NEW CROSS ALDOL REACTIONS. THE REACTIONS OF SILYL ENOL ETHERS WITH KETO ESTERS PROMOTED BY TITANIUM TETRACHLORIDE

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It was found that, in the presence of TiCl₄, keto esters such as ethyl pyruvate, ethyl 2,2-dimethyl acetoacetate, ethyl levulinate and ethyl 5-oxohexanoate react with various trimethylsilyl enol ethers derived from ketones at room temperature to afford cross aldols, i.e., hydroxy keto esters, in good yields.

The aldol condensation has long been recognized to be one of the most versatile synthetic tools in organic synthesis. However, synthetic utility of this reaction is severely curtailed, as it normally proceeds by the promotion of bases under equilibrium conditions.

Recently, it has been reported from our laboratory that the $TiCl_4$ -promoted reactions of silyl enol ethers with carbonyl compounds have elegant and broad utility in the preparation of cross aldols as illustrated in the following schemes.^{2,3)}



In the present experiment, the preparation of cross aldols by the reactions of silyl enol ethers with keto esters was investigated. A typical reaction procedure is shown in the following: To a dichloromethane solution (15 ml) of ethyl pyruvate (392 mg, 3 mmol) and TiCl₄ (567 mg, 3 mmol) was added a dichloromethane solution (10 ml) of 3-trimethylsiloxy-2-pentene (474 mg, 3 mmol) at room temperature under an argon atmosphere, and the mixture was kept at room temperature for 3 hr with stirring. After hydrolysis with cold water (30 ml), the resulting organic layer was extracted with ether (70 ml), and the extract was concentrated under reduced pressure. The aldol, ethyl 2,3-dimethyl-2-hydroxy-4-oxohexanoate, was obtained in 87% (526 mg) yield after purification by column chromatography (silica gel).

In a similar manner, the reactions of various silyl enol ethers with ethyl pyruvate were carried out in the presence of TiCl₄, and the corresponding aldols were obtained in good yields (see Table 1).



R ¹	R ²	isolated yield $(\%)^4$
CH ₃ CH ₂	CH ₃	87
CH ₃	Н	55
-(CH ₂)	3	76
-(CH ₂)	4	88
C ₆ H ₅	H	63

Table 1. The Reactions of Sily1 Enol Ethers with Ethy1 Pyruvate

Further, the reactions of various silyl enol ethers with a variety of keto esters, such as ethyl 2,2-dimethyl acetoacetate, ethyl levulinate, and methyl 5-oxohexanoate, were run in the presence of TiCl_4 , and the corresponding aldols were obtained in good yields as shown in Table 2. In the case of the reaction of ethyl acetoacetate with 1-trimethylsiloxy-1-cyclohexene, no reaction was observed, and ethyl acetoacetate was recovered along with cyclohexanone produced by the

Keto Ester	Silyl Enol Ether	Product ⁴⁾ (isolated yield %)
сн ₃ сос(сн ₃) ₂ соос ₂ н ₅	OSiMe ₃	$CH_{3}-C-C(CH_{3})_{2}COOC_{2}H_{5}$
сн ₃ со(сн ₂) ₂ соос ₂ н ₅	Me ₃ SiO C ₆ H ₅ C=CH ₂	$CH_{3} - C - C (CH_{3})_{2} COOC_{2}H_{5}$ $CH_{2}COC_{6}H_{5} (38)$
	Me ₃ SiO C ₆ H ₅ >C=CHCH ₃	$CH_{3}^{0H} - C(CH_{2})_{2}COOC_{2}H_{5}$ $CH_{3}^{-CHCOC}_{6}H_{5}$ (86)
	OSiMe ₃	$CH_{3}-C(CH_{2})_{2}COOC_{2}H_{5}$
сн ₃ со(сн ₂) ₃ соосн ₃	^{Me₃SiO} C ₆ H ₅ >C=CH ₂	$CH_{3}^{-C} - (CH_{2})_{2}COOC_{2}H_{5}$ $CH_{2}COC_{6}H_{5}$ (41)
	OSiMe ₃	$CH_{3}-C-(CH_{2})_{3}COOCH_{3}$ $O = (69)$
	Me ₃ SiO C ₂ H ₅ C=CHCH ₃	$CH_{3}^{OH} CH_{3}^{-C-} (CH_{2})_{3}^{-COOCH} CH_{3}^{-C-} (CH_{2})_{3}^{-COOCH} CH_{3}^{-C-} (71)$

Table 2. The Reactions of Sily1 Enol Ethers with Keto Esters

hydrolysis of 1-trimethylsiloxy-1-cyclohexene. This may be due to the preferential formation of stable enol structure of ethyl acetoacetate to decrease the carbonyl activity to react with the enol ether.

It is noted that silyl enol ethers react only with the ketone function of keto esters at room temperature to give aldols, i.e., hydroxy keto esters, and none of dehydrated product from hydroxy keto ester, i.e., unsaturated keto ester, was given.

REFERENCES

- Present address: The First Research Laboratory, Tokushima Factory, Otsuka Pharmaceutical Company, Ltd., 463-10 Kagasuno, Kawauchi-cho, Tokushima 770-01.
- 2) a) T. Mukaiyama, K. Narasaka, and K. Banno, Chem. Lett., 1011 (1973).
 - b) T. Mukaiyama, K. Banno, and K. Narasaka, J. Amer. Chem. Soc., <u>96</u>, 7503 (1974).
- 3) T. Mukaiyama and M. Hayashi, Chem. Lett., 15 (1974).
- 4) The products were confirmed by ir and nmr spectra and elemental analysis.

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