CHEMISTRY LETTERS, pp. 1011-1014, 1973. Published by the Chemical Society of Japan

NEW ALDOL TYPE REACTION

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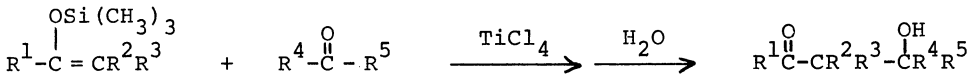
In the presence of $TiCl_4$, trimethylsilyl enol ethers of ketones react smoothly with ketones or aldehydes at room temperature to give the aldol type addition products, β-hydroxyketones, in good yields.

We investigated the useful method for the preparation of β-hydroxyketones [2] by the reaction of trimethylsilyl enol ethers[1] [1] with ketones or aldehydes in the presence of $TiCl_4$ at room temperature.[2]

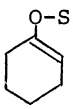
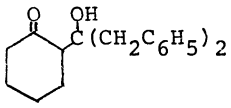
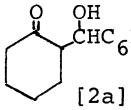
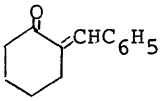
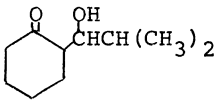
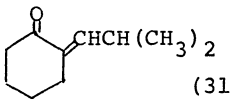
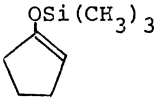
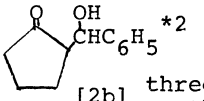
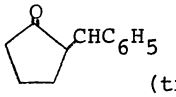
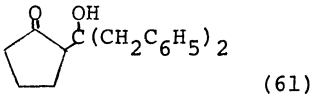
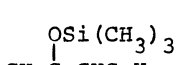
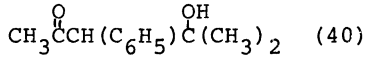
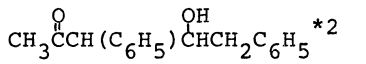
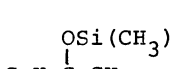
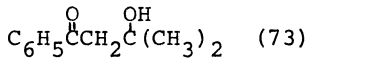
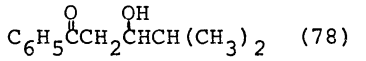


[1] [2]

The typical procedure is described for the reaction of trimethylsilyl enol ethers of acetophenone [1d] with phenylacetaldehyde: To a CH_2Cl_2 (20 ml) solution of $TiCl_4$ (5.1 mmol) and phenylacetaldehyde (5.0 mmol) was added CH_2Cl_2 solution of [1d] (5.0 mmol) under an argon atmosphere at room temperature, and the reaction mixture was stirred for 2 hr. After hydrolysis, the resulting organic layer was extracted with ether and the extract was condensed under reduced pressure. The residue was chromatographed on silica gel and the addition product, 1,4-diphenyl-3-hydroxybutan-1-one, was isolated in 78% yield along with a small amount of unreacted phenylacetaldehyde and acetophenone (10%).

In a similar manner, the reactions of silyl enol ethers of cyclohexanone [1a], cyclopentanone [1b], phenylacetone [1c] and acetophenone [1d] with various ketones or aldehydes were tried and the results are listed in the table. In all cases, the

Table. The reactions of silyl enol ethers with ketones or aldehydes

Silyl enol ether [1]	Ketone or Aldehyde	Reaction time(hr)	Product [2]*1 (Isolated yield, %)
 [1a]	$(C_6H_5CH_2)_2CO$	1	 (62)
	C_6H_5CHO	2	 [2a] threo (63) erythro (19)  (6)
	$(CH_3)_2CHCHO$	5	 (50)  (31)
 [1b]	C_6H_5CHO	5	 [2b] threo (37) erythro (37)  (trace)
	$(C_6H_5CH_2)_2CO$	18	 (61)
 [1c]	$(CH_3)_2CO$	5	 (40)
	$C_6H_5CH_2CHO$	5	 [2c] threo (24) erythro (53)
 [1d]	$(CH_3)_2CO$	5	 (73)
	$(CH_3)_2CHCHO$	5	 (78)

*1 The products have ir and nmr spectra and elemental analysis in accord with the assigned structures.

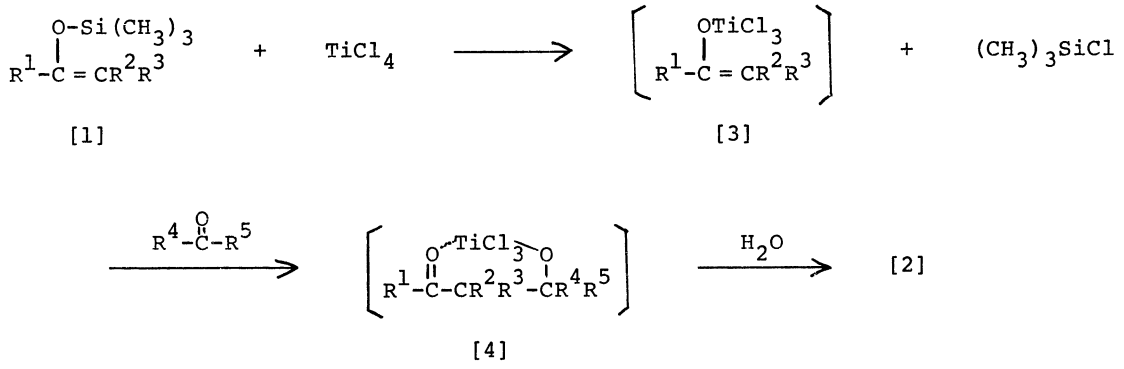
*2 The threo- and erythro- isomers were separated by silica gel column chromatography, and the stereochemistry of the stereo-isomers was determined by nmr spectrum. Each of the isomers of [2a,b,c] has a simple doublet due to the proton (Ha) of the CH-O- group or the other tertiary hydrogen (Hb), and the comparison of the coupling constant (Jab) of the isomers suggests the stereochemistry.[3]

	Chemical Shift(δ) Ha	Hb*3	Coupling Constant Jab(Hz)	
2a (threo)	4.83	——	9.0	in $CDCl_3$
2b (erythro)	5.40	——	2.5	in $CDCl_3$
2b (threo)	4.68	——	9.0	in CCl_4
2b (erythro)	5.16	——	2.0	in CCl_4
2c (threo)	4.43	3.70	9.0	in CCl_4
2c (erythro)	4.40	3.43	6.0	in CCl_4

*3 Signal not sufficiently resolved from methylene signals.

cross-aldol addition type products [2] were obtained in good yields, and none of the self-addition or condensation product of ketone or aldehyde was detected.

This reaction may proceed through an initial formation of titanium enol ether [3],[1a,4] produced from [1] and $TiCl_4$, which in turn reacts with ketone or aldehyde to give addition product [4]. The [4] is then hydrolyzed to β-hydroxyketone [2].



In general, mixed aldol reactions afford a mixture of self- and cross-addition products, therefore, the yield of the cross-addition product is rather low.[5] On the other hand, it was established by the present reaction that the cross-aldol addition type products are obtained selectively in good yields from silyl enol ethers and ketones or aldehydes. It is further noted that, in the case of the reaction of silyl enol ether of unsymmetrical ketone such as phenylacetone, the addition reaction proceeds selectively at the olefinic position originated in the silyl enol ether.

Further development is now in progress.

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3) M. Stiles, R. P. Winkler, Y. Chang, and L. Traynor, J. Amer. Chem. Soc., 86, 3337 (1964); J. E. Dubois and M. Dubois, Tetrahedron Lett., 4215 (1967).

4) J. H. Haslam, U. S. P. 2,708,205, Chem. Abstr., 50, 4211 (1956); L. Vuitel and A. Jacot-Gillarmod, Synthesis, 608 (1972).

The ir spectrum of the CH_2Cl_2 solution of equimolar amounts of [1c] and $TiCl_4$ has strong absorption at 1653 cm^{-1} (C=C), and the spectrum has the absorptions at 850, 820 and 460 cm^{-1} which also appear in the ir spectrum of CH_2Cl_2 solution of $(CH_3)_3SiCl$.

5) A. T. Nielsen and W. J. Houlihan, "Organic Reactions", 16, John Wiley and Sons, Inc., New York (1968), p.1.

(Received June 28, 1973)