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Aldol Reactions of Formaldehyde in Non-aqueous Media

VIII.* Acid-catalyzed Reactions of α,β-Unsaturated Ketones with Formaldehyde

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α,β-Unsaturated ketones were found to react with formaldehyde in refluxing chloroform and in the presence of boron trifluoride etherate, two molecules of the aldehyde being added to the C=C bond of the ketone with the formation of 1,3-dioxanes.

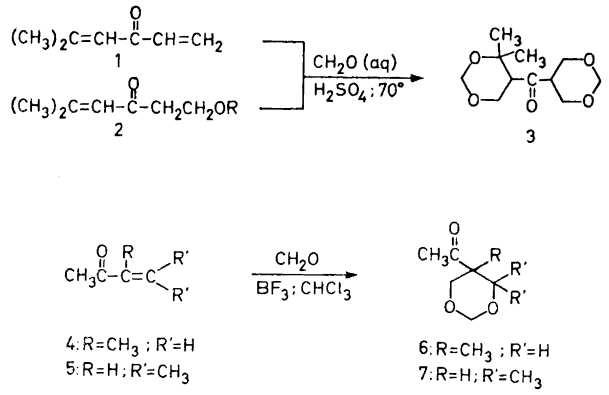
Formaldehyde reacts with olefinic double bonds under the influence of acid catalysts to yield 1,3-glycols and 1,3-dioxanes.[1] This reaction, which was first described by Prins,[2] is known as the Prins reaction. Aldehydes other than formaldehyde react in a similar manner,[3] but with greater difficulty. In some cases the addition of formaldehyde is stereospecific.[3] The mechanism of the reaction has received particular attention.[4–7] Blomquist [4] and Dolby [6] proposed mechanisms involving electrophilic attack by the conjugate acid of formaldehyde on the olefinic double bond with the formation of a three-membered [6] or four-membered [4] cyclic positive ion. Nucleophilic back-side attack on this cyclic intermediate by formaldehyde, water or, in the case of acetic acid as a solvent, by acetate ion, would account for the specific formation of *trans* products.

Only a few examples of reactions of formaldehyde with compounds containing carbonyl conjugated double bonds are given in the literature. *trans*-Cinnamic acid, for example, has been reported to react with formaldehyde in acetic acid containing considerable amounts of sulfuric acid to give 4-phenyl-5-carboxy-1,3-dioxane in a moderate yield.[8] Similarly, the reactions between the α,β-unsaturated ketones *1* and *2* (Scheme 1) and aqueous formaldehyde in the presence of sulfuric acid have been shown to give the 1,3-dioxane *3*.[9]

In the course of investigations regarding aldol reactions of formaldehyde in non-aqueous media it was found that the α,β-unsaturated ketones *4* [10]

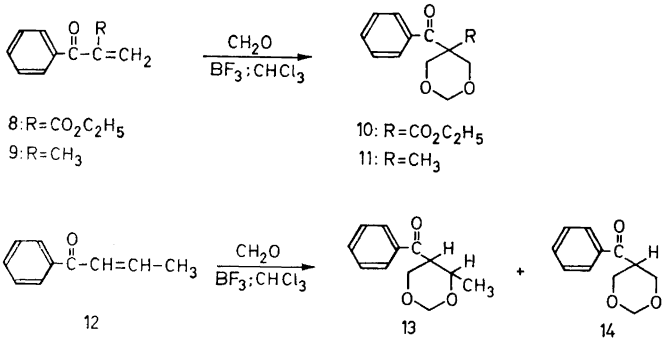
* Part VII: See Ref. 12.

SCHEME 1



and *5* [11] (Scheme 1) react with formaldehyde in refluxing chloroform solution and in the presence of boron trifluoride etherate at low rates, the 1,3-dioxanes *6* and *7*, respectively, being formed. Under similar conditions, however, the reaction of ethyl 2-benzoylacrylate (*8*) to give 1,3-dioxane *10* proceeded much more rapidly (Scheme 2).[12] With regard to these observations it was of interest

SCHEME 2



to investigate the reactions of some other α,β-unsaturated ketones with formaldehyde in the chloroform-BF_3 system. Two alternative mechanisms for the addition of formaldehyde to the C=C bond of an α,β-unsaturated ketone are proposed and discussed in this communication.

RESULTS AND DISCUSSION

As already mentioned, the aliphatic α,β-unsaturated ketones *4* and *5* reacted very slowly and incompletely with formaldehyde in refluxing chloroform under the influence of boron trifluoride etherate.[10,11] Replacement of

the acetyl group of *4* by a benzoyl group gives phenyl isopropenyl ketone (*9*; Scheme 2). The latter was found to be somewhat more reactive than ketone *4* towards formaldehyde, with 5-benzoyl-5-methyl-1,3-dioxane (*11*) being obtained in a yield of 4.3 % after 35 min reaction, as compared with 0.7 % of 1,3-dioxane *6* from methyl isopropenyl ketone (*4*). Ethyl 2-benzoylacrylate (*8*), which carries an ethoxycarbonyl group instead of the α-methyl group of *9*, has previously been shown to react easily with formaldehyde to give 1,3-dioxane *10* (Scheme 2).[12] This high reactivity towards formaldehyde has also been found for an isomer of ketone *9*, phenyl propenyl ketone (*12*; Scheme 2). The latter compound reacted rapidly with formaldehyde to give 4-methyl-5-benzoyl-1,3-dioxane (*13*) and 5-benzoyl-1,3-dioxane (*14*), the latter compound lacking the β-methyl group of the starting material.

By following the reaction of ketone *12* by vapour phase chromatography it was found that the concentration of 1,3-dioxane *13* reached a maximum

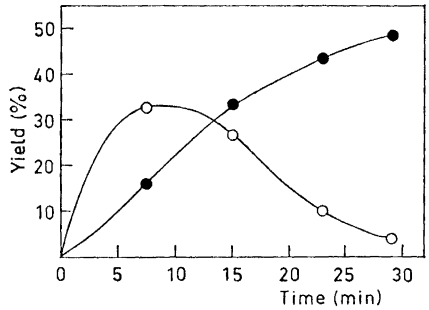


Fig. 1. Formation of 4-methyl-5-benzoyl-1,3-dioxane (*13*, ○) and 5-benzoyl-1,3-dioxane (*14*, ●) from phenyl propenyl ketone (*12*) and trioxane.

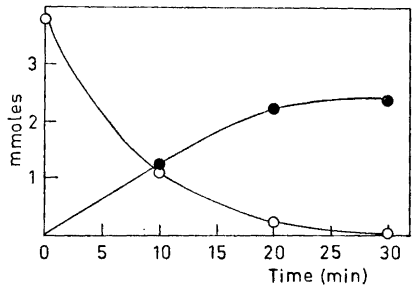
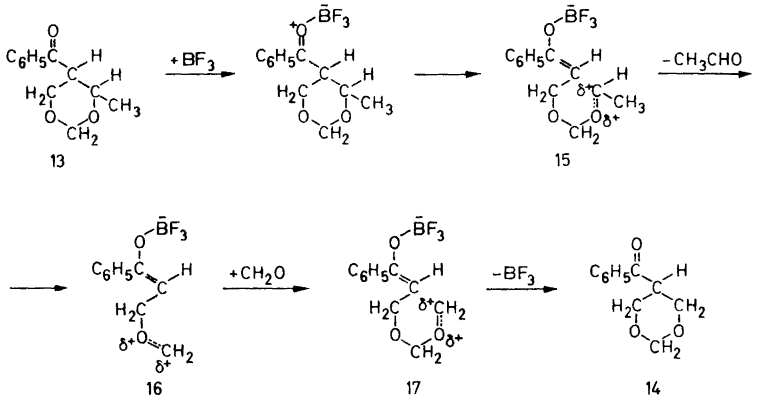


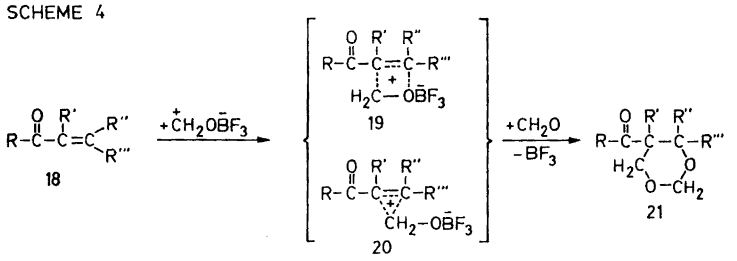
Fig. 2. Formation of 5-benzoyl-1,3-dioxane (*14*, ●) from 4-methyl-5-benzoyl-1,3-dioxane (*13*, ○) and trioxane under the influence of boron trifluoride etherate.

shortly after the start of the reaction (Fig. 1), and then decreased with a simultaneous increase in the concentration of compound *14*. This observation indicated that compound *13* was a precursor of *14*. Treatment of 1,3-dioxane *13* with trioxane and boron trifluoride etherate in refluxing chloroform provided evidence for the correctness of this view, compound *14* being formed rapidly and in a good yield (Fig. 2). A reaction path for the conversion of *13* to *14* is proposed in Scheme 3. According to this scheme, addition of boron trifluoride to the keto group causes de-aldolization of compound *13* with the formation of *15*. Expulsion of one molecule of acetaldehyde followed by reaction of the resulting intermediate *16* with formaldehyde gives *17*, which by intramolecular electrophilic attack forms the end product, 1,3-dioxane *14*. Small amounts of the liberated acetaldehyde have been detected by vapour phase chromatography.

SCHEME 3

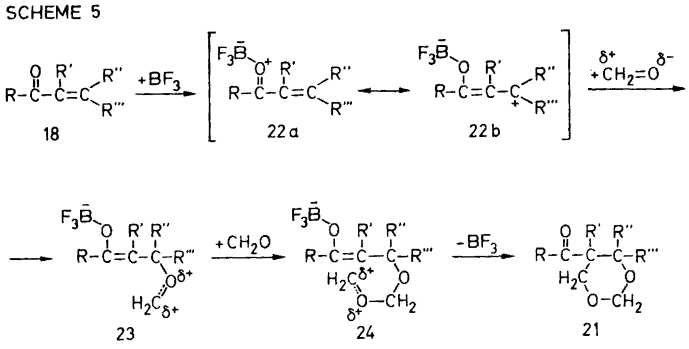


SCHEME 4



The addition of formaldehyde to the C=C bond of an α,β-unsaturated ketone may be formulated in two different ways (*cf.* Ref. 12), either as a Prins reaction at the ethylenic double bond (Scheme 4), or as a 1,4-addition of the conjugate acid of formaldehyde to the conjugated system, *i.e.* addition of boron trifluoride at the keto group followed by addition of formaldehyde at the β-carbon atom of the ketone (Scheme 5). The latter mechanism would be analogous to other 1,4-additions to α,β-unsaturated ketones, *e.g.* addition of hydrogen bromide.[13,14]

SCHEME 5



Some of the experimental facts obtained may be in agreement with both mechanisms. As mentioned before, the isomeric ketones *9* and *12* showed largely different reactivities towards formaldehyde, ketone *12* being the more reactive one. Due to electron release from the β-methyl group, the cyclic intermediate (*19* or *20*) formed from ketone *12* according to the mechanism of the Prins reaction (Scheme 4) [4,6] should be more stabilized than the corresponding intermediate from ketone *9*. Similarly, the positive charge at the β-carbon atoms in their conjugate acids (Scheme 5) should more easily be developed in the case of ketone *12*, due to the stabilizing effect of the β-methyl group.

There are, however, other facts that are not easily reconciled with the mechanism of the Prins reaction (Scheme 4), but which are in agreement with the mechanism of the 1,4-addition given in Scheme 5. According to the former mechanism the conjugate acid of formaldehyde would add to the ethylenic double bond in an electrophilic manner to give a cyclic intermediate (*19* or *20*), which by reaction with a further molecule of formaldehyde would give the 1,3-dioxane *21*. Electron withdrawing substituents on the double bond should decrease its reactivity in the electrophilic attack (*cf.* Ref. 14, p. 659), but, contrary to the predicted behaviour, substitution of the electron-withdrawing ethoxycarbonyl group for the electron-releasing α-methyl group of *9* was found to greatly enhance the reactivity of the double bond towards formaldehyde.

Furthermore, α,β-unsaturated ketones are comparatively strong bases,[15] and should be converted to their conjugate acids by complex formation with boron trifluoride to a high degree under the conditions used. The ethylenic double bond of the conjugate acid (*22 a*; Scheme 5) is deactivated for electrophilic attack by the adjacent positively charged carbonyl group, and is not likely to be attacked by the conjugate acid of formaldehyde in a Prins reaction.

On the other hand, the β-carbon atom of the resonance hybrid *22* [13,14] offers a possibility for a nucleophilic attack by the partially negatively charged oxygen atom of formaldehyde with the formation of the intermediate *23*. Further reaction with formaldehyde would give *24*, which on intramolecular electrophilic attack would give the 1,3-dioxane *21*, according to Scheme 5.

EXPERIMENTAL

Trioxane was supplied by Perstorp AB, Perstorp, Sweden. Phenyl isopropenyl ketone (*9*) was prepared according to Burckhalter and Fuson,[16] and phenyl propenyl ketone (*12*) according to Kohler.[17] Commercially available organic chemicals were usually distilled before use. IR spectra were recorded on a Beckman IR-9 spectrophotometer, and NMR spectra on a Varian A-60 instrument. Vapour phase chromatography (VPC) was performed using a Perkin Elmer 800 instrument. Boiling and melting points are uncorrected.

Reaction of phenyl isopropenyl ketone (9) *with formaldehyde.* A solution of phenyl isopropenyl ketone (1.5 g, 10 mmoles) and trioxane (0.9 g, 10 mmoles) in chloroform (25 ml) was heated to reflux, and boron trifluoride etherate (1.25 ml) was added. A sample was withdrawn 35 min after addition of the catalyst and neutralized with sodium bicarbonate. The yield of the reaction product, 5-benzoyl-5-methyl-1,3-dioxane (*11*),[18] was determined by VPC and found to be 88 mg (4.3 %).

Reaction of methyl isopropenyl ketone (4) *with formaldehyde.* In an experiment similar to that with ketone *9* a yield of 10 mg (0.7 %) of 5-acetyl-5-methyl-1,3-dioxane (*5*) was obtained from methyl isopropenyl ketone (*4*).

Reaction of phenyl propenyl ketone (12) *with formaldehyde.* A. A solution of phenyl propenyl ketone (1.5 g, 10 mmoles) and trioxane (0.9 g, 10 mmoles) in chloroform (25 ml) was heated with stirring to 55°. Boron trifluoride etherate (1 ml) was added, and after 16 min the reaction was interrupted by the addition of water. The mixture was neutralized with sodium bicarbonate, dried over anhydrous calcium sulfate, and the solvent removed under reduced pressure. By means of thin layer chromatography and VPC on two different stationary phases one of the two reaction products was identified as 5-benzoyl-1,3-dioxane (*14*).[18] The other product was separated by means of chromatography on silica gel (eluent benzene-ethyl acetate 4:1). A colourless oil (0.41 g) was obtained, which was characterized by IR and NMR spectra (NMR spectrum is given in Fig. 3) as 4-methyl-5-benzoyl-1,3-dioxane (*13*). (Found: C 69.78; H 6.72. Calc. for $C_{12}H_{14}O_3$: C 69.88; H 6.84).

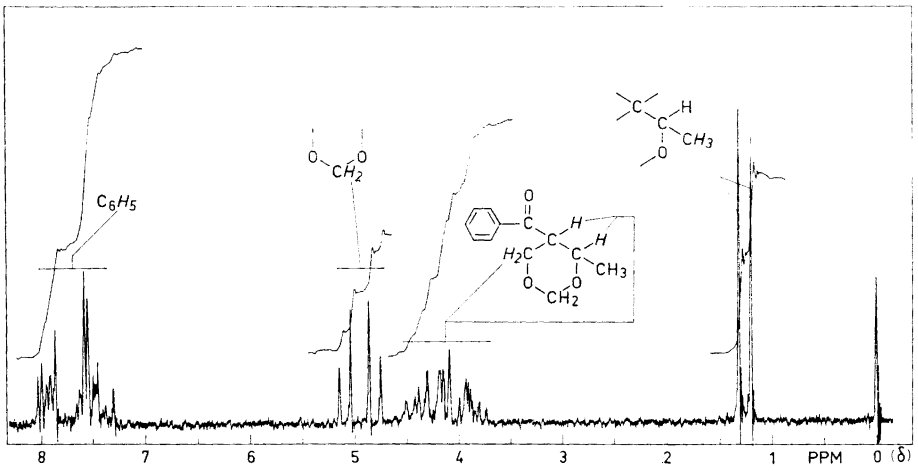


Fig. 3. NMR spectrum of 4-methyl-5-benzoyl-1,3-dioxane (*13*).

B. An experiment similar to that described under A was carried out in refluxing chloroform and with 1.25 ml of boron trifluoride etherate; samples were withdrawn 7.5, 15, 23, and 29 min after the addition of the catalyst, neutralized with sodium bicarbonate, and the yields of 1,3-dioxanes *13* and *14* determined by VPC. Results obtained are given in Fig. 1.

C. In an experiment similar to that described under B the reaction was interrupted after 25 min by the addition of water. The mixture was worked up as described under A, and chromatography on silica gel (eluent benzene-ethyl acetate 4:1) gave colourless crystals of 1,3-dioxane *14*, m.p. 49—50° (lit.[18] 49—50°) after recrystallization from isopropyl ether. Mixed m.p. with authentic 1,3-dioxane *14* gave no depression. IR and NMR spectra were identical with those of the authentic material.

D. In an experiment similar to B, a stream of nitrogen was passed over the refluxing solution, through the reflux condenser, and through a wash bottle containing chloroform (15 ml). The wash bottle was immersed in an ice bath. After 30 min reaction small amounts of acetaldehyde present in the chloroform solution were detected and identified by means of VPC on two different stationary phases.

Treatment of 1,3-dioxane 13 *with trioxane and boron trifluoride etherate.* A solution of 1,3-dioxane *13* (80 mg, 3.8 mmoles) and trioxane (75 mg, 8.3 mmoles) in chloroform (2.5 ml) was heated to reflux, and boron trifluoride etherate (0.1 ml) was added. Samples

were withdrawn 10, 20, and 30 min after addition of the catalyst, neutralized with sodium bicarbonate, and the amounts of starting material (*13*) and the reaction product, 1,3-dioxane *14*, were determined by VPC. Results obtained are given in Fig. 2.

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