Thermolysis of 2-Methoxy-2,5,5-trimethyl-Δ^3-1,3,4-oxadiazoline. Carbenes from Thermal Fragmentation of a Carbonyl Ylide Intermediate

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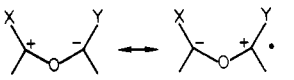
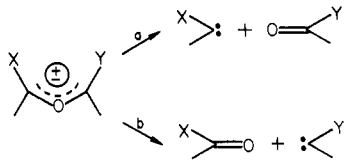
The properties and synthetic applications of carbonyl ylides constitute an active area of chemical research.[1] Very recently, Griffin, Houk, and their co-workers[2] published results of theoretical studies of structures and reactions of substituted carbonyl ylides



One of the questions addressed in that paper concerns their fragmentation (eq 1), and the authors' conclusions about frag-

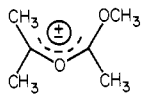


(1)

mentation, on the basis of their studies and the literature, included the following:[3] (a) Fragmentation of carbonyl ylide (X = Y = H) is endothermic by about 38 kcal/mol. (b) One amino substituent (X = NH_2) decreases the thermodynamic barrier to fragmentation in either sense and path a, leading to aminocarbene, may actually be exothermic.[4] (c) Thermal fragmentation of a carbonyl ylide from a coplanar ground state (0°,0° conformation[5]) is a disallowed process.

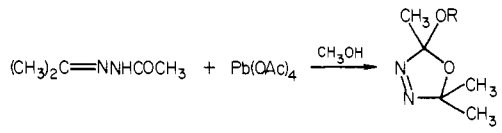
Experimental evidence for thermal fragmentation of carbonyl ylides is meager. The one unambiguous example known to us is the observation that a photolysis warmup procedure produces more fragmentation products from aryloxiranes than does photolysis alone.[6]

We wish to report experimental results which indicate that a methoxy-substituted carbonyl ylide



fragments in a thermal process by both pathways. The results are discussed in terms of the theoretical predictions cited above.[2]

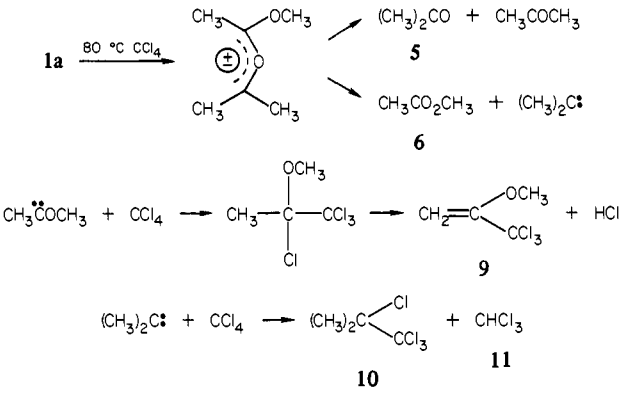
2-Methoxy-2,5,5-trimethyl-Δ^3-1,3,4-oxadiazoline (**1a**) was prepared by oxidation of acetone acetylhydrazone with lead tetraacetate in methanol (eq 2).[7] The crude product, which



(2)

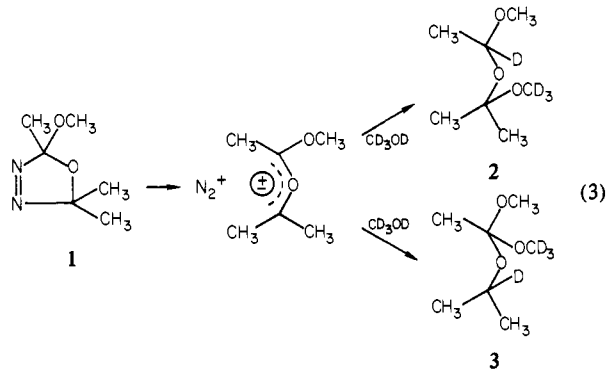
1a, R = CH_3
b, R = $COCH_3$
c, R = H

Scheme I



contained **1b** (ca. 30%), was treated with KOH in methanol to hydrolyze **1b** to **1c**, which decomposes.[8] Addition of water, extraction with CH_2Cl_2, drying of the extract, evaporation of the solvent, and distillation at 10^{-2} torr (pot temperature 40–45 °C) gave pure **1a** as a faintly yellow liquid: ^{1}H NMR ($CDCl_3/Me_4Si$) δ 1.43 (s, 3 H), 1.55 (s, 6 H), 3.06 (s, 3 H); ^{13}C NMR ($CDCl_3/Me_4Si$) δ 23.4, 24.0, 25.1, 50.4 (OCH_3), 119.9 (C5), 133.7 (C2).

Oxadiazoline **1a** decomposes with first-order kinetics in methanol-d_4 ($k^{79.5}_{CD_3OD} = 5.3 \times 10^{-6}$ s^{-1}) and carbon tetrachloride ($k^{79.5}_{CCl_4} = 1.4 \times 10^{-5}$ s^{-1}).[9] Products **2** and **3** from decomposition of **1a** in CD_3OD are shown in eq 3, which also depicts the probable



(3)

mechanism by which they are formed.[10] Compounds **2** and **3** were not separated, but their structures could be inferred from the ^{1}H NMR spectrum of the mixture. Thus a singlet at δ 1.19 was assigned to the ketal methyl groups of **2** and a multiplet ($^3J_{HD}$ = 1.2 Hz) was assigned to the deuterium coupled acetal methyl group of **2**. Similarly, a multiplet at δ 1.00 ($^3J_{HD}$ = 1.2 Hz) and a singlet at δ 1.92 were assigned to the *gem*-dimethyl and the orthoester methyl groups, respectively, of **3**. Integrals of the above-mentioned signals corresponded to a product ratio **2**/**3** ≃ 3:7, and that ratio was used to assign the methoxy singlets at δ 3.56 and 3.26 to **2** and **3**, respectively.

Addition of aqueous HCl to a mixture of unlabeled **2** and **3** (from thermolysis of **1a** in CH_3OH) gave rise to acetone, acet-

(1) The history of carbonyl ylides and their most common reactions are reviewed briefly by Griffin, Houk, and their co-workers.[2] Many references cited in that paper[2] are not repeated here.

(2) Houk, K. N.; Rondau, N. G.; Santiago, C.; Gallo, C. J.; Gandour, R. W.; Griffin, G. W. *J. Am. Chem. Soc.* **1980**, *102*, 1504.

(3) For additional conclusions about substituent effects on fragmentation pathways and for discussion of their origins, see ref 2.

(4) The calculated value is −17 kcal mol^{-1} but the authors[2] emphasize that absolute values of the energies, unlike relative values, may be unreliable.

(5) The 0°,0° conformation is that in which the central oxygen, the two carbons attached to it, and the other immediate substituent atoms at those carbons lie in the same plane.

(6) Do-Minh, T.; Trozzolo, A. M.; Griffin, G. W. *J. Am. Chem. Soc.* **1970**, *92*, 1402.

(7) For a review of oxidative cyclization of derivatives of carbonyl compounds, (hydrazones, semicarbazones, etc.) see: Warkentin, J. *Synthesis* **1970**, 279 and references therein.

(8) Knittel, P.; Warkentin, J. *Can. J. Chem.* **1975**, *53*, 2275.

(9) Reaction was monitored in each case by following the decrease in the integrals from the methoxy group signals at δ 3.1 in the ^{1}H NMR spectrum, to at least 80% completion. Dichloromethane and benzene were used as internal standards for normalizing the integrals. Correlation coefficients from a least-squares treatment of the ln (integral) and time data were 0.997 or better.

(10) For precedent for capture of a carbonyl ylide by methanol see, for example: (a) Shimizu, N.; Bartlett, P. D. *J. Am. Chem. Soc.* **1978**, *100*, 4260. (b) Ege, S. N.; Gess, J. E.; Thomas, A.; Umrigar, P.; Griffin, G. W.; Das, P. K.; Trozzolo, A. M.; Leslie, T. M. *J. Chem. Soc., Chem. Commun.* **1980**, 1263.

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aldehyde dimethyl acetal, isopropyl alcohol, and methyl acetate, all of which were identified from their GLPC retention times.[11] Those components could also be recognized in the ^1H NMR spectrum of the mixture. The carbonyl compounds and isopropyl alcohol were also identified from their gas-phase IR spectra.[12] These results confirm that **1a** decomposes via a carbonyl ylide intermediate in methanol.

Thermolysis of **1a** at 82 °C in 1,1-diphenylethylene (**4**) gave acetone (**5**), methylacetate (**6**), 2,2-dimethyl-1,1-diphenylcyclopropane (**7**)[13] [^1H NMR (CCl_4/Me_4Si) δ 1.12 (s, 2 H), 1.25 (s, 6 H), 7.20 (m, 10 H)], and a compound tentatively identified as 1-methoxy-1-methyl-2,2-diphenylcyclopropane (**8**) [^1H NMR (CCl_4/Me_4Si) δ 1.16 (m, 4 H), 1.25 (d, ^2J = 9 Hz, 1 H), 3.10 (s, 3 H), 7.30 (m, 10 H); MS, m/z 238 (M^+)]. Those products are readily explained in terms of dimethyl- and methylmethoxycarbene intermediates. Dimethylcarbene was also suggested by the finding of propene from thermolysis of **1a** in benzene.[14] The decomposition of **1a** in CCl_4, which gives products **5**, **6**, and **9-11** (Scheme I),[15] provided further support for carbenic JA5M89Ci

Although the only direct evidence for formation of a carbonyl ylide pertains to methanol solvent, it is very likely that the same intermediate is formed in CCl_4 and C_6H_6. The similar magnitudes of the first-order rate constants (above) would have to be fortuitous if different mechanisms were in operation.[17] Moreover, it is now fairly clear[19] that the very similar **1b** forms a carbonyl ylide intermediate in CCl_4 and the intermediate undergoes an intramolecular H transfer as proposed by Shimizu and Bartlett[10a] for analogous processes involving carbonyl ylide intermediates, which can be trapped. Thus **1a** is unlikely to be mechanistically different in the rate-determining step. The sharp difference between **1a** and **1b**, insofar as the product-determining steps are concerned, can be accounted for nicely in terms of the expected donor substituent effect of the OCH_3 group, analogous to that of the NH_2 group.[2]

In order for the ylide intermediate to fragment thermally to carbenes and carbonyl compounds, it must either have a nonplanar ground state[2] or a nonplanar state must be readily accessible from a planar ground state. Calculations[2] indicate that a donor substituent reduces the barriers to rotation of 0°,0° conformations to 0°,90° conformations. It is interesting that there is apparently little preference for one fragmentation over the other (CCl_4 results). The theory[2] for amino-substituted carbonyl ylide predicts that the 0°,90° conformation would have the shorter bond between amino-substituted carbon and carbonyl oxygen. This feature is presumably offset in the presence case by the greater stabilization that the donor substituent affords to a carbene as compared to a carbonyl compound.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council for financial support of this research and to a referee for alerting us to a reference.

(11) These products were separated by GLPC, and their structures were assigned by injecting aliquots to which pure standards had been added, one at a time.

(12) Nicolet, Model 7199, FT-IR instrument fitted with Varian Aerograph 3700 gas chromatograph. Authentic samples were injected under the same conditions to obtain reference spectra.

(13) The ^1H NMR spectrum of **7** is in good agreement with that of a model compound, 1-(hydroxymethyl)-1-methyl-2,2-diphenylcyclopropane: Dreibelbis, R. L.; Khatri, H. N.; Walborsky, H. M. *J. Org. Chem.* **1975**, *40*, 2074.

(14) Identified from its ^1H NMR spectrum and also by bromination to 1,2-dibromopropane.

(15) Yields and characterization of **9-11**. **9**: 31%; ^1H NMR (δ, CCl_4/Me_4Si) 5.2 (d, $^2J_{HH}$ = 4 Hz, 1 H), 4.4 (d, $^2J_{HH}$ = 4 Hz, 1 H), 4.0 (s, 3 H); MS, m/z 178, 176, 174 in ratio 0.3:1.0:1.0 (M^+), 121, 119, 117 in ratio 0.3:1.0:1.0 (CCl_3^+), 57 ($C_3H_5O^+$). **10**: 33%; ^1H NMR (δ, $CDCl_3/Me_4Si$) 2.0 (s); MS, m/z 163, 161, 159 in ratio 0.3:1.0:1.0 [$(CH_3)_2CCCl_3^+$], 79, 77 in ratio 0.3:1.0 [$(CH_3)_2CCl^+$], mp 180 °C (lit.[16] mp 178.6-179.6 °C). **11**: 30%.

(16) Rogers, A. O.; Nelson, R. E. *J. Am. Chem. Soc.* **1936**, *58*, 1028.

(17) A small decrease of the rate constant for thermolysis of a cis azo compound as solvent polarity is increased is now well-known and explicable in terms of the large dipole moment of the substrate.[18]

(18) Schulz, A.; Rüchardt, C. *Tetrahedron Lett.* **1976**, 3893.

(19) Before the paper of Shimuzu and Bartlett[10a] appeared, one of us[20] had proposed a diradical intermediate to account for the thermolysis products of **1b**.

(20) Yeung, D. W. K.; MacAlpine, G. A.; Warkentin, J. *J. Am. Chem. Soc.* **1978**, *100*, 1962.

Biosynthesis of Macrolide Antibiotics. 3.[1] Regiochemistry of Isotopic Hydrogen Labeling of Brefeldin A by Acetate†

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Although the biosynthesis of 14- and 16-membered macrolide antibiotics by microorganisms has been studied for many years, most of the knowledge gained has been about the biochemically simple C_2-C_4 carbon precursors.[2] Scant information is available about the biochemical transformations subsequent to the chain-forming condensation of the C_2-C_5 thioesters leading to the aglycons[3] of these macrolides. This is in distinct contrast to fatty acid biosynthesis in living systems for which a comprehensive mechanistic and enzymological picture can be drawn[4,5] and from which bioorganic mechanisms of macrolide antibiotic formation[2d] have been formulated by analogy.

As the structural intricacies of macrolide antibiotics[2b,6] imply complex biosynthetic routes, it is of fundamental importance to map their anabolic pathways. The 16-carbon macrolide antibiotic brefeldin A (**1**) has been chosen for study, because its biochemical precursors are acetate and malonate.[7] Thus comparisons are possible with the biochemistry of fatty acids which also share these precursors. We summarize in this and the following paper the regio- and stereochemical results obtained about its biosynthesis by isotopically labeling **1** with [2-^{13}C,2-$^2H_3$]-, [1-^{14}C,2-^{3}H]-, and [2-$^2H_3$]acetate.

In our initial experiments we wished to determine whether enrichment from [^{2}H]- and [^{3}H]acetate produced a labeling pattern for **1** similar to that observed for fatty acids.[8] Radioactively labeled **1**, obtained from the metabolism of sodium [1-^{14}C,2-^{3}H]acetate ($^3H/^{14}C$ ratio = 9.18) by *Penicillium brefel-*

† NRCC No. 19055.

(1) Part 2: Mabuni, C. T.; Garlaschelli, L.; Ellison, R. A.; Hutchinson, C. R. *J. Am. Chem. Soc.* **1979**, *101*, 707-714.

(2) Reviews: (a) Vanek, Z.; Majer, J. In "Antibiotics"; Gottlieb, D., Shaw, P. D., Eds.; Springer Verlag: New York, 1967; Vol. 2, pp 154-188. (b) Omura, S.; Nakagawa, A. *J. Antibiot.* **1975**, *28*, 401-433. (c) Martin, J.-F. *Annu. Rev. Microbiol.* **1977**, *31*, 13-38. (d) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585-607. (e) Corcoran, J. W. *Annu.* Rep. *Med. Chem.* **1977**, *12*, 130-139.

(3) Most of our knowledge is about post-aglycon biochemical processing such as oxidation, glycosidation, and methylation: cf. ref 2 d,e.

(4) Reviews: (a) Volpe, J. J.; Vagelos, P. R. *Annu. Rev. Biochem.* **1973**, *42*, 21-60. (b) Numa, S.; Yamashita, S. *Curr. Top. Cell. Regul.* **1974**, *5*, 198-246. (c) Bloch, K.; Vance, D. *Annu. Rev. Biochem.* **1977**, *46*, 263-298.

(5) (a) Sedgwick, B.; Cornforth, J. W. *Eur. J. Biochem.* **1977**, *75*, 465-479. (b) Sedgwick, B.; Cornforth, J. W.; French, S. J.; Gray, R. T.; Kelstrup, E.; Willadsen, P. *Ibid.* **1977**, *75*, 481-495. (c) Sedgwick, B.; Morris, C.; French, S. J. *J. Chem. Soc., Chem. Commun.* **1978**, 193-194. (d) Sedgwick, B.; Morris, C. *Ibid.* **1980**, 96-97.

(6) Mallams, A. K. *Kirk-Othmer Encycl. Chem. Technol. 3rd Ed.* **1978**, *2*, 937-961.

(7) (a) Handschin, U.; Sigg, H. P.; Tamm, Ch. *Helv. Chim. Acta* **1968**, *57*, 1943-1965. (b) Coombe, R. G.; Foss, P. S.; Watson, T. R. *Chem. Commun.* **1967**, 1229-1230. (c) Coombe, R. G.; Foss, P. S.; Jacobs, J. J.; Watson, T. R. *Aust. J. Chem.* **1969**, *22*, 1943-1950.

(8) (a) Rous, S. *Adv. Lipid Res.* **1971**, *9*, 73-118. (b) Reference 5a and citations therein. (c) White, R. H. *Biochemistry* **1980**, *19*, 9-15. (d) McInnes, A. G.; Walter, J. A.; Wright, J. L. C. *Tetrahedron Lett.* **1979**, 3245-3248.

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