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THE VINYLOGOUS CONIA REARRANGEMENT : A MASKED ENE REACTION

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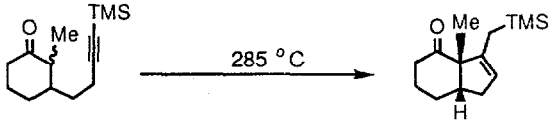
SUMMARY: *A novel carbocyclic thermal rearrangement of 4-substituted 2-cyclohexen-1-ones is suggested to involve a 'masked' ene reaction and provides a facile route to spirocyclic cyclohexenone systems.*

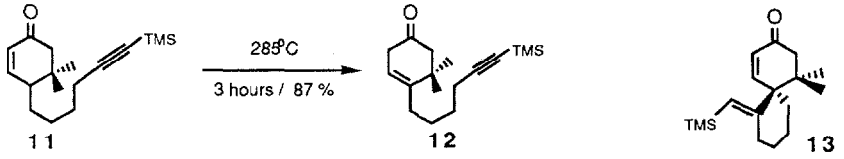
The thermal cyclization of unsaturated carbonyl compounds, or Conia reaction, is a useful means of generating rings α to an aldehyde or ketone.[1] A shortcoming of this reaction has been that an olefin is the maximum functionality produced in the newly formed ring. We have recently described a general route to bicyclic keto-silanes by the thermal rearrangement of β-substituted silylacetylenic cycloalkanones, a variant which should greatly enhance the utility of this process.[2]



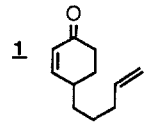
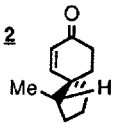
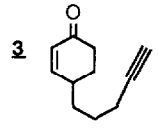
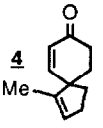
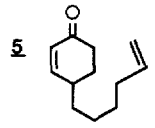
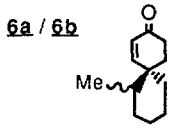
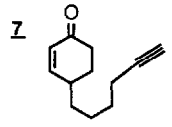
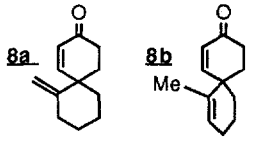
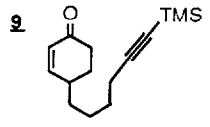
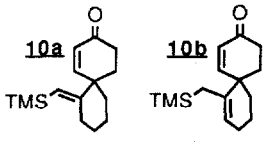
We now report a hitherto unknown thermal rearrangement which results in the formation of spirocyclic enones upon heating certain γ-substituted α,β-unsaturated cyclic ketones.[3] A summary of our findings is given in the Table.[4] Formally these transformations correspond to "vinylogous" Conia rearrangements. Yields for these reactions are moderate to good (48-72%), and in the cyclization of **1** a single diastereomer was formed, shown by nOe studies to have the methyl syn to the enone double bond.[5] These reactions can be conducted on gram-scale by sealing a neat sample (in vacuo) in a heavy-walled glass tube, or alternatively the starting enone may be sealed in a medium-walled NMR tube containing toluene-d8.[6] Purification of the product was achieved by flash[7] or thin layer preparative chromatography on silica gel using 3:1 hexane / ether as eluent.

Preliminary evidence discussed below suggests that the mechanism for this novel rearrangement involves the sequence: (1) C-4 enolization of the enone, (2) deconjugative ketonization to a β,γ-unsaturated enone, and (3) an ene-reaction involving transfer of a C-2 hydrogen to the side chain. Thus the cyclization step is actually a "masked" ene-reaction.[8]

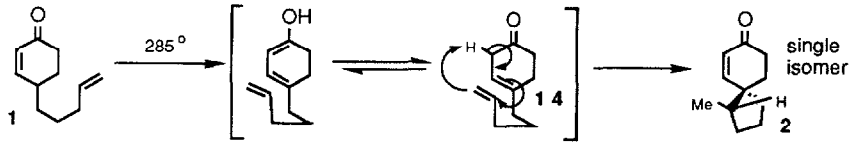
Evidence for the enolization/deconjugation mechanism was provided when compound **11** was heated to 285° for three hours.[9] The only isolated product (87% isolated yield) was the deconjugated isomer **12**.[10] In this instance the formation of spirocycle **13** was sterically prohibited by the presence of the geminal methyl groups α to the potential quaternary center, as previously established by Davis and Halsall.[15]



11 12 13

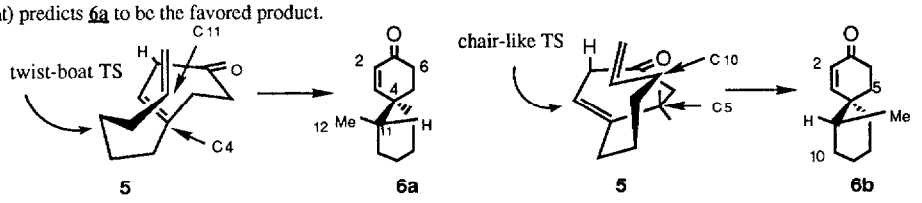
Starting Enone	Conditions	Product (s)	Total Isolated Yield
	285° C 5 hours		58% [5] single diastereomer
	285° C 1.5 hrs.		72% [11]
	285° C 48 hrs.		48% [12] (3 : 1)
	285° C 5-6 hrs.		23% (60%) [13] (2 : 1)
	285° C 48 hrs.		42 - 54% [14] (3 : 1)

Evidence favoring the subsequent intramolecular ene reaction step derives from the formation of the single diastereomer **2** starting from **1**. This reaction is expected to proceed by way of intermediate **14**, for which the stereochemistry of the subsequent ene-reaction transition state leads uniquely to the observed stereoisomer **2**. Further support for our mechanism was obtained by heating authentic enone **14** [16] to 285° C; the only product formed was the single isomer **2**, identical to the spirocycle prepared from **1**. Enone **1** was not detected during this process (using 300 MHz NMR and analytical gas chromatography), indicating that cyclization is significantly faster than re-enolization.[17] Finally, NMR monitoring of the rearrangement of **1** at 285° C showed the generation and subsequent disappearance of intermediate **14**, consistent with the consecutive first-order reactions proposed.



The formation of a 3 : 1 ratio of diastereomeric enones **6** from reactant **5** may be rationalized by a slightly more complicated analysis, illustrated below. In this case, the increase in chain length permits cyclization to either face of the terminal double bond, and this is borne out in the observed 3 : 1 ratio of product stereoisomers. Although no **nOe's** were observed for products **6a/6b**, *tentative*

structural assignments were made as follows. Examination of Dreiding models and the use of the MM2 program MacroModel[18] indicate that the minor isomer, presumably **6b**, is best obtained through a chair transition state, even though there exists a significant steric interaction between the methylene hydrogens at C-5 and C-10. Alternative conformations do not correct for this interaction without compromising the necessary proximity between C-4 and C-11, and C-12 with the axial hydrogen at C-2. The formation of the major isomer (assumed to be **6a**) appears to proceed best through a twist boat conformation for the C-4 side chain. This conformation minimizes the unfavorable steric interactions present in both the conventional chair and boat forms, while still maintaining good C-4 to C-11 proximity for the formation of the incipient σ bond. Either transition state conformation (chair or twist-boat) predicts **6a** to be the favored product.



Further studies of the mechanism, scope and limitations[19] of these and related rearrangements, and of their use in complex molecule synthesis, are in progress.[20]

References:

(1) For a review of this reaction, see Conia, J. M.; Le Perchec, P. *Synthesis*, **1975**, 1.

(2) Kende, A. S.; Hebeisen, P.; Newbold, R. C. *J. Amer. Chem. Soc.*, **1988**, *110* , 3315.

(3) The monocyclic enones were prepared by the procedure of Stork, G.; Danheiser, R.L. *J. Org. Chem.*, **1973**, *38*, 1775.

Alkylation of 3-ethoxycyclohexenone with the appropriate alkyl iodide provided the corresponding 6-alkyl-3-ethoxycyclohexenones in 40 - 76% isolated yield. Reduction with 1.2 equivalents of DIBAL-H in toluene, followed by acidic workup provided the desired 4-alkyl-2-cyclohexenones in 80 - 96% yields (see Kende, A. S.; Fludzinski, P. *Org. Syn.*, **1985**, *64*, 68).

(4) All new compounds exhibited IR, ^{1}H and ^{13}C NMR spectra (including APT studies), mass spectral or combustion data in agreement with the structures indicated.

(5) Enone **2**: **^{1}H NMR** (300MHz, $CDCl_3$, partial) δ 6.80 (1 H, d, J = 10.3 Hz), 5.94 (1 H, d, J = 10.3 Hz), 0.94 (3 H, d, J = 6.9 Hz); **^{13}C NMR** ($CDCl_3$) δ 199.92 (C=O),156.18 (C-3), 127.68 (C-2), 46.57, 44.00, 38.42, 35.88, 35.75, 34.19, 22.14, 15.46; **IR** (film) 2960, 1680 cm^{-1} (unsaturated ketone); **Anal.** Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.25; H, 9.91. Structure **2** was firmly established by **nOe** studies: irradiation of the C-3 hydrogen produced a 9.7% enhancement of the the methyl signal, whereas irradiation of the methyl group produced a 30% enhancement of the β-vinyl proton.

(6) All reaction vessels were thoroughly base washed and oven dried (140 ^{0}) for at least 48 hours. The glass tubes were sealed under a vacuum of 0.01 mm Hg by means of a freeze--thaw technique employing liquid nitrogen. All reactions were carried out at 285 ^{0} C, and were initially monitored using the NMR technique to determine the time required for the reaction to completely consume starting material. Samples larger than one gram were turned frequently to ensure thorough heat transfer.

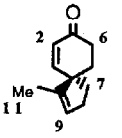
(7) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* , **1978**, *43*, 2923.

(8) Hoffman, H. M.R. *Angew. Chem. Int. Ed.*, **1969**, *8*, 556. For a review containing several examples of spirocyclizations structurally related to those observed here, see Oppolzer, W.; Snieckus, V. *Angew. Chem. Int. Ed.*, **1978**, *17*, 476.

(9) Enone 11: **^{1}H NMR** (300MHz, $CDCl_3$, partial) δ 6.76 (1 H, d, J = 10.2 Hz), 5.96 (1 H, d, J = 10.2 Hz), 0.10 (9 H, s, $Si(Me)_3$); **^{13}C NMR** ($CDCl_3$, partial) δ 199.58 (C=O), 152.20 (C-2), 128.36 (C-3), 46.56 (C-4); **IR** (film) 2960, 2170 (acetylene), 1678 (unsaturated ketone), 1248 cm^{-1} ($Si(Me)_3$ stretch); **MS** (70 ev) m/e 276 (M^+).

(10) Enone 12: **^{1}H NMR** (300MHz, $CDCl_3$, partial) δ 5.33 (1 H, br. t, C-3), 2.83 (2 H, C-2 methylene), 2.34 (2 H, s, C-6 methylene), 0.11 (9 H, s, $Si(Me)_3$); **^{13}C NMR** ($CDCl_3$, partial) δ 210.64 (C=O), 39.25 (C-2), 116.79 (C-3), 145.79 (C-4); **IR** (film) 2960, 2178 (acetylene), 1720 (unconjugated ketone), 1250 cm^{-1} (TMS stretch); **MS** (70 ev) m/e 276 (M^+).

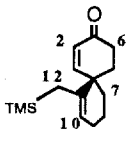
(11) Enone 4: **^{1}H NMR** (300MHz, $CDCl_3$) δ 6.66 (1 H, d, J = 9.8 Hz), 5.95 (1 H, d, J = 10.1 Hz), 5.48 (1 H, s, $J_{allylic}$ = 1.18 Hz, 2.49 (t, 2 H), 2.16 (m, 2 H), 2.32 (m, 2 H), 1.91 (1 H, m), 1.80 (1 H, m), 1.65 (3 H, s, $J_{allylic}$ = 1.45 Hz); **^{13}C NMR** ($CDCl_3$) δ 199.56 (C=O), 157.28 (C-3), 144.04 (C-10), 128.07 (C-2), 126.85 (C-9), 51.45 (C-4), 35.50, 35.31, 30.41, 29.71 (C-5 to C-8), 13.30 (C-11). **IR** (film) 2938, 1678 (unsaturated ketone), 1610 cm^{-1}. **HRMS** Calcd. for $C_{11}H_{14}O$: 162.1045. Found: 162.1025.



(12) Enone 6a: **^{1}H NMR** (300MHz, $CDCl_3$, partial) δ 7.06 (1 H, d, J = 10.4 Hz), 6.00 (1 H, d, J = 10.4 Hz), 0.86 (3 H, d, J = 6.3 Hz); **^{13}C NMR** ($CDCl_3$) d 199.76 (C=O), 155.60 (C-3), 129.02 (C-2), 39.20, 38.79, 37.18, 33.73, 33.43, 30.57, 25.44, 22.31, 16.97; **IR** (film) 2938, 1668 cm^{-1} (unsaturated ketone); **HRMS** Calcd. for $C_{12}H_{18}O$: 178.1358. Found: 178.1364. Enone 6b: **^{1}H NMR** (300MHz, $CDCl_3$, partial) δ 6.59 (1 H, d, J = 10.4 Hz), 5.92 (1 H, d, J = 10.4 , 0.84 (3 H, d); **^{13}C NMR** ($CDCl_3$) d 200.14 (C=O), 161.36 (C-3), 127.82 (C-2), 39.20, 38.73, 37.18, 33.73, 33.05, 29.16, 25.73, 21.55, 17.09.

(13) Enone 8: 60% yield based on recovered starting material at 38% conversion. **^{1}H NMR** (major, exocyclic) (300 MHz, $CDCl_3$, partial) δ 6.67 (1 H, d), 6.02 (1 H, d), 4.89 and 4.65 (2 H, (s) each). **IR** (film) 2938, 1668 cm^{-1} (unsaturated ketone); **MS** (70 ev) m/e 177 (M^{+1}), 176 (M^+, 34.4%), 77 (100%). **HRMS** Calcd. for $C_{12}H_{16}O$: 176.1201. Found: 176.1190. **^{1}H NMR** (minor, endocyclic) (300 MHz, $CDCl_3$, partial) δ 6.88 (1 H, d), 5.91 (1 H, d), 5.58 (1 H, br. s), 1.68 (3 H, d).

(14) Enone 10 (allylsilane isomer): **^{1}H NMR** (300MHz, $CDCl_3$) δ 6.66 (1 H, d, J = 10.3 Hz), 6.01 (1 H, d, J = 10.2 Hz), 5.18 (1 H, s), 2.52 (1 H, dt), 2.32 (2 H, m), 2.26 (1 H, dt), 1.87 (2 H, m), 1.66 (5 H, complex m), 1.38 (1 H, m), 0.09 (9 H, s); **^{13}C NMR** ($CDCl_3$) d 200.59 (C=O), 158.40 (C-3), 128.54 (C-2), 157.74 (C-11), 124.86 (C-10), 45.33, 39.59, 34.07, 31.24, 30.94, 27.68 (C-9), 21.01, 0.16 ($Si(Me)_3$); **IR** (film) 2940, 1688 (unsaturated ketone), 1605, 1250 cm^{-1} ($Si(Me_3)$ stretch); **HRMS** Calcd. for $C_{15}H_{24}OSi$: 248.1596. Found: 248.1588.



(15) Davis, B. R.; Halsall, T. G. *J. Chem. Soc.* **1962**, 1833.

(16) β,γ-Unsaturated enone 14 was prepared by Birch reduction of p-(4-pentenyl)-anisole using lithium in $NH_3(l)$, hydrolyzed by oxalic acid or 3M HCl, and purified by preparative gas chromatography. **^{1}H NMR** (300MHz, $CDCl_3$, partial) δ 5.81 (1H, m, terminal olefin methine), 5.45 (1H, s, β-methine of β,γ-unsaturated ketone), 4.99 (2H, t, terminal methylene), 2.86 (2H, s, methylene α to ketone). **IR** (film) 2940, 1722 (β,γ-unsaturated ketone), 1645, 1445, 1195 cm^{-1}.

(17) Enone 14: **^{1}H NMR** (300MHz, $CDCl_3$, partial) δ 5.81 (1H, m, terminal olefin methine), 5.45 (1H, s, β-vinyl proton), 4.99 (2H, m, terminal olefin), 2.86 (2H, s, methylene α to ketone) **IR** (film) 2940, 1722 cm^{-1} (β,γ-unsaturated ketone)

(18) See for example: Still, W.C. et al. *J. Org. Chem.* **1987**, *52*, 951 and references cited therein.

(19) We have observed that at 285° C, 4-(4-pentenyl)-2-cyclopenten-1-one simply undergoes double bond migration to give 3-(4-pentenyl)-2-cyclopenten-1-one. No spirocycle is observed even upon prolonged heating.

(20) Partial support of this research by Grant CA-18846, awarded by the National Cancer Institute, USPHS, is gratefully acknowledged. R.C.N. is grateful to the University of Rochester for an Arnold Weissberger Fellowship.

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