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Communications

The Ozonolysis of Alkenylidenecyclopropanes

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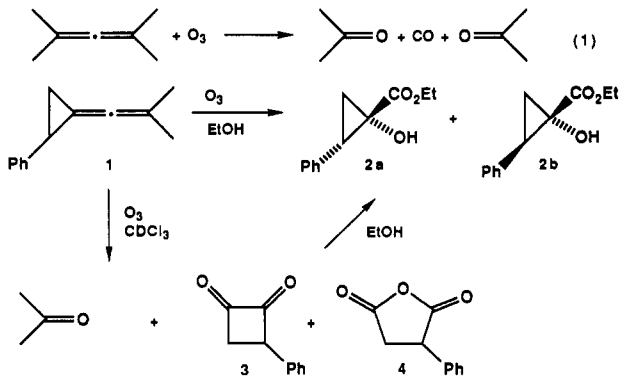
Summary: The ozonolysis of alkenylidenecyclopropanes has been shown to generate cyclobutane-1,2-diones by a novel ring-expansion process which occurs at some point during oxidative cleavage of the allene unit.

The oxidative cleavage of allenes by ozone, first described by Favorskii,[1] has frequently been used in structure determinations for this class of compounds.[2] However, it was not until the critical study of Kolsaker and Teige[3] that the major reaction pathway was appreciated to involve a single equivalent of each reactant in the overall conversion to two carbonyl fragments plus carbon monoxide (eq 1).[4] Attempts to trap hypothetical reactive intermediates in this process with hydroxylic solvents, an efficient process in the ozonization of simple olefins,[5] have not been successful with allenes.[3] The only instance in which this appears to have been accomplished was described by Hartzler,[6] who reported that alkenylidenecyclopropane **1** was converted to cyclopropyl ester **2** by ozone in ethanol. This product is unique in that it retains the central carbon of the starting allene. We have examined this intriguing transformation in greater detail and now report on the unusual course of this deceptively simple transformation.



Repetition of the Hartzler experiment clearly demonstrated that the two diastereomeric cyclopropyl esters **2a** and **2b** (4:1 mixture)[7] were indeed formed when the ozonolysis of **1** was performed in ethanol in the conventional manner. However, the addition of **1** to a saturated solution of ozone (1 equiv) in $CDCl_3$ at −61 °C gave a pink reaction mixture which was shown by ^1H and ^{13}C NMR analyses to contain starting material, acetone, and two new compounds in the relative proportions of 1:2.6:1.7:0.5. Although attempts to isolate the unknown materials by chromatographic methods failed owing to decomposition, the addition of an excess of ethanol to a portion of the reaction mixture, followed by concentration after a few minutes, caused bleaching of the color with concomitant conversion of the first unknown to esters **2a** and **2b**, clearly indicating that this compound is a precursor to the esters. Exposure of a second portion of the ozonolysis mixture to

(1) Favorskii, A. E.; Bone, M. D. *Chem. Abstr.* **1937**, *31*, 5752; *Dokl. Akad. Nauk. SSSR* **1937**, *14*, 499.
(2) Taylor, D. R. *Chem. Rev.* **1967**, *67*, 336.
(3) (a) Kolsacker, P.; Teige, B. *Acta Chem. Scand.* **1970**, *24*, 2101. (b) Kolsacker, P.; Børresen, S. *Acta Chem. Scand.* **1979**, *B33*, 133.
(4) Sterically hindered allenes react by transfer of a single oxygen atom from ozone in certain instances, leading to allene oxides, cyclopropanones, and their further reaction products:[3b,5] Crandall, J. K.; Conover, W. W.; Komin, J. B.; Machleder, W. H. *J. Org. Chem.* **1974**, *39*, 1723.
(5) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1978; Vol. 1.
(6) Hartzler, H. D. *J. Am. Chem. Soc.* **1961**, *83*, 4990.
(7) Compound **2a** shows: ^1H NMR ($CDCl_3$) δ 7.34–7.24 (m, 5), 4.26 (q, 2, J = 7 Hz), 2.73 (dd, 1, J = 10, 8 Hz), 2.65 (s, 1), 1.88 (dd, 1, J = 10, 6 Hz), 1.60 (dd, 1, J = 8, 6 Hz), and 1.32 (t, 3, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 173.1, 135.0, 128.7, 128.2, 126.8, 61.7, 58.8, 35.2, 20.2, and 14.2; IR 3450, 1735 cm^{-1}. Isomer **2b** shows: ^1H NMR ($CDCl_3$) δ 7.24–7.11 (m, 5), 3.74 (q, 2, J = 6 Hz), 2.69 (dd, 1, J = 10, 9 Hz), 1.90 (dd, 1, J = 9, 6 Hz), 1.65 (dd, 1, J = 10, 6 Hz), and 0.76 (t, 3, J = 6 Hz) ^{13}C NMR ($CDCl_3$) δ 172.4, 135.9, 128.9, 127.9, 126.6, 61.1, 60.8, 34.5, 18.6, and 13.5.

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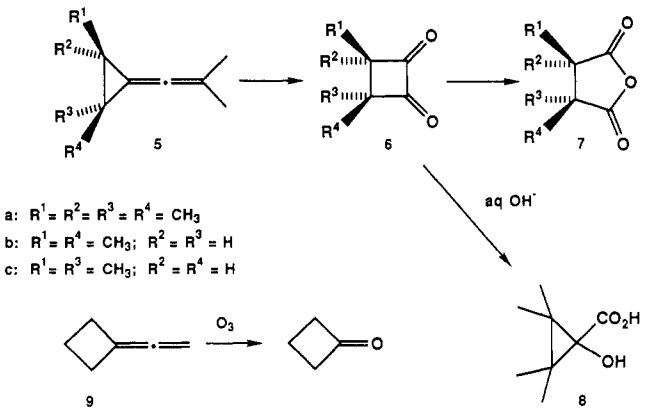
sunlight likewise led to the selective decomposition of this same component to form styrene efficiently. This information is fully consistent with the anticipated chemical behavior[8,9] of 3-phenylcyclobutane-1,2-dione (**3**), as are the spectroscopic properties of this component.[10] Support for this hypothesis was found in the unequivocal identification of the second, stable unknown as phenylsuccinic anhydride (**4**) by comparison of the spectra with those of an authentic sample.[11]

Confirmation of these results was obtained from a study of the related alkenylidenecyclopropane **5a**. Addition of **5a** to 3 equiv of ozone as a saturated solution in CH_2Cl_2 at −78 °C gave a mixture of dione **6a**, anhydride **7a**, and acetone. In this case, dione **6a** was stable enough for isolation by preparative GC, which permitted full characterization of both **6a** and **7a**.[12] Furthermore, dione **6a** was converted to anhydride **7a** as the major product by an excess of ozone under the usual reaction conditions. In another experiment 1 N NaOH was added to the reaction mixture obtained from equimolar amounts of allene **5a** and ozone after warming to 0 °C. The pink color of **6** disappeared rapidly, and crystalline acid **8**[13] was recovered in 48% yield upon acidification of the aqueous extract. Starting material (25%) and anhydride **7a** (25%) were obtained from the resulting CH_2Cl_2 solution.

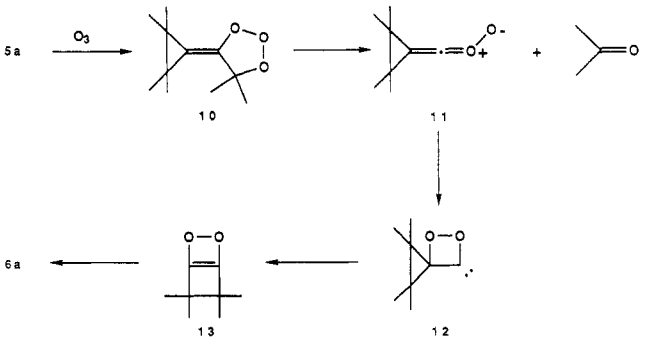


Finally, information concerning the stereochemistry of the ring expansion process was secured by examination of the isomeric *cis*- and *trans*-alkenylidenecyclopropanes **5b** and **5c**.[14] For this purpose it was convenient to exhaustively ozonize the allenes in CH_2Cl_2 at −78 °C so that conversion to the anhydrides was complete.[15] These transformations proceeded with retention of stereochemistry; thus, **5b** gave **7b** and **5c** yielded **7c** cleanly. In experiments conducted on **5b** or **5c** in $CDCl_3$ at −78 °C with 1 equiv of ozone, the intermediacy of the corresponding dione **6b** or **6c**, respectively, was demonstrated by ^{13}C and ^1H NMR.[16] However, several attempts to isolate these diones or to transform them to ring-contracted products were not successful.

A similar transformation was not observed with ethenylidenecyclobutane **9**. In this instance, ozonolysis gave cyclobutanone as the only significant product derived from the carbocyclic unit.

The reaction originally reported by Hartzler is thus shown to proceed by a disguised ring expansion–ring contraction sequence. The second step of this process is well-precedented,[8] but the generation of the cyclobutanedione intermediate is less obvious. Nonetheless, a plausible hypothesis for the observed conversion can be based on the mechanism put forth to explain the oxidative fragmentation shown in eq 1.[3]

This scenario is initiated by the 1,3-dipolar addition of ozone to the more electron-rich double bond[17] of the alkenylidenecyclopropane to give trioxolane **10**, which subsequently fragments to acetone and a ketene *O*-oxide of structure **11**. Isomerization of **11** to the dioxetane carbene **12** is proposed as the next step. A species of this type has



been suggested as an intermediate in the transformation of eq 1, where it serves as a source of carbon monoxide and a carbonyl compound by [2 + 2]-cycloreversion. In the case of **12**, the presence of the strained cyclopropane ring retards a similar fragmentation and permits a competitive ring expansion to generate dioxetene **13**. Electrocyclic opening of **13** to the cyclobutanedione, as would be expected[18] completes the process. This description, while somewhat speculative, has the virtue of incorporating common steps for the cleavage reactions of simple allenes and alkenylidenecyclopropanes. Analogy for the **12** to **13** transformation is found in the well-established ring expansion of cyclopropylcarbenes to cyclobutenes,[19] a process

(8) (a) Barnier, J. P.; Denis, J. M.; Salaun, J.; Conia, J. M. *Tetrahedron* **1974**, *30*, 1397, 1405. (b) Salaun, J.; Garnier, B.; Conia, J. M. *Tetrahedron* **1974**, *30*, 1413, 1423.

(9) (a) de Groot, A.; Oudman, D.; Wynberg, H. *Tetrahedron Lett.* **1969**, 1529. (b) Heine, H. G.; Wendisch, D. *Justus Liebigs Ann. Chem.* **1976**, 463.

(10) Cyclobutanedione **3** shows: ^1H NMR ($CDCl_3$) δ 7.8–7.0 (m), 4.47 (dd, 1, J = 13, 10 Hz), 3.60 (dd, 1, J = 19, 13 Hz), and 3.30 (dd, 1, J = 19, 10 Hz); ^{13}C NMR ($CDCl_3$) δ 206.7, 206.0, 135.6, 127.7, 127.0, 58.7, and 49.2; IR 1805, 1780, and 1710 cm^{-1}.

(11) Anhydride **4** gave: ^1H NMR ($CDCl_3$) δ 7.40–7.24 (m, 5), 4.32 (dd, 1, J = 10, 7 Hz), 3.43 (dd, 1, J = 19, 10 Hz), and 3.09 (dd, 1, J = 19, 7 Hz); ^{13}C NMR ($CDCl_3$) δ 171.7, 169.2, 134.6, 129.4, 127.2, 46.5, and 35.5; IR 1870 and 1800 cm^{-1}.

(12) Cyclobutanedione **6a** is an orange liquid: ^1H NMR ($CDCl_3$) δ 1.16; ^{13}C NMR ($CDCl_3$) δ 214.9, 58.8, and 12.3; IR 1805, 1775 cm^{-1}. Barnier, J. P.; Conia, J. M. *Bull. Soc. Chim. Fr.* **1976**, 281. Anhydride **7a** is a white solid: mp 142–144 °C; ^1H NMR δ ($CDCl_3$) 1.23; ^{13}C NMR ($CDCl_3$) δ 176.5, 48.3, and 20.7; IR 1860 and 1790 cm^{-1}. Auwers, K.; Ungemach, O. *Ber. Dtsch. Chem. Ges.* **1935**, *68*, 349.

(13) Acid **8** is a white solid: mp 122–124 °C; ^1H NMR (acetone-d_6) δ 4.5 (br s, 2), 1.21 (s, 6), and 1.12 (s, 6); ^{13}C NMR (acetone-d_6) δ 174.1, 63.3, 31.7, 17.7, and 17.4; IR 1730 and 1710 cm^{-1}. Heine, H.G.; Wendisch, D. *Justus Liebigs Ann. Chem.* **1976**, 463.

(14) (a) Hartzler, H. D. *J. Am. Chem. Soc.* **1961**, *83*, 4997. (b) Pasto, D. J.; Borchardt, J. K. *J. Org. Chem.* **1976**, *41*, 1061.

(15) Anhydride **7b** shows: ^1H NMR ($CDCl_3$) δ 3.20 (m, 2) and 1.30 (m, 6); ^{13}C NMR ($CDCl_3$) δ 174.0, 39.0, 11.3; IR ($CDCl_3$) 1852, 1800, 1784 cm^{-1}. The anhydride **7c** is a white solid: mp 86.5–87 °C; ^1H NMR ($CDCl_3$) 2.73 (m, 2), 1.40 (m, 6); ^{13}C NMR ($CDCl_3$) δ 173.0, 43.2, 14.1; IR ($CDCl_3$) 1844, 1789 cm^{-1}. Dozen, Y.; Hatta, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2842.

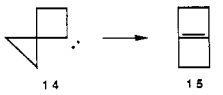
(16) Cyclobutanedione **6b** shows: ^1H NMR ($CDCl_3$) δ 3.31 (m, 2) and 1.19 (m, 6); ^{13}C NMR ($CDCl_3$) δ 212.1, 52.2, and 8.9. **6c** shows: ^1H NMR ($CDCl_3$) δ 2.73 (m, 2) and 1.38 (m, 6); ^{13}C NMR ($CDCl_3$) δ 211.6, 57.4, and 14.3.

(17) (a) Crombie, L.; Maddocks, P. J.; Pattenden, G. *Tetrahedron Lett.* **1978**, 3483. (b) Pasto, D. J.; Fehlner, T. P.; Schwartz, M. E.; Barney, H. F. *J. Am. Chem. Soc.* **1976**, *98*, 530.

(18) Turro, N. J.; Ramamurthy, V.; Liu, K. C.; Krebs, A.; Kemper, R. *J. Am. Chem. Soc.* **1976**, *98*, 6758.

(19) *Carbenes*; Moss, R. A., Jones, M., Eds.; Wiley: New York, 1973; Vol. 1.

which has been shown to occur with retention of configuration at the migrating carbon center.[20] Finally, the directly analogous hydrocarbon carbene **14** is known to isomerize to **15**.[21]



14 **15**

(20) Guarino, A.; Wolf, A. P. *Tetrahedron Lett.* **1969**, 655.

Further studies are currently underway to further develop our understanding of the ozonolysis of allenes and to test the mechanistic hypotheses put forth.

Acknowledgment. Support for this work was generously provided by the National Institute of Health (Grant GM 39988).

(21) Wiberg, K. B.; Burgmaier, G. J.; Warner, P. *J. Am. Chem. Soc.* **1971**, *93*, 246.

A Method for the Synthesis of Alkynyl Phenyl Sulfides from Alkynyltrimethylsilanes. A Novel, Efficient Synthesis of the Thienamycin Intermediate from 3(*R*)-Hydroxybutyric Acid

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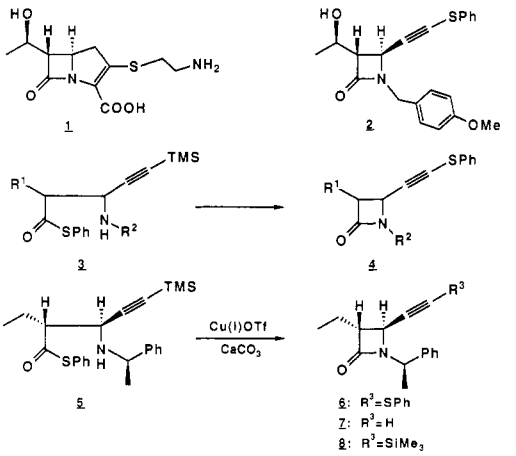
Summary: The mechanism of the one-pot conversion of β-amino thiol esters of type **3** to β-lactams of type **4** has been clarified, and it is proposed that the actual active species is a PhSSPh–CuOTf complex. Through the use of this novel reaction, an efficient synthesis of the thienamycin intermediate **2**, starting with 3(*R*)-hydroxybutyric acid, has been achieved. Furthermore, the combined reagents (PhSSPh–CuOTf) have been demonstrated to be a powerful source of PhS^+ through the conversion of several alkynyltrimethylsilanes to alkynyl phenyl sulfides.

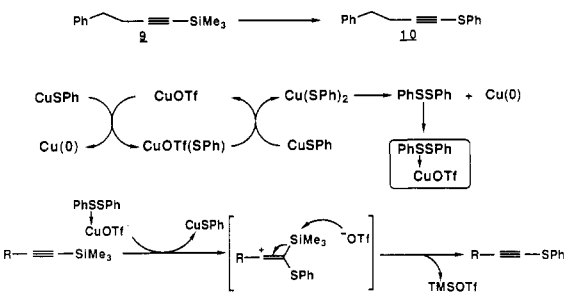
The carbapenem skeleton can be constructed efficiently via two synthetic routes. One uses an intramolecular carbene insertion reaction,[1] and the other proceeds via an intramolecular Wittig reaction.[2] The key synthetic intermediate for the synthesis of (+)-thienamycin (**1**) utilizing the latter process is the alkynyl phenyl sulfide **2**,[2c,d] whose novel and efficient synthesis starting with 3(*R*)-hydroxybutyric acid is reported herein. In addition, the detailed mechanism of the direct conversion of β-amino thiol esters of type **3** to β-lactams of type **4** and the method for the synthesis of alkynyl phenyl sulfides from alkynyltrimethylsilanes are also described (Scheme I).

We have recently found that treatment of the β-amino thiol ester **5** with CuOTf (1.2 equiv) and $CaCO_3$ (2 molar equiv) in refluxing dioxane for 5 h affords the alkynyl phenyl sulfide **6** in one pot (34%), together with **7** (28%). On the other hand, using toluene instead of dioxane provided none of **6**, giving instead a mixture of **7** and **8** in 89% yield.[3] We decided to initiate mechanistic studies on the conversion of **5** to **6**, because alkynyl phenyl sulfides of type **4** are known to be useful intermediates for the synthesis of carbapenem antibiotics.[2] The reagents which appeared to play a key role in the above transformation were CuOTf, $CaCO_3$, and CuSPh, formed by reaction of CuOTf with the β-amino thiol ester. It was found that treatment of the simple model compound **9** with CuSPh (1.2 equiv) afforded

Scheme I



Scheme II



none of **10**. On the other hand, treatment of **9** with the combined reagents (1.2 equiv of CuSPh and 1.2 equiv of CuOTf) in refluxing dioxane provided **10** in 30% yield, indicating that both reagents are essential in the conversion of alkynyltrimethylsilanes to alkynyl phenyl sulfides. When the above reaction was carried out at 45 °C, phenyl disulfide was formed in 100% yield and no **10** was produced. These results implied that the actual reagent for the above transformation is phenyl disulfide. After several attempts, it was found that treatment of **9** with 1.2 equiv of phenyl disulfide, 1.2 equiv of CuOTf, and 2.0 molar equiv of $CaCO_3$ in refluxing dioxane gave **10** in 82% yield.[4]

(1) (a) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31. (b) Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Ibid.* **1980**, *21*, 2783.

(2) (a) Ponsford, R. J.; Roberts, P. M.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1979**, 847. (b) Yoshida, A.; Tajima, Y.; Takeda, N.; Oida, S. *Tetrahedron Lett.* **1984**, *25*, 2793. (c) Maruyama, H.; Shiozaki, M.; Oida, S.; Hiraoka, T. *Ibid.* **1985**, *26*, 4521. (d) Maruyama, H.; Hiraoka, T. *J. Org. Chem.* **1986**, *51*, 399.

(3) Miyachi, N.; Kanda, F.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 3511.

(4) Exposure of **9** to phenyl disulfide only afforded none of **10**.

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