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ERYTHRO SELECTIVE CROSS ALDOL REACTION VIA α-SILYL TRIMETHYLSILYL ESTERS.

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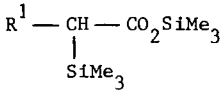
ABSTRACT.- *Various fluoride ion mediated reactions of aliphatic α-silyl trimethylsilyl esters 1 with benzaldehyde have been investigated. Moderate erythro stereoselectivity is observed.*

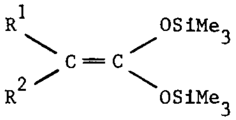
In a previous study (1), we investigated the development of ketene bis (trimethylsilyl) acetals (2) 2 as synthetic carboxylic acid dianions and their practical utility in selective carbon-carbon bond formation in their $TiCl_4$- mediated reactions. Recently, Heathcock and co-workers (3) extended this to diastereofacial selectivity work with chiral aldehyde. Aldol type reactions promoted by fluoride ion with α-silyl carbonyl compounds are much less known than those with enol silyl ethers (4). α-Silyl ketones as a source of the enolate anion gave the aldol product (5). Under all conditions, moderate erythro selectivities are observed. Furthermore, titanium (IV) chloride catalyzed asymmetric aldol- type reactions with α-trimethylsilyl ketones via acetals were also obtained recently (6). A reaction of ethyl trimethylsilylacetate with carbonyl compounds catalyzed by TBAF was reported previously (7). Our desire to develop an efficient method to control the stereochemistry of the aldol reaction led us to explore the role of α-silyl esters (8) 1 as nucleophilic reagents.



$$R^1-\underset{\displaystyle SiMe_3}{\underset{|}{CH}}-CO_2SiMe_3$$

1

R^1 = Me,Et

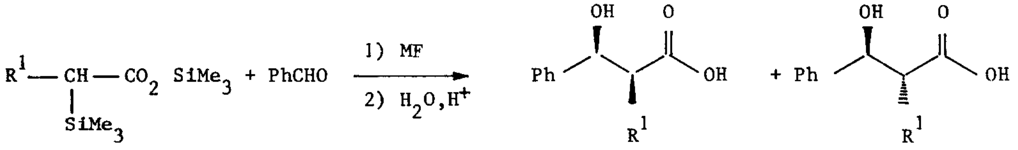


2

R^1 = alkyl, allyl

R^2 = H, alkyl

We now report that α-silyl esters 1, useful synthetic reagents, react with benzaldehyde to give erythro β-hydroxyacids in good yields under fluoride ion catalysis (eq.1).



(1)

1 2 M = NBu_4,Cs 3 erythro 4 threo

The results are summarized in Table I.

Table I : DIASTEREOMER RATIOS IN THE F^- MEDIATED REACTIONS OF α-SILYL TRIMETHYLSILYL ESTERS 1 WITH BENZALDEHYDE (eq.1)

Entry	R^1	Conditions	% Yield	Ratio 3:4 a)
1	Me	TBAF, RT	45	81:19
2	Me	TBAF, Reflux	82	77:23
3	Me	CsF, Reflux	84	74:26
4	Et	TBAF, -78°C	34	70:30
5	Et	TBAF, Reflux	70	74:26
6	Et	CsF, Reflux	76	78:22

a) Determined by ^1H NMR at 60 MHz.

As shown in Table I, the α-silyl esters studied exhibit moderate erythro selectivity. The counterions Cs^+ and NBu_4^+ lead to an almost identical stereoselectivity. In order to know if aldolate erythro-threo equilibration exists, the reaction of 1 at -78°C (entry 4), was undertaken. The isomers erythro and threo were obtained in a ratio of 70:30. Entries 4 and 5 show that the aldol addition proceeds with kinetic stereoselection.

In the case of fluoride ion promoted reactions of enol silyl ethers (9) and silyl acetate (7), quaternary ammonium enolate has been proposed as a synthetic intermediate. It is reasonable to believe that our reactions proceed through a series of equilibria shown below, centered upon quaternary ammonium or caesium carboxylic dianion.

To test this hypothesis, we examined the reaction of 2 with benzaldehyde under basic conditions. Data are listed in Table II.

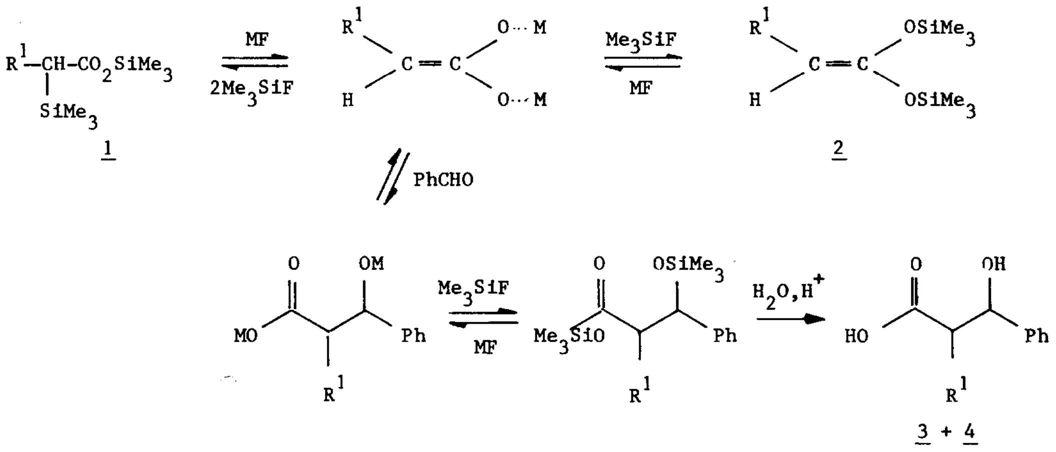


Table II : DIASTEREOMER RATIOS IN THE F$^-$ MEDIATED REACTIONS OF KETENE BIS (TRIMETHYLSILYL) ACETALS 2 WITH BENZALDEHYDE

Entry	R^1	Conditions	% Yield	Ratio 3:4 a)
7	Me	TBAF, Reflux	75	79:21
8	Et	TBAF, Reflux	60	74:26
9	Et	CsF, Reflux	78	78:22

a) Determined by ^{1}H NMR at 60 MHz.

Thus, all reactions (entries 7-9) proceed with erythro diastereoselectivity. The same stereoratios are obtained regardless of the nature of organic silicon compounds. In view of the results, we consider the existence of quaternary ammonium and caesium carboxylic dianions as the intermediates in these reactions. We have not yet any direct evidence of them.

The reaction of 1 with benzaldehyde was examined in the presence of Lewis acids. Surprisingly, under such conditions, α-silyl ester (R^1 = Me) did not effect the aldol reaction. With an equivalent amount of $TiCl_4$, $ZnBr_2$ and BF_3 etherate. 2,3 Dimethyl succinic acid was obtained in yields of 82, 35 and 76%, respectively.

To sum up, the research reported in this paper shows that compounds 1 behave similarly to the corresponding ketene bis (trimethylsilyl) acetals 2 under basic conditions, except in the presence of a Lewis acid, affording a stereoselective synthesis of β-hydroxyacids with good yields. We are now working on the application of 1 to other types of carbon-carbon bond reactions.

General procedure for the preparation of β-hydroxyacids

To a solution 1M of TBAF in THF (2 ml, 10 mol %) under nitrogen at room temperature was added a mixture of silyl compound (20 mmol) and benzaldehyde (2.2 g 20 mmol) in 20 ml of THF. The reaction mixture was then stirred at reflux for twenty four hours, cooled at the end of this time and hydrolyzed with dilute HCl, and the solution was extracted with ether three times. The ether extracts were poured into dilute HCl and stirred for 15 mn, then washed with brine, dried ($MgSO_4$), concentrated in vacuo to afford a mixture of crude erythro and threo adducts. For the reaction catalyzed by CsF (10 mol %) in DMF, a solution of silyl compound (20 mmol) in 10 ml of DMF and a solution of benzaldehyde (2.2 g, 20 mmol) in 10 ml of DMF were added in sequence ; then the procedure was followed as above.

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