

Mechanistic Studies on Alcoholysis of α -Keto esters

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α -Keto ester is an important family of organic compounds in biochemistry¹ and in synthetic organic chemistry.² While the compounds are stable in non polar solvents, they readily form hydrates and hemiacetals of keto carbonyls in the presence of water and alcohols, respectively.³

In the course of our studies on the solvent effect in photochemistry of phenacyl carboxylates, we had a chance to prepare and work with 2-methylphenacyl phenylglyoxylate (**1a**), which we found it very unstable in methanol even at standing in ambient temperature. The resulting products of the decomposition turned out to be α -hydroxy-2-methylacetophenone and methyl phenyl-glyoxylate, methanolysis products of **1a** (Scheme 1). The seemingly simple conversion, however, turned out to have a twist in reaction pathways according to our further investigation into the chemical change. The reaction occurred by way of a hemiacetal of the keto carbonyl of **1a**. Such a reaction pathway for the alcoholysis of α -keto esters has not been documented in the literature to the best of our knowledge. Here we report our preliminary findings on the unprecedented reaction pathway.

A hint that the above reaction may not have occurred by direct methanolysis of the ester group was given to us when a ¹H NMR spectrum of methanol-*d*₄ solution of **1a** was taken. Besides the peaks of the starting keto ester, appearance of a new set of peaks, which seemed to come from one compound, was observed. The new set of peaks were similar to those of **1a** except that a singlet at 5.6 ppm corresponding to the methylene protons alpha to the phenacyl C=O in the starting keto ester was replaced by an AB quartet at 5.2 ppm, and the ortho protons of the benzoyl group were shifted upfield. The new compound was assigned to a hemiacetal of the benzoyl carbonyl group of **1a** judging from known reactivities of α -keto esters with alcohols and the characteristic spectroscopic data. The fact that the new product was too unstable to isolate and returned to the starting keto ester supported our structural assignment.

When the sample was monitored by taking its ¹H NMR spectrum at regular intervals, we found that the peaks for the hemiacetal decreased in compensation for the increase of

several new peaks. The growing peaks turned out later to be from the methanolysis products of **1a** by the spectroscopic analysis of the isolated product obtained from a large scale experiment. Even though the methanolysis products seemed to come from the hemiacetal in our initial experiment, one had to be careful to draw the conclusion because it could just result from coincidental matchup of kinetics of two separate events: formation of the hemiacetal from **1a** and the simple methanolysis of **1a**. Thus, we decided to do the kinetic evaluation of the methanolysis.

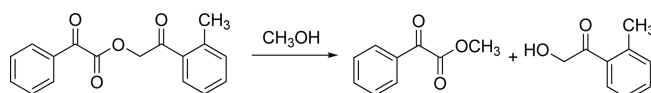
The consecutive reaction through the hemiacetal can be modelled by a simple scheme as $S \xrightleftharpoons[k_{-1}]{k_1} H \xrightarrow{k_2} A$ where S, H, and A represent the starting keto ester, the hemiacetal intermediate and the alcoholysis product. Rate equations can be exactly solved and the concentrations of all species are determined analytically as functions of time. The same is applied to the parallel reaction of $A \xrightleftharpoons[k_{-1}]{k_2} S \xrightleftharpoons[k_{-1}]{k_1} H$ since

two reactions are associated with each other by exchanging H and S and replacements of k_1 with k_{-1} and *vice versa* in one result would thus lead to the other. Results of the consecutive reaction with $[H]_0 = [A]_0 = 0$ have been reported.⁴ Whether the above methanolysis follows the consecutive or the parallel pathway can be easily determined by measuring the concentration changes experimentally. Behavior of $d[A]/dt$ in time, if it is compared with $[H]$ or $[S]$, determines the corresponding methanolysis to be consecutive or parallel. Difference between $d[H]/dt$ and $d[S]/dt$ is, however, more conspicuous than between $[H]$ and $[S]$, we rather use $d^2[A]/dt^2$ to specify reaction type. Often $d[S]/dt$ is increasing monotonously while $d[H]/dt$ is mostly decreasing or with a minimum which justifies our choice of the second-order derivative to identify a possible pathway. Furthermore, rate constants k_1 , k_{-1} , and k_2 are estimated accurately for reactions by comparing experimental concentration changes with theory. Detailed calculations show for consecutive reactions when $[S]_0 \neq 0$ and $[H]_0 = [A]_0 = 0$;

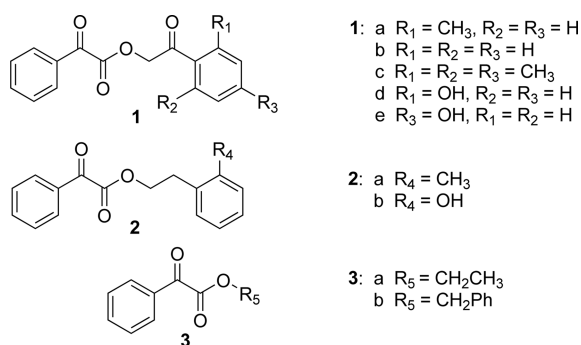
$$k_1 = -\frac{S_{10}}{[S]_0}, k_{-1} = \frac{S_{10}}{[S]_0} - \frac{S_{20}}{[S]_{10}}, k_2 = \frac{S_{20}}{S_{10}} - \frac{H_{20}}{H_{10}}.$$

where $S_{10} = \left. \frac{d[S]}{dt} \right|_0$ and $S_{20} = \left. \frac{d^2[S]}{dt^2} \right|_0$. Same holds for H. For parallel reactions, rate constants are;

$$k_1 = \frac{H_{10}}{[S]_0}, k_{-1} = \frac{S_{20}H_{10} - H_{20}S_{10}}{D_{10}H_{10}}, k_2 = -\frac{D_{10}}{[S]_0}$$



Scheme 1. Methanolysis of 2-Methylphenacyl Phenylglyoxylate (**1a**).

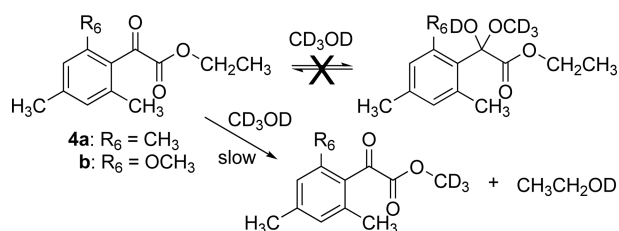
Scheme 2. α -Keto Esters Used in This Study.

where $D_{10} = S_{10} + H_{10}$. Rate constants and concentrations for reactions both with non-vanishing $[S]_0$ and $[H]_0$ are given elsewhere⁵. The apparent rate constant k_{obs} is equal to k_2 for the parallel reaction whereas in the consecutive reaction, $k_{\text{obs}} = k_1k_2/k_{-1} + k_2$ or $k_{\text{obs}} = k_1k_2/k_{-1}$ depending on whether a particular reaction system supports a steady-state or a fast equilibrium.

Having the kinetic analysis in hand, we were ready to evaluate which pathway is the right mechanism for the methanolysis of α -keto esters. Thus, we prepared several α -keto esters shown in Scheme 2 and took ^1H NMR spectra of each compound in methanol- d_4 at regular time intervals with an internal standard present.

Then we applied the kinetic analysis mentioned above to the concentration vs. time data that we obtained from each experiment. To our surprise, we found that the consecutive pathway is operating for all the ketones that we have tested. The kinetic analysis results tell us that the methanolysis products are formed from the hemiacetal intermediates. We strongly suspect that 1,2-shift of the methoxy group from the hemiacetal is involved in the formation of the methanolysis products, even though we have no definite evidences to support it at this point. Neighboring group participation of a carbonyl group has been proposed in a nucleophilic substitution reaction of α -halocarbonyl systems before, in which a nucleophile attacks the carbonyl carbon before migrating to the neighboring carbon to kick out the leaving group.⁷ But, the analogous mechanism has not been discussed in any reactions of α -keto esters in the literature.

According to the consecutive mechanism, the methanolysis does not occur without going through the hemiacetal intermediate, or classical methanolysis of ester portion occurs at much slower rate than the methanolysis *via* the hemiacetal does. Thus, we have prepared two sterically hindered α -keto esters, **4** in Scheme 3, where both ortho positions of the benzoyl moiety are substituted with either methyl or methoxy group and investigated their reactivities in methanol. The carbonyl group of 2,4,6-trimethylphenyl group is known to be highly resistant to nucleophilic attack.⁸ The compounds **4** did not show any sign of formation of the hemiacetal in their NMR spectra and the methanolysis products were formed in less than five percent conversion at long standing up to one week at room temperature. In comparison, the unsubstituted ester, ethyl glyoxylate (**3a**), is

Scheme 3. Methanolysis of Sterically Hindered α -Keto esters.

converted into the methanolysis products over 50 percents in less than a period of one day. Apparently the ortho substituents effectively block the nucleophilic attack at the benzoyl carbon to prevent from forming the hemiacetal, and instead the methanolysis occurs *via* a classical alcoholysis path of esters which seems to be much slower than the consecutive mechanism.

The above result tells us that methanolysis of the α -keto ester occurs mainly *via* the hemiacetal intermediate and other pathway involving direct attack at its ester moiety is much slower and minor path.

In summary, we have found that alcoholysis of α -keto esters proceeds *via* their hemiacetal intermediates as a major pathway from kinetic studies. Blocking formation of the hemiacetal by introducing steric hindrance slowed down the alcoholysis dramatically, which proved again the hemiacetal was a key intermediate for the alcoholysis of α -keto esters. Involvement of 1,2-shift of alkoxy group in the hemiacetal to complete the alcoholysis has been suggested in our mechanism, whose evidences we are currently actively looking for.

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