

THE TANDEM MICHAEL-ALDOL REACTION CATALYZED BY TRITYL PERCHLORATE [#]

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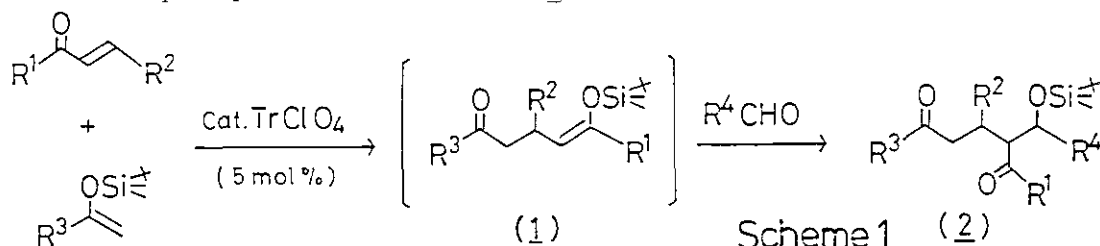
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Abstract—In the presence of a catalytic amount of trityl perchlorate, the tandem reaction of conjugate addition of silyl enol ethers to α,β -unsaturated ketones, and the sequential aldol reaction with aldehydes is carried out smoothly to afford γ -acyl-substituted δ -hydroxy ketone derivatives stereoselectively in high yields. The ketones thus obtained are easily converted to tetrahydropyran or δ -valerolactone derivatives.

Recently, we have demonstrated new possibilities of various trityl salts in synthetic reactions,¹ for example, trityl salts efficiently catalyze the aldol reaction between silyl enol ethers and acetals, orthoesters, or aldehydes.^{1c,d,j} Trityl perchlorate also effectively catalyzes the Michael reaction of silyl enol ethers with α,β -unsaturated ketones, and the adducts, synthetically valuable γ -keto silyl enol ethers, are isolated in high yields.^{1f} Another advantage of this reaction is that trityl perchlorate is regenerated owing to the recycle system to coexist with this silyl enol ether after the Michael reaction has completed. Thus, it is assumed that, if appropriate electrophiles are added to the reaction system, it is possible to obtain the adducts by further reactions of the intermediate silyl enol ethers with various electrophiles. In this paper, we wish to disclose our finding on the trityl perchlorate catalyzed tandem Michael-aldol reaction, and also the utilization of this reaction for the stereoselective syntheses of tetrahydropyran and δ -valerolactone derivatives.²

[#] Dedicated to Professor Gilbert Stork, on the occasion of his 65th birthday.

The tandem Michael-aldol reaction is composed of the following two steps sketched in Scheme 1. In the first step (the Michael reaction), silyl enol ethers react with α,β -unsaturated ketones to afford the intermediate silyl enol ethers (1) in the presence of a catalytic amount of trityl perchlorate (5 mol%). In the second step (the aldol reaction), the silyl enol ethers (1) initially formed further react with aldehydes by the promotion of trityl perchlorate to afford the γ -acyl-substituted δ -hydroxy ketone derivatives (2).

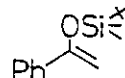
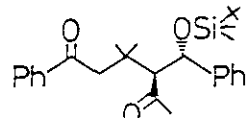
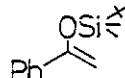
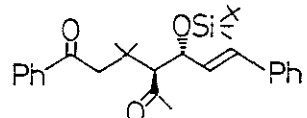
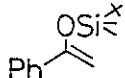
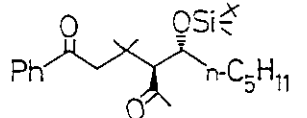
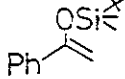
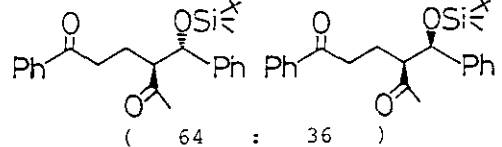
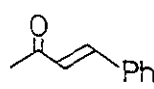
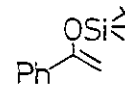
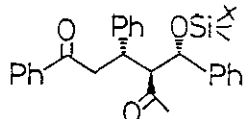
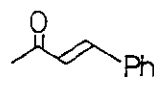
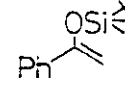
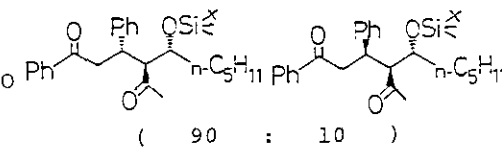
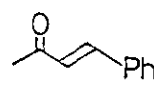
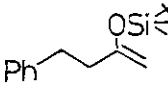
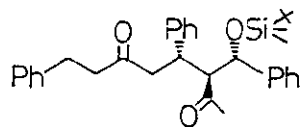
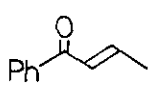
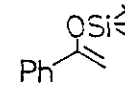
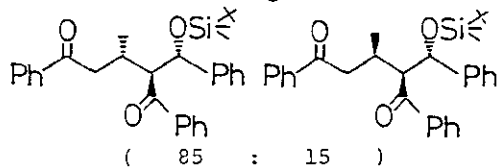


Several examples are shown in Table 1. In every case, γ -acyl-substituted δ -hydroxy ketone derivatives are obtained in high yields. In this reaction, a catalytic amount of trityl perchlorate effectively catalyzes both the Michael and the successive aldol reaction, and the formation of two carbon-carbon bonds at the α and β positions of α,β -unsaturated ketones is realized in one pot. Moreover, the products of this reaction are easily isolated as O-protected tert-butyl dimethyl silyl ethers, though it is well-known that δ -hydroxy ketones are in an equilibrium with hemiacetals and the separation of both isomers is difficult.

In addition, remarkable stereocontrol was achieved in the present reaction. Concerning the relative configuration of the γ and δ positions of the δ -hydroxy ketone derivatives, the anti products³ were obtained exclusively (except for entry 4 (Table 1)). Further, as shown in entries 5 and 7, in the cases of mono β -substituted α,β -unsaturated ketones, only one of four diastereomers was obtained. In the cases of entries 6 and 8, two of four diastereomers are obtained and one of them, the anti-anti adduct³ is produced predominantly.

A typical procedure for the preparation of γ -acyl-substituted δ -hydroxy ketone derivatives is as follows; the mixture of a silyl enol ether (0.50 mmol), an α,β -unsaturated ketone (0.53 mmol), and trityl perchlorate (0.03 mmol, 5 mol%) in dichloromethane (3 ml) was stirred at -78°C for an appropriate time (15-60 minutes). Then an aldehyde (0.47 mmol) in dichloromethane (1 ml) was added to this reaction mixture and further stirred at -78°C overnight. After the reaction

Table 1. Stereoselective syntheses of γ -acyl-substituted δ -hydroxy ketone derivatives^{a)} (Scheme I)

Entry	α,β -Unsaturated ketone	Silyl enol ether	Aldehyde	Product ^{b)} (Diastereomer ratio)	Yield/%
1			PhCHO		91
2			PhCH=CHCHO		93
3			<i>n</i> -C ₅ H ₁₁ CHO		83
4			PhCHO	 (64 : 36)	67
5			PhCHO		93
6			<i>n</i> -C ₅ H ₁₁ CHO	 (90 : 10)	98
7			PhCHO		72
8			PhCHO	 (85 : 15)	85

a) All products gave satisfactory spectral data.

b) Each compound was separated by silica gel column chromatography.

was completed, aqueous sodium hydrogen carbonate was added. The aqueous layer was extracted with dichloromethane and the organic layer was dried. After the solvent was removed under reduced pressure, the residue was separated by silica gel column chromatography.

The γ -acyl-substituted δ -hydroxy ketone derivatives thus obtained were easily converted to the tetrahydropyran derivatives. Namely, the treatment of the δ -hydroxy ketones with trifluoroacetic acid in dichloromethane gave dihydropyran derivatives in excellent yields (Scheme 2). The reduction with triethylsilane in the presence of a catalytic amount of trityl perchlorate^{1e} yielded 4-acyl-substituted 2,3,5-tri-substituted tetrahydropyran derivatives in high yields (Table 2).⁴

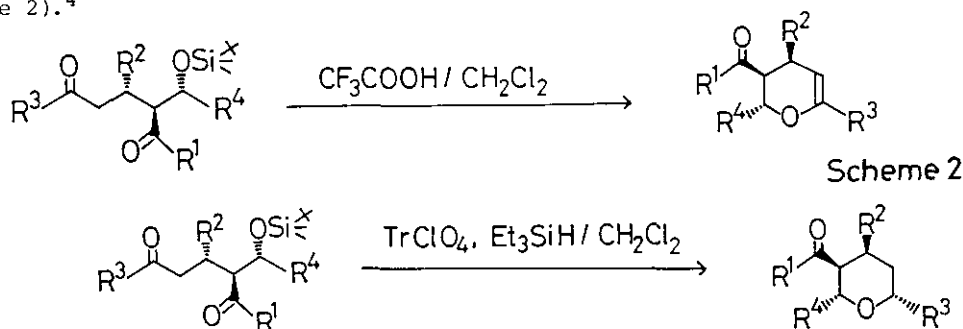
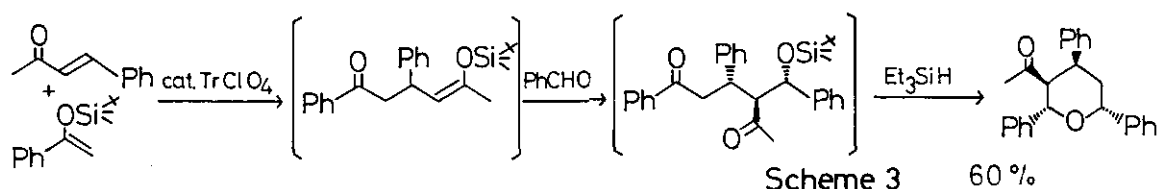


Table 2. A synthesis of acyl-substituted tetrahydropyrans^{a)}

Entry	δ -Hydroxy ketone derivative	Tetrahydropyran derivatives	Yield/%
1			86
2			93
3			quant.

a) All the products gave satisfactory spectral data.

The latter compound was also prepared from a silyl enol ether, an α,β -unsaturated ketones, and an aldehyde by one pot procedure as shown in Scheme 3.



Acetals or orthoesters are also successfully employed as electrophiles, and the reactions proceed smoothly at -78°C in the presence of a catalytic amount of trityl perchlorate, and the corresponding δ -hydroxy ketone derivatives are obtained stereoselectively in high yields (Table 3).

Table 3. A stereoselective synthesis of γ -acyl-substituted δ -hydroxy ketone derivatives^{a)}

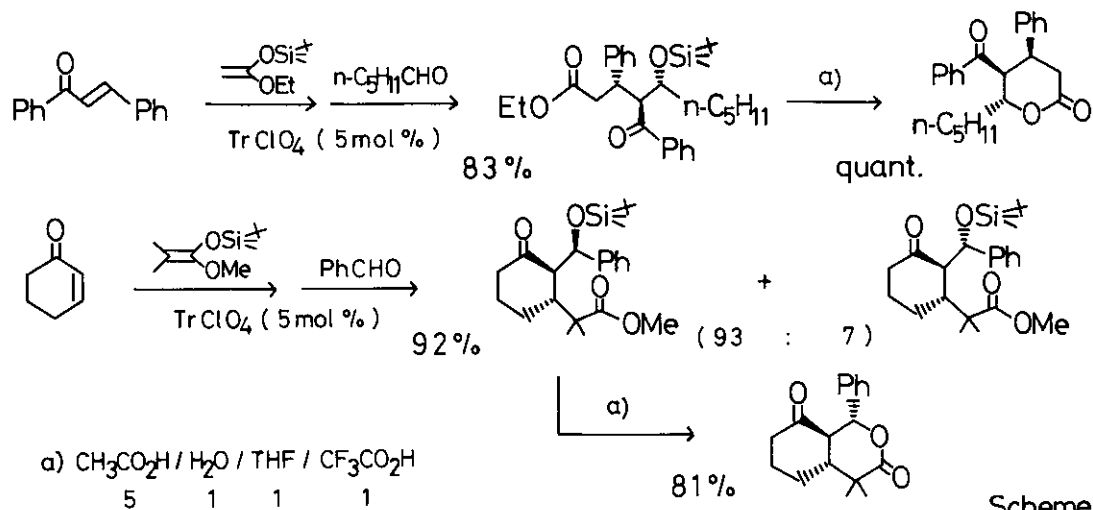
Entry	α,β -Unsaturated ketone	Silyl enol ether	Acetals or orthoformate	Product ^{b)}	Yield/%
1			PhCH(OMe)_2		89
2			$\text{PhCH}_2\text{CH}_2\text{CH(OMe)}_2$		85
3			$\text{CH(OCH}_3)_3$		71

a) All the products gave satisfactory spectral data.

b) Diastereomer ratio $>20:1$ (determined by ^{13}C nmr). Relative configuration assignment was not made.

Synthetically valuable acyl-substituted δ -valerolactone derivatives⁵ are prepared based on this procedure. That is, the tandem Michael-aldol reaction between α,β -

unsaturated ketones, silyl enol ethers derived from esters, and aldehydes gave γ -acyl-substituted δ -hydroxy ester derivatives stereoselectively in high yields. Desilylation and lactonization of these esters under acidic conditions produced δ -valerolactone derivatives in good yields (Scheme 4).



Scheme 4

This method is expected to be possibly applied to the syntheses of various natural products.

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