HIGHLY COORDINATE ORGANOSILICON COMPOUNDS IN SYNTHESIS: NEW ENTRY TO S,N-ACETALS BY SELECTIVE REDUCTION OF ALKYLTHIOMETHYLENIMINIUM SALTS BY USE OF TRIMETHOXYSILANE AND DILITHIUM 2,3-BUTANDIOLATE¹

Yoshinori Tominaga, Yoshiki Matsuoka, Hisashi Hayashida, Shinya Kohra, and Akira Hosomi*

Faculty of Pharmaceutical Sciences, Nagasaki University, Nagasaki 852, Japan

Summary: Reduction of alkylthiomethyleniminium iodides proceeds smoothly by use of trimethoxysilane and dilithium 2,3-butandiolate in tetrahydrofuran at $0^{\circ}C$ to give the corresponding S,N-acetals selectively in high yield.

Much attention has been directed to synthetic chemistry by use of various α, α -diheteroatom-substituted alkanes (R¹R²CXY; X, Y = 0, N, S, halogen). Among them, S,N-acetals² as well as O,O-acetals,³ O,N-acetals,⁴ O,S-acetals,⁵ N, N-acetals,⁶ and S,S-acetals⁷ are one of the most useful and important intermediates in organic synthesis, in particular, from standpoint of both protecting groups and active reagents, and are of interest in their biological activities.⁸ Therefore efficient synthetic methods are highly desirable.⁹ Previously we reported that carbonyl compounds such as aldehydes and ketones were conveniently reduced with pentacoordinate hydridosiliconate derived from trialkoxysilane and alkali metal salt of alcohol in highly chemo- and stereoselective modes.¹⁰ In the extension of the studies on highly coordinate silicon compounds in synthesis,¹¹ we have found that alkylthiomethyleniminium salts (1) can be readily reduced by use of trimethoxysilane (2) and dilithium 2,3-butandiolate (4) under mild conditions to afford S,N-acetals (3) selectively (eq. 1), whereas reduction with sodium borohydride¹² and lithium aluminum hydride proceeds to give the corresponding tertiary amines (5) or a mixture of **3** and **5**. Since starting materials (1) are readily available from thioamides and alkyl iodide,¹³ the new method should find a wide application.

$$\begin{array}{c} \text{HSi(OMe)}_{3}(2) \ / \ (\text{LiOCHMe})_{2}(4) \\ \text{R}^{1}-\text{C}=\text{N}^{+}\text{R}^{2}\text{R}^{3} & \longrightarrow \text{R}^{1}-\text{CH}-\text{NR}^{2}\text{R}^{3} \ (+ \ \text{R}^{1}\text{CH}_{2}\text{NR}^{2}\text{R}^{3}) \ (1) \\ \text{I}_{SR}^{4} \ \text{I}^{-} & \text{THF, 0°C} & \text{I}_{SR}^{4} \end{array}$$

Representative results are listed in Table 1. A typical experimental

procedure is given for the preparation of benzaldehyde S,N-acetal (3a) from iminium salt (1a). Treatment of methylthiomethyleniminium iodides (1a) (1 mmol), readily prepared by the reaction of phenylthiomorpholide (6a) with methyl iodide, with trimethoxysilane (2) (1.5 mmol) in the presence of dilithium 2,3-butandiolate (4a) (1 mmol) in tetrahydrofuran (10 ml) at 0° C for 4 h afforded selectively the corresponding S,N-acetal (3a) in 88% yield, after hydrolysis with aqueous NaHCO3, extraction with CHCl3, followed by the usual anhydrous workup. The S,N-acetal (3a) was pure by GLC and NMR analyses. Except for reduction of the salt (1h) of N,N-dimethylthioamide, no amine (5), derived by further reduction, was found in the reaction mixture, irrespective of careful examinations and spectroscopic and GLC analyses (entry 12). We examined and found bidentate dilithium diolates (4), in particular, simple and readily available dilithium 2,3-butandiolate (4a), to be most effective and suitable among most commonly used various alkoxides. Thus when lithium ethanolate (4c) was used as an activator in the reaction of p-anisylmethylthiomethylenemorpholinium iodide (1b), the yield of S,N-acetal (3b) did not raise up more than 30%. However, with 4a, 3b was obtained in 98% yield.

When 1 was treated with lithium aluminum hydride under the similar conditions, only tertiary amine $(R^1CH_2NR^2R^3, 5)$ was obtained in quantitative yield.¹⁴ Moreover, in contrast with the results of other iminium salts in the previous papers,¹² reduction with sodium borohydride in ethanol took place in non-selective way, giving a mixture of S,N-acetal (3) and tertiary amine (5) in good total yields.

The some significant features of the present reduction by using pentacoordinate hydridosiliconate are as follows: (1) Various aromatic and aliphatic substrates (1) including heteroaromatic derivative can enter the reaction to give the corresponding S,N-acetals (3) under mild conditions. (2) Reduction occurs with almost complete product selectivity to give 3, not amine (5), in all cases, with an exception in the case of $NR^2R^3 = NMe_2$, although reduction of 1 with sodium borohydride gave a mixture of 3 and 5 in almost all cases and, with lithium aluminum hydride, 5 was the predominant product. (3) Chemoselective reduction takes place by use of pentacoordinate hydridosiliconate.

In addition, the synthetic utility of the present reaction was mostly displayed by the ready accessibility of starting materials, easy manipulation of the conversion, and mild conditions of the reduction.

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Entry	Imin	nium Salt	(1)	Conditions ^{a)}	Yield of 3 ^{b)}
	R ¹	NR ² R ³	R ⁴		
1	p-Me2NC6H4	NO	Me (1c)	A, 3 h	74
2	$p-MeOC_6^{H}_4$	NO	Me (1b)	A, 4 h	98
3		1b		B, 16 h	36
4		1b		C, 3 h	28
5	p-MeOC ₆ H ₄	NO	Et (1d)	A, 3 h	91
6	p-MeOC ₆ H ₄	N	Me (1e)	A, 4 h	82
7	o-MeOC ₆ H ₄	NO	Me (1f)	A, 2 h	81
8		1f		B, 3 h	57
9	Ph	NO	Me (1a)	A, 4 h	88
10		1a		B, 4 h	66
11	Ph	N	Me (1g)	A, 4 h	66
12	Ph	NMe2	Me (1h)	A, 3 h	47 ^c)
13	Ph	NO	Et (1i)	A, 4 h	83
14	p-ClC ₆ H ₄	NO	Me (1j)	A, 2 h	76
15	p-ClC ₆ H ₄	N	Me (1k)	A, 4 h	83
16	p-CNC6H4	NO	Me (11)	A, 4 h	74
17	p-NO2C6H4	NO	Me (1m)	A, 5 h	79 ^d)
18	2-Thienyl	NO	Me (1n)	A, 17 h	82
19	n-Bu	NO	Me (1o)	A, 3 h	52

Table 1. Reduction of alkylthiomethyleniminium iodides (1) with trimethoxysilane (2) and lithium alkoxide (4)

(Captions of the table)

a) All reactions were carried out in THF at 0° C in the ratios of 1 : 2 : 4 = 1: 1.5 : 1. Condition A: (LiOCHMe)₂ (4a), B: LiOCH₂CH₂NMe₂ (4b), C: LiOEt (4c). b) Satisfactory spectroscopic data were obtained for all 3. The yield was determined by NMR after isolation. The corresponding aldehydes were obtained quantitatively after hydrolysis or TLC treatment. c) N,N-Dimethylbenzylamine (5a) was obtained in 52% yield. d) In dioxane.

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