The Reaction of Ketene with Carbon–Carbon σ Bonds. The Case of Moore's Ketene[1,2]

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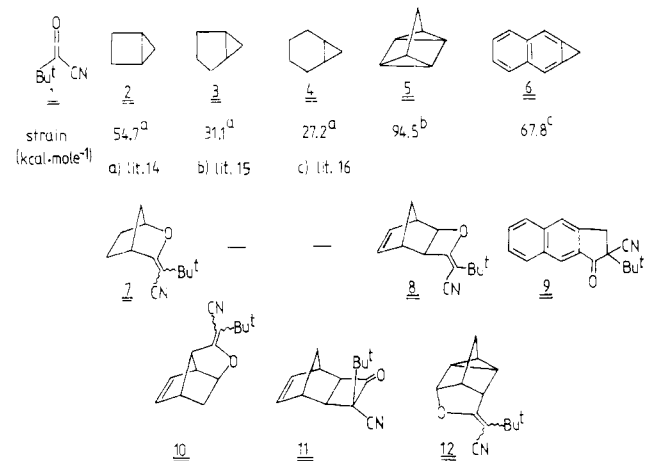
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Summary: Moore's ketene (*tert*-butylcyanoketene) reacts with strained cyclopropanes (strain energy more than 31 kcal mol^{-1}) to give oxetane, tetrahydrofuran, or cyclopentanone derivatives. The ketenophiles which react with Moore's ketene are bicyclo[2.1.0]pentane, quadricyclane, and naphtho[*b*]cyclopropane.

Ketenes were discovered in 1905 by Staudinger.[3] Since then their chemistry has been illustrated by reactions with homo- and heteronuclear double and triple bonds.[4] Many of these studies have been directed to a landmark in the chemistry of ketenes, i.e., the $_2\pi_s + _2\pi_a$ reaction mode proposed by Woodward and Hoffman[5] for concerted cycloadditions. Illustrations for ketene insertion into σ bonds such as C–H (ene reactions),[6a-e] C–metal,[6f] C–Cl,[6f] C–O[6f] bonds, etc., are encountered nevertheless in a few publications, while the implications of their reactions with σ C–C bonds were not realized as a property per se.[7] Indeed the reactions of ketene with C–C σ bonds were virtually ignored during eight decennia following Staudinger's discovery. While the heteronuclear bonds which react with ketenes have no particular requirements, the C–C σ bonds must be strained,[8] as we shall point out. Accordingly, the present paper is aimed to draw attention to this novel property of C–C σ bonds in the reaction with ketenes,

which we intend subsequently to elaborate further in order to reveal factual and rational dimensions of this reaction. The ketene chosen for our initial studies is Moore's ketene.[9] As ketenophiles, compounds containing cyclopropane units such as bicyclo[2.1.0]pentane (2),[10] bicyclo[3.1.0]hexane (3),[11] bicyclo[4.1.0]heptane (4),[11] quadricyclane (5),[12] and naphtho[*b*]cyclopropane (6)[13] were selected. The results of this study are presented below.

Bicyclo[2.1.0]pentane (2) reacted with Moore's ketene across the central bond, giving 2-oxabicyclo[2.2.1]heptane (7).[17] Other electrophilic additions to the central bond

(1) (a) Taken in part from the B.Sc. Thesis of RAC (Polytechnic Institute Bucharest, 1980). Presented in part at the Conference of Chemistry and Chemical Engineering, Bucharest, 22–23 October, 1987, Abstract p.32. (b) We[2] have named *tert*-butylcyanoketene as Moore's ketene, as a tribute to its discoverer for the opportunity given to chemists throughout the world to enjoy the marvelous and fruitful chemistry of this ketene.

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(3) Staudinger, H. *Ber.* 1905, *38*, 1735. See also: Staudinger, H. *Die Ketene*; Verlag von Ferdinand Enke: Stuttgart, 1912.

(4) For a large variety of topics related to the chemistry of ketenes, see: (a) *The Chemistry of Ketenes, Allenes and Related Compounds*; Patai, S., Ed.; J. Wiley: New York, 1980; Parts 1 and 2. (b) Ghosez, L.; O'Donnell, M. J. In *Pericyclic Reactions*; Marchand, A. P., Lehr, R. E., Eds.; Academic Press: New York, 1980; pp 79–140. (c) March, J. *Advanced Organic Chemistry: Reactions, Mechanism and Structure*, 2nd ed.; McGraw-Hill: London, 1977; p 780. (d) Moore, H. W.; Gheorghiu, M. D. *Chem. Soc. Rev.* 1981, *10*, 289. (e) Carey, F. A.; Sunberg, R. J. *Advanced Organic Chemistry*, 2nd ed.; Plenum Press: New York, 1984; p 330.

(5) Woodward, R. B.; Hoffman, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, Germany, 1971; p 163.

(6) For ene reactions in the case of Moore's ketene, see the following. (a) With 2-methylpropene: Brook, P.; Hunt, K. J. *J. Chem. Soc., Chem. Commun.* 1974, 989. (b) With 1-methylcyclopropene: Aue, D. H.; Helvig, G. S. *J. Chem. Soc., Chem. Commun.* 1975, 604. (c) With ethers and esters of 2-hydroxymethyl: Becker, D.; Brodsky, N. C. *J. Chem. Soc., Chem. Commun.* 1978, 237. In the case of bis(trifluoromethyl)ketene: (d) With propene, 1-butene, 1-hexene, 2-methylpropene, 2-phenylpropene, see: England, D. C.; Krespan, C. G. *J. Org. Chem.* 1970, *35*, 3300. (e) With 2-methylpropene, see: Charbukov, Yu. A.; Mukhamadaliev, N.; Knunyants, I. D. *Tetrahedron* 1968, *24*, 1341. (f) Ulrich, H. *Cycloaddition Reactions of Heterocumulens*; Academic Press: New York, 1967; p 89.

(7) The reaction of quadricyclane with diphenylketene was reported in 1978. Apparently the authors did not realized that this was the first known reaction of a ketene with C–C σ bonds: Becherer, J.; Hanel, N.; Hoffman, R. W. *Justus Liebigs Ann. Chem.* 1978, 312.

(8) For a present state of art regarding the concept of molecular strain, see: Cramer, D.; Kraka, E., to be published. Strain-assisted syntheses have became a powerful synthetic method in organic chemistry, see: Tetrahedron-Symposia, –in print number 28; *Tetrahedron* 1989, *45*(10), Ghosez, L., guest Editor. Trost, B. M. *Top. Curr. Chem.* 1986, *133*, 5. de Meijere, A. *Bull. Soc. Chim. Belg.* 1984, *93*, 241.

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(12) Smith, C. D. *Org. Synth.* 1971, *51*, 133.

(13) Billups, W. E.; Chow, W. Y. *J. Am. Chem. Soc.* 1973, *95*, 4099. We have improved the overall yield of preparation from 10% to 26% using ethyl trichloroacetate instead of chloroform and sodium methoxide instead of potassium *tert*-butoxide. For review on cycloproparenes, see: Billups, W. E.; Rodin, W. A.; Haley, M. M. *Tetrahedron* 1988, *44*, 1305.

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(16) Billups, W. E.; Chow, W. Y.; Lavell, K. H.; Lewis, E. S.; Margrave, J. L.; Sass, R. L.; Shieh, J. J.; Werness, P. G.; Ward, J. L. *J. Am. Chem. Soc.* 1973, *95*, 7878.

(17) Moore's ketene was generated by thermolysis of 2,5-diazido-3,6-di-*tert*-1,4-benzoquinone,[2] in anhydrous benzene, at reflux, under argon. All reactions were carried out in this solvent, unless otherwise stated. Relevant analytical data are presented below (IR data are quoted in cm^{-1}; chemical shifts in δ ppm; for MS in parentheses are given the relative intensities). **Compound 7**: IR (CCl$_4$) 1640, 2210, 2980; ^{1}H NMR (CCl$_4$) 0.73–2.17 (6 H, m), 1.2 (9 H, s), 3.45 (1 H, br s); MS 191 (72.5), 176 (33.9), 108 (100), 67 (12.3), 57 (15.6). **Compound 8**: IR (CCl$_4$) 1670, 2210, 2970; ^{1}H NMR (CDCl$_3$) 1.17 (9 H, s), 1.66 (1 H, d, *J* = 9 Hz), 1.86 (1 H, d, *J* = 9 Hz), 3.17 (2 H, m), 3.23 (1 H, br s), 4.72 (1 H, m), 6.17 (2 H, m); ^{13}C NMR (CDCl$_3$) 29.44 (q), 32.37 (s), 40.88 (t), 45.04 (d), 46.97 (d), 84.55 (s), 92.81 (t and d), 118.56 (s), 131.72 (d), 139.77 (d), 171.84 (s); MS 215 (34.6), 200 (100), 182 (22.2), 172 (10.6, 155 (14), 108 (98.1), 92 (71.4), 91 (96.9), 77 (13.3), 66 (40.9). Anal. Calcd for C$_{14}$H$_{17}$ON: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.21; H, 7.91; N, 6.83. **Compound 9**: mp 191–192 °C (uncorrected); IR (CHCl$_3$) 1630, 1720, 2220, 2940; ^{1}H NMR (CDCl$_3$) 1.12 (9 H, s), 3.65 (2 H, s), 7.35–8.0 (5 H, m), 8.3 (1 H, s); ^{13}C NMR (CDCl$_3$) 25.82, 35.82, 38.0, 56.06, 119.93, 124.35, 126,25, 126.81, 127.92, 129.54, 130.50, 132.41, 132.69, 137.75, 143.04, 198.06. Anal. Calcd for C$_{18}$H$_{17}$ON: C, 82.13; H, 6.46; N, 5.3. Found: C, 82.87; H, 6.39; N, 4.86.

in 2 are well documented.[18] The higher homologues 3 and 4 did not react with Moore's ketene. For example bicyclo[4.1.0]heptane (4) and Moore's ketene showed no reaction (reflux in toluene, 20 h), when monitored by IR and ^{1}H NMR spectroscopy.

Quadricyclane (5) gave the oxetane 8, as the sole reaction product (quantitative yield) when treated with Moore's ketene.[17] At 19 °C, the cycloaddition occurred in 2 min. Norbornadiene was reported to react with Moore's ketene with comparable readiness[19] as its valence isomer quadricyclane, resulting the cyclobutanone 11 and the ether 12, both isomers of oxetane 8. Tentatively, the configurations of the exo-methylene fragment and of the four-membered ring is provided by ^{1}H NMR spectra without and with $Eu(fod)_3d_{27}$.

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Naphtho[b]cyclopropane (6) gave the benzoindanone 9 when treated with Moore's ketene (90% yield). However, the reactivity of the cyclopropane ring annelated to the naphthalene was less than of quadricyclanic rings. For example at room temperature the cycloaddition took ca. 24 h as compared to 2 min in the case of quadricyclane.

The strain energy prerequisite threshold established with the present array of ketenophiles was estimated at about 31 kcal mol^{-1}.

We are actively engaged in testing new substrates and other ketenes in order to illustrate phenomenologically the reaction of ketenes with C–C σ bonds, as well as to uncover various aspects of the reaction mechanism.

# Biomimetic Total Synthesis of (±)-Methyl Homodaphniphyllate[1]

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Summary: Bis-carbamoyl derivative 4, prepared from the known amino alcohol 3 by reaction with phenyl isocyanate, is converted into carbamate 5 in refluxing formic acid. A similar process, involving carbamoyl phosphate as the carbamoylating agent, might operate in the biosynthesis of the daphniphylline skeleton.

It has been suggested that the daphniphylline skeleton 2 might arise by cyclization of an unsaturated amine 1.[2] We have attempted to bring about this transformation in vitro by treatment of compounds of type 1 under various acidic conditions, without success. This failure to cyclize presumably results from preferential protonation of the amine under the attempted acidic conditions.
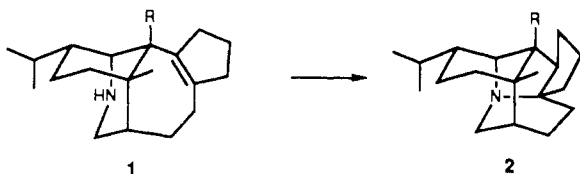
In contrast, the bis-carbamoyl derivative 4, obtained by treatment of amino alcohol 3[3] with phenyl isocyanate, cyclizes smoothly in refluxing formic acid to provide the carbamate 5. Saponification of 5 affords alcohol 6 in 94% overall yield for the three-step conversion. Amino alcohol 6 is converted into (±)-methyl homodaphniphyllate (7) by Jones oxidation and Fischer esterification (73% yield). The conversion of 3 into 7 completes a 13-step stereo-

controlled total synthesis of the alkaloid (13% overall yield) and completely solves our earlier problem in controlling the stereochemistry at the isopropyl-bearing carbon.[4]
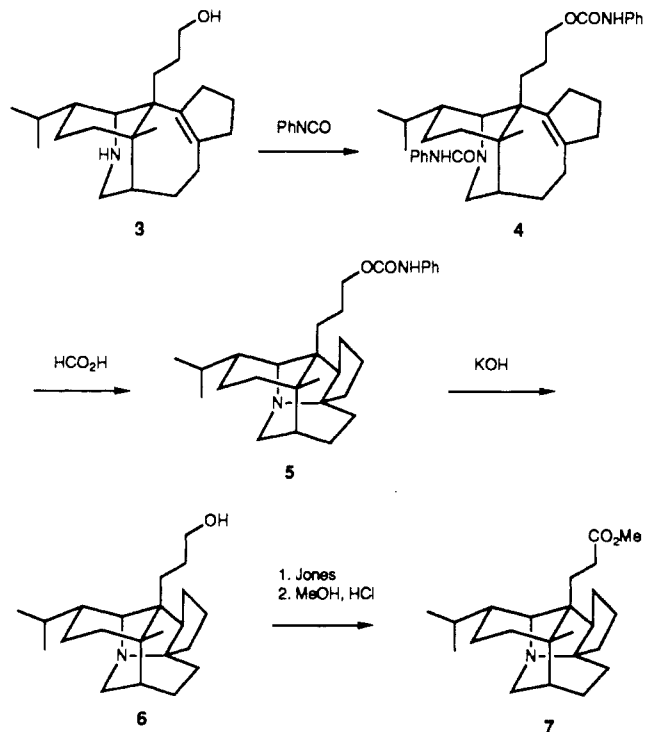
The ease of cyclization of 4 raises the interesting question of whether a similar process might be involved in the actual biosynthetic formation of the daphniphylline

(1) Part 7 in a series of papers on the Daphniphyllum alkaloids. For part 6, see: Piettre, S.; Heathcock, C. H. Science (Washington, D.C.), in press.

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(4) Heathcock, C. H.; Davidsen, S. K.; Mills, S.; Sanner, M. A. J. Am. Chem. Soc. 1986, 108, 5650.