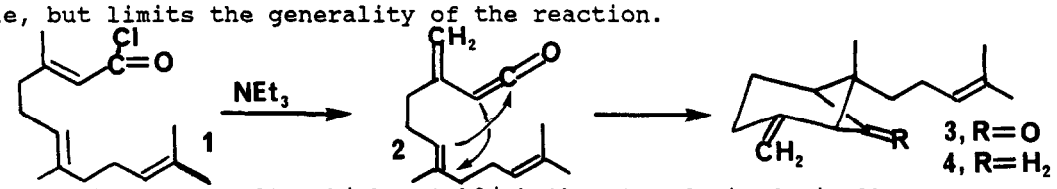
Tetrahedron Letters,Vol.26,No.46,pp 5619-5622,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

INTRAMOLECULAR [2 + 2] CYCLOADDITION REACTIONS OF VINYLKETENES. STEREO- AND REGIOSPECIFIC PREPARATION OF VINYLKETENES FROM α,β-UNSATURATED ACID CHLORIDES.

Yashwant S. Kulkarni, Beverly W. Burbaum and Barry B. Snider*
Department of Chemistry, Brandeis University, Waltham, MA 02254

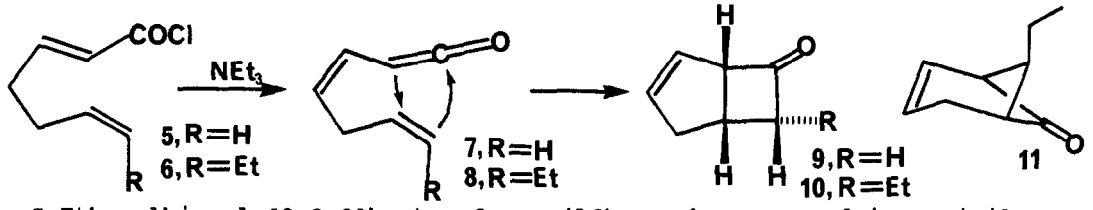
Abstract: Treatment of α,β-unsaturated acid chlorides 5, 6, 14, 17, and 18 with NEt_3 in toluene at reflux generates, stereo- and regiospecifically, the vinylketene which undergoes a facile intramolecular [2 + 2] cycloaddition.

The stereospecific [2 +2] cycloaddition of ketenes to alkenes is a valuable method for the synthesis of cyclobutanones and compounds which can be derived from them; it is one of the few general methods for carbofunctionalization of alkenes. We have recently shown that the intramolecular cycloaddition of alkoxyketenes or chloroketenes with alkenes is a general synthetic method in which electronic effects of substituents on the alkene, rather than the connectivity pattern, controls the regiochemistry of the cycloaddition.[1,2] We have also shown that vinylketenes[3] are suitable substrates for the intramolecular [2 + 2] cycloaddition. The cycloaddition of vinylketene 2, which can be easily prepared regiospecifically from E,E-farnesoyl chloride (1) by treatment with NEt_3 in toluene at reflux, cyclizes to give 3 which is converted to β-trans-bergamotene (4) by Wolff-Kishner reduction.[3] Chrysanthenone, β-pinene and β-cis-bergamotene have been prepared similarly, and ketone 3 has been converted to β-copaene, β-ylangene and lemnalol.[4] Ghosez, Greuter et al., have reported the preparation and cycloaddition of vinylketenes from α,β-unsaturated acid chlorides containing two identical alkenyl side chains.[2] The symmetry of the substrate makes only one vinylketene possible, but limits the generality of the reaction.

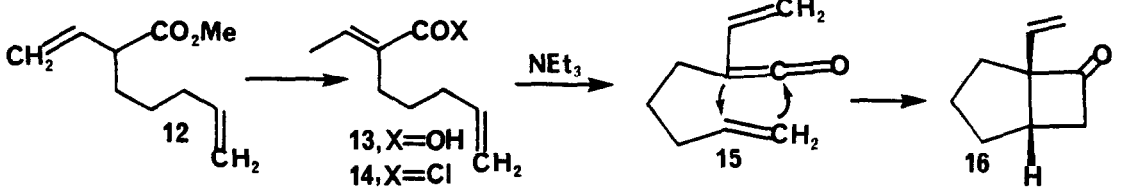


We report here results which establish that the desired vinylketenes are readily prepared stereo- and regiospecifically by treatment of a variety of α,β-unsaturated acid chlorides with NEt_3 in toluene at reflux, and that

these cycloadditions lead efficiently to alkenylcyclobutanones. Treatment of 5[5] with NEt_3 in benzene at reflux for 8 h gave the bicycloheptenone 9[6] in 48% yield. The selective formation of the cis-vinylketene 7, which is required for the cycloaddition, was anticipated from Kende and Toder's observation that deconjugative protonation of the kinetic dienolate generated from ethyl trans-2-hexenoate gave an 81:13 mixture of cis:trans ethyl 3-hexenoate.[8] The kinetic deprotonation of the acid chloride 5 apparently proceeds in a manner similar to that of the ester studied by Kende. Treatment of the α,β-unsaturated acid chloride 6[9] with NEt_3 in toluene at reflux for 20 min gave the ketene 8 which reacted analogously to give a 46% yield of 10[6] and a 5% yield of an unstable isomer which may be 11.

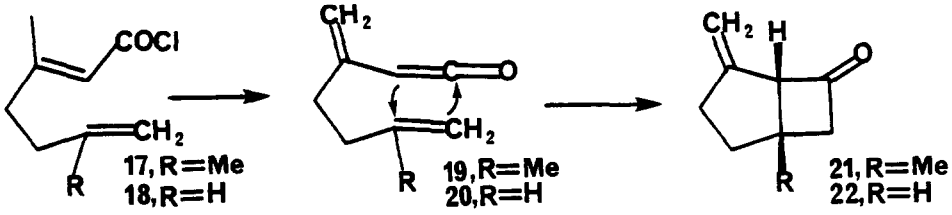


5-Ethenylbicyclo[3.2.0]heptan-6-one (16) can be prepared in a similar fashion. Reaction of methyl crotonate with LDA in THF at 0 °C followed by the addition of 1 equivalent of HMPA, cooling to -78 °C, and addition of 5-iodo-1-pentene gave 12 in 65% yield.[10] Hydrolysis of 12 in 20% aqueous KOH gave the conjugated acid 13 in 96% yield which was converted to the acid chloride 14 (oxalyl chloride, benzene 50 °C) in quantitative yield. Reaction of 14 with NEt_3 in toluene at reflux for 1.25 h gave ketene 15 which underwent an intramolecular cycloaddition to give 16[6] in 51% yield. Vinylcyclobutanones such as 16 are versatile intermediates for the construction of a variety of ring systems.[11] The 2-methyl homologue, prepared by a 12 step route is a key intermediate in Gadwood's synthesis of poitediol.[12]



The selective formation of 2 from acid chloride 1 makes this route to vinylketenes very attractive; further studies indicate that it is generally applicable. Reaction of 17[13] with NEt_3 in toluene at reflux for 1 h gave 21[6] in 43% yield. Reaction of 18[13] under identical conditions gave 22[6] in 41% yield. The formation of 22 indicates that vinylketenes undergo intramolecular cycloaddition with unreactive monosubstituted double bonds. The intramolecular cycloaddition of the related saturated ketene lacking the methylene group has been reported to give only a 3% yield of cycloadduct.[2]

The selective formation of the exomethyleneketene appears to result from two reinforcing factors. Katzenellenbogen and Crumrine have shown that kinetic deprotonation of related α,β-unsaturated acids occurs on the methyl group regardless of the double bond geometry.[14] On this basis, the formation of ketenes 2, 19 and 20 was expected regardless of the geometry of the α,β-unsaturated acid chloride. More recently, Harris and Weiler have shown, by the use of labeled substrates, that deprotonation of methyl 3-methyl-2-butenoate or 3-methyl-2-butenoic acid occurs regioselectively on the methyl group syn to the acid function under kinetic conditions.[15] Since the predominant isomer of acid chlorides 1, 17 and 18 is the E-isomer, the syn effect should also favor the formation of the exomethylene ketene. Further study will be necessary to determine the regioselectivity of the deprotonation of α,β-unsaturated acid chlorides in which these two effects do not reinforce each other.



After this work was completed, Corey, Desai and Engler reported a vinylketene cycloaddition related to that of 7 and 8 as the key step in the synthesis of retigeranic acid,[16] and Corey and Desai reported the cyclization of 2 to give 3.[17] In both cases, the vinylketenes were prepared by treatment of the less readily available β,γ-unsaturated acid chloride with NEt_3. The preparation of these versatile intermediates from α,β-unsaturated acid chlorides which we have described here makes a wide variety of bicyclic 2-alkenylcyclobutanones readily available from easily accessible precursors by a procedure which is applicable to large-scale preparations.

Acknowledgment. We are grateful to the National Institutes of Health for financial support.

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6. The spectral data follow: 9: H NMR is identical to that previously

reported;[7] ^{13}C NMR 25.8, 40.4, 53.2, 73.7, 125.4, 133.5, 216.1. **10**: H NMR 0.97 (t, 3, J = 7.5), 1.52 (ddq, 1, J = 7.5, 8.7, 14.1), 1.66 (ddq, 1, J = 7.2, 7.5, 14.1), 2.46-2.65 (m, 2), 3.11 (dddd, 1, J = 2.5, 8.0, 9.1, 9.6), 3.21 (dddd, 1, J = 3.3, 7.2, 8.7, 9.6), 4.24 (dddd, 1, J = 2.1, 3.0, 3.3, 8.0), 5.60 (dddd, 1, J = 2.1, 2.1, 3.0, 5.7), 5.92 (dddd, 1, J = 2.1, 2.4, 2.4, 5.7); ^{13}C NMR 12.9, 20.0, 30.2, 32.6, 63.2, 71.5, 125.3, 134.7, 211.0. **16**: H NMR 1.45-1.95 (m, 5), 2.15 (dd, 1, J = 6.1, 13.0), 2.49 (dd, 1, J = 4.7, 18.6), 2.75-2.85 (m, 1), 3.24 (dd, 1, J = 9.8, 18.6), 5.07 (d, 1, J = 10.8), 5.22 (d, 1, J = 17.6), 5.94 (dd, 1, J = 10.8, 17.6); ^{13}C NMR 25.1, 32.7, 35.3, 36.3, 49.2, 78.3, 114.0, 135.9, 214.4. **21**: H NMR 1.45 (s, 3), 1.74 (ddd, 1, J = 8.1, 13.0, 13.0), 1.93 (ddd, 1, J = 2.5, 7.1, 13.0), 2.52 (m, 2), 2.84 (dd, 1, J = 4.4, 18.3), 2.95 (dd, 1, J = 2.4, 18.3), 3.44 (m, 1), 4.87 (br s, 1), 4.92 (br s, 1); ^{13}C NMR 24.7, 33.3, 38.2, 39.3, 56.6, 75.4, 108.9, 147.8, 206.5. **22**: H NMR 1.78 (br ddd, 1, J = 2.5, 7.5, 12.8), 1.90 (dddd, 1, J = 6.5, 7.5, 12.8, 12.8), 2.37 (br dd, 1, J = 7.5, 15.0), 2.49 (m, 1), 2.68 (ddd, 1, J = 3.1, 5.0, 18.2), 2.93 (m, 1), 3.16 (ddd, 1, J = 5.0, 8.9, 18.2), 3.85 (m, 1), 4.87 (br s, 1), 4.90 (br s, 1); ^{13}C NMR 29.7, 31.7(2), 51.2, 70.8, 108.7, 147.6, 207.1.

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(Received in USA 7 August 1985)