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A NOVEL RING EXPANSION OF 1-CARBOETHOXY-1,1-TRIMETHYLENE-3-DIAZO-2-PROPANONE

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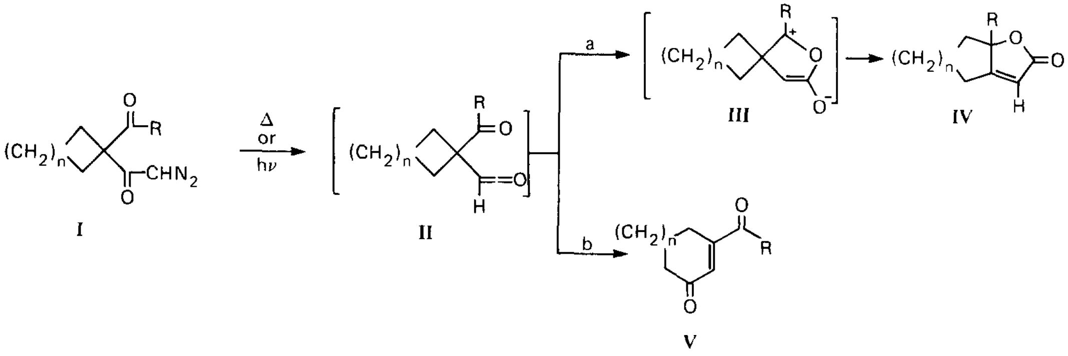
SUMMARY: The title compound undergoes an unusual thermal cyclobutyl to cyclopentyl rearrangement initiated by the intramolecular reaction of a ketene moiety produced in situ with the pendant functionality.

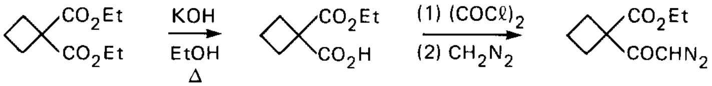
For some time we have been investigating the reaction of strained ring derivatives with various electrophiles resulting in rearranged products with multiple, chemically differentiated functionalities.[1] During the course of this study, we became interested in bifunctional reagents which contained an electrophile-nucleophile combination within the same molecule.[2] It seems that the electrophilic ketene moiety is capable of fulfilling such a dual role under certain reaction conditions,[3] and accordingly we have described an unusual ring contraction of a α-ketenyl substituted cyclobutanone which is apparently initiated by electrophilic attack of the ketene substituent on the cyclobutanone carbonyl group.[4]

This result suggested that ketene derivatives might also be utilized to initiate Demjanov-type ring expansions of appropriate strained ring derivatives containing geometrically proximate nucleophilic functionality as shown in Scheme I. One potential complication for small rings derivatives (n=0,1) is the possibility of a competing vinyl cycloalkane-cycloalkene rearrangement to yield enones such as V.[5] We now report here the observation of such an intramolecular ketene initiated ring expansion which produces a highly functionalized butenolide derivative rather than the corresponding cyclic enone.

Scheme I



1,1-Dicarboethoxycyclobutane 1 can be selectively hydrolyzed to the half acid ester 2 using potassium hydroxide in ethanol. The ester is converted *via* the acid chloride by treatment with excess diazomethane to the desired diazoketone 3 which was purified by column chromatography (silica gel, ethyl acetate-hexane).



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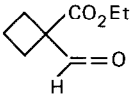

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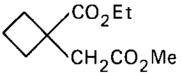

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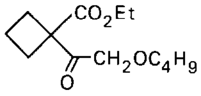

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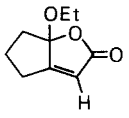

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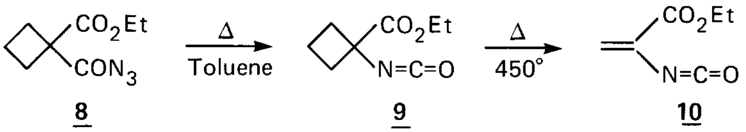
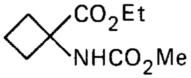
Photolysis of 3 (450 watt Hg lamp, Vycor filter) in methanol led to the isolation of the homologated ester 5 in 82% yield[6] *via* the desired ketene 4. However, photolysis in the absence of trapping reagents at room temperature or below produced no evidence of the desired ring expansion and resulted instead in a complex high boiling product mixture. The presence of a high frequency IR band at ~1830 cm^{-1} suggests that ketene dimers may comprise a portion of this mixture. Under these reaction conditions, intramolecular rearrangement is apparently not competitive with alternative bimolecular reactions of the ketene such as dimerization. A similar high boiling product mixture was produced in the solution pyrolysis of 3 in high boiling solvents such as xylene. In an attempt to detect the presence of 4 in the thermal process, the diazoketone was slowly added to a refluxing mixture of 85/15 xylene/n-butanol. In this case, a new product was isolated (60%), but spectral characterization indicated that it was not the expected ester derived from the ketene 4 but was instead the butyl ether 6[6] apparently resulting from the displacement of nitrogen from 3 without rearrangement.

In an effort to generate the desired ketene 4 under conditions of high dilution to minimize any intermolecular reactions, 3 was pyrolyzed in the gas phase through a hot tube at 350°C (0.1 mm). The injection of a ketene trapping agent such as methanol into the cold trap prior to warmup did not produce any of the ester 5. Instead a new stable product was isolated in ~40% yield after glpc purification. The spectral data of this material was completely consistent with the proposed butenolide structure 7.[7] Particularly significant in this regard was the presence of a complex ABX_3 diastereotopic pattern at $\delta 3.38$ in the NMR for the methylene protons of the ethyl group which is consistent with the close proximity of an asymmetric center.





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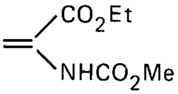

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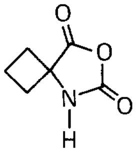

13

Since the isocyanate functionality is a known electrophile which shares many common reactions with ketenes,[8] the isocyanate derivate 9 (IR (neat) 2260, 1735 cm^{-1}) was prepared by thermolysis of the acid azide 8. Unlike the corresponding ketene, however, the isocyanate 9 proved to be quite thermally stable and was recovered virtually unchanged under the conditions used for the pyrolysis of the diazoketone 3. The use of higher temperatures and pressures (580°C, 4 mm) resulted in considerable decomposition of 9 as evidenced by the apparent broadening of both the isocyanate and ester absorptions in the IR of the pyrolysate. In addition, the ^{1}H NMR of the crude pyrolysate showed what appeared to be olefinic hydrogens at δ 5.40 and 5.78. When the pyrolysate was quenched with MeOH, the urethane 11 formed from the starting isocyanate 9 was isolated in 14% yield.[9] In addition, however, another urethane was isolated (28%) which was identified by its spectral and analytical data as 12.[9] Apparently, under the more vigorous pyrolysis conditions, the four membered ring undergoes a fragmentative loss of ethylene to produce 10.

Although no evidence for the desired ring expansion of 9 could be garnered, careful spectral examination of the crude pyrolysate indicated the presence of a small amount of an additional, methanol labile product which had infrared absorptions at 1780 and 1850 cm^{-1}. The relative yield of this material increased somewhat at lower temperatures and pressures (*e.g.*, 450°C, 0.1 mm). The characteristic infrared absorptions[10] coupled with its reactivity toward methanol suggested that this material might be the N-carboxyanhydride of 1-aminocyclobutane carboxylic acid 13. This hypothesis was confirmed by comparison of the spectral data of the crude pyrolysate with that of an authentic sample of 13 prepared by reaction of the amino acid with phosgene.[10] It thus seems that some intramolecular attack on the ester moiety of 9 occurs to some extent, but the nitrogen anion thus formed undergoes protonation rather than ring expansion.

In summary, we have demonstrated for the first time an intramolecular Demjanov-type ring expansion initiated by attack of a ketene electrophile on a geometrically proximate ester carbonyl. Attempts to extend this reaction to the corresponding isocyanate were unsuccessful and led predominantly to fragmentation of the four membered ring particularly at higher temperatures.

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5. Willcott, R. M.; Cargill, R. L.; Sears, A. B.; "Progress in Physical Organic Chemistry," Streitweiser, A.; Taft, R. W.; eds., 1972, Wiley-Interscience, New York.
6. Spectral and analytical data consistent with the proposed structures were obtained for all new compounds.
7. Spectral data: 7, IR (neat) 2980, 1780, 1765, 1660, 1180, 1085, 1055, 965, 900 and 730 cm^{-1}; ^{1}H NMR δ($CDCl_3$) 1.26 (t,J=7.5 Hz,3H), 1.2-3.0 (m,6H), 3.38 (m,2H) and 5.77 (t,J=1.5 Hz,1H), ^{13}CMR δ($CDCl_3$) 14.98, 22.04, 23.51, 32.02, 58.75, 112.63, 114.3, 171.54 and 173.3; mass spectroscopic molecular weight 168.079.
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9. Spectral data: 11; ^{1}H NMR δ($CDCl_3$) 1.27 (t,J=7.5 Hz,3H), 1.7-2.7 (m,6H), 3.68 (s,3H), 4.2(q,J=7.5 Hz,2H) and 5.38 (brs,1H); IR($CDCl_3$) 3340 (m) and 1725 (s)cm^{-1}; 12; ^{1}H NMR ($\delta CDCl_3$) 1.28 (t,J=7.5 Hz,3H), 3.76 (s,3H), 4.25 (q,J=7.5 Hz,2H), 5.78 (brs,1H), 6.20 (brs,1H) and 7.2 (brs,1H); IR($CDCl_3$) 3410 (m), 1735 (m), 1710 (s), 1640 (w) cm^{-1}; 13; mp 109°C(dec); ^{1}H NMR δ($CDCl_3$) 1.5-2.9 (m,6H) and 7.2 (brs,1H); IR($CDCl_3$) 3450 (w), 3300 (w), 1850 (m) and 1780 (s) cm^{-1}.
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