ATTEMPTS AT NEW METHODS OF BUILDING UP NON-AROMATIC CYCLIC SYSTEMS

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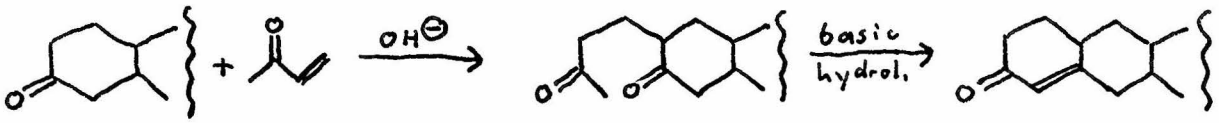
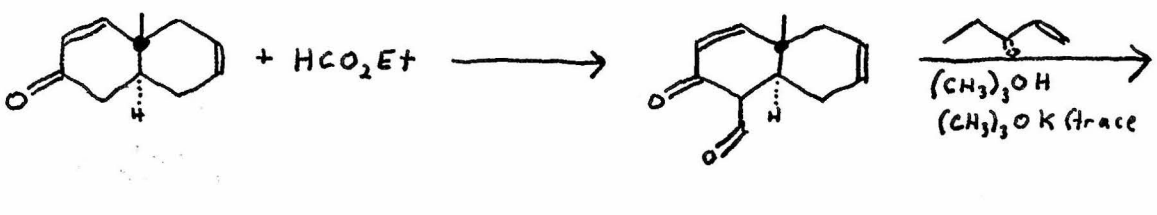
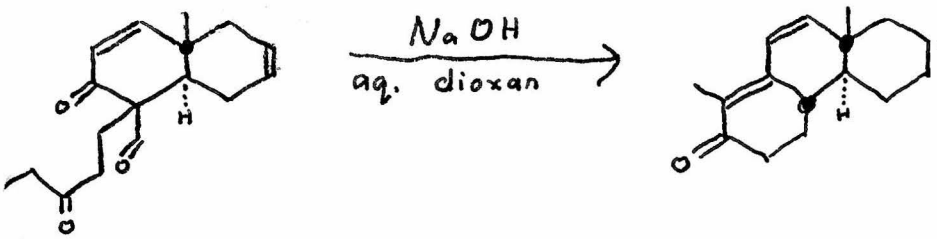
The major problem in the development of useful synthetic schemes for steroids is that of fusing additional rings onto a cyclic substrate. Reactions that are used for this purpose are usually modifications of;



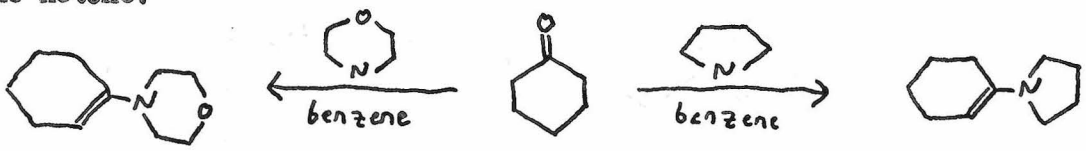
This reaction as written can be made to work only in exceptional cases. If one attempts to condense 2-octalone or most other non-aromatic cyclic ketones with methyl vinyl ketone, no adduct is obtained as conditions sufficiently basic to form the enolate anions of these ketones cause the methyl vinyl ketone to polymerize rapidly. This problem has been avoided in some instances by the conversion of the substrate ketone into a β-keto aldehyde or β-keto ester,[1] whose enolate could be formed with very weak base.



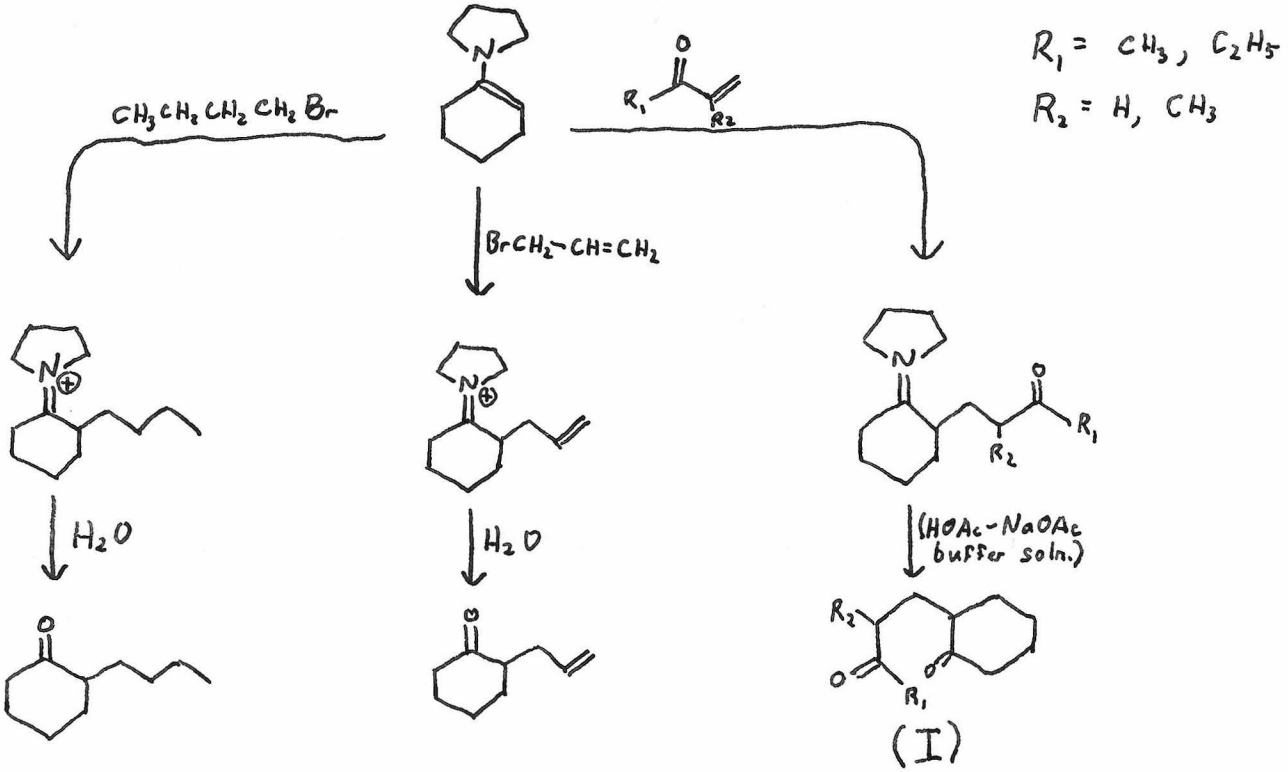


Alkylations in which the methyl vinyl ketone is formed slowly in-situ by an elimination reaction have also found some success.

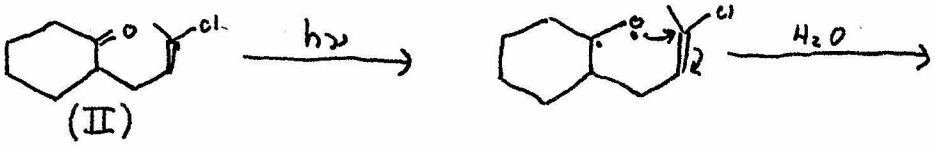
Recently, however, Stork[2] has shown that many alkyl halides and electrophilic olefins will add under neutral conditions to the enamines of aliphatic ketones. First, the substrate ketone is condensed with a secondary amine such as pyrrolidine or morpholine to give the enamine of the ketone:



The enamine is then isolated and alkylated to give the iminium salt, which is then hydrolized in H_2O or weakly acidic solution. In this manner, Stork was able to condense enamines of cyclohexanone with methyl vinyl ketone, ethyl vinyl ketone, methyl isopropenyl ketone, alkyl halides and aryl halides in good yield (60-70%).



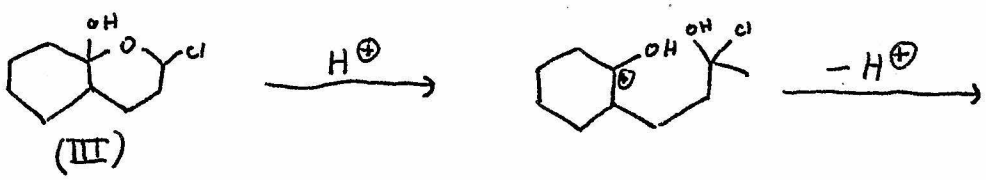
An alternative method has been proposed for forming diketones of the type I. The pyrrolidine enamine of the substrate ketone is alkylated with 1,3-dichloro-2-butene, yielding a compound of the type II. II is then irradiated with ultra-violet light in the presence of water. The carbon-oxygen double bond of the ketone is excited to its diradical triplet state, and through the mechanism shown, a α-chloro hemi-ketal is formed.



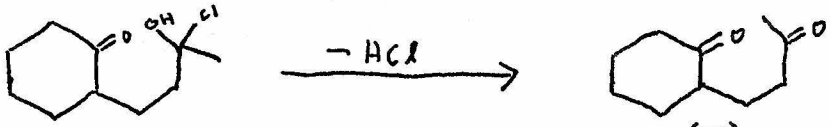
(II)

(III)

III is then hydrolized in dilute acid to yield I.



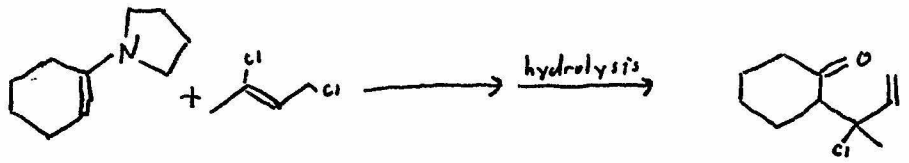
(III)



(I)

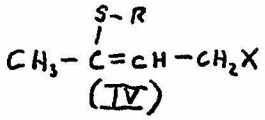
II was prepared following the method of Stork[3] and the photolysis was attempted in a number of solvents and in the presence of Ag^{+}. In all cases it appeared that no detectible amount of III was formed (although side reactions did occur in some cases).

The possibility was considered, that in the alkylation, substitution did not occur at the expected site (#1 carbon), but rather at the #3 carbon, through a S_N2' type of mechanism. This would yield, instead of II:



This possibility was discounted, however, as a similar alkylation has been reported[4] in which the expected S_N2 product was obtained.

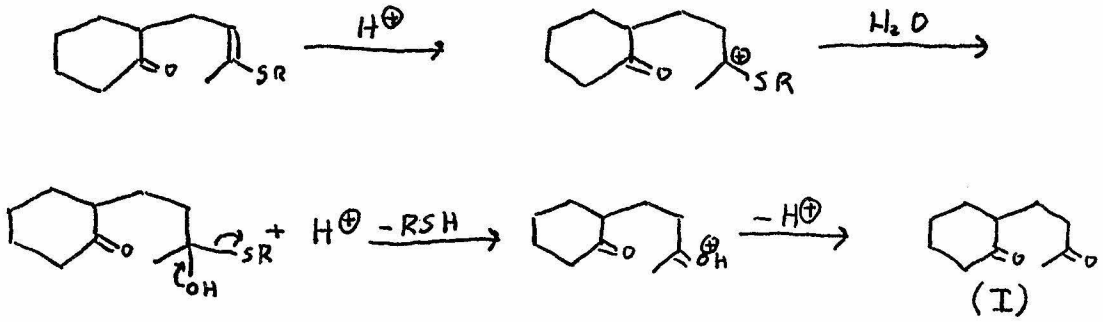
A variant on the above procedure has been proposed in which the substrate ketone is alkylated with a thio-enol ether of the type:



(IV)

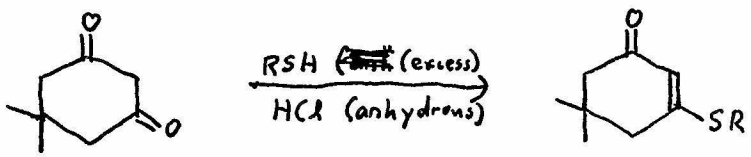
R = alkyl or aryl group
X = Cl, Br, I

The alkylation product is then hydrolized with water or dilute acid to yield II:



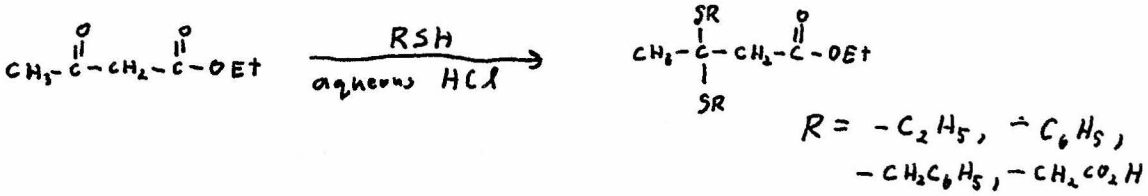
(I)

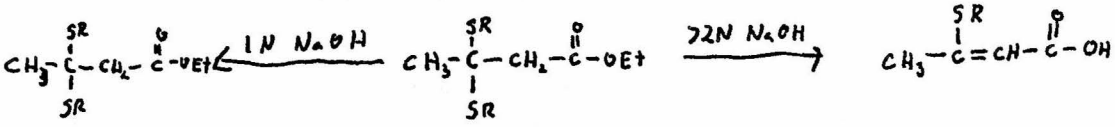
Thio-enol ethers similar to IV have not been reported in the literature. However, the following syntheseis of a -keto thio-enol ether has been reported by Kendall[5]:



R = $-C_2H_5$, $-C_6H_5$, $-CH_2C_6H_5$

It has also been reported[6,7]:





In hopes of obtaining the thio-enol ether directly, anhydrous HCl was bubbled through some methyl acetoacetate containing an excess of benzyl mercaptan. Distillation of the reaction product indicated that about 10% thio-enol ether had been formed, with the remaining product being the dithio ketal. This material was then hydrolized in aqueous methanol which was 3N in NaOH. Acidification of this mixture yielded a crystalline material which was the thio-enol ether acid. This acid was then reduced to the corresponding alcohol with Lithium Aluminum Hydride. The small amount of product obtained prevented distillation and a complete analysis, but an infrared spectrum indicated the expected product had been obtained. The alcohol was then converted to the corresponding bromide with PBr_3 in $CHCl_3$. Infrared and NMR spectra of the product here indicated that the expected bromide was not obtained, and so no attempt to alkylate cyclohexanone was made. Another attempt to make IV is now being made using ethyl mercaptan instead of the benzyl compound.

EXPERIMENTAL

Pyrrolidine enamine of cyclohexanone: 103 ml. (1.0 mole) distilled cyclohexanone and 92 ml. (1.1 mole) distilled pyrrolidine were refluxed for 16 hours in 400 ml. benzene. The water produced in the reaction was separated by azeotropic distillation into a water separator. The solvent was removed at reduced pressure, and the enamine was distilled under nitrogen, yielding an almost colorless liquid, b. p. 145-150° (30-50 mm). The enamine became colored rapidly upon exposure to air, so it was necessary to keep it under nitrogen at all times.

Alkylation of the cyclohexanone enamine: 12 ml. distilled 1,3-dichloro-2-butene was added dropwise to 15 ml. of the cyclohexanone enamine in 100 ml. reagent acetonitrile under nitrogen, and the mixture refluxed for 24 hours. The solvent was then removed at reduced pressure yielding a red-violet liquid which solidified upon standing. This was dissolved in 60 ml. water and stirred for 20 hours. The alkylation product was extracted from the hydrolysis with 2 portions of ether, washed with distilled water and saturated NaCl solution, and dried over anhydrous sodium sulfate. The ether was removed at reduced pressure, and the residue was distilled, yielding 9 ml. of an almost colorless liquid, b. p. 95-100° (2.5 mm); reported[8] b. p. 120-130° (12 mm). Characteristics of infrared spectrum: no absorption in region 2.5 to 3.2 microns; strong absorption at 5.84 microns; weak absorption at 6.0 microns.

PHotolysis of 2-(3-chloro-2-butenyl)cyclohexanone in acetonitrile: 1.6 g. 2-(3-chloro-2-butenyl)cyclohexanone in 150 ml. 98% aqueous acetonitrile was irradiated using a Hanovia lamp for 48 hours. It was noticed that the solution had turned yellow during the photolysis. The solvent was removed at reduced pressure and the residue dissolved in ether. The ether solution was washed and dried over anhydrous sodium sulfate. The ether was removed at reduced pressure. An infrared spectrum of the residue was unchanged from starting material. A thin layer chromatograph (carrier solvent 95% benzene, 5% ether) showed an unmoved spot which was taken to be polymerized starting material and/or solvent.

Photolysis of 2-(3-chloro-2-butenyl)cyclohexanone in methanol: 1.7 g. 2-(3-chloro-2-butenyl)cyclohexanone in 100ml. 98% aqueous methanol was irradiated for 48 hours using a germicidal lamp. The solvent was removed at reduced pressure, the residue dissolved in ether, and the ether solution was washed and dried. The ether was removed at reduced pressure. An infrared spectum and thin layer chromatograph (solvent same as above) of the product showed it to be unchanged from starting material.

Photolysis of 2-(3-chloro-2-butenyl)cyclohexanone in the presence of Ag^+: 1.4 g. 2-(3-chloro-2-butenyl)cyclohexanone and 2.0 g. silver nitrate (equimolar ratio) were dissolved in 100 ml. 90% aqueous methanol. The mixture was irradiated for 24 hours, after which it was noticed that considerable silver metal was present. The mixture was filtered, and the solvent was removed from the filtrate at reduced pressure. The residue was dissolved in ether, washed, dried, and the ether removed at reduced pressure.

The infrared spectrum of the product was identical to that of starting material, with the exception of the appearrance of a new weak absorption at 5.70 microns. A thin layer chromatograph showed considerable quantities of starting material to still be present, but presence of a different material was also shown. On the basis of the position of the infrared absorption, it was decided that the new compound was not any of the expected reaction products.

Photolysis of 2-(3-chloro-2-butenyl)cyclohexanone in the presence of acetone: 1.1 g. 2-(3-chloro-2-butenyl)cyclohexanone was added to a mixture of 88 ml. methanol, 10 ml. acetone, and 2 ml. water. This mixture was then irradiated for 120 hours on the Germicidal lamp. The solvent was removed at reduced pressure, the residue dissolved in ether, washed, dried, and the ether removed at reduced pressure. The infrared spectrum showed considerable change; characteristics: strong absorption at 2.92 microns; absorption at 5.84 microns much weaker than with starting material; continuous weak absorption throughout the range 7.5 to 12 microns. A thin layer chromatograph showed a continuous smear indicative of the presence of many compounds. A sample of the product was hydrolized in 0.5N HCl for 24 hours, and another sample was hydrolized in 0.5N NaOH for 24 hours. Infrared spectra of both samples showed no change. A vapor phase chromatogram of the photolysis product (silicone oil column; oven temp. 190°) showed 9 distinct peaks, demonstrating that the product was indeed a bad mixture.

Attempt at the synthesis of 1-bromo-3-thiobenzyl-2-butene: Anhydrous HCl was bubbled through a mixture of 10 ml. distilled methyl acetoacetate and 100 ml. benzyl mercaptan which was cooled by an ice-salt bath. After 30 minutes the addition of HCl was stopped and the mixture was stirred for 24 hours. HCl was then added for an additional 30 minutes, after which the mixture was again stirred for 24 hours. The mixture was then washed with sodium bicarbonate solution and water, and dried over sodium sulphate. The excess mercaptan was distilled off at aspirator pressure, and the residue was distilled at vacuum pump pressure, yielding 2 ml. of a nearly colorless liquid, b. p. 85° (0.08 mm); and 12 ml. of a yellow liquid, b. p. 178-179° (0.08 mm).

The higher boiling liquid was hydrolized in 67% aqueous methanol which was 3N in NaOH. Acidification of this mixture produced a white precipitate which was filtered out and recrystallized from ethanol, m. p. 120-125°; reported[9] for 3-thiobenzyl-2-butenoic acid, m. p. 130°. Yield: 8.4 g. The acid was reduced with Lithium Aluminum Hydride in 200 ml. purified tetrhydrofuran. The excess hydride was expended with ethyl acetate, and the solution was acidified. The alcohol was extacted with ether, and the ether solution was washed and dried. The ether was removed at reduced pressure, yielding 5 ml. of a yellow liquid, which had an infrared spectrum that fit the expected product.

The alcohol was dissolved in 125 ml. chloroform, and 3.0 g. of phosphorous tribromide was added dropwise to this solution. The mixture was stirred for 24 hours, and then washed with sodium bicarbonate solution and distilled water. It was dried over sodium sulfate and the solvent was removed at reduced pressure. The residue was a yellow liquid which turned red upon being stored overnight in a refrigerator. The infrared spectrum of this crude product showed a moderate absorption at 5.82 microns (corresponds

to an unconjugated ketone). The bromide was distilled, b. p. 50-80° (1.0 mm) yield: approx. 1.5 ml. of a nearly colorless but cloudy liquid. The infrared of the distillate was nearly identical to that of the crude product. A NMR spectrum showed a complicated pattern which could not be correlated to the expected bromide. A thin layer chromatograph showed the distillate to consist of two compounds, in the approximate ratio 4:1. It is considered highly doubtful that either of these two componds were the expected bromide.

The high boiling point of benzyl mercaptan made purification of the various compounds extremely difficult in some cases.

FOOTNOTES

1 - See R. B. Woodward, et al. JACS 74, 4227 (1952), the steps between his compound XXXIII and his compound XXXVI.

2 - G. Stork, et al. JACS 85, 207 (1963)

3 - Stork's procedure for 2-allyl cyclohexanone.

4 - Sylvestre Julia. Bull. Soc. Chem. France, 785 (1954). Julia alkylated cyclohexanone with 1,3-dichloro-2-butene using tert-amyl sodium, and obtained only 2-(3-chloro-2-butenyl)cyclohexanone.

5 - Kendall, et al. Chem. Abs. 42, 4764 (1948)

6 - R. Escales and E. Baumann. Berichte 19, 1787 (1886)

7 - H. Hauptmann and A. C. Giora. Tetrahedron Letters no. 11, pp. 1-4, 1960.

8 - V. Prelog, et al. Chem. Abs. 43, 7907 (1943).

9 - Op. cit. Hauptmann and Giora.