## AGGREGATIVE ACTIVATION IN HETEROCYCLIC ELIMINATION - ADDITIONS I. DEHYDRO DIHYDROPYRAN NUCLEOPHILIC CONDENSATIONS

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<u>Summary</u>: It is shown that by nucleophilic Aggregative Activation of NaNH<sub>2</sub>, dehydro dihydropyrans may be easily generated and condensed with ketone enolates in good yields.

Although strained cycloalkynes and cyclo-1,2 dienes were discovered many years ago,<sup>1</sup> they long remained of little use in synthesis. The most convenient generation of these transient species consists in reacting the corresponding vinyl halides with a very strong base.<sup>2</sup> However, with classical bases. condensation of nucleophiles on these very reactive intermediates is impeded by their self-condensation or by the competitive attack of the generating bases themselves.<sup>3</sup> Aggregative activation<sup>4</sup> by the use of complex bases<sup>5</sup> has now allowed us to solve this problem.

For the synthesis of pyran derivatives the elimination-addition symbolized in Scheme I could constitute an attractive pathway. Examination of the literature showed that generation of dehydro dihydro-pyrans is only rarely described<sup>6</sup> and that nothing is known about their chemistry.

Our previous work on dehydrocyclohexenes<sup>5</sup> firmly established that nonnucleophilic complex bases reacted with halo-cyclohexenes to generate mainly cyclohexynes.<sup>7</sup> On the contrary, nucleophilic complex bases strongly favour cyclohexa 1.2-diene formation.<sup>8</sup>

### Scheme I



We have now found that when one uses cyclohexanone enolate as activating agent<sup>9</sup> of sodamide, the condensations reported in Scheme II are easily performed. Scheme II



The alcohol 1 was obtained predominantly (50 % yield) after 300 h when performed the reaction in DME at -15°C. The three compounds formed were separated by preparative HPLC. The unreacted cyclohexanone is recovered almost totally.

Solvent	<u> </u>	<u>t (h)</u>	overall yield %(a)	1% (a)	<b>2%</b> (a)	<b>3</b> %(a)
THF	35	66	50	30	-	20
DME	0	66	50	26	16	8
DME	-15	300	68	50	11.	7

(a) Isolated yield calculated from 3-bromo 4,5-dihydro-4H-pyran

The functionalization of 1 was also briefly explored (Scheme III).

Alcohol 2 polymerizes rapidly and was isolated as a para-nitrobenzoate derivative. This property could be due to the condensation of the hydroxyl group on the dihydropyran function; this potentially useful possibility is presently being studied. The structure of 2 is tentatively assigned by spectroscopic comparison with 1, the structure of which was established by X-ray diffraction analysis of the corresponding epoxide.

### Scheme III



The same cis epoxide 4 (Scheme IV) was obtained by two different procedures using respectively <u>m</u>-chloroperoxybenzoic acid (MCPBA)<sup>10</sup> and Mo(CO)<sub>6</sub>-Bu<sup>t</sup>OOH<sup>11</sup> as oxidative agents, the first one giving the best yield. The formation of the cis epoxide with Mo(CO)<sub>6</sub> was very surprising. Indeed, according to Chong, A. et al.<sup>12</sup> the catalyzed epoxidation would take place after first complexation of the double bond by the molybdenum. In the present case, we could expect such a complexation on the less hindered side directing the hydroperoxide towards the most hindered one and would lead to the trans epoxide.

On the contrary MCPBA was expected to directly attack the double bond on the less hindered side and give the cis epoxide. The last result was in agreement with those obtained some years ago in the laboratory when we performed the synthesis of an analogous non oxygenated ring compound.<sup>13</sup>

The stereochemistry of the glycol **6** (prepared using procedures described in the literature 14.15) has not yet been determined.

Finally we performed the same kind of dehydro dihydropyran condensation with the enolates of cyclopenta and cycloheptanone (Scheme IV).



At the present time, we have no explanation for the absence of 3,4-cyclo adducts

analogous to 2 or for the formation of cis and trans isomer mixtures from cyclopentanone and cycloheptanone, but not with cyclohexanone.

These first very encouraging results show that dehydro dihydropyrans may be easily used as synthetic intermediates and the field opened by these condensations is under active investigation in our laboratory.

General procedure and identification. The reactions were carried out with magnetic stirring under a nitrogen atmosphere and monitored by GLC analysis. To a suspension of NaNH<sub>2</sub> (150 mmol) in the reaction solvent (40 mL), the ketone (50 mmol) in 40 mL of the same solvent was added dropwise at room temperature for cyclohexa - and cycloheptanone or at  $-17^{\circ}$ C for the cyclopentanone. The mixture was stirred mechanically 2 h at 35-40°C for cyclohexa - or cycloheptanone or at  $-17^{\circ}$ C for the cyclopentanone or at  $-17^{\circ}$ C for the cyclopentanone. The mixture was stirred mechanically 2 h at 35-40°C for cyclohexa - or cycloheptanone or at  $-17^{\circ}$ C for the cyclopentanone. Then 3-bromo 4,5-dihydro-4H-pyran<sup>16</sup> (25 mmol) diluted in the solvent (20 mL) was added and the reaction was performed for the time and at the temperature given in scheme II and scheme IV . After completion the mixture was poured on ice and extracted with 3 x 75 mL of ether. The different products thus obtained were separated by HPLC chromatography. All compounds were identified by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR data ; melting point and combustion analysis or mass spectra and by X ray diffraction analysis for the epoxide 4. These X ray data permit us to confirm the stereochemistry of 4 and by deduction that of 1.

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