## **Ring Enlargement-Annulation via Thermal Oxy-Cope Rearrangement**

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Abstract: Thermal oxy-Cope rearrangement of substrates 5,7 and 11 resulted in ring expansion and annulation. The effect of alkene substituents and variation in the ring systems on the reaction has been studied.

Recently, we reported cyclopentane annulation via ring enlargement involving the thermal rearrangement of the substrate 1  $(eq.1)^1$ . An initial oxy-Cope rearrangement followed by a transannular ene reaction was invoked to explain the formation of the product 3.



Our studies revealed that the second chemical event namely the transannular ene reaction depends upon the interatomic distance between  $C_1$  and  $C_5$  (eq. 1)<sup>1</sup>. We now present herein a related chemistry with a study on the effect of alkene substitutent on the mode of ene reaction and the outcome of the thermal rearrangement of 5. Incidentally this study brought to light the facts that the transannular ene reaction not only depends upon interatomic distance between the  $C_1$  and  $C_5$ , but also the proximity of the allylic hydrogen<sup>2</sup> to the carbonyl oxygen. An extension of this study was made to a system containing an allenic and alkyne function as one of the participating  $\pi$ -system.

Addition of lithium acetylide (3 equivalents) to 2-methyl-2-(cyclohexen-1' -y1)-cyclohexanone in THF at -78°C gave the known ethynyl carbinol<sup>3</sup>4 in almost quantitative yield as a single diastereomer (mp 110-111°C;  $CCl_4$ -hexane).



The stereochemical relationship of the substituents in compund 4 was obtained by single crystal X-ray analysis. Reduction of the ethynyl carbinol<sup>3</sup> 4 with 5% Pd-BaSO<sub>4</sub> in pyridine at 35 psi, H<sub>2</sub> atmosphere gave the known vinyl carbinol 5 in 90% yield<sup>3</sup>. Refluxing 5 in ortho-dichloro benzene (o-DCB) for 12h in inert atmosphere (N<sub>2</sub>) and then removal of o-DCB under reduced pressure (< 0.5 Torr) followed by column chromatography gave compound 7 in 90% yield.

Compound 7 showed absorptions for hydroxyl group and double bond in the IR ( $u_{0-H} = 3520$  and  $u_{C-C} = 1610 \text{ cm}^{-1}$ ); and a characteristic vinylic hydrogen signal at  $\delta$  5.4 and also the appearance of angular methyl signal at  $\delta$  1.15 in the <sup>1</sup>H NMR (400 MHz) spectrum. In <sup>13</sup> C NMR (100.6 MHz) the vinyl carbon resonates at 145.35(s) and 121.61 (d), the hydroxyl bearing quaternary carbon resonates at 73.65 (s), the methyl bearing quaternary carbon resonates at 32.01(d). The stereochemical relationship as indicated in compound 7 was based on mechanistic considerations and further confirmed by differential NOE studies. Irradiation of angular methyl at  $\delta$  1.15 causes 16.9% enhancement of -OH signal at  $\delta$  3.38 thus establishing a cis relationship between the two. The formation of compound 7 can be rationalised as involving an initial oxy-Cope rearrangement to give the ring enlarged dione 6 and subsequent transannular ene reaction to give compound 7. After the initial oxy-Cope rearrangement an alternative mode of transannular ene reaction occurs (eq 2) due to the unfavourable bond distance between C-1 and C-5 atoms<sup>4</sup> and the proximity of one of the protons at C-11 to the carbonyl oxygen<sup>5.6</sup>. The net result is the formation of a C-C bond between the termini of the  $\pi$  systems with no apparent skeletal change. It differs from the base catalysed rearrangement which gives rise to only compound<sup>3</sup> 6.

Attention was then focussed on the rearrangement studies of a substrate incorporating an allenyl moiety. A survery of the literature showed that there are only two examples of thermal oxy-Cope rearrangement involving allenic systems<sup>7</sup>. Recently, we reported<sup>8</sup> the base catalysed oxy-Cope rearrangement of an allenic system. The studies indicated the greater reactivity of the allenyl system as compared to the vinyl system due to the strain arising from the cumulated bonds which reduces the strength of the  $\pi$  bond relative to a vinyl system and also the excellent overlap of the olefinic  $\pi$  bond with the p AO's of the central carbon atom of the allenic moiety. From our model studies thermal rearrangement of the substrated 8 seemed a worthwhile objective. The substrate 8 was prepared in 65% yield from the known 1-ethynyl-1-hydroxyl-6-oxo-8a-methyl-1,2,3,4,6,7,8,8a octahydronapthalene<sup>9</sup> by the method of Dikshit<sup>10</sup>, however as a mixture of diastereomers (eq. 3).



Refluxing the mixture 8 in o-DCB at reflux temperature for 14 h then removal of solvent at reduced pressure followed by column chromatography gave a major product 11 in 65% yield as a solid (mp 117°,

hexane-ethyl acetate) and an inseparable mixture of products. The major compound 11 was characterized by spectral data. It showed the presence of a -OH, conjugated carbonyl and double bond in IR spectrum ( $v_{0-H} = 3580$ ,  $v_{C=0} = 1660$ ,  $v_{C=C} = 1625$  and  $1600 \text{ cm}^{-1}$ ). In <sup>1</sup>H NMR (400 MHz) spectrum the vinylic hydrogen H<sub>7</sub> and H<sub>a</sub> appeared at  $\delta$  6.55 and  $\delta$  5.91 respectively. The vinylic methyl signal appears at  $\delta$  2.04 as a singlet and the saturated methyl group as a doublet at  $\delta$  1.23 and the methine proton H-6 appears at  $\delta$  3.0 as a multiplet (ddq). In <sup>13</sup>C NMR (100.6 MHz) spectrum the vinyl carbon resonates at 155.79 (d) (C-7), 147.9 (s) (C-11), 137.01 (s) (C-10) and 129.87 (d) (C-8), the hydroxyl bearing quaternary carbon resonates at 87.37(s) (C-1) and the conjugated carbonyl resonatesat 189.52 (s) (C-9). The formation of compound 11 can be rationalized by involving an initial oxy-Cope rearrangement to give compound 9 followed by a transannular ene reaction<sup>5</sup> and then isomerization to give compound 11. This methodology provides an easy entry into an angularly fused tricycle.

This methodology was extended to the substrate 12 in which one of the  $\pi$  systems is an alkyne (eq. 4). The known ethynyl carbinol<sup>11</sup> 12 on refluxing in o-DCB at reflux temperature for 12h and removal of solvent at reduced pressure gave a mixture of products 14 and 15 in the ratio of 90:10. They were separated by preparative HPLC. The structures of the compounds 14<sup>13</sup> and 15 were confirmed based on <sup>1</sup>H NMR (300 MHz), <sup>13</sup>C NMR including DEPT studies and NOE studies. An initial oxy-Cope rearrangement followed by transannular ene reaction results in a cyclopentene annulation. This method should prove to be a useful alternative to existing cyclopentene annulation<sup>12</sup>. All new compounds reported showed satisfactory spectral data<sup>13</sup>.



In summary with proper insight, well designed carbocyclic frame work can be synthesized from this strategy. The greater utility of the rearrangement is the ease with which the rearrangement can be effected and also the ready availability of starting material. Further the study clearly established the difference in the base and thermal catalysed rearrangement of the substrates.

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7: <sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.4 (s, 1H, H<sub>11</sub>), 2.38 (br s, 1H, OH), 2.04 - 1.06 (m, 19H, methylenes) and 1.15 (s, 3H, angular methyl). <sup>13</sup>C NMR (100.6MHz, CDCl<sub>3</sub>) 145.34 (C<sub>7</sub>), 121.61 (C<sub>11</sub>), 73.65, 43.32, 34.07, 33.10, 32.01, 31.63, 30.72, 30.02, 26.03, 21.95, 21.14, 21.02 and 20.64.

11 : <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.55 (d(t), J = 10.25 and 2.44 Hz, 1H, H<sub>7</sub>), 5.91 (d(t), J = 10.25 and 2.93 Hz, 1H, H<sub>8</sub>), 3.00 (m, 1H, H<sub>6</sub>), 2.68 (m,3H, methylene and OH), 2.01 (s, 3H, vinylic methyl) 2.05-1.27 (m, 6H, methylene) and 1.23 (d, J = 7.42 Hz, 3H, methyl). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) 189.522 (C<sub>9</sub>), 155.794 (C<sub>7</sub>), 147.90 (C<sub>11</sub>), 137.018 (C<sub>10</sub>), 129.869 (C<sub>8</sub>), 87.367 (C<sub>1</sub>), 64.963, 57.161, 43.044, 36.259, 31.129, 21.885, 16.861, 15.692.

14 : IR (CCl<sub>4</sub>,  $v_{max}$ /cm<sup>-1</sup>) 3560, 3080, 1735, 1650 and 1610. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  5.915 (dd, J = 5.6 and 2.53 Hz, 1H, H<sub>3</sub>), 5.70 (dd, J = 5.6 and 1.86 Hz, 1H, H<sub>2</sub>), 4.92 (d, J = 1.4, 1H, H<sub>13b</sub>), 4.86 (s, 1H, H<sub>13b</sub>) 4.175 (q, J = 7.3, 2H, -COO CH<sub>2</sub> CH<sub>3</sub>); 3.37 (d(t), J = 8.13 and 2.13 Hz, 1H, H<sub>4</sub>), 2.88 (d, J = 8.13, 1H, H<sub>5</sub>), 2.00 (s, 2H, H<sub>7</sub>); 1.76 (d, J = 14.46, 1H, H<sub>9a</sub>), 1.32 (s, 1H, 0H), 1.31 (d, J = 14.46, 1H, H<sub>9b</sub>), 1.29 (t, J=7.36, 3H, -COO CH<sub>2</sub>CH<sub>3</sub>), 1.00 (s, 3H, -CH<sub>3</sub>), 0.93 (S, 3H, -CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>); 176.201 (C<sub>10</sub>), 143.869 (C<sub>6</sub>), 142.009 (C<sub>3</sub>), 127.643 (C<sub>2</sub>), 113.472 (C<sub>13</sub>), 84.809 (C<sub>1</sub>), 60.923, 57.256, 53.544, 47.229, 45.062, 31.729, 31.081, 26.971 and 14.21.

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