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The Highly Stereoselective Michael Reaction of α,β-Unsaturated Ketones with Silyl Enol Ethers of Thioesters Catalyzed by Trityl Salts. A Facile Stereoselective Synthesis of 5-Oxocarboxylic Acid Ester Derivatives

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In the presence of a catalytic amount of trityl salts, silyl enol ethers of thioesters stereoselectively react with α,β-unsaturated ketones to afford the Michael adducts in high yields. 5-Oxocarboxylic acid ester derivatives, useful synthetic precursors of various naturally occurring compounds, are stereoselectively obtained by this procedure.

Recently we have demonstrated that trityl salts efficiently catalyze the Michael reaction between silyl enol ethers and α,β-unsaturated ketones.[1-4] This new reaction proved to have many advantages over the conventional Michael reactions: (1) The reaction proceeds under non-basic, very mild reaction conditions, and undesired side reactions are suppressed. (2) The Michael adducts are obtained in high yields, in high regioselectivity (no 1,2-adducts are obtained) and in relatively high stereoselectivity.[2] (3) A catalytic amount of trityl salt is sufficient to complete this Michael reaction. (4) The Michael adducts are respectively isolated as 1,5-diketones or synthetically valuable silyl enol ethers depending on the working up procedure. (5) The tandem reactions such as the Michael-aldol,[3] the Michael-Michael[4] reactions are easily carried out in one-pot.

Now we wish to describe here the highly stereoselective synthesis of 5-oxocarboxylic acid esters, useful intermediates for the synthesis of various natural products,[5] according to the present Michael reaction employing the suitable ester enolate equivalents and α,β-unsaturated ketones.

Recently, some methods have been reported towards an efficient synthesis of these Michael adducts, however, the realization of high stereoselectivity and the suppression of 1,2-addition products still remained as serious problems. For examples, RajanBabu reported[6] the TASF (tris(dimethylamino)sulfonium difluorotrimethylsiliconate) catalyzed Michael reaction of ketene silyl acetals with α,β-unsaturated ketones afforded the Michael adducts non-stereoselectively. Heathcock et al. reported[7] the Lewis acid mediated Michael reaction between ketene silyl acetals and α,β-unsaturated ketones with low stereoselectivity except for acyclic t-butyl enones, and the competition between 1,2- and 1,4-addition reactions caused a severe problem. They also reported[8] that the Michael reaction between the lithium enolate of t-butyl propionate and α,β-unsaturated ketones resulted in the formation of desired 1,4-addition product along with the 1,2-addition product and that the diastereoselectivity was strongly dependent on substrates. Based on these results, the development of the new procedure is strongly desired for the stereoselective Michael reaction of ester enolate equivalents with α,β-unsaturated ketones, which leads to 5-oxocarboxylic acid ester derivatives.

In the first place, the reaction of (Z)-1-t-butyldimethylsiloxy-1-methoxypropene derived from methyl propionate with 1-phenyl-2-buten-1-one was carried out in the presence of a catalytic amount of trityl perchlorate. The corresponding Michael adduct was obtained in 65% yield with low selectivity (ul/lk = 62/38[9]). Then ester and siloxy groups and the geometry of enolates were further screened, however, selectivity was not improved. While, it was found that the Michael reaction proceeded in good yields with good selectivities when silyl enol ethers of thioesters were employed as an equivalent of ester enolate, especially excellent selectivity was achieved by the use of (Z)-1-t-butyldimethylsiloxy-1-t-butylthiopropene[10] (Table 1).

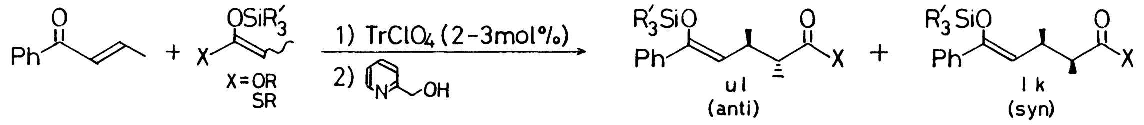


Table 1. The reaction of 1-phenyl-2-buten-1-one with silyl enol ethers of a ester and thioesters

Entry	X	R'_3		Yield/%	ul / lk
1	OMe	^{t}BuMe$_2$	Z	65	62 / 38
2	SEt	^{t}BuMe$_2$	Z	66	80 / 20
3	SPh	^{t}BuMe$_2$	Z	84	89 / 11
4	S^{t}Bu	Me$_3$	Z	73	71 / 29
5	S^{t}Bu	^{t}BuMe$_2$	Z	82	95 / 5
6	S^{t}Bu	^{t}BuMe$_2$	E	77	31 / 69

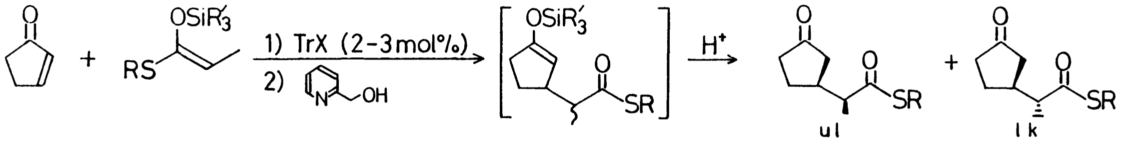


Table 2. The reaction of 2-cyclopentenone with silyl enol ethers of thioester

Entry	R	R'_3		TrX	Temp/ ℃	Yield/%	ul / lk
1	^{t}Bu	^{t}BuMe$_2$	Z	TrClO$_4$	-78	43	66 / 34
2	^{t}Bu	Me$_3$	E	TrClO$_4$	-78	56	23 / 77
3	^{t}Bu	Me$_3$	E	TrOTf	-78	70	21 / 79
4	Et	^{t}BuMe$_2$	Z	TrSbCl$_6$	-78	58	82 / 18
5	Et	PhMe$_2$	Z	TrSbCl$_6$	-78	76	88 / 12
6	Et	PhMe$_2$	Z	TrSbCl$_6$	-100	84	92 / 8

Next, the reaction of 2-cyclopentenone, an example of cyclic α,β-unsaturated ketones, with (Z)-1-t-butyldimethylsiloxy-1-t-butylthiopropene was carried out to produce the corresponding Michael adduct in 43% yield, ul/lk = 66/34. In order to improve the yield and diastereoselectivity, several reaction parameters such as solvent, reaction temperature, thioester and siloxy groups, the geometry of enolates, and the kind and the amount of trityl salts were screened. And finally, it was proved that the ul Michael adduct was predominantly obtained when (Z)-1-dimethylphenylsiloxy-1-ethylthiopropene was employed in the presence of a catalytic amount of *trityl hexachloroantimonate*.[11)] On the other hand, the lk adduct was preferentially obtained when (E)-1-t-butylthio-1-trimethylsiloxypropene was employed in the presence of a catalytic amount of *trityl triflate* (Table 2).

Several examples of this reaction are shown in Table 3. The ul adducts were stereoselectively obtained in high yields.

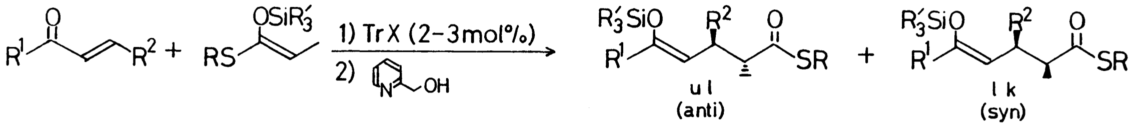
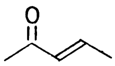
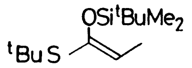
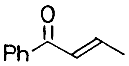
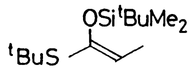
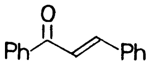
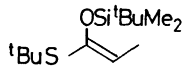
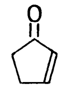
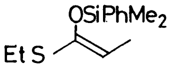
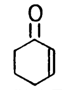
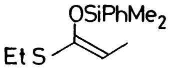
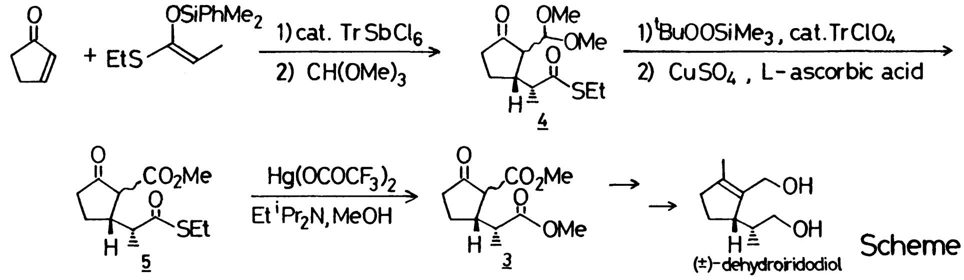


Table 3. The reaction of α,β-unsaturated ketones (A) with silyl enol ethers of thioesters (B)

Entry	A	B	TrX	Temp/°C	Yield/%	ul / lk
1			$TrClO_4$	-78	67	>95 / 5
2			$TrClO_4$	-78	82	95 / 5
3			$TrClO_4$	-78	80	92 / 8
4			$TrSbCl_6$	-100	84	92 / 8
5			$TrSbCl_6$	-100	94	88 / 12

A typical procedure is described for the reaction of (E)-1-phenyl-2-buten-1-one (1) with (Z)-1-t-butyldimethylsiloxy-1-t-butylthiopropene (2, Z/E = 95/5); the mixture of 1 (0.5 mmol), 2 (0.55 mmol), and trityl perchlorate (2-3 mol%) in dichloromethane (3 ml) was stirred at -78 °C for 1 h. 2-Pyridinemethanol (0.1 mmol) was added and the reaction mixture was diluted with dry low-to-medium-boiling petroleum ether (10 ml). After filtration, the solvent was removed under reduced pressure, and the residue was separated by deactivated silica gel[12)] column chromatography to afford S-t-butyl 5-t-butyldimethylsiloxy-2,3-dimethyl-5-phenyl-4-pentenethioate (82%, ul/lk = 95/5[13)]).

Then, in order to demonstrate the utility of the present reaction, the stereoselective synthesis of the (±)-dehydroiridodiol intermediate (3)[14)] was studied according to the following equations (Scheme 1). The tandem Michael-aldol reaction[3)] between 2-cyclopentenone, (Z)-1-dimethylphenylsiloxy-1-ethylthiopropene, and methyl orthoformate was carried out in the presence of a catalytic amount of trityl hexachloroantimonate to afford the corresponding adduct (4). Oxidation of 4 with *t*-butyl trimethylsilyl peroxide in the presence of a catalytic amount of trityl perchlorate, followed by treatment with CuSO$_4$ and L-ascorbic acid[15)] produced the methyl ester (5), which was in turn easily converted to the intermediate for the synthesis of dehydroiridodiol (3) by treatment with mercuric trifluoroacetate and ethyldiisopropylamine in methanol.[16)]



Scheme 1.

It should be noted that synthetically valuable 5-oxocarboxylic acid ester derivatives are prepared in high yields with high stereoselectivity from α,β-unsaturated ketones and silyl enol ethers of thioesters by appropriate choice of trityl salts and thioester and siloxy groups.

References

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9) For definition of the ul/lk convention, see, D. Seebach and V. Prelog, Angew. Chem., Int. Ed. Engl., 21, 654 (1982).
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11) Commercially available from Aldrich Chemical Company.
12) A mixture of silica gel (WAKO GEL C-200) and water (6:1).
13) For the assignment of the stereochemistry, see, Ref. 2 and Ref. 7 .
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