Pergamon

Tetrahedron Letters 39 (1998) 2585–2588

TETRAHEDRON LETTERS

Uncatalyzed Aldol Reaction Using a Dimethylsilyl Enolate and α-Dimethylsilyl Ester in *N,N*-Dimethylformamide[1]

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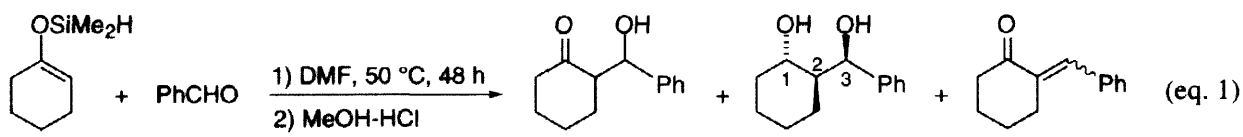
Received 22 December 1997; revised 21 January 1998; accepted 23 January 1998

Abstract: Dimethylsilyl enolates and α-dimethylsilyl esters reacted with aldehydes in *N,N*-dimethylformamide without an activator to give aldol adducts in moderate to good yields. Under the same conditions, the corresponding trimethylsilyl derivatives exhibited lower reactivities toward the aldol reaction.

The Mukaiyama crossed-aldol reaction is a powerful and selective method for the construction of carbon-carbon bonds.[2] This well-established transformation involves the reaction of silyl enolates, particularly trimethylsilyl (TMS) enolates, with carbonyl compounds usually in the presence of an activator such as a Lewis acid or fluoride ion. Recently, it has turned out that the elaboration of the substituent on silicon allows an uncatalyzed aldol reaction.[3,4] Myers and Denmark *et. al.* have reported that enoxysilacyclobutanes readily add to aldehydes without an activator, and their high reactivities are due to the increased Lewis acidity of the silicon bearing an angle strain.[3a-d] In this context, we envisioned that introduction of a less sterically demanding substituent such as hydrogen on silicon might enhance the Lewis acidity of the silicon center, making silyl enolates reactive enough to cause an aldol reaction even in the absence of an activator. As the result of investigation based on this working hypothesis, it was found that the dimethylsilyl (DMS) enolates **1** and α-DMS ester **7** added to aldehydes in *N,N*-dimethylformamide (DMF) without a catalyst. We herein report the details of this uncatalyzed aldol reaction.



1a **2a**, 79% **3a**, 14% **4a**, 4% (eq. 1)

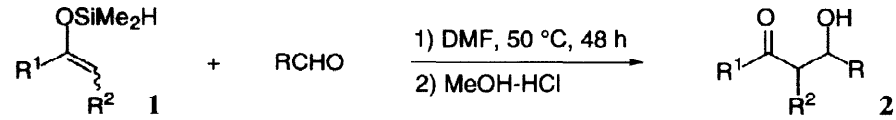
Initially, the reaction of the DMS enolate **1a** (1.1 mmol),[5] derived from cyclohexanone, with benzaldehyde (1.0 mmol) was conducted in various solvents for 12-18 h at room temperature. The use of DMF gave the aldol adduct **2a** in 24% yield after desilylation with HCl-MeOH. Other solvents (toluene, dichloromethane, tetrahydrofuran, acetonitrile, methanol, dimethylsulfoxide, and hexamethylphosphoramide[6]) were less effective in promoting the aldol reaction. An increased amount of **1a** and an elevated reaction temperature also work to improve the yield of **2a**. Thus, treatment of **1a** (2.0 mmol) with benzaldehyde (1.0

0040-4039/98/$19.00
PII: S0040-4039(98)00275-5

mmol) in DMF (2 mL) for 48 h at 50 °C followed by desilylation with HCl-MeOH provided **2a** in 79% yield (*syn* : *anti* = 58 : 42) along with the diol **3a** (14%, 1,2-*anti*-2,3-*syn*-isomer : other isomers = >30 : 1) and α,β-unsaturated ketone **4a** (4%, eq. 1). The formation of **3a** can be explained by intramolecular hydrosilylation of the carbonyl group in the DMS ether of *syn*-**2a**.[6] Under the same conditions, the TMS enolate of cyclohexanone also reacted with benzaldehyde, although the yield of **2a** dropped to 38% (*syn* : *anti* = 71 : 29).

Next, we examined the applicability of the present uncatalyzed aldol reaction. The results are summarized in Table 1. Not only aromatic aldehydes but also less bulky aliphatic aldehydes such as 3-phenylpropanal and butanal, which easily cause self-condensation in basic or acidic media, underwent the aldol reaction with **1a-c** in good yields. In contrast, no adducts were observed in the reactions of pivalaldehyde and ketones. It was also revealed that the DMS enolate **1d**, derived from acetophenone, was less reactive than **1a-c**.

Table 1. Reactions of Dimethylsilyl Enolates with Aldehydes[a]



Entry	Silyl Enolate R¹	Silyl Enolate R²	Aldehyde R	Yield / % (*syn* : *anti*[b])
1	$(CH_2)_4$ (**1a**)		Ph	79 (58 : 42)
2[c]	**1a**		*p*-$O_2NC_6H_4$	66 (60 : 40)
3[d]	**1a**		(*E*)-PhCH=CH	60 (42 : 58)
4	**1a**		$Ph(CH_2)_2$	70 (37 : 63)
5	**1a**		Pr	67 (34 : 66)
6	**1a**		*c*-C_6H_{11}	50 (27 : 73)
7	**1a**		*i*-Pr	24 (18 : 82)
8	**1a**		*t*-Bu	0
9	Et	Me (**1b**)[e]	Ph	82 (66 : 34)
10	**1b**		$Ph(CH_2)_2$	77 (57 : 43)
11	Ph	Me (**1c**)[f]	Ph	81 (71 : 29)
12	**1c**		$Ph(CH_2)_2$	57 (66 : 34)
13	Ph	H (**1d**)	Ph	52
14	**1d**		$Ph(CH_2)_2$	25

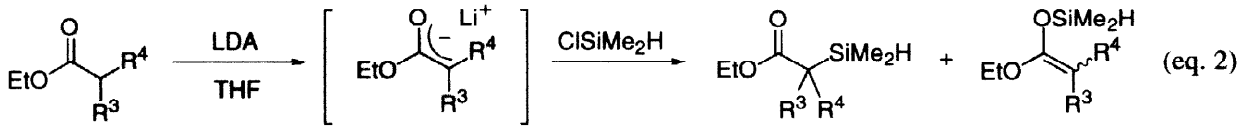
[a]All reactions were performed with a silyl enolate (2.0 mmol) and an aldehyde (1.0 mmol) in DMF (5 mL) at 50 °C for 48 h unless otherwise noted. The crude product was treated with 2 M HCl aq. (2 mL) in MeOH (5 mL) at rt for 15 min. [b]Determined by ^{1}H NMR analysis of the isolated product. [c]The reaction time is 25 h. [d]Desilylation of the crude product was carried out with HCl-MeCN instead of HCl-MeOH. [e]*E*:*Z* = 2:1. [f]*E*:*Z* = <1:30

Judging from the stereochemical outcome of the reaction of **1a-c**, contrary to our initial expectation, the present aldol reaction would not proceed *via* a cyclic transition state organized by the Lewis acidity of a tetra- or penta-coordinated silicon, which promises stereospecific conversion of silyl enolates.[3] The critical solvent effect implies that the coordination of DMF to silicon enhances the nucleophilicity of **1** to induce the aldol reaction *via* an open transition state.[2b,7,8] DMF seems to play a similar role on the fluoride ion catalyst used in the reaction of silyl enolate with aldehydes.[9] The observed difference in reactivity between DMS- and TMS-substituted compounds can be explained by the ease of the DMF coordination.

For further extension of the present reaction, the synthesis of the DMS ketene acetals **8** was attempted. However, treatment of the lithium enolate **6a**, generated by the deprotonation of ethyl acetate (**5a**), with chlorodimethylsilane (DMSCl) did not give the expected ketene silyl acetal **8a** by *O*-silylation but the α-silyl

esters **7a** by *C*-silylation (eq. 2). The enolate **6b**, derived from ethyl propanoate (**5b**), also reacted with DMSCl at the *C*-terminus, while the enolate **6c** from ethyl isobutyrate (**5c**) underwent both *O*- and *C*-silylation to give a 42:58 mixture of **7c**[10] and **8c**. These results stand in marked contrast to the exclusive formation of ketene silyl acetals in the reaction of lithium enolates with trimethylsilyl chloride.[11] The regioselectivity observed with DMSCl is similar to that with chloromethyldiphenylsilane, which also effects *C*-silylation of **6a** and **6b**.[12,13] DMSCl, however, has higher *C*-silylation ability, because **6c** undergoes only *O*-silylation with chloromethyldiphenysilane unlike the present results with DMSCl.

To our surprise, these α-silyl esters **7** as well as **1** react with various aldehydes in DMF with no catalyst, affording the β-hydroxyesters **9** in moderate to good yields (Table 2). Ethyl trimethylsilylacetate (Me_3Si-CH_2CO_2Et, **10**) also served as an enolate equivalent in DMF, although the reactivity is lower than that of **7a**. For example, the reaction of **7a** with benzaldehyde gave the aldol adduct **9a** ($R^3 = R^4 = H$, R = Ph) in 81% yield (entry 1), while the use of **10** resulted in 44% yield. When aliphatic aldehydes bearing α-hydrogens were employed, the aldol reaction of **7** proceeded without self-condensation of the aldehydes in contrast to the fluoride ion-catalyzed reaction of **10**.[14]



5a: R^3, R^4 = H
5b: R^3 = H, R^4 = Me
5c: R^3, R^4 = Me

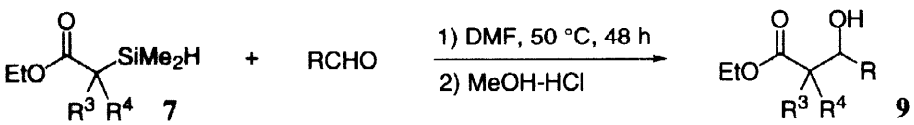
6

7a, 66%
7b, 64%
7c + **8c**, 55% (**7c** : **8c** = 42 : 58)

7

8

Table 2. Reactions of α-Dimethylsilyl Esters with Aldehydes[a]



7 **9**

Entry	α-Silyl Ester R^3	α-Silyl Ester R^4	Aldehyde R	Yield / %
1	H	H (**7a**)	Ph	81
2	**7a**		*p*-$O_2NC_6H_4$	75
3	**7a**		(*E*)-PhCH=CH	67
4	**7a**		$Ph(CH_2)_2$	58
5	**7a**		Pr	53
6	**7a**		*i*-Pr	39
7	H	Me (**7b**)	Ph	87 (68 : 32)
8	**7b**		$Ph(CH_2)_2$	56 (60 : 40)
9	Me	Me (**7c**)	Ph	93
10	**7c**		$Ph(CH_2)_2$	65

[a,b]See footnotes a and b in Table 1.

In conclusion, we have demonstrated that the introduction of hydrogen on silicon enhances the reactivities of silyl enolates and α-silyl esters. We are now studying the reactions of **1** and **7** with imines for the highly stereoselective synthesis of β-amino ketones. The results will be reported in due course.

Acknowledgments: Financial support for our work is provided by Grants-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Japan, Teikoku Chemical Industries Inc., and Pfizer

Pharmaceuticals Inc. We thank Dow Corning Toray Silicone Co. Ltd., Chisso Co. Ltd., and Shin-Etsu Chemical Co. Ltd. for gifts of organosilicon compounds.

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