CHEMISTRY LETTERS, pp. 1189-1192, 1974. Published by the Chemical Society of Japan

A CONVENIENT METHOD FOR THE SYNTHESIS OF δ-ALKOXY-β-KETOESTER
THE TITANIUM TETRACHLORIDE-ACTIVATED REACTION OF DIKETENE WITH ACETAL

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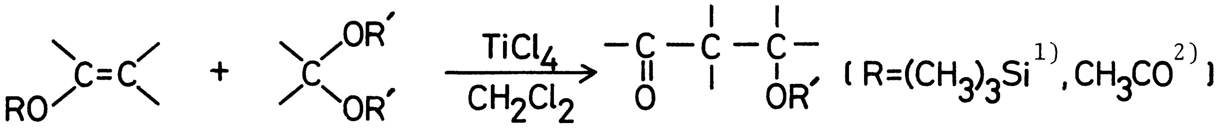
It was established that, in the presence of $TiCl_4$, diketene [1] reacts with acetals [2] at -78 ∿ -20°C to afford δ-alkoxy-β-ketoesters [3] in good yields. This reaction provides a novel method for the introduction of $-COCH_2COCH_2-$ unit to an electrophile as acetal activated by $TiCl_4$.

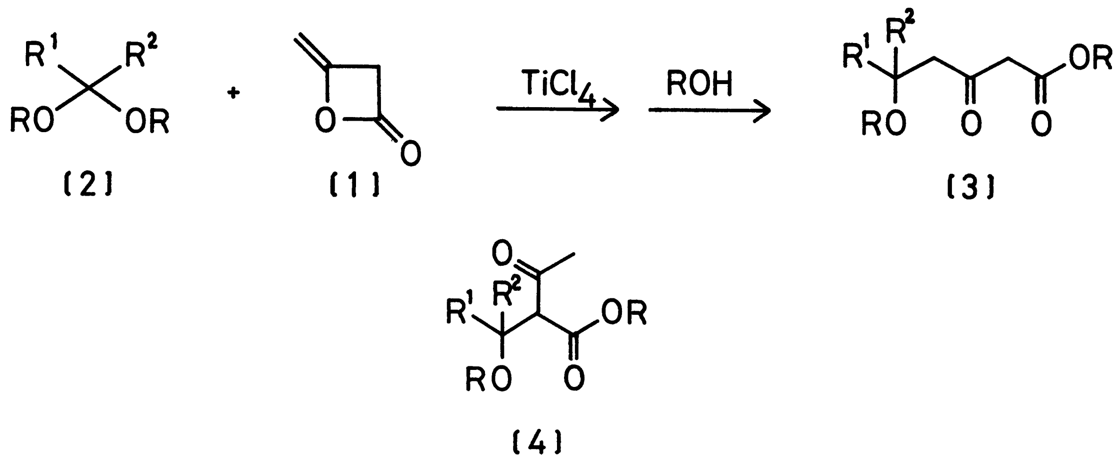
As a part of our continuing studies on the exploration of useful synthetic reactions by using $TiCl_4$, it was found recently that β-alkoxyketones were produced in good yields when silyl enol ethers1) or enol acetates2) were allowed to react with acetals.



In the present study, the reactions of diketene [1], chosen as an appropriate nucleophile in place of silyl enol ethers or enol acetates in the above experiments, with various acetals [2] activated by $TiCl_4$ were examined.

Concerning the reactions of diketene with acetaldehyde diethyl acetal in the presence of Lewis acid as $BF_3 \cdot O(C_2H_5)_2$, it was reported by Kucherov and Yufit3) that only ethyl α-(1-ethoxyethyl)acetoacetate is obtained along with some by-products.

Contrary to the above result, it was found by the present experiment that δ-alkoxy-β-ketoesters [3] were obtained exclusively by the treatment of diketene [1] with acetals [2] at -78 ∿ -20°C and none of α-(1-alkoxyalkyl)acetoacetic esters [4] were isolated. For example, ethyl 5-ethoxy-3-oxohexanoate was produced in good yield when acetaldehyde diethyl acetal was used as an acetal in the following equation.

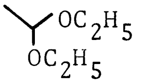
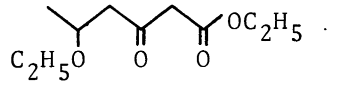
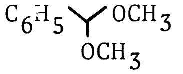
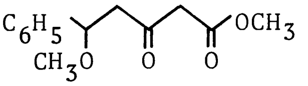
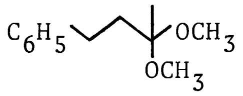
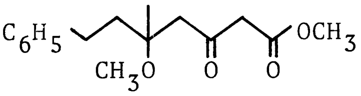
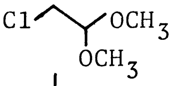
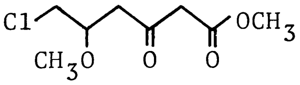
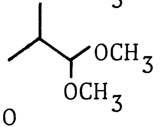
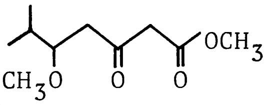
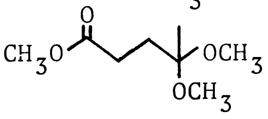
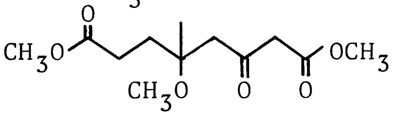
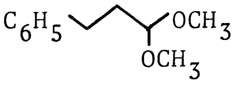
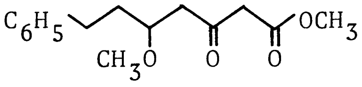


The following experiment provides details of a typical preparation of δ-alkoxy-β-ketoester. A solution of benzylacetone dimethyl acetal (0.486 g, 2.5 mmol) in dichloromethane (4 ml) was added dropwise to a vigorously stirred solution of $TiCl_4$ (0.57 g, 3.0 mmol) in dichloromethane (10.5 ml) at -78°C and successively a solution of diketene (0.420 g, 5.0 mmol) in dichloromethane (0.5 ml) was injected at once. The reaction mixture was stirred for 1 hr at -78°C, and then 2 ml of dry methanol was added. After being stirred for 0.5 hr at -20 ∿ -10°C, the reaction mixture was poured into an ice-cooled aqueous potassium carbonate (ca. 1 g, 7 mmol) solution. After the removal of insoluble yellow precipitate by filtration, the filtrate was extracted with ether. The ether solution was washed with water and saturated brine, and dried over anhydrous sodium sulfate. After the removal of the solvent, the residue was warmed at ca. 35°C under reduced pressure (2 mm Hg) in order to remove excess diketene and methyl acetoacetate, produced from diketene and methanol, and separated by column chromatography (silica gel). Thus, methyl 5-methoxy-5-methyl-3-oxo-7-phenylheptanoate was obtained in 87 % yield (0.608 g).

In a similar manner, various δ-alkoxy-β-ketoesters were prepared in good yields by the treatment of diketene [1] with various acetals [2] derived from acetaldehyde, benzaldehyde, benzylacetone, chloroacetaldehyde, isobutyraldehyde, methyl levulinate and β-phenylpropionaldehyde, and the results are listed in the following table.

As shown in the table, acetals [2] having chlorine atom or carboxylic ester group in the same molecule similarly react with diketene [1] to afford the corresponding δ-alkoxy-β-ketoesters [3] in good yields. For example, methyl levulinate dimethyl acetal reacted with diketene at -78°C by the action of $TiCl_4$ to give dimethyl 5-methoxy-5-methyl-3-oxooctanedioate in 76% yield. In the case of chloroacetaldehyde dimethyl acetal, the reaction did not take place at -78°C, but the use of 4.0 mole excess of diketene and 2.0 mole excess of $TiCl_4$ at -20°C led to the formation of methyl 6-chloro-5-methoxy-3-oxohexanoate in 58% yield.

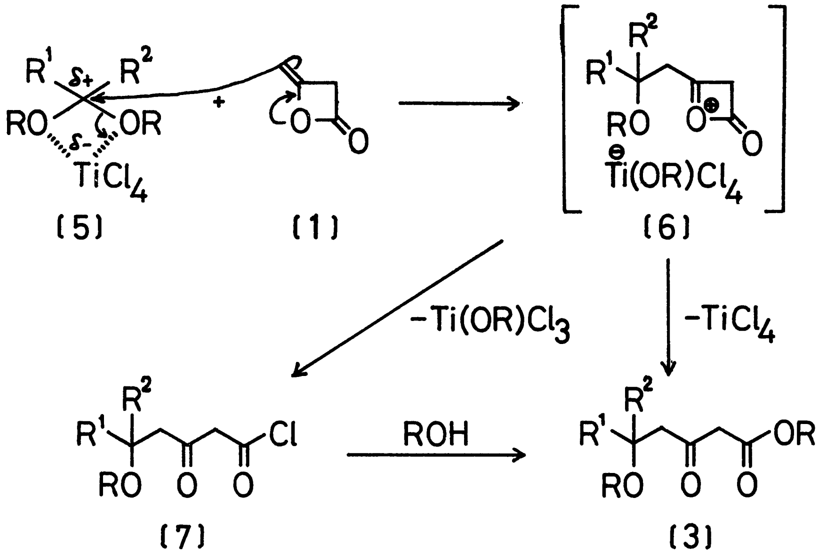
Table. The Reactions of Diketene [1] with Various Acetals [2]

Acetal[2]	Molar Ratio		Temp. (°C)	Time (hr)	δ-Alkoxy-β-ketoester[3]^a)	Yield^b) (%)
	Diketene[1]	$TiCl_4$				
	2.0	1.2	-78	1		67
	2.0	1.2	-78	1		84^c)
	2.0	1.2	-78	1		87
	4.0	2.0	-20	1		58
	2.0	1.2	-78	1		77
	4.0	1.5	-78	1		76
	1.5	1.2	-78	1		87

a) All compounds exhibited ir and nmr spectrum data in accordance with assigned structures.
b) Yield of isolated product.
c) Methyl 5-chloro-3-oxo-5-phenylpentanoate was isolated in 9% yield as a minor product.

The reaction can be reasonably explained by considering an initial formation of a highly active acetal-$TiCl_4$ complex [5] from acetal [2] and $TiCl_4$. A nucleophilic attack of exo-double bond of diketene [1] on the complex [5] forms a new carbon-carbon bond to give an intermediate [6] as sketched below. The intermediate [6] was immediately converted to δ-alkoxy-β-ketoester [3] accompanying the elimination of $TiCl_4$ and/or δ-alkoxy-β-ketoacyl chloride [7] with the elimination of

$Ti(OR)Cl_3$. The acyl chloride [7] was converted to δ-alkoxy-β-ketoester [3] by the treatment with alcohol (ROH).



It is noted that the present reaction is carried out under acidic conditions in great contrast with that of 1,3-dianion[4] generated from acetoacetic ester under strongly basic conditions. Therefore, different from the well-known reactions of 1,3-dianion, diketene is used as a new reagent for the introduction of $-COCH_2COCH_2-$ unit to an electrophile as acetal activated by $TiCl_4$.

Further reactions of diketene with other electrophiles, such as aldehydes, ketones are now in progress.

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(Received August 3, 1974)