NEW DEVELOPMENT OF THE MUKAIYAMA REACTION : ONE POT SYNTHESIS OF B-CHLORO ACIDS AND ESTERS Moncef BELLASSOUED\*\*, Jacques-Emile DUBOIS\* and Emmanuel BERTOUNESQUE

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ABSTRACT.- The titanium tetrachloride reaction of ketene silyl acetals with benzaldehyde has been investigated. Through an aldolization-chlorination process, using two equivalents of TiCl<sub>a</sub>,  $\beta$ -chloro acids and esters are obtained in good yields.

 $\beta$ -halogeno acids are very often used for the synthesis of  $\beta$ -lactones<sup>1</sup>. Among the methods for the preparation of  $\beta$ -chloro acids, the most convenient and regio selective is the addition of hydrogen chloride to  $\alpha$ ,  $\beta$ -unsaturated acids<sup>2</sup>. To our knowledge, two papers reported the use of titanium tetrachloride as chlorination reagent for the synthesis of  $\alpha$ -chloronitriles<sup>3</sup> and  $\beta$ -chlorohydrocinnamic ester<sup>4</sup>.

It is known that the Mukaiyama reaction applied to ketene silyl acetals yields  $\beta$ -hydroxy acids<sup>5</sup> and esters<sup>6</sup> when one equivalent of  ${\rm TiCl}_{4}$  is used at -78°. We wish to report herein that the same reaction carried out with two equivalents of TiCl, at room temperature leads to B-chloro acids and esters in good yield. We first carried out our investigation of the reaction of ketene bis(trimethylsilyl) acetals 1 with benzaldehyde' (eq.1).



The results and the reaction conditions are summarized in the Table.

## TABLE

Yields of Products 2 in the reaction of Ketene Silyl Acetals 1 with Benzaldehyde in the Presence of  $TiCl_{4}$ .

R	Molar ratio	Reaction conditions	Yield <sup>a,b</sup> of <u>2</u>
	of TiCl <sub>4</sub>		
Me	10%	-60°, 1 h	0(80) <sup>c</sup>
Me	10%	-60°, l h ; 20°, 24 h	0(87) <sup>C</sup>
Me	I	-60°, 1 h	0(91) <sup>c</sup>
Me	1	-60°, l h ; 20°, 3 days	50 <sup>d</sup> (33) <sup>c</sup>
Me	1	-60°, 1 h ; 40°, 24 h	53 <sup>d</sup> (25) <sup>c</sup>
Me	2	-60°, 14 h	20 <sup>d</sup> (70) <sup>c</sup>
Me	2	-60°, l h ; -10°, l h	87 <sup>e</sup>
Me	2	-60°, 1 h ; 20°, 2 h	90 <sup>e</sup>
Et	2	-60°, l h ; 20°, 2 h	80 <sup>e</sup>
i-Pr	2	-60°, 1 h ; 20°, 2 h	82 <sup>e</sup>
Ph	2	-60°, 1 h ; 20°, 2 h	75 <sup>e</sup>
	R Me Me Me Me Me Et i-Pr Ph	RMolar ratio of TiCl4Me10%Me1Me1Me1Me2Me2Me2Me2Me2Ph2	RMolar ratio of TiCl4Reaction conditionsMe $10\%$ $-60^{\circ}$ , 1 hMe $10\%$ $-60^{\circ}$ , 1 h; 20°, 24 hMe1 $-60^{\circ}$ , 1 h; 20°, 3 daysMe1 $-60^{\circ}$ , 1 h; 20°, 3 daysMe1 $-60^{\circ}$ , 1 h; 40°, 24 hMe1 $-60^{\circ}$ , 1 h; 40°, 24 hMe2 $-60^{\circ}$ , 1 h; 40°, 24 hMe2 $-60^{\circ}$ , 1 h; 20°, 2 hMe2 $-60^{\circ}$ , 1 h; 20°, 2 hEt2 $-60^{\circ}$ , 1 h; 20°, 2 hi-Pr2 $-60^{\circ}$ , 1 h; 20°, 2 hPh2 $-60^{\circ}$ , 1 h; 20°, 2 h

a) the structures of compounds  $\underline{2}$  were established by <sup>1</sup> H-NMR, elemental analysis and acido-basic titration

- b) mixtures of diastereoisomers
- c) yield of β-hydroxyacid recovered
- d) yields were determined by <sup>1</sup>H-NMR signals of CH-OH and CH-Cl protons
- e) isolated product yields.

As shown in the Table, a molar ratio of  $\text{TiCl}_4$  equal to 2 gives, at 20°, exclusively  $\beta$ -chloroacids <u>2</u> in good yield (entries 8-11). Reaction with R = Me occurs very well at -10° (entry 7). Furthermore, the reaction of dimethyl ketene bis(trimethylsilyl) acetal with benzaldehyde and two equivalents of TiCl<sub>4</sub> (-60°, 1 h ; 40°, 3 h) leads to 3-chloro 2,2-dimethyl 3-phenyl propionic acid in 72% isolated yield.

It is to be observed that the notion of the substitution of the trimethylsiloxy group by a halogen atom comes from a study by Ayi and coworkers<sup>8</sup> who investigated the reaction of  $\beta$ -trimethylsiloxy esters with PhPF<sub>4</sub>. On the other hand, Kuwajima and coworkers<sup>9</sup> reported the formation of trichlorotitanium enolates at 20-30° by the reaction of enol silyl ethers and TiCl<sub>4</sub>. In these conditions we propose to interpret the reaction pathway of chlorination reaction with two equivalents of TiCl<sub>4</sub> by a Lewis acid-base interaction between  $OSi \equiv$  groups and TiCl<sub>4</sub> followed by a subsequent cleavage of  $O-Si \equiv$  bond leading to the formation of  $O-TiCl_3$  bond and finally to the  $\beta$ -chlorosubstitution (scheme).



Since  $\beta$ -chloroacids are formed in good yields from ketene bis(trimethylsilyl) acetals <u>1</u>, we have also examined the reaction described by Chan<sup>6</sup> : two alkyl ketene ethyl(trimethylsilyl) acetals <u>3</u> are condensed with benzaldehyde in the presence of two equivalents of TiCl<sub>4</sub>. The expected  $\beta$ -chloroesters <u>4</u> are obtained exclusively (eq.2).





The effect of another potential chlorination reagent  $(SnCl_4)$  was also examined using the same ketene bis(trimethylsilyl) acetals  $\underline{l}$ :  $\beta$ -chloroacids  $\underline{2}$  are obtained in yields of only 47-60% without by products after silicagel chromatography (hexane-ether = 1/1) of the reaction mixtures. The use of TiBr<sub>4</sub>, TiI<sub>4</sub> and TiF<sub>4</sub> with various carbonyl compounds is currently in progress.

## REFERENCES

- 1. H.E. Zaugg, Org. Reactions, 8, 305 (1954).
- 2. H.H. Guest, J. Am. Chem. Soc., <u>69</u>, 300 (1947).
- 3. S. Kiyooka, R. Fujiyama and K. Kawaguchi, Chem. Lett., 1979 (1984).
- 4. H. Suzuki, H. Manabe, R. Emokiya and Y. Hanazaki Chem. Lett., 1339 (1986).
- J.E. Dubois and G. Axiotis, Tetrahedron Lett., <u>25</u>, 2143 (1984); J.E. Dubois
  G. Axiotis and E. Bertounesque, ibid., <u>25</u>, 4655 (1984); M. Bellassoued,
  J.E. Dubois and E. Bertounesque, ibid, 27, 2623 (1986).
- 6. T.H. Chan, T. Aida, P.W.K. Gory and D.N. Harpp, Tetrahedron Lett., 4029 (1979).
- 7. A typical experiment is as follows : A solution of benzaldehyde (20 mmol, 2.2 g) in 10 ml  $CH_2Cl_2$  was added rapidly to a  $CH_2Cl_2$  solution (0.66 M) of TiCl<sub>4</sub> (40 mmol, 60 ml) under a nitrogen atmosphere at -60°C and the mixture was stirred at the same temperature for 10 mn. Then the ketene silyl acetal (20 mmol) in 10 ml  $CH_2Cl_2$  was added dropwise at -60°C. After the addition was complete, the reaction mixture was removed from the cold bath and allowed to warm slowly to room temperature over a period of 2 hours (24 hours for the  $\beta$ -chloroesters). The reaction mixture was then quenched with water, extracted with  $CH_2Cl_2$ , washed with brine, dried over anhydrous magnesium sulfate and solvent evaporated to give a crude product. The NMR analysis of the crude product showed the exclusive formation of halogen compound.
- 8. A.I. Ayi, R. Condom, P.C. Maria, T.N. Wade and R. Guedj, Tetrahedron Lett., 4507 (1978).
- 9. E. Nakanura and I. Kuwajima, Tetrahedron Lett., 24, 3343 (1983).

(Received in France 21 October 1987)