of the excited chromophore was suggested to initiate the sensory signal transduction in *Stentor*.[17] It was recently reported that 2- or 2'-hydroxyl is the preferred site of deprotonation of hypericin.[18] It is reasonable to speculate that similar deprotonation of stentorin could serve as the initial photosensory transduction step. Photoinduced electron transfer, however, is also possible. A complete understanding of the photosensory transduction mechanism of *Stentor* awaits further characterization of the native stentorin.

Acknowledgment. This work was supported by grants from the National Institutes of Health (RO1-NS15426), the U.S. Army Research Office (28748-LS-SM and 29597-LS-EPS), and the National Science Foundation (DIR-9017262). We thank Dr. Rich Shoemaker for his assistance with NMR, Dr. J. S. Rhee for preliminary mass spectrometric measurements, and Dr. David Berkowitz and Dr. Desmond Wheeler for helpful discussions.

(15) Kim, I.-H.; Rhee, J. S.; Huh, J. W.; Florell, S.; Faure, B.; Lee, K. W.; Kahsai, T.; Song, P.-S.; Tamai, N.; Yamazaki, T.; Yamazaki, I. *Biochim. Biophys. Acta* **1990**, *1040*, 43-57.
(16) Song, P.-S.; Suzuki, S.; Kim, I.-D.; Kim, J. H. In *Photoreceptor Evolution and Function*; Holmes, M. G., Ed.; Academic Press: London, 1991; pp 21-63.
(17) Song, P.-S. *Biochim. Biophys. Acta* **1981**, *639*, 1-29.
(18) Falk, H.; Meyer, J.; Oberreiter, M. *Monatsh. Chem.* **1992**, *123*, 277-284.

α- versus β-Elimination of (*Z*)-(β-Halovinyl)iodonium Salts: Generation of (α-Haloalkylidene)carbenes and Their Facile Intramolecular 1,2-Migration

Masahito Ochiai*

Faculty of Pharmaceutical Sciences
University of Tokushima
1-78 Shomachi, Tokushima 770, Japan

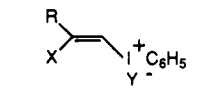
Koji Uemura and Yukio Masaki

Gifu Pharmaceutical University
5-6-1 Mitahora Higashi, Gifu 502, Japan

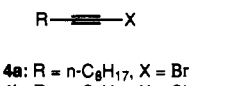
Received November 2, 1992
Revised Manuscript Received February 11, 1993

Base-induced dehydrohalogenation of vinyl halides leading to the formation of alkynes can take place through either α- or β-elimination.[1,2] The kinetic results for E2-type dehydrohalogenation of vinyl halides show that the relative rates of elimination decrease in the order anti β- > syn β- ≫ α-elimination.[3] We report herein competition between the base-induced α- and β-eliminations of (*Z*)-(β-halovinyl)phenyliodonium salts, which make possible the generation of (α-haloalkylidene)carbenes (Scheme I).

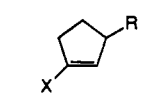
Exposure of (*Z*)-(β-bromovinyl)iodonium bromide **1a** (Y = Br) to $NaHCO_3$ in CH_2Cl_2–MeOH–H_2O at 0 °C for 4 h afforded the rearranged 1-bromoalkyne **4a** in high yield (Table I). Similarly, **2a** (Y = Br) and **3a** (Y = Br) produced exclusively **5a** and **6a**, respectively. These experiments were the first to show that (α-bromoalkylidene)carbenes could be generated and undergo 1,2-migration of α-bromine to terminal carbons more rapidly than the intramolecular 1,5-carbon–hydrogen insertion yielding 1-bromocyclopentenes.[4,5] The relative rates of 1,2-migration and



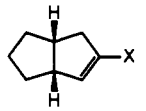
1a: R = n-C_8H_{17}, X = Br
1b: R = n-C_8H_{17}, X = Cl
1c: R = n-$C_{14}H_{29}$, X = F
2a: R = c-$C_5H_9CH_2$, X = Br
2b: R = c-$C_5H_9CH_2$, X = Cl
3a: R = t-Bu, X = Br
3b: R = t-Bu, X = Cl



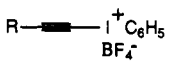
4a: R = n-C_8H_{17}, X = Br
4b: R = n-C_8H_{17}, X = Cl
5a: R = c-$C_5H_9CH_2$, X = Br
5b: R = c-$C_5H_9CH_2$, X = Cl
6a: R = t-Bu, X = Br
6b: R = t-Bu, X = Cl
7a: R = C_6H_5, X = I
7b: R = C_6H_5, X = Br
7c: R = C_6H_5, X = Cl



8a: R = n-C_5H_{11}, X = Br
8b: R = n-C_5H_{11}, X = Cl
8c: R = n-$C_{11}H_{23}$, X = F



9a: X = Br
9b: X = Cl



10: R = n-C_8H_{17}
11: R = c-$C_5H_9CH_2$
12: R = C_6H_5

1,5-C–H insertion depend on the α-halogen atoms of alkylidenecarbenes. Thus, in the case of (α-chloroalkylidene)carbenes, 1,2-chlorine shift competes with 1,5-C–H insertion yielding 1-chlorocyclopentenes: treatment of **1b** (Y = Cl) with $NaHCO_3$ or *n*-Bu_4NF gave a 59:41 mixture of the 1-chloroalkyne **4b** and the 1-chlorocyclopentene **8b** in high yields. Similar ratios of 1,2-shift to 1,5-C–H insertion were obtained in the reaction of **2b** (Y = Cl). Most importantly, the level of selectivity does not depend on the base used. This strongly suggests that the same intermediates are involved in the reactions. On the other hand, 1-fluorocyclopentene **8c** was obtained selectively in the reaction of **1c** (Y = Cl), albeit in low yield.[6]

Base-induced α-elimination of the phenyliodonio group with super nucleofugalities from (*Z*)-(β-halovinyl)phenyliodonium salts would directly generate (α-haloalkylidene)carbenes.[4] However, the following mechanistic alternative should be considered for the generation of (α-haloalkylidene)carbenes: (1) stereoelectronically preferable anti β-elimination of hydrogen halides by base yielding alkynyliodonium salts, (2) Michael type addition of the halide ions, and (3) reductive elimination of the phenyliodonio group (Scheme I). It appears that the intermolecular crossover experiments shown in Scheme II could distinguish between these two reaction pathways. Both the vinyliodonium-derived product **4a** and the alkynyliodonium-derived product **5a** were obtained in a ratio of 70:30 from the reaction of a 1:1 mixture of **1a** (Y = BF_4) and **11** with $NaHCO_3$. With a 1:1 mixture of **1b** (Y = BF_4) and **11**, the ratio of the alkynyliodonium-derived products (**5b** and **9b**) decreased to the extent of one-third. The same holds true for a combination of **2a,b** (Y = BF_4) and **10**. These results clearly demonstrate that the generation of (α-haloalkylidene)carbenes involves not only α-elimination of phenyliodonio groups but also anti β-elimination of hydrogen halides. Furthermore, (β-bromovinyl)iodonium salts show a greater tendency toward anti β-elimination of hydorgen halides than (β-chlorovinyl)iodonium salts. These were further supported by the intramolecular version of the crossover experiments using **1a** (Y = Cl) and **1b** (Y = Br), as shown in Scheme II.[7]

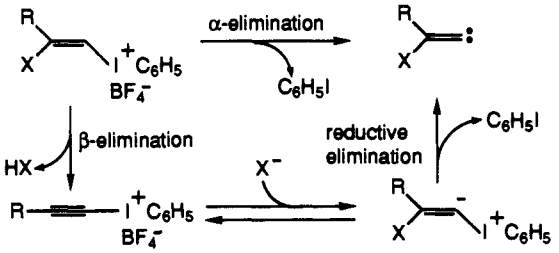
The earlier reports that 1,5-C–H insertion of alkylidenecarbenes cannot compete with 1,2-aryl migration,[8,9] combined with the

(1) (a) Ben-Efraim, D. A. *The Chemistry of the Carbon–Carbon Triple Bond*; Patai, S., Ed.; Wiley: New York, 1978; Chapter 18. (b) Kobrich, G.; Buck, P. *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; Chapter 2.
(2) (a) Fritsch, P. *Justus Liebigs Ann. Chem.* **1894**, *279*, 319. (b) Buttenberg, W. P. *Justus Liebigs Ann. Chem.* **1894**, *279*, 324. (c) Wiechell, H. *Justus Liebigs Ann. Chem.* **1894**, *279*, 337.
(3) Cristol, S. J.; Whittemore, C. A. *J. Org. Chem.* **1969**, *34*, 705.
(4) For generation of alkylidenecarbenes by base-induced α-elimination of vinyliodonium salts, see: Ochiai, M.; Takaoka, Y.; Nagao, Y. *J. Am. Chem. Soc.* **1988**, *110*, 6565.
(5) For excellent reviews of alkylidenecarbenes, see: (a) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383. (b) Stang, P. J. *Acc. Chem. Res.* **1982**, *15*, 348.

(6) The rearranged 1-fluoroalkyne was not detected. However, the selective formation of **8c** does not necessarily exclude the intervention of 1,2-fluorine migration of (α-fluoroalkylidene)carbene, since the rearranged 1-fluoroalkynes have been shown to be highly labile even at 0 °C and would escape detection: Delavarenne, S. Y.; Viehe, H. G. *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; Chapter 10. However, the activation energy for isomerization of difluorovinylidene to difluoroacetylene has been calculated to be prohibitively large: (a) Strausz, O. P.; Norstrom, R. J.; Hopkinson, A. C.; Schoenborn, M.; Csizmadia, I. G. *Theor. Chim. Acta* **1973**, *29*, 183. (b) Norstrom, R. J.; Gunning, H. E.; Strausz, O. P. *J. Am. Chem. Soc.* **1976**, *98*, 1454. (c) Brahms, J. C.; Dailey, W. P. *J. Am. Chem. Soc.* **1990**, *112*, 4046.
(7) The relative rate of the reaction of bromide and chloride anions with **10** was found to be 3.5:1.
(8) (a) Wolinsky, J.; Clark, G. W.; Thorstenson, P. C. *J. Org. Chem.* **1976**, *41*, 745. (b) Ochiai, M.; Kunishima, M.; Nagao, Y.; Fuji, K.; Shiro, M.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 8281.

0002-7863/93/1515-2528$04.00/0

Scheme I



Scheme II

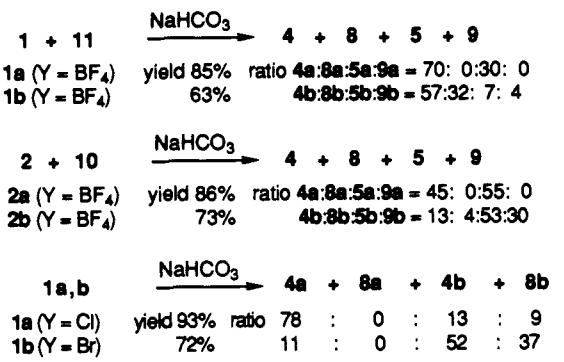


Table I. Reaction of (*Z*)-(β-Halovinyl)iodonium Salts with Bases[a]

substrate	reactn time, h	product, % yield[b] alkyne	olefin	ratio[c]
1a (Y = Br)	4	**4a**, 98	**8a**, 0	100:0
1b (Y = Cl)	5	**4b**, 52	**8b**, 36	59:41
1b (Y = Cl)	4[d]	**4b**, 59	**8b**, 41	59:41
1c (Y = Cl)	10[d]		**8c**, 17[e]	
2a (Y = Br)	5	**5a**, 95	**9a**, 0	100:0
2b (Y = Cl)	5	**5b**, 54	**9b**, 33	62:38
2b (Y = Cl)	19[d]	**5b**, 41	**9b**, 25	62:38
3a (Y = Br)	5.5	**6a**, 77		
3b (Y = Cl)	6	**6b**, 92		

[a] Unless otherwise noted, reactions were carried out using 1.2 equiv of $NaHCO_3$ at 0 °C in CH_2Cl_2–MeOH–H_2O. [b] Determined by gas chromatography using an internal standard. [c] Ratios of 1,2-shift of halogens to 1,5-C–H insertions. [d] Reactions were carried out using 2–4 equiv of *n*-Bu_4NF at room temperature in CH_2Cl_2. [e] Isolated yield.

finding that 1,2-chlorine migration of alkylidenecarbenes competes with 1,5-C–H insertion, make the comparison between the migratory aptitude of an α-phenyl group and α-halogen atoms very interesting. Because of the instability of (β-halo-β-phenylvinyl)iodonium salts,[10] (α-halo-α-phenylalkylidene)carbenes were directly generated from **12** through Michael type addition–reductive elimination sequences.[8b] The reaction of [2-^{13}C]-**12** (99% enriched) with LiX (X = Cl, Br, and I) in CH_2Cl_2–MeOH at −78 °C afforded good yields of 1-halo-2-phenylacetylenes **7**. The ^{13}C-enrichment at C-2 of **7** was found to be more than 98% by ^{13}C NMR spectra. While there is no report concerning the migratory aptitude of α-halogen atoms of alkylidenecarbenes,[11] these results clearly indicate that the rate of 1,2-migration of α-halogen atoms (I, Br, and Cl) of alkylidenecarbenes is much greater than that of an α-phenyl group.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan.

(9) For 1,2-migration of α-aryl groups of alkylidenecarbenes, see: (a) Newman, M. S.; Kutner, A. *J. Am. Chem. Soc.* **1951**, *73*, 4199. (b) Stang, P. J.; Mangum, M. G.; Fox, D. P.; Haak, P. *J. Am. Chem. Soc.* **1974**, *96*, 4562. (c) Brown, R. F. C.; Eastwood, F. W.; Harrington, K. J.; McMullen, G. L. *Aust. J. Chem.* **1974**, *27*, 2393. (d) Stang, P. J.; Fox, D. P.; Collins, C. J.; Watson, C. R. *J. Org. Chem.* **1978**, *43*, 364. (e) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837.

(10) Beringer, F. M.; Galton, S. A. *J. Org. Chem.* **1965**, *30*, 1930.

(11) For 1,2-migration of halogen atoms of (α-haloalkyl)carbenes, see: (a) Bevan, W. I.; Haszeldine, R. N.; Young, J. C. *Chem. Ind. (London)* **1961**, 789. (b) Liu, M. T. H.; Bonneau, R. *J. Org. Chem.* **1992**, *57*, 2483.

Encoded Combinatorial Peptide Libraries Containing Non-Natural Amino Acids

Janice M. Kerr, Steven C. Banville, and Ronald N. Zuckermann*

Chiron Corporation, 4560 Horton Street Emeryville, California 94608

Received December 22, 1992

Methods for the synthesis and screening of diverse peptide libraries have recently been developed for the rapid discovery of biologically-active lead compounds.[1-4] We describe here a method for encoding[5] non-natural components[6] in a diverse combinatorial library with standard amino acids by the parallel and alternating synthesis of two polymer chains: a binding ligand and a coding peptide. The use of a peptide tag allows the sequence of any isolated binding ligand to be identified by conventional peptide analyses and thus circumvents the problems sometimes associated with the analysis of novel biopolymers.

This combinatorial encoding strategy utilizes a resin-splitting peptide synthesis method[7,8] to alternately synthesize a "binding" strand and a "coding" strand (Figure 1). Orthogonal protecting groups are used to allow for the individual and alternating extension of both polymer strands on each resin bead. Specifically, base-labile, N^{α}-[(9-fluorenylmethyl)oxy]carbonyl-protected (Fmoc-protected) monomers and acid-labile, N^{α}-[[2-(3,5-dimethoxyphenyl)prop-2-yl]oxy]carbonyl-protected (Ddz-protected)[9] amino acids are used to synthesize the binding and coding strands, respectively. Although these two groups are orthogonal, the use of *tert*-butyl ester or trityl side chain protecting groups may require the use of an N^{α} protecting group with greater acid lability than Ddz.

The relationship between the binding and coding strands can assume a variety of configurations. The number of Fmoc monomers that can be represented depends on both the number of different Ddz amino acids used and on the length of the Ddz code. An efficient coding strategy requires the addition of Ddz amino acids only at a mixture position (where $n > 1$ in Figure 1). In the example presented here, four Ddz-protected amino acids were used in trimer sequences to allow for the representation of up to 64 non-natural monomers. Ddz-protected leucine, phenylalanine, glycine, and alanine were chosen as encoding monomers because they do not require side chain protection, and they give reproducibly strong signals upon Edman sequencing.

The isolation of receptor-binding ligands from a solution-phase or solid-phase encoded library can be performed by affinity selection[4] or bead-staining techniques.[2] The identity of the binding sequence can then be determined by Edman sequencing of the coding strand. To avoid ambiguity, only the coding strand should be sequenced; the binding sequence must be acetylated or otherwise made nonsequenceable. Binding sequences of identical molecular weight can be distinguished by using different codes, allowing

(1) Fodor, S. P. A.; Read, J. L.; Pirrung, M. C.; Stryer, L.; Lu, A. T.; Solas, D. *Science* **1991**, *251*, 767-773.

(2) Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmiersky, W. M.; Knapp, R. J. *Nature* **1991**, *354*, 82-84.

(3) Houghten, R. A.; Pinilla, C.; Blondelle, S. E.; Appel, J. R.; Dooley, C. T.; Cuervo, J. H. *Nature* **1991**, *354*, 84-86.

(4) Zuckermann, R. N.; Kerr, J. M.; Siani, M. A.; Banville, S. C.; Santi, D. V. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 4505-4509.

(5) Brenner, S.; Lerner, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 5381-5383.

(6) Simon, R. J.; Kania, R. S.; Zuckermann, R. N.; Huebner, V. D.; Jewell, D. A.; Banville, S.; Ng, S.; Wang, L.; Rosenberg, S.; Marlowe, C. K.; Spellmeyer, D. C.; Tan, R.; Frankel, A.; Santi, D. V.; Cohen, F. E.; Bartlett, P. A. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 9367-9371.

(7) Furka, A.; Sebestyén, M.; Asgedom, M.; Dibó, G. *Int. J. Pept. Protein Res.* **1991**, *37*, 487-493.

(8) Zuckermann, R. N.; Kerr, J. M.; Siani, M. A.; Banville, S. C. *Int. J. Pept. Protein Res.* **1992**, *40*, 498-507.

(9) Voss, C.; Birr, C. *Hoppe-Seyler's Z. Physiol. Chem.* **1981**, *362*, 717-725.

0002-7863/93/1515-2529$04.00/0