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One-Pot Synthesis of α,β-Unsaturated Ketones from *tert*-Butyldimethylsilyldibromomethane and Two Different Aldehydes

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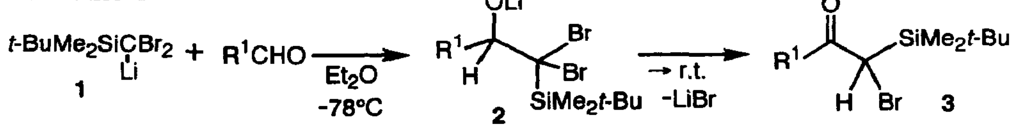
Abstract: An addition of benzaldehyde to an ethereal solution of *tert*-butyldimethylsilyldibromomethyllithium provided α-bromo-α-silyl ketone. Further treatment of the α-bromo-α-silyl ketone with butyllithium afforded enolate which provided β-hydroxy-α-silyl ketone upon treatment with aldehyde in ether. The enolate gave α,β-unsaturated ketone or monosilyl ether of 2-acyl-1,3-diol in THF instead of ether.

We have reported[1] that treatment of a THF solution of *tert*-butyldimethylsilyldihalomethyllithium with aldehyde (R^1CHO) followed by an addition of second aldehyde (R^2CHO) and HMPA gave the corresponding monosilyl ether of 1,3-diol ($R^1CH(OSiMe_2\text{-}t\text{-}Bu)CX_2CH(OH)R^2$). The use of ether instead of THF as a solvent has proved to change the reaction pathway dramatically and treatment of *tert*-butyldimethylsilyldibromomethyllithium (**1**) with aldehyde (R^1CHO) gave α-bromo-α-silyl ketone ($R^1COCHBrSiMe_2\text{-}t\text{-}Bu$). We wish to report here a synthetic method for formation of (*E*)-α,β-unsaturated ketones and 2-acyl-1,3-diol monosilyl ether in one-pot based on organosilicon chemistry which involves 1,2-migration of hydrogen followed by 1,3-rearrangement of silicon.

Treatment of *tert*-butyldimethylsilyldibromomethyllithium (**1**), derived from $t\text{-}BuMe_2SiCHBr_2$ and lithium diisopropylamide, with benzaldehyde in ether at −78 °C provided α-bromo-α-silyl ketone **3a**[2] in 76% yield upon warming the reaction mixture to room temperature. The representative results are shown in Scheme 1. The reaction obviously involves initial formation of adducts **2** followed by 1,2-migration of hydrogen[3,4] giving α-bromo-α-silyl ketones.

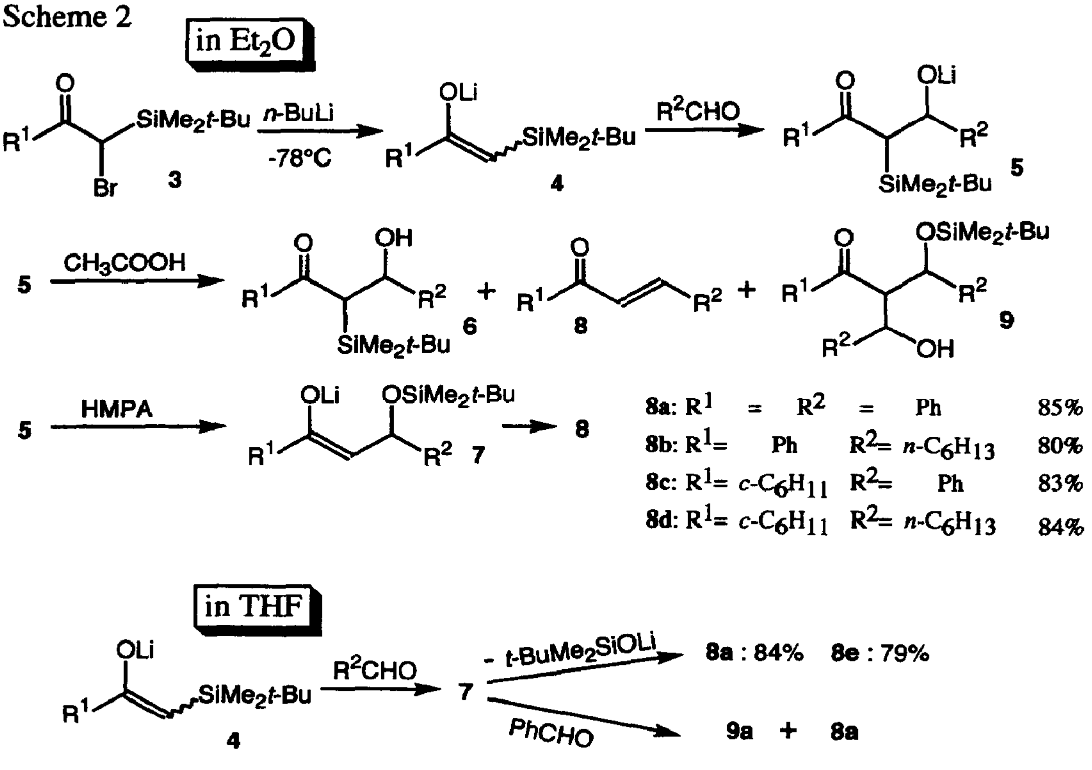
Scheme 1



R^1 = Ph	**3a** : 76%	R^1 = $c\text{-}C_6H_{11}$	**3b** : 72%
R^1 = PhCH=CH	**3c** : 62%	R^1 = $t\text{-}C_4H_9$	**3d** : 49%
R^1 = $n\text{-}C_6H_{13}$	**3e** : 42%		

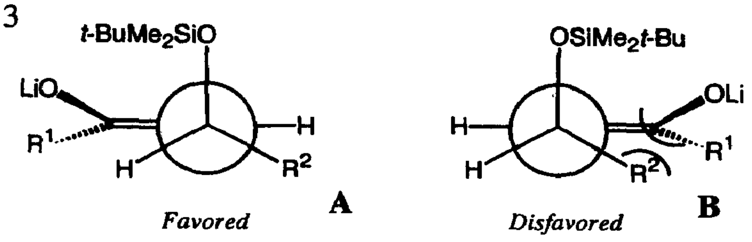
An addition of butyllithium to an ether or a THF solution of α-bromo-α-silyl ketone **3** at −78 °C caused lithium-bromine exchange to afford an enolate **4**[5] which was quenched with diluted hydrochloric acid to give α-silyl ketone ($R^1COCH_2SiMe_2$-*t*-Bu) quantitatively. Again, reaction solvent played a critical role in the reaction of enolate **4** with aldehydes (Scheme 2). The enolate **4** was treated with aldehyde in ether and quenching the reaction with acetic acid yielded *β*-hydroxy-*α*-silyl ketone **6**, which was contaminated by (*E*)-α,β-unsaturated ketone **8** and monosilyl ether of 2-acyl-1,3-diol **9** (**6**:**8**:**9** = 7:1:1).[6] An addition of HMPA to **5** before quenching provided only (*E*)-α,β-unsaturated ketone **8** with high stereoselectivity in good yields. Four examples are shown below. In contrast, the reaction of enolate **4** in THF with aldehyde (1.1 equiv) provided (*E*)-α,β-unsaturated ketone **8** directly without an addition of HMPA. For instance, the enolate **4a** (R^1 = Ph) or **4b** ($R^1 = c\text{-}C_6H_{11}$) gave α,β-unsaturated ketone **8a** or **8e** ($R^2 = n\text{-}C_4H_9$) in 84% or 79% yield, respectively, upon treatment with benzaldehyde or pentanal. An addition of an excess of PhCHO to **4a** gave monosilyl ether of 2-acyl-1,3-diol **9a** ($R^1 = R^2$ = Ph),[7] derived from two molecules of aldehyde, in addition to α,β-unsaturated ketone **8a**. The yield of **9a** increased with increase of an amount of benzaldehyde employed and the use of four molar equivalents of benzaldehyde per one mol of enolate gave a mixture of **8a** and **9a** in 23% and 73% yields, respectively. Thus, the 1,3-rearrangement[8] of silyl group (**5**→**7**) takes place readily in THF and an addition of **7** to the second molecule of aldehyde competes with elimination of *t*-BuMe$_2$SiOLi to give α,β-unsaturated ketone. Stereoselective formation of (*E*)-α,β-unsaturated ketone could be explained by relative stabilities of the rotamer A of the intermediate enolate **7**, which is more stable than B (Scheme 3).[8]

Scheme 2



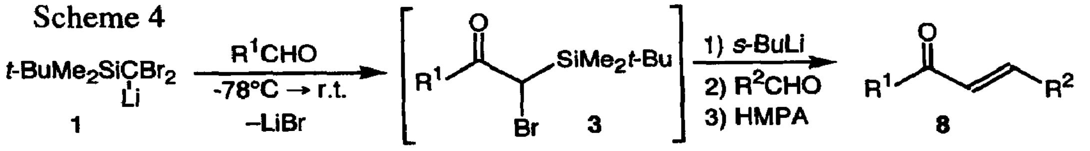
8a: R^1 =	R^2 =	Ph	85%
8b: R^1= Ph	R^2=	$n\text{-}C_6H_{13}$	80%
8c: R^1= $c\text{-}C_6H_{11}$	R^2=	Ph	83%
8d: R^1= $c\text{-}C_6H_{11}$	R^2=	$n\text{-}C_6H_{13}$	84%

Scheme 3



Then we turned out our attention toward one-pot synthesis of α,β-unsaturated ketone starting from *tert*-butyldimethylsilyldibromomethyllithium (**1**). An addition of aldehyde to ethereal solution of **1** gave α-bromo-α-silyl ketone which was further converted into enolate with base and then treated with second aldehyde and successively with HMPA to afford α,β-unsaturated ketone. A typical experiment is as follows. Benzaldehyde (1.2 mmol) was added to **1** (1.0 mmol) in ether at –78 °C and the reaction mixture was warmed up to room temperature over 10 h to provide **3a**. The reaction mixture was cooled to –78 °C and *sec*-butyllithium (2.5 mmol)[9] was added. After the reaction mixture was stirred at –78 °C for 1 h, the second aldehyde (PhCHO or heptanal, 3.0 mmol) was added. The mixture was stirred for another 30 min and then HMPA (2.5 mmol) was added. The resulting mixture was stirred at –78 °C for 1 h, then at 0 °C for 10 min and poured into sat. ammonium chloride. Extractive workup followed by silica-gel column chromatography gave α,β-unsaturated ketone **8a** or **8b** in 59% or 57% yield, respectively (Scheme 4).[10]

Scheme 4



8a : 59% **8b** : 57% **8c** : 56% **8d** : 53%

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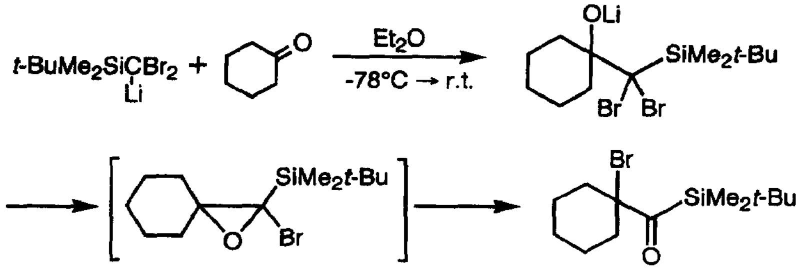
2. **3a**: Mp 55.0-56.0 °C; IR (neat before crystallization) 2952, 2926, 2856, 1676, 1465, 1448, 1261, 832, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ -0.01 (s, 3H), 0.24 (s, 3H), 0.95 (s, 9H), 4.90 (s, 1H), 7.40–7.65 (m, 3H), 7.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ -6.11, 5.67, 17.96, 27.03, 35.73, 128.49, 128.77, 133.37, 136.61, 196.32. Found: C, 53.37; H, 6.79%. Calcd for $C_{14}H_{21}OBrSi$: C, 53.67; H, 6.76%.
3. Decomposition of β-oxido carbenoid to a lithium enolate has been reported. Taguchi, H.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1972**, 4661; idem *J. Am. Chem. Soc.* **1974**, *96*, 6510; idem *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1592; Villieras, J.; Bacquet, C.; Normant, J. F. *J. Organomet. Chem.* **1972**, *40*, C1; idem *Bull. Soc. Chim. Fr.* **1975**, 1797; Köbrich, G.; Grosser, J. *Tetrahedron Lett.* **1972**, 4117.
4. The use of ketone such as cyclohexanone in place of aldehyde gave α-bromoacylsilane. The reaction might proceed via silyl epoxide formation followed by rearrangement. This was confirmed by the

following experiment. Treatment of 1-bromo-1-trimethylsilyl-1-octene with m-chloroperoxybenzoic acid afforded α-bromoacylsilane (n-$C_6H_{13}CHBrCOSiMe_3$) in 50% yield. For the preparation of α-haloacylsilanes, see Kuwajima, I.; Abe, T.; Minami, N. *Chem. Lett.* **1976**, 993; Sato, T.; Abe, T.; Kuwajima, I. *Tetrahedron Lett.* **1978**, 259; Page, P. C. B.; Rosenthal, S. *Tetrahedron* **1990**, *46*, 2573; Hewkin, C. T.; Jackson, R. F. W. *J. Chem. Soc. Perkin Trans. I*, **1991**, 3103.



5. A regioselective enolate formation from trimethylsilylmethyl ketones has been reported. Matsuda, I.; Okada, H.; Sato, S.; Izumi, Y. *Tetrahedron Lett.* **1984**, *25*, 3879.
6. The distribution of the products was influenced by fine reaction conditions and varied from **6**:**8**:**9** = 7:1:0 to 7:2:1.
7. **9a** (a mixture of two diastereomers). Major product: ^{1}H NMR ($CDCl_3$) δ −0.36 (s, 3H), −0.23 (s, 3H), 0.51 (s, 9H), 4.11 (dd, J = 2.7, 9.7 Hz, 1H), 4.43 (dd, J = 2.7, 10.4 Hz, 1H), 4.88 (d, J = 10.4 Hz, 1H), 5.37 (d, J = 9.7 Hz, 1H), 6.95–7.75 (m, 15H); ^{13}C NMR ($CDCl_3$) δ −5.74, −4.84, 17.69, 25.31, 60.00, 72.72, 76.50, 124.90, 126.81, 127.00, 128.02, 128.45, 128.52, 133.12, 138.67, 142.43, 142.49. Minor one: ^{1}H NMR ($CDCl_3$) δ −0.16 (s, 3H), 0.17 (s, 3H), 0.92 (s, 9H), 4.08 (dd, J = 9.5, 3.3 Hz, 1H), 4.61 (d, J = 9.5 Hz, 1H), 5.24 (d, J = 9.1 Hz, 1H), 5.46 (dd, J = 9.1, 3.3 Hz, 1H), 6.95–7.50 (m, 15H); ^{13}C NMR ($CDCl_3$) δ −5.21, −4.63, 18.19, 25.79, 62.04, 72.14, 74.20, 125.14, 126.70, 126.81, 127.51, 127.67, 128.02, 132.62, 137.93, 142.17, 142.98.
8. Yamamoto, K.; Tomo, Y. Suzuki, S.; *Tetrahedron Lett.* **1980**, *21*, 2861; Larchevêque, M.; Debal, A. *J. Chem. Soc. Chem. Commun.* **1981**, 877; Larson, G. L.; de Kaifer, C. F.; Seda, R.; Torres, L. E.; Ramirez, J. R. *J. Org. Chem.* **1984**, *49*, 3385.
9. Butyllithium was not so effective as *sec*-BuLi for the formation of enolate in one-pot procedure.
10. Financial supports by the Ministry of Education, Science and Culture of Japan (Grant-in-Aid for Scientific Research No. 05650877) and Asahi Glass Foundation for Industrial Technology are acknowledged.

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