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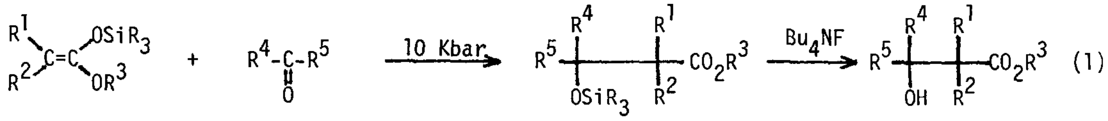
ALDOL REACTIONS, CONJUGATE ADDITIONS, AND ALKYLATION REACTIONS OF O-SILYLATED KETENE ACETALS UNDER NEUTRAL CONDITIONS[1]

Yoshinori Yamamoto,*[a] Kazuhiro Maruyama,[a] and Kiyoshi Matsumoto[b]

[a] Department of Chemistry, Faculty of Science, Kyoto University, and [b] College of Liberal Arts and Science, Kyoto University, Kyoto 606, Japan

Summary: Aldol reactions, conjugate additions, and alkylation reactions of O-silylated ketene acetals take place under neutral conditions by using a high pressure technique.

Recent publication[2] on conjugate additions of O-silylated ketene acetals to enones by using a high pressure technique has prompted us to report our own findings in this area. Aldol reactions, conjugate additions, and alkylation reactions of silyl enol ethers or silyl ketene acetals are normally carried out with acids or bases as the catalyst.[3] We have been seeking a new method which enables the reactions to take place under neutral conditions. Recently, we reported that the aldol reaction of silyl enol ethers under neutral conditions was realized by using a high pressure technique.[4] Unfortunately, however, the carbonyl compounds were limited to aromatic aldehydes, and the reaction with aliphatic aldehydes or ketones was sluggish. We now report that the neutral aldol condensations of aldehydes and ketones take place with O-silylated ketene acetals (1) by using a high pressure technique (10 Kbar)(eq 1),



1 a; R^1= H, R^2= Me, R^3= Et, R = Me

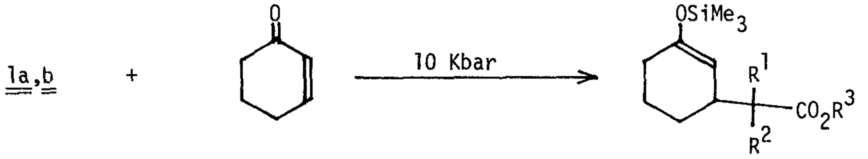
b; R^1= R^2= Me, R^3= Et, R = Me

c; R^1= R^2= H, R^3= Me, R_3 = Me_2(t-Bu)

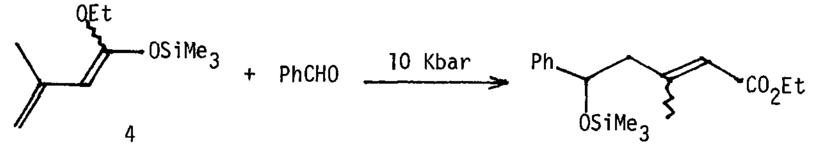
2

3

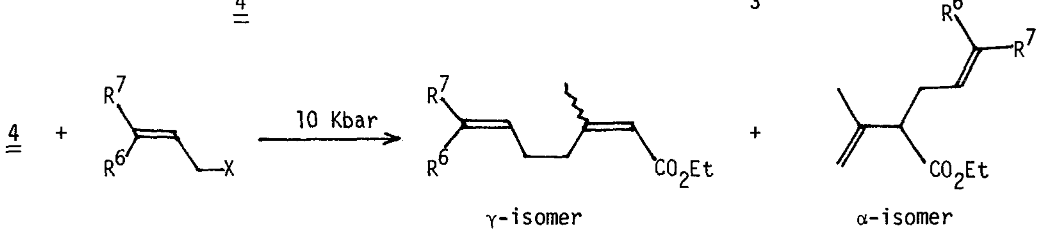
and that conjugate addition to cyclohexenone (eq 2) and the reactions of O-silyl-O-alkyl dienol ether (4) at the γ position (eqs 3 and 4) are realized through this technique.



(2)



(3)

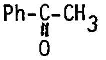
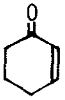
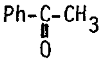
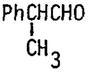
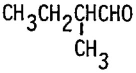
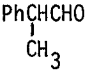
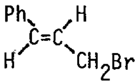
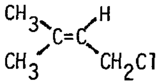


(4)

The results are summarized in Table 1. The reaction was generally very clean, and the carbonyl compounds were recovered without change when the reaction was incomplete (see Table). The reaction also proceeded in ether, but the yield of aldol products was generally higher in CH_2Cl_2 than in ether. As apparent from Table 1, the condensation of the hindered ketene acetal (1b) with acetophenone, as well as aldehydes, proceeded smoothly, giving aldol products in high yield. Unfortunately, however, the stereoselectivity was low; the threo/erythro isomers were formed in a ratio of ca. 1 : 1. The Cram/anti-Cram problem in the high pressure aldol reaction was also examined. Although the ratio of the Cram product was enhanced in the BF_3-catalyzed reaction of O-silyl ketene acetals,[5] the ratio was not so high in the high pressure reaction. The Cram product ratio in the reaction of 1c with α-phenylpropanal decreased in comparison with that in the reaction of the corresponding lithium enolate; the BF_3 catalyzed reaction[5], 15 : 1; the high pressure reaction, 2.4 : 1; the lithium enolate reaction, 2.8 : 1 (3 : 1)[5].

The regioselective γ-alkylation of silyl dienol ethers is an important problem in organic synthesis and primarily investigated by Fleming's group.[6] The high pressure reaction produced a similar regioselectivity (γ : α = ca. 80 : 20). On the other hand, the high pressure induced condensation with benzaldehyde took place at the γ-position exclusively. Since the corresponding reaction with the lithium dienolate produces 5,6-dihydro-α-pyrone

Table 1. High pressure reactions of O-silylated ketene acetals[a]

Silyl ketene acetal	Electrophile	Conditions	Yield (%)[b]	Isomer ratio[c]
				erythro/threo
1a	PhCHO	room temp., 6 d	~100	55/45
	PhCHO	50°C, 6 d	~100	56/46
	$(CH_3)_2CHCHO$	room temp., 6 d	~100	34/66
	$CH_3(CH_2)_3CHO$	room temp., 6 d	~100	50/50
	 $Ph-C(=O)-CH_3$	50°C, 6 d	85(15)[d]	55/45[e]
		room temp., 6 d	80(20)[d]	50/50[e]
1b	PhCHO	room temp., 6 d	~100	
	 $Ph-C(=O)-CH_3$	50°C, 6 d	80(20)[d]	
		50°C, 6 d	80(20)[d]	
				Cram/anti-Cram
	 $PhCH(CH_3)CHO$	50°C, 6 d	80[f]	80/20
	 $CH_3CH_2CH(CH_3)CHO$	50°C, 6 d	91[f]	64/36
1c	 $PhCH(CH_3)CHO$	50°C, 6 d	73[f]	71/29
				γ-isomer/α-isomer
4	PhCHO	50°C, 2 d	85[f]	100/-
		50°C, 2 d	80[f]	85/15
		50°C, 2 d	82[f]	81/19

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[a] In a Teflon capsule were placed the electrophile (1 mmol), O-silylated ketene acetal

(Table 1. continued)

(1.5 mmol), and CH_2Cl_2 (ca. 1 ml). High pressure experiments were performed in a stainless steel die and compressed via a piston. After the period indicated in Table 1, the pressure was released and the solvent removed in vacuo. The product (2) was directly analyzed by ^1H NMR spectroscopy. [b] By ^1H NMR spectroscopy,except where otherwise indicated. [c] The ratio of erythro/threo isomers was determined by ^1H NMR spectroscopy of the hydrolysis product (3). The other ratios were determined by GLPC and/or HPLC. [d] (Recovery of ketones). [e] The ratio of two isomers. The relative configuration was not determined. [f] Isolated yield.

derivative,[7] the high pressure aldol reaction may be useful for the synthesis of δ-hydroxy-α,β-unsaturated carbonyl compounds.

References and Notes.

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