Pergamon

Tetrahedron Letters, Vol. 38, No. 32, pp. 5631-5634, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01267-7

High Pressure Induced Mukaiyama Type Aldol Reaction of bis Trimethylsilyl Ketene Acetals

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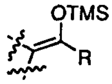
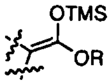
Abstract: The Mukaiyama type aldol reaction of bis trimethylsilyl ketene acetals 3 was investigated under high pressure conditions. Silyl aldols 5 were obtained with a *syn* stereoselectivity, significantly correlated upon the steric bulk of R substituent. In the case of unsaturated bis trimethylsilyl ketene acetal 4, a pressure dependance of the regioselectivity was observed, the desired linear adducts 8 being formed at lower pressure. © 1997 Elsevier Science Ltd.

The Mukaiyama aldol reaction of silyl enol ethers **1** and silyl ketene acetals **2** is recognized as an important reaction in modern synthetic chemistry, normally carried out in the presence of acids or bases as catalyst.[1] The success of this procedure hinges on the fact that the reactions are carried out in such a way that the newly formed aldol is trapped as a neutral silyl compound and is thus protected from wasteful side reactions, particularly from dissociation into the free carbonyl components which could in turn undergo non selective condensation. One of us has established that *bis* trimethylsilyl ketene acetals **3** reacted efficiently and stereoselectively under these conditions.[2a]



1



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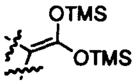
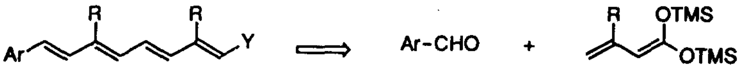


3

In connection with our work on the total synthesis of retinoids,[3] we were interested in the high pressure induced aldol condensation of *bis* silyl ketene acetals **4**, allowing a rapid assembly of the polyene units of these biomolecules.



Y = COOTMS, COOH
R = H, alkyl

4

Indeed, Yamamoto[4] reported the high pressure activation of such reaction, using silyl enol ethers **1**. Three important points were observed: (1) the reaction proceeds without catalyst even at room temperature; (2) the

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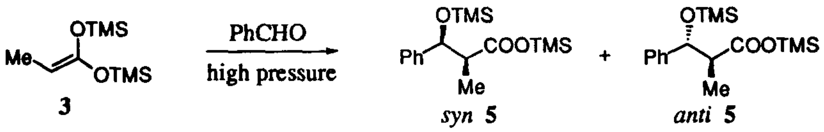
adducts do not isomerize under the reaction conditions; (3) the stereoselectivity of *syn/anti* aldol reverses in comparison with that of the corresponding titanium tetrachloride catalyzed Mukaiyama condensation. Silyl ketene acetals **2** are also converted into ß-silyloxyesters under these conditions, although *without stereoselectivity*.[5]

In a preliminary study, the reactivity of *bis* silyl ketene acetals **3** towards aromatic aldehydes was tested, in order to investigate the role of the additional silyl substituent on the diastereoselectivity. These *bis* silyl ketene acetals **3** were synthesized from the corresponding carboxylic acids according to known procedures.[2b,6] Methyl substituted *bis* silyl ketene acetal **3** reacted with benzaldehyde,[7] furnishing a mixture of *syn* and *anti* silyl aldols **5** in good yields (Table 1). The reaction was very clean yielding only aldol products, the unreacted starting materials being removed under vacuum.

Table 1: High Pressure Mediated Condensation of 1,1-Bis(trimethylsiloxy)-1-propene **3** with Benzaldehyde



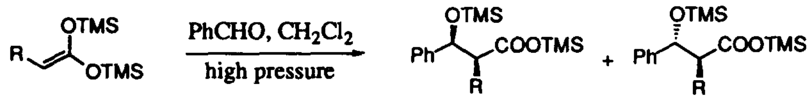
Entry	Solvent	Conditions	*syn* 5 :	*anti* 5	Yield %
1	CH_2Cl_2	5 kbar, 23° C, 6 days	65	35	78
2	CH_2Cl_2	5 kbar, 64° C, 5 days	62	38	86
3	CH_2Cl_2	10 kbar, 23° C, 5 days	63	37	75
4	CH_2Cl_2	14 kbar, 64° C, 4 days	63	37	85
5	THF	14 kbar, 64° C, 2 days	64	36	86
6	none	14 kbar, 64° C, 2 days	67	33	75

A relatively modest *syn* diastereoselectivity was obtained, regardless the temperature (20 to 65 °C, entries 1 and 2) and the solvent (entries 4,5 and 6) in a range of pressure from 5 to 14 kbar. Increasing the pressure or the temperature resulted in an increase of the yield of bis silyl aldols **5**.

The diastereoselectivity of crude reaction mixtures was deduced from ^1H NMR spectra (deuterobenzene), through integration of H_β doublets in silyl aldols **5**. No isomerization of the adducts was observed under high pressure conditions as the reflect of a positive activation volume for the retroaldol reaction. The *syn* and *anti* relative configuration in silyl aldols **5** were established after hydrolysis into known ß-hydroxyacids[2b,6] and by comparison with the corresponding compounds **5** obtained through bis silylation (LiHDMS, THF, -40 °C to RT, 5 min then TMSCl, -40 °C to RT, 15 min) of known pure *syn* and *anti* ß-hydroxyacids.

This *syn* diastereoselectivity was shown to be significantly correlated upon the steric bulk of R substituent in the bis silyl ketene acetals 3 (Table 2).

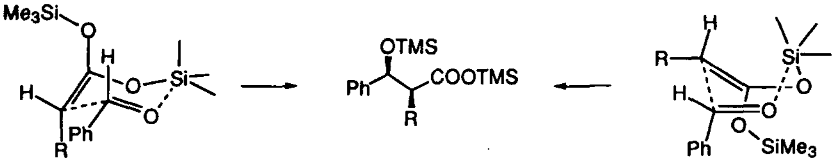
Table 2: High Pressure Mediated Condensation of Substituted bis Silyl Ketene Acetals 3 with Benzaldehyde



3 *syn* **5** *anti* **5**

Entry	R	Conditions	*syn* **5**	: *anti* **5**	Yield %
1	Me	5 kbar, 23° C, 6 d	65	35	78
2	Me	5 kbar, 64 °C, 5 d	62	38	86
3	Me	14 kbar, 64 °C, 4 d	63	37	85
4	Et	5 kbar, 23° C, 6 d	80	20	90
5	Et	5 kbar, 64 °C, 3 d	67	33	80
6	Et	14 kbar, 23 °C, 2 d	80	20	85
7	Et	14 kbar, 64 °C, 4 d	68	32	83
8	*i* Pr	8 kbar, 64° C, 3 d	84	16	85
9	*i* Pr	14 kbar, 64 °C, 2 d	80	20	81

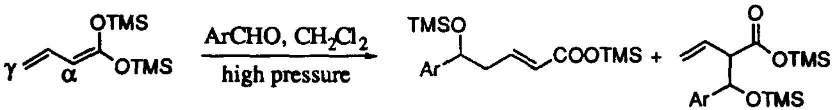
Although allowing a shorter reaction time, thermal conditions (64 °C) resulted in a slight decrease in stereoselectivity (entries 1 / 2, 4 / 5 and 6 / 7) while increasing the pressure has almost no effect. Thus, replacement of an O-alkyl group in silyl ketene acetals 2 by a O-silyl group in bis silyl ketene acetals 3 resulted in a noticeable increase in stereoselectivity.[5] The preference for *syn* bis silyl aldols 5 may be attributed to reaction pathway involving *compact* chair-like 6 or boat-like 7 transition states[4,8] in which steric interaction between the R substituent of bis silyl ketene acetals 3 and the phenyl group of benzaldehyde are minimized.



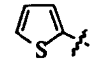
6 *syn* **5** **7**

We further studied the condensation of unsaturated bis silyl ketene acetal 4 (R = H) as a model in the synthesis of retinoid compounds. As shown in table 3, the differentiation of α and γ carbon centers in **4** occured to be dependant on the reaction pressure.

Table 3: High Pressure Induced Condensation of Unsaturated Silyl Ketene Acetal **4** with Aromatic Aldehydes



4 γ adduct **8** α adduct **9**

Entry	Ar	Conditions	γ Adduct **8** :	α Adduct **9**	Yield %
1	Ph	17 kbar, 65° C, 3 days	25	75	68
2	Ph	12 kbar, 65° C, 3 days	35	65	51
3	Ph	5 kbar, 65° C, 6 days	83	17	57
4	Ph	2 kbar, 65° C, 3 days	88	12	41
5		5 kbar, 23° C, 10 days	92	8	63

The desired γ adducts **8** were the major compound at 5 kbar while, at 17 kbar, the reverse preference was observed, the α adduct **9** being predominant. This pressure dependance of the regioselectivity may imply that the transition state leading to the linear aldol **8** is less compact than the one implied in the formation of branched aldol **9**. Work is in progress to extend the scope of this high pressure induced Mukaiyama type reaction.

Acknowledgment: We are grateful to Professor Jean d'Angelo for support in high pressure chemistry.

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7. General procedure: a mixture of bis trimethylsilyl ketene acetal and electrophile (1.5 eq) in a solvent (0.5 mL/mmol) was introduced by means of a syringe into a 1-, 3- or 4-mL Pyrex glass cell (1.5 mm wall thickness) fitted with a 1 mm inner diameter capillary orifice. Cells are immersed in hexane, used as piezotransmitter liquid, in a piston-cylinder apparatus and pressurized. After depressurization, a sample was analyzed by ^{1}H NMR to determine the conversion of bis silyl ketene acetals. The solvent and unreacted materials were removed under vacuum to yield pure bis silyl aldols.
8. See in relation: Isaacs, N. S.; Marshall, R. L.; Young, D. J. *Tetrahedron Lett.* **1992**, *33*, 3023-3024.

(*Received in France* 26 *March* 1997; *accepted* 19 *June* 1997)