The Cyclization of 5-isopropyl-3-methyl-2(3-n-pentenyl)-2-cyclohexene-1-one

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CONTENTS

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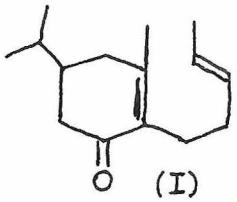
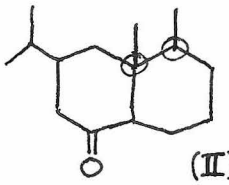
I. Introduction

This work is directed toward the total problem of bringing about the cyclization of 5-isopropyl-3-methyl-2(3-n-pentenyl)-2-cyclohexene-1-one (I) to the decanone (II), in a stereospecific manner. It is mainly an investigation of several possible approaches of effecting the cyclization.



(I)

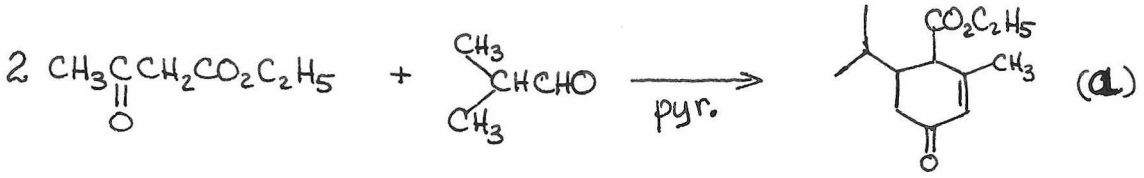


(II)

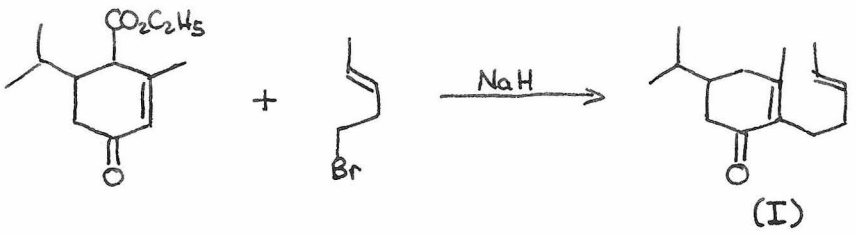
The basic problem faced is to find a way to activate the molecule at position 3, in order to induce the intramolecular alkylation which gives the cyclized product.

II. Background

Compound (I) has been prepared by Dr. David Chan, at Caltech, through the following sequence of reactions:



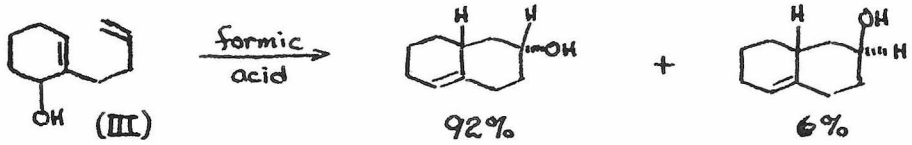
(a)



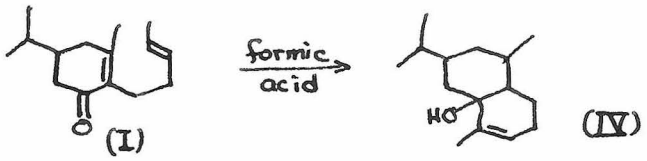
(b)

This is basically just a modication of Hagemann's ester formation followed by C-alkylation, which is preferentially directed by the location of the substituents.

Johnson and co-workers (1) have found that 2(3-n-butenyl)-cyclohexene-1-ol (III), when treated with anhydrous formic acid, underwent cyclization in the manner described below, giving a preferential yield of one



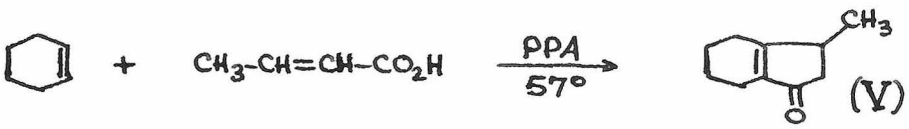
of the isomers. However, when this method was applied to compound (I) by Dr. Chan, cyclization occurred pre-



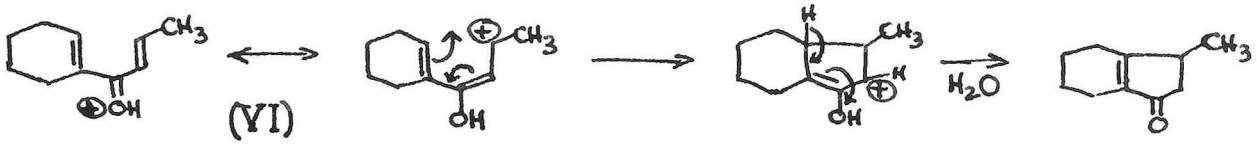
ferentially at the carbonyl carbon, giving the undesired alcohol (IV). It appears from this that the main blocking force is the presence of the two bulky methyl groups at the points where cyclization is desired, thus necessitating the passage through a tertiary carbonium ion. This problem could conceivably be overcome by the use of stronger acid-catalysts, ones which did a better job of

blocking the carbonyl carbon, while at the same time withdrawing the electrons from the site of preferred intramolecular attack.

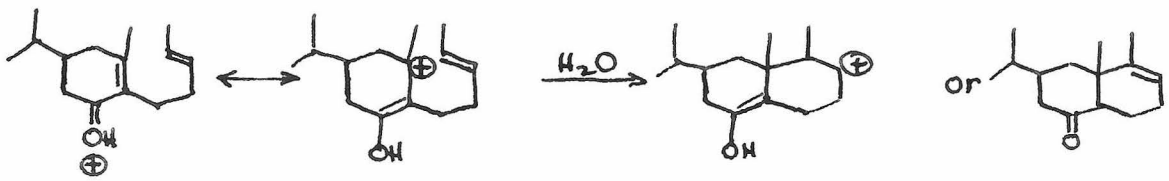
Johnson (1) found that polyphosphoric acid in 80% aqueous acetone at 75°C yielded similar results on the cyclohexenol (III) as did formic acid. Dev (2) found that cyclohexene reacted with crotonic acid in polyphosporic acid to give the substituted cyclopentenone (V):



If this reaction proceeds through an initial attack of the carboxyl function followed by cyclization, the intermediate is somewhat analogous to that which would be expected in the case of the compound under question(I). Thus, for the Dev reaction, the intermediate (VI) would be important:

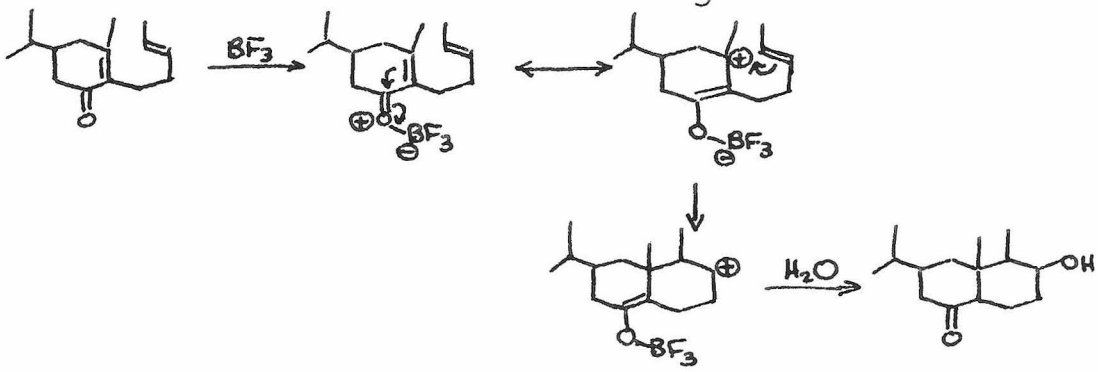


Similarly, for (I) the following can be visualized:



There still exists, of course, the problem of bulky groups at the point of cyclization, as well as the lack of conjugation through the second double bond as occurs in Dev's compound.

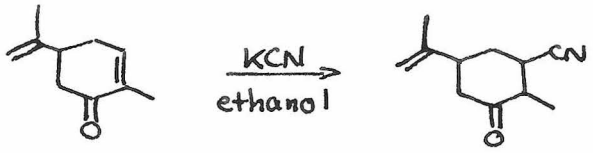
Boron trifluoride is also an effective acid catalyst in certain types of reactions involving attack of olefins at activated sites. Thus, for compound (I), one possible reaction in the presence of BF_3 is the following:



Another possible approach to the problem is to alter the functionality of the compound, in such a way as to enhance the cyclization reaction. In this study, only one modification was attempted, namely, the formation of the cyanohydrin of compound (I). The cyanide reaction of a conjugated ketone can yield two possible products, the cyanohydrin, and the keto-nitrile obtained from 1,3-addition. Nagata, et al (3) have reported the cyanation of a conjugated system as shown below:

The rest of the material was a mixture of compounds including the cyanohydrin. Djerassi has also reported the

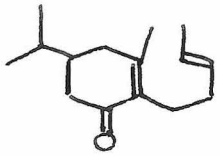
formation of the 1,3-addition product, as below: (4)



III. Experiments and Results

A. Preliminary

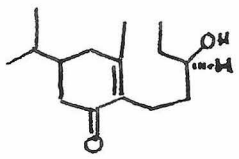
The cyclohexenone (I) used in these tests was prepared by Dr. David Chan, and was reported to have a purity of approximately 95%. Its infrared spectrum showed strong peaks at 3.39, 6.01, 6.13, 7.27, and 10.37μ. The peaks at 6.01 and 6.13 are due to the ketone and the conjugated double bond, respectively. The NMR spectrum showed a doublet at 0.9 for 6 protons, a 2-electron doublet at 1.6, a 2-electron doublet at 1.8, a 6-electron singlet at 1.9, a 6-electron doublet at 2.2, and a 2-electron quintuplet at 5.35 ppm. This data fits with the proposed structure of the compound:

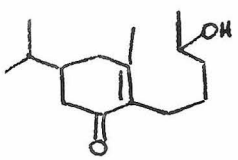


B. Polyphosphoric Acid

Five (5) grams of polyphosphoric acid (113 g P_2O_5/ 100 cc H_3PO_4) was heated to 70° C. 300 mg of the cyclohexenone (I) were added to the above, and the mixture was heated for 30 minutes. The hot product was poured over

ice and water (15 g), and diluted to 20 ml. with water following decomposition of the reaction complex. 3.8 g of $(NH_4)_2SO_4$ was dissolved in the solution, and the mixture was then extracted with petroleum ether. The solvent extract was washed with water, then with 5% aqueous NH_4OH, and finally with brine, and dried over anhydrous sodium sulfate. The ether was then evaporated, yielding approximately 250 g of a clear yellow liquid. The infrared spectrum showed peaks at 2.91, 3.41, 6.05, 6.15, 6.86, 7.29, and 8.97μ. From this information alone, it would appear that the double bond on the pentenyl side chain has been hydrolyzed to give the alcohol. This would account for the disappearance of the peak at 10.37, which is present in the starting material, and is probably accounted for as a C=H out of plane bend of the trans-1,2-disubstituted double bond in the side chain. The existence of the conjugated ketone function in the product, as indicated by the two peaks around 6μ, would imply that no cyclization has occurred, since cyclization would eliminate the conjugation. Thus, the product of this reaction is a mixture of the following, in addition to some starting material.





C. Boron Trifluoride

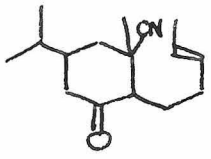
310 mg of the cyclohexenone (I) were dissolved in 4 ml of ether, and the solution was cooled to 0° in an ice bath. Approximately 0.1 g of $BF_3(Et_2O)$ was added to the solution, and the mixture was stirred for about 15 minutes, after which time the mixture was poured over ice water. 2 g of $NaHCO_3$ were added to the reaction mixture to neutralize the acid. The product was extracted with ether. The extract was washed with saturated $NaHCO_3$, then water, and finally dried over anhydrous sodium sulfate. The ether was evaporated from the extract. The resulting product was similar in color and consistency to the starting material. An infrared spectrum of the product proved to be identical to that of the starting material.

D. Cyanide Reaction

To a reaction vessel were added 300 mg (1.4 mmole) of the cyclohexenone (I), 200 mg KCN (3 mmole), 3 ml of ethanol (95%), and 1 ml of water. 140 mg of glacial acetic acid was added dropwise over a period of 5 minutes. The mixture was stirred for 30 minutes, after which time 4 ml of water were added. The solution was extracted with chloroform, the extract was washed with water, and then dried over Na_2SO_4 (anhydrous). The chloroform was evaporated, yielding about 260 mg of a pale yellow liquid. The infrared spectrum showed major peaks at 3.36, 5.99,

6.13, 7.27, and 10.37μ. There was no indication of any nitrile present in the product.

To a reaction vessel were added 310 mg of the cyclohexenone (I), 190 mg of KCN, 0.5 ml of saturated NH_4Cl, 16 ml of N,N-dimethylformamide, and 2 ml of water. The reaction mixture was stirred at 100°C for six hours, during which time there was some evolution of ammonia. After cooling, the solvent was distilled off in vacuo, water was added, and the mixture extracted with chloroform. The extract was washed with water, then by $NaHCO_3$, and finally dried over anhydrous sodium sulfate. The chloroform was evaporated, yielding 280 mg of a yellow liquid as product. This liquid was redistilled to give 250 mg of a yellow liquid boiling at 152-154°C. The infrared spectrum of this material showed absorptions at 3.39, 4.25(weak), 5.82, 5.97, 6.13, 7.24, 9.20, and 10.35μ. The peak at 4.25 is indicative of some nitrile addition. However, the fairly strong peak at 5.82μ, which is due to the unconjugated cyclohexanone, implies that addition occurred across the double bond to give compound (VII). A thin-



(VII)

layer chromatogram of the product substantiates the lack of any cyanohydrin formation (see Figure 1). Thus, if there were any cyanohydrin in the product, it should have

travelled further along the plate than did the starting material.

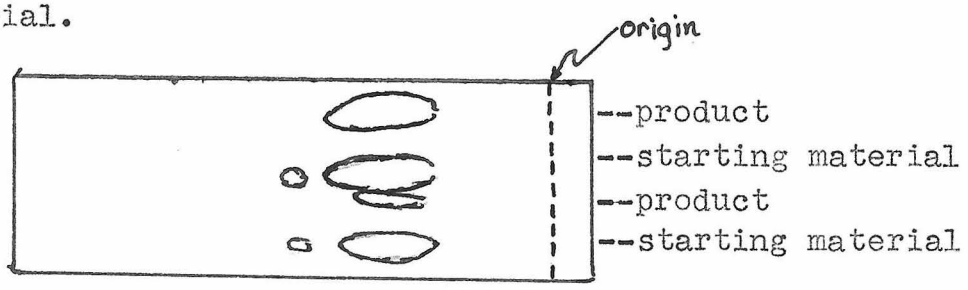


Figure 1.

IV. Discussion of Results

It is apparent from the above results that the cyclization of the cyclohexenone(I) directly through acid-catalysis is impossible. This is probably due in part to the presence of the two methyl groups at the points of cyclization. In addition, the length of the side chain as well as the inactivity of the double bond contribute to inactivity in the cyclization reaction. The inability to prepare the cyanohydrin in preference to the 1,3-addition product eliminates this particular possibility for activating the molecule.

V. Conclusion

It seems most likely from this work that a modification of the cyclohexenone (I) is necessary in order to effect the cyclization. This modification could be made at the ketone function, such as forming the oxime or the semi-carbazone, followed by acid-catalyzed cyclization.

Another possibility is to add something at the carbonyl carbon, as was hoped for in the case of the cyanide reaction. One likely approach might be to alkylate the molecule at the carbonyl carbon, such as with methyllithium. The resulting alcohol would probably be more subject to activation by any of the acid-catalysts than the ketone. Finally, activation could be brought about by conversion of the pentenyl side chain, say by adding a carboxyl function to the double bond, thus, pulling the electrons in the preferred direction. This latter approach would probably be less realizable than one of the others, due to its greater inspecificity.

VI. Abstract

Several possible approaches toward effecting the cyclization of 5-isopropyl-3-methyl-2(3-n-pentenyl)-2-cyclohexen-1-one (I) to the decanone (II) are studied. Acid-catalysts, such as polyphosphoric acid and boron trifluoride, are found to be ineffective acting directly on the cyclohexenone. The cyanohydrin of (I) was found to be the unpreferred product in the cyanide reaction, thus eliminating that activated form as a means to effecting the cyclization.

References

1. W.S. Johnson, W.H. Lunn, and K. Fitzi, JACS 86, 1972 (1964).

2. S. Dev, J. Indian Chem. Soc., 34, 169 (1957).

3. W. Nagata, et. al., J. Org. Chem., 26, 2413 (1961).

4. C. Djerassi, et. al., J. Org. Chem., 28, 1632 (1963).