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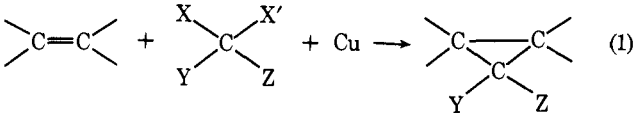
A Novel Synthetic Route to Cyclopropane Derivatives from Olefins

Sir:

We wish to report a new, versatile, and convenient method for the synthesis of cyclopropane derivatives by the reaction of olefins with organic *gem*-dihalides and copper.[1] The reaction



(1)

(X, X′ = halogen)

is usually free from serious side reactions, and appears to be applicable to wide ranges of olefins and organic *gem*-dihalides. The reaction proceeds smoothly at moderate temperature and gives cyclopropane derivatives often in good yields. An aromatic hydrocarbon is the most suitable solvent for the reaction. Reactions were carried out in a flask fitted with a reflux condenser and a magnetic stirrer.[3] Some experimental results are given in Table I. All products were identified by comparison of their ^1H NMR and ir spectra with those of authentic samples, or showed satisfactory analytical data and expected spectra.

Reaction 1 with dihalomethanes gives cyclopropane derivatives in good yields as the corresponding Simmons–Smith reaction.[7] Reaction 1 with trihalomethanes is useful in the synthesis of monohalocyclopropane derivatives from olefins, and shows syn stereoselectivity.[9] The reaction with dibromoacetic esters shows syn selectivity when steric repulsion between the alkoxycarbonyl group and the substituents of the olefin is not significant, contrary to the reaction of diazoacetic esters with olefins.[10] The cis isomer is obtained predominantly from terminal olefins such as 1-hexene, 1-octene, and styrene. Although the exo isomer predominated over the endo isomer in the reaction with cyclic olefins, the anti selectivity is much lower than that of the corresponding reaction of ethyl diazoacetate.[11]

Except for the case with cyclohexene and methyl dibromoacetate,[12] isomeric olefins, which would be expected from the insertion of the corresponding free carbenes into C–H bonds, were not detected in the reaction mixture. Reaction 1 seems to proceed via organocopper intermediates rather than free carbenes.

The reaction of pure *trans*-stilbene with diiodomethane and copper in ethylbenzene gave *trans*-1,2-diphenylcyclopropane.[13] *cis*-1,2-Diphenylcyclopropane and *cis*-stilbene were not detected in the reaction mixture. On the other hand, the corresponding reaction with pure *cis*-stilbene gave a 97.1:2.9 mixture of *cis*- and *trans*-1,2-diphenylcyclopropane.[13] The recovered stilbene was also a 98.1:1.9 mixture of cis and trans isomers. These experimental results show that reaction 1 loses the stereospecificity to some extent probably by the action of copper(I) halide.

Table I. Synthesis of Cyclopropane Derivatives from Olefins, Organic *gem*-Dihalides, and Copper[a]

Olefin	Halide	Temp (°C)	Time (h)	Product	Yield (%)[b]	Isomer ratio
Cyclohexene	CH_2I_2	70	50	Bicyclo[4.1.0]heptane[c]	85–87	—
Cyclohexene	CH_2BrI	70	50	Bicyclo[4.1.0]heptane[c]	69	—
Cyclohexene	$CHCl_2I$	70	25	*endo/exo*-7-Chlorobicyclo[4.1.0]heptane[d]	48	2.1
Cyclohexene	$CHCl_2I$	70	50	*endo/exo*-7-Chlorobicyclo[4.1.0]heptane[d]	14	2.2
Cyclohexene	$Br_2CHCOOCH_3$	55	50	*exo/endo*-7-Methoxycarbonylbicyclo[4.1.0]-heptane[e]	31	2.4
1-Hexene	$Br_2CHCOOCH_3$	60	98	*cis/trans*-1-Butyl-2-methoxycarbonylcyclo-propane[e]	25	2.7
Cycloheptene	$Br_2CHCOOCH_3$	80	50	*exo/endo*-8-Methoxycarbonylbicyclo[5.1.0]-octane[e]	46	1.9
cis-Cyclooctene	CH_2I_2	100[f]	50	*cis*-Bicyclo[6.1.0]nonane[c]	77	
cis-Cyclooctene	$Br_2CHCOOCH_3$	55	50	*exo/endo*-9-Methoxycarbonyl-*cis*-bicyclo-[6.1.0]nonane[e]	71	1.3
1-Octene	CH_2I_2	70	47	Hexylcyclopropane[c]	86	—
1-Octene	$Br_2CHCOOCH_3$	70	50	*cis/trans*-1-Hexyl-2-methoxycarbonylcyclo-propane[e]	21	2.7
Styrene	CH_2I_2	70	92	Phenylcyclopropane[c]	90	—
Styrene	$Br_2CHCOOCH_3$	100[f]	48	*cis/trans*-1-Methoxycarbonyl-2-phenylcyclo-propane[e]	22	1.6
trans-Stilbene	CH_2I_2	125[g]	50	*trans*-1,2-Diphenylcyclopropane[c]	27	—
cis-Stilbene	CH_2I_2	125[g]	50	*cis/trans*-1,2-Diphenylcyclopropane[c,e]	22	33

[a] Reactions were carried out with 4.0 mmol of olefin, 8.0 mmol of organic *gem*-dihalide, 18.0 mmol of copper, and 0.2 mmol of iodine in 3.0 ml of benzene. [b] Based on the olefin. [c] Authentic samples were prepared by the Simmons–Smith reaction.[7] [d] Authentic samples were prepared by the reaction of lithium carbenoid.[8] [e] Complete spectral and elementary analyses of these compounds are included in the supplementary material. [f] Toluene was used instead of benzene. [g] Ethylbenzene was used instead of benzene.

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Supplementary Material Available: Spectral and elementary analysis of the derivatives (5 pages). Ordering information is given on any current masthead page.

References and Notes

(1) During the course of study on the preparation of tetracyanoethylene, Cairns and co-workers[2] obtained 7-cyano-7-ethoxycarbonylbicyclo[4.1.0]heptane in 10% yield by the reaction of ethyl dibromocyanoacetate with copper in the presence of cyclohexene. The reaction of dibromomalononitrile with copper in the presence of cyclohexene was also suggested to afford 7,7-dicyanobicyclo[4.1.0]heptane, although the structure of the product was not finally elucidated. These experiments are previous examples of reaction 1, but details are not available in the literature.
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(3) Bromoiodomethane,[4] chlorodiiodomethane,[5] dichloroiodomethane,[5] and methyl dibromoacetate[6] were prepared by minor modification of literature methods. Diiodomethane, olefins, and solvents were purified by distillation. The ordinary commercial grade of copper powder (particle size was 5–15 μ) provided by Nakarai Chemicals, Ltd., Kyoto, was used without further purification. Copper powder was allowed to react with a small amount of iodine in solvent at room temperature. After the brown color of iodine disappeared, olefin and organic *gem*-dihalide were added, and the mixture was heated at the prescribed temperature with stirring. After the reaction, the inorganic products were separated by filtration, and the organic layer was analyzed. Yields were determined by VPC analysis of the reaction mixture.
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(13) These reactions were carried out with the aid of Mr. Ichiro Kameura.

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Oligopeptides as Potential Antiaggregation Agent for Proteins: Hemoglobin S Gel and Insulin Dimer

Sir:

The ordered aggregation of certain proteins requires specific contact areas between associating protein molecules. Oligopeptides mimicking a portion of the amino acid sequence at the contact region has been proposed as potential antiaggregation agents.[1] This is based on a working hypothesis that such oligopeptides (A) might compete for the binding sites on the protein (P) molecules if they are energetically favorable or if their concentrations are sufficiently high, thereby shifting the equilibria:

$$P + P \overset{K_P}{\rightleftarrows} P_2 \ldots \rightleftarrows P_n; \quad P + A \overset{K_A}{\rightleftarrows} PA \qquad (1)$$

toward the monomeric complex PA which is incapable of association. Reaction 1 does not rule out the possibility that P aggregates to form a nucleus P_m ($m \ll n$),[2] but stops at P_m·PA instead of polymeric P_n. To test this idea, we present some preliminary studies of the influence of antiaggregation agents on two proteins: deoxygenated hemoglobin (Hb) S which gels and insulin which dimerizes.

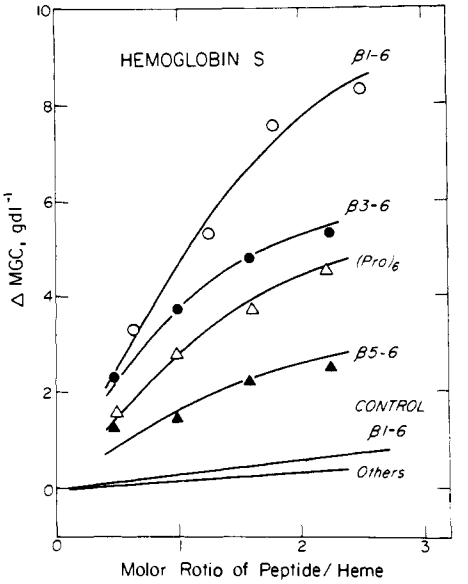

Figure 1. Increase in the minimum gelling concentration of deoxyhemoglobin S in the presence of various oligopeptides in phosphate buffer (pH 6.8; ionic strength 0.1) at 37 °C. The MGC of deoxyHb S alone is 9.5 g dl^{-1}. The baselines refer to the correction of additional ionic strength due to positively charged oligopeptide amides. See text.

Hb S: Out of 574 amino acid residues Hb S differs from normal Hb A in only two mutation sites, that is, two β6 valine residues instead of glutamic acid. It is highly suggestive that the β1–6 region:

1 6

Val His Leu Thr Pro Val . . .

might constitute one of the contact areas between neighboring molecules when deoxyHb S gels. Thus, we have synthesized a series of oligopeptide amides containing β1–6, β3–6, β5–6, and also a hexa-L-prolineamide (the latter is to test the specificity of these peptides). The effectiveness of these oligopeptides is determined by comparing the minimum gelling concentration (MGC)[3] of deoxyHb S in phosphate buffer (pH 6.8; I = 0.1) at 37 °C. For control, the MGC of Hb S alone was found to be 9.5 g/dl at I = 0.1; addition of NaCl to increase its ionic strength raised the MGC to 10.3 g/dl at I = 0.16. Figure 1 shows the increase in MGC of deoxyHb S in the presence of various oligopeptides. (The imidazole·HCl in the hexapeptide was first neutralized with concentrated NaOH, which produced additional NaCl. This accounts for the difference in the baselines.) The most prominent feature is that the MGC increases almost linearly with the molar ratio of the hexapeptide β1–6 amide to Hb S. At a molar ratio of 2.5 peptide per heme, the increment in MGC amounts to 75%. Shorter peptides such as tetrapeptide β3–6 and dipeptide β5–6 amides are less effective than the hexapeptide amide β1–6. These results are consistent with the view that the oligopeptides compete for the binding site at the contact area. Hexa-L-prolineamide also raises the MGC of deoxyHb S, although it is not as effective as β1–6 amide. It is possible that $(Pro)_6$ might interfere with some other contact area, thus making gelation difficult. (We also attempted to use $(Gly)_6$ and $(Ser)_6$, but their low solubilities at neutral pH made meaningful measurements of ΔMGC difficult.) Hemoglobin which is much larger than our other example, insulin, may provide locations other than those involved in intersubunit contacts which can associate less specifically with oligopeptides but with subsequent modification of aggregation tendencies. Recently, small quantities (3.8 mM) of L-homoserine, L-glutamine, and L-asparagine, but no other amino acids, have been reported to inhibit and reverse the sickling of erythrocytes.[4] Our preliminary studies