids into Alkenyl Bromides with Inversion of Configuration. Striking Differences in the Stereochemistry of the Replacement of the Boronic Acid Substituent by Bromine and Iodine and Its Significance in Terms of the Reaction Mechanism

Sir:

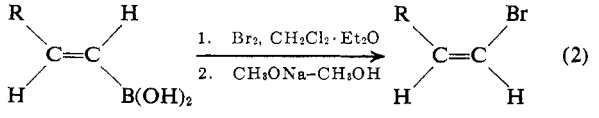
Alkenylboronic acids add bromine readily at low temperatures to produce intermediates which are converted by base into alkenyl bromides of 99% isomeric stereochemical purity in essentially quantitative yields. The replacement of the boronic acid substituent by bromine proceeds with inversion of configuration. This is in striking contrast to the retention of configuration observed in the base-induced iodination of alkenylboronic acids.[1] The catechol esters of alkenylboronic acids, readily synthesized *via* the hydroboration of alkynes with catecholborane,[2] can be converted directly into these alkenyl bromides. Consequently, this procedure provides a remarkably simple means for the conversion of alkynes into alkenyl bromides of high stereochemical purity.

We recently reported that *trans*-1-alkenylboronic acids are converted by iodine under the influence of base into the corresponding *trans*-1-alkenyl iodides of >99% stereochemical purity in almost quantitative yields[1] (eq 1). We undertook to synthesize the corresponding bromide by a similar procedure utilizing bromine. However, the results proved unsatisfactory. For example, the addition of bromine to a solution of *trans*-1-octenylboronic acid in the presence of aqueous sodium hydroxide at 0° provided a 65:35 mixture of *cis*- and *trans*-1-octenyl bromide in a yield of ~50%.[3] However, when the bromine was added first to the boronic acid, followed by the base, an essentially quantitative yield of the isomerically pure *cis*-1-octenyl bromide[4] was obtained (eq 2).



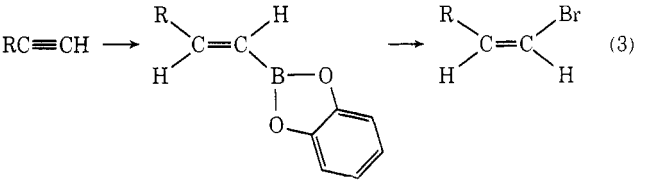
(1)

The observation that the replacement of the boronic acid group by bromine proceeds with inversion of configuration, whereas the earlier replacement by iodine proceeds with retention of configuration, was of major interest and stimulated a detailed study. The reaction appears to be general. Thus, *trans*-2-cyclohexylethenylboronic acid also undergoes substitution with inversion (eq 2).

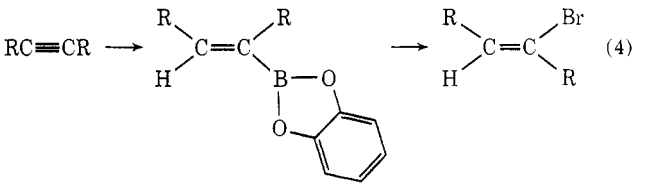


(2)

The catechol esters of *trans*-1-alkenyl- and internal *cis*-alkenylboronic acids are conveniently prepared by the hydroboration of the corresponding alkynes with catecholborane.[2] There would be an obvious advantage in utilizing these catechol esters directly. Use of 1 molar equiv of bromine resulted in a low yield. Evidently the catechol moiety was reacting competitively with the bromine. However, use of 2 molar equiv of bromine solved this problem. Consequently, treatment of the catechol esters of the alkenylboronic acids with 2 molar equiv of bromine in methylene chloride, followed by treatment with base, provides a simple, practical procedure for the conversion of both terminal and internal alkynes into stereochemically pure vinyl bromides (eq 3 and 4).



(3)



(4)

Representative results are summarized in Table I. The following experimental procedure was utilized. The alkyne, 25.0 mmol, was hydroborated with 25.0 mmol of catecholborane as described previously[2] to produce the catechol ester of the alkenylboronic acid. The product was dissolved in 25 ml of methylene chloride and cooled to the appropriate reaction temperature (Table I), and 50 mmol of bromine was added. The reaction mixture was stirred for 1 hr, and then 50 mmol of base (aqueous sodium hydroxide or sodium methoxide in methanol) was added. The mixture was stirred for 1 hr and then brought to room temperature. Water, 25 ml, was added and the organic phase was separated. The aqueous phase was extracted twice with methylene chloride and the combined organic phase was dried over magnesium sulfate. Distillation yielded the vinyl bromide. Thus, from 25.0 mmol of 1-octyne, there was obtained 3.94 g of *cis*-1-octenyl bromide [bp 90–91° (35 mm); n^{20}D 1.4619], a yield of 82%. The product was characterized by ir (700 cm^{-1}), pmr (δ 5.8–6.4 (2 H, m), 1.8–2.9 (2 H, m), 0.8–1.8 (11 H, m)), and mass spectrometry [*m/e* 192 (100), 190 (100)].

It is possible to account for the inversion of configuration in the present reaction in terms of the usual trans addition of bromine to the double bond,[5] followed by a

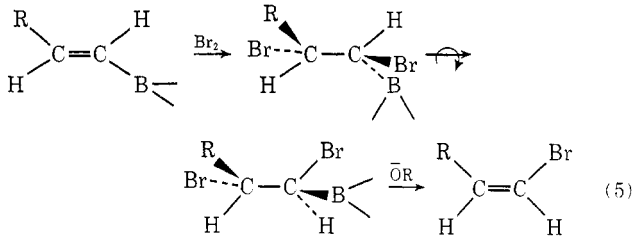
(1) H. C. Brown, T. Hamaoka, and N. Ravindran, *J. Amer. Chem. Soc.*, **95**, 5786 (1973).
(2) H. C. Brown and S. K. Gupta, *ibid.*, **94**, 4370 (1972).
(3) Another product, more volatile than the bromides, was noted in the gas chromatogram. The reaction mixture revealed strong >C=O absorption in the ir spectrum. Possibly octanal is formed *via* oxidation of the vinylboronic acid by hypobromite (from bromine and the base).
(4) Hydroalumination–bromination of alkynes gives vinyl bromides of opposite stereochemistry: see G. Zweifel and C. C. Whitney, *ibid.*, **89**, 2753 (1967).
(5) (a) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, pp 150, 523; (b) S. Winstein, *J. Amer. Chem. Soc.*, **64**, 2792 (1942); (c) D. H. R. Barton and E. Miller, *ibid.*, **72**, 1066 (1950); (d) E. L. Eliel and R. G. Haber, *J. Org. Chem.*, **24**, 143 (1959).

Table I. Stereospecific Conversion of Alkynes to Alkenyl Bromides *via* Hydroboration–Bromination–Elimination

Alkyne	Intermediate brominated (yield, %)[a]	Temp,[b] °C	Base used	Stereochemical purity[c]	Yield of alkenyl bromide,[c] %
1-Octyne	Boronic acid (90)	−20	MeONa–MeOH	99% cis	94,[d] 85[e]
	Catechol ester (90)	0	Aq NaOH	99% cis	100,[d] 90[e] (91,[d] 82[e])
Cyclohexylethyne	Boronic acid (93)	−40	MeONa–MeOH	99% cis	95,[d] 88[e]
	Catechol ester (93)	−40	MeONa–MeOH	99% cis	91,[d] 85[e]
Phenylethyne	Catechol ester	−40	MeONa–MeOH	99% cis	90[e]
3-Hexyne	Catechol ester (92)	−20	MeONa–MeOH	99% trans	92,[d] 85[e]
4,4-Dimethyl-2-pentyne	Catechol ester (97)	−20	MeONa–MeOH	98% trans	99,[d] 96[e]

[a] See ref 2. [b] At higher temperatures the stereochemical purity of the product is lower. [c] The alkenyl bromides were identified and characterized by means of gc, ir, pmr, and mass spectrometry. The stereochemistry of the internal alkenyl bromides was determined by preparation of the lithio derivatives (A. S. Dreiding and R. J. Pratt, *J. Amer. Chem. Soc.*, **76**, 1902 (1954); D. Y. Curtin and J. W. Crump, *ibid.*, **80**, 1922 (1958)), followed by protonolysis and the identification of the resulting olefin by gc. [d] Based on the intermediate boronic acid or its ester. [e] Based on the alkyne. The yields by isolation are given in parentheses.

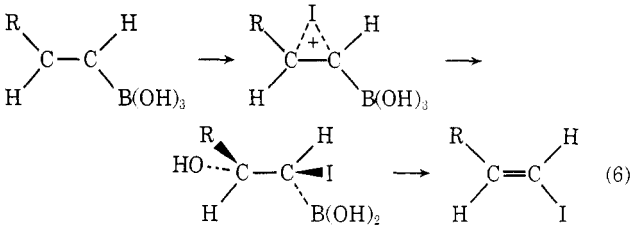
base-induced trans elimination of boron and bromine to give the product[6] (eq 5).



(5)

In the case of the iodine reaction,[1] the interpretation must be less definite at this time. The intermediate undergoing reaction is postulated to be the neutralized boronic acid. It was observed that the vinyl iodide is formed at a rate slower than that at which the iodine disappears.[1] Consequently, the reaction cannot involve a direct electrophilic attack of iodine on the carbon–boron bond.

We wish to propose that there is a trans addition of the elements of hypoiodous acid *via* an iodonium ion intermediate,[7] followed by a cis elimination (eq 6).



(6)

It was suggested earlier that β-substituted organoborane derivatives undergo cis eliminations preferentially when the substituent is one involving oxygen (alkoxy, acetate, etc.) capable of forming a dative bond from oxygen to boron.[6c,8]

A number of modifications of this mechanism can be suggested. However, it is preferable to defer more detailed consideration until such a time as more mechanistic data become available.

Irrespective of the precise mechanism involved, it is evident that we are now in a position to convert alkynes into vinyl bromides and iodides of opposite configurations, very conveniently *via* hydroboration with catecholborane. These vinyl bromides and iodides are readily converted into vinyl Grignard[9] and vinyllithium[10,11] derivatives with retention of their stereochemistry. Consequently, the present developments open up highly practical routes from the readily available alkynes to these valuable vinyl metallics of known stereochemistry.

(6) (a) D. S. Matteson and J. D. Liedtke, *J. Amer. Chem. Soc.*, **87**, 1526 (1965); (b) H. C. Brown, D. H. Bowman, S. Misumi, and M. K. Unni, *ibid.*, **89**, 4531 (1967); (c) D. J. Pasto and Sr. R. Snyder, O. S. F., *J. Org. Chem.*, **31**, 2773 (1966).

(7) (a) G. Zweifel, H. Arzoumanian, and C. C. Whitney, *J. Amer. Chem. Soc.*, **89**, 3652 (1967); (b) G. Zweifel, N. L. Polston, and C. C. Whitney, *ibid.*, **90**, 6243 (1968).

(8) (a) H. C. Brown and E. F. Knights, *ibid.*, **90**, 4439 (1968); (b) H. C. Brown and O. J. Cope, *ibid.*, **86**, 1801 (1964); (c) H. C. Brown and R. M. Gallivan, Jr., *ibid.*, **90**, 2902 (1968).

(9) H. Normant, *Advan. Org. Chem.*, **2**, 1 (1960).

(10) See references in footnote *c* of Table I.

(11) (a) E. J. Corey and D. J. Beames, *J. Amer. Chem. Soc.*, **94**, 2710 (1972); (b) A. F. Kluge, N. G. Untch, and J. H. Fried, *ibid.*, **94**, 9256 (1972).

(12) Visiting scholar on funds provided by Fuji Photo Film Co., Ltd., Tokyo, Japan.

(13) Postdoctoral research associate on grants provided by G. D. Searle and Co., Chicago, Ill., and the National Science Foundation (Grant No. 27742X).

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Determination of the Preferred Conformations Constrained along the C-4′–C-5′ and C-5′–O-5′ Bonds of β-5′-Nucleotides in Solution. Four-Bond ^{31}P–^{1}H Coupling[1]

Sir:

The Newman projections I–III and IV–VI respectively illustrate the preferred conformations constrained along the C-4′–C-5′ and C-5′–O-5′ bonds of a β-5′-nucleotide. An important stereochemical consequence of a β-5′-nucleotide existing in the gg–g′g′ (I and IV) conformation is that the atoms H-4′, C-4′, C-5′, O-5′, and P-5′ are in the same plane and that the four bond coupling path between H-4′ and P is the familiar "W" (VII). When the molecule is rotated into *any* other conformation this W relationship is destroyed. Studies by Hall, *et al.*,[2–4] indicate that the magnitude of

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(2) L. D. Hall and R. B. Malcolm, *Can. J. Chem.*, **50**, 2092 (1972).

(3) L. D. Hall and R. B. Malcolm, *Can. J. Chem.*, **50**, 2102 (1972).

(4) B. Donaldson and L. D. Hall, *Can. J. Chem.*, **50**, 2111 (1972).