

## Condensation of Ketene Acetals derived from Glycolates with Aldehydes and Ketones: Synthesis of $\alpha,\beta$ -Dialkoxy Esters

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Deprotonation of glycolate esters, followed by trapping with trimethylsilyl chloride, affords ketene acetal derivatives which undergo condensation (accompanied by silyl group transfer) with aldehydes and ketones in the presence of zinc chloride to give  $\alpha,\beta$ -dialkoxy esters.

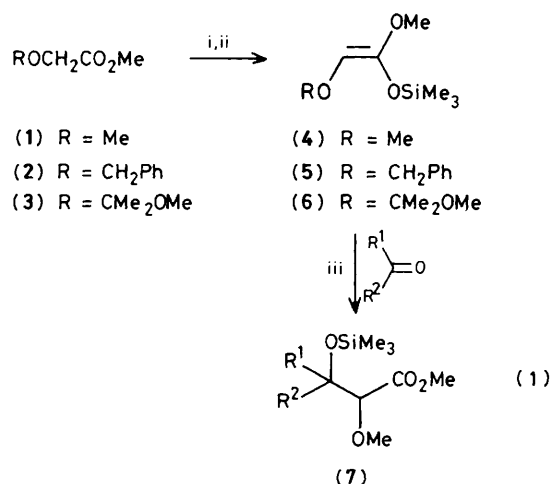
Variations of the mixed aldol condensation which employ an enol derivative of one of the carbonyl reactants have become widely used.<sup>1</sup> By contrast, the reaction of aldehydes and ketones with ketene acetals, the analogous enol derivatives of esters, has been less extensively investigated,<sup>2</sup> although acylation of silyl ketene acetals has long been known to give  $\beta$ -keto esters.<sup>3</sup> In searching for a route to  $\alpha,\beta$ -dialkoxy esters which could be used to synthesize segments of structures such as pederin<sup>4</sup> and boromycin,<sup>5</sup> we have found that (4), the silyl ketene acetal derived from methyl  $\alpha$ -methoxyacetate (1), reacts cleanly with aldehydes and ketones in the presence of zinc chloride to give  $\alpha$ -methoxy- $\beta$ -siloxy esters (7), according to equation (1).

The condensation of (4) (2 equiv.), prepared by deprotonation of (1) with lithium hexamethyldisilazide followed by quenching with trimethylsilyl chloride, with the carbonyl compound takes place in dichloromethane solution containing anhydrous zinc chloride (0.1 equiv.) at room temperature during 12–16 h. Products were isolated by dilution of the mixture with hexane, filtration, and chromatography of the residual oil on silica. Yields are given in Table 1.

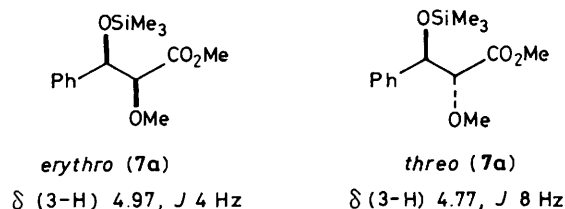
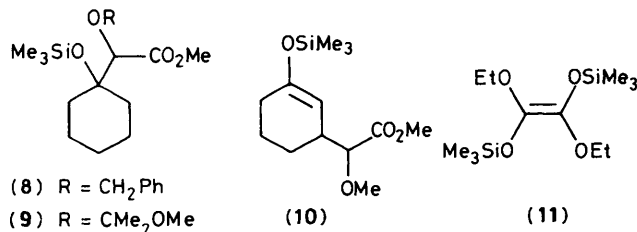
The reaction of (4) with aldehydes (7a–d) gave in all cases a mixture of diastereoisomers, with little or no stereoselectivity apparent. In one instance, that of (7a), stereoisomers were separated and *erythro* and *threo* configurations were assigned on the basis of the chemical shift of the C-3 proton and its vicinal coupling constant.<sup>6</sup>

Ketene acetals (5) and (6) were prepared from methyl

$\alpha$ -benzyloxyacetate (2) and methyl  $\alpha$ -(methoxyisopropoxy)-acetate (3) respectively. The ester (2) was obtained by displacement of methyl  $\alpha$ -bromoacetate with sodium benzyloxide and (3) was secured by treatment of methyl glycolate with 2-methoxypropene in the presence of phosphorus



Scheme 1. Reagents: i, lithium hexamethyldisilazide, ii, trimethylsilyl chloride, iii, zinc chloride.



oxychloride.<sup>5</sup> The low yield of (9) from the condensation of cyclohexanone with (6) is attributed to the acid-sensitive nature of the methoxyisopropyl substituent in this case.

When cyclohex-2-enone was treated with (4), the sole product (10) (mixture of diastereoisomers) resulted from conjugate addition, accompanied by a silyl group transfer, to give the enol ether regiospecifically. This sequence, which parallels an observation made by Reetz in the reaction of cyclohex-2-enone with (11)<sup>7</sup> has obvious potential for the attachment of carbon chains in tandem to the α and β positions of a conjugated enone.

The condensation of ketene acetals (4), (5), and (6) with aldehydes and ketones extends a previous study by Wissner,<sup>8</sup> who showed that (4) can be acylated with acid chlorides to give (transiently) α-hydroxy-β-keto acids. In a recent report, Reetz has described the condensation of the highly reactive (11) with aldehydes and ketones to give, after hydrolysis, α-keto esters.<sup>7</sup> The sequence exemplified herein complements these

**Table 1.** Products from zinc chloride-catalysed condensation of ketene acetals with aldehydes and ketones.

R <sup>1</sup> C(:O)R <sup>2</sup>	Ketene acetal	Product (Yield, %)
R <sup>1</sup> = Ph, R <sup>2</sup> = H	(4)	(7a) (75)
R <sup>1</sup> = C <sub>6</sub> H <sub>13</sub> , R <sup>2</sup> = H	(4)	(7b) (83)
R <sup>1</sup> = CHMe <sub>2</sub> , R <sup>2</sup> = H	(4)	(7c) (72)
R <sup>1</sup> = CH(Me)Et, R <sup>2</sup> = H	(4)	(7d) (71)
R <sup>1</sup> , R <sup>2</sup> = -[CH <sub>2</sub> ] <sub>5</sub> -	(4)	(7e) (85)
R <sup>1</sup> = R <sup>2</sup> = Et	(4)	(7f) (77)
R <sup>1</sup> = Ph, R <sup>2</sup> = Me	(4)	(7g) (85)
R <sup>1</sup> , R <sup>2</sup> = -[CH <sub>2</sub> ] <sub>5</sub> -	(5)	(8) (81)
R <sup>1</sup> , R <sup>2</sup> = -[CH <sub>2</sub> ] <sub>5</sub> -	(6)	(9) (36)
R <sup>1</sup> , R <sup>2</sup> = -CH=CH[CH <sub>2</sub> ] <sub>3</sub> -	(4)	(10) (70)

two processes by providing access to esters functionalized on a lower oxidation level at α and β positions.

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