ORGANIC LETTERS

2011
Vol. 13, No. 6
1440–1443

Addition of TMS-Substituted Oxiranyl Anions to Acylsilanes. A Highly Stereoselective Approach to Tetrasubstituted (*Z*)-β-Hydroxy-α-TMS Silyl Enol Ethers

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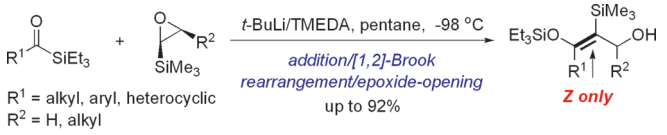
Received January 14, 2011

ABSTRACT



A highly stereoselective approach to novel tetrasubstituted (*Z*)-β-hydroxy-α-TMS silyl enol ethers is described. The reaction proceeds via a sequential addition/[1,2]-Brook rearrangement/epoxide-opening process of TMS-substituted oxiranyl anions with acylsilanes.

Silyl enol ethers as important building blocks have shown wide utility in many synthetic transformations.[1] As the configuration of double bonds is crucial for high facial selectivity, preparation of geometrically defined silyl enol ethers has been in long-standing demand in organic synthesis.[2] Although good configurational control has been achieved in the formation of di- and trisubstituted silyl enol ethers, stereoselective accessibility of the *acyclic tetrasubstituted one*, which possesses great potential in the construction of various stereogenic quaternary carbon centers,[3] still remains quite a challenging task.[4]

Silyl-substituted oxiranyl anion **2**, first introduced by Eisch and Galle, has presented good nucleophilicity to various electrophiles.[5] However, to our knowledge, no addition of this species to acylsilanes **1**[6] has been

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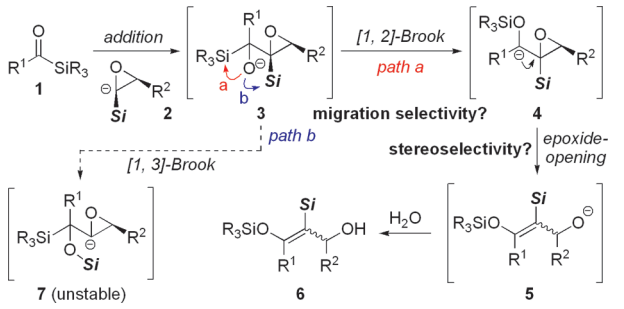
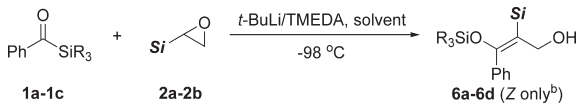
10.1021/ol200116f
Published on Web 02/22/2011

Scheme 1



investigated. Additionally, despite the preparation of silyl enol ethers from acysilanes having been reported,[7] there are only limited examples describing the synthesis of tetrasubstituted one. We envisioned that such an addition might initiate an efficient approach to tetrasubstituted β-hydroxy-α-TMS silyl enol ethers **6** based on the consideration of the following selectivity issues (Scheme 1). First, for the potential two C_{sp^3} to O silyl migration paths of alkoxide intermediate **3**, we presumed that the desired [1,2]-Brook rearrangement[8] (path a) should be energetically more favorable due to the relief of epoxide ring strain.[9] Moreover, despite the fact that the competitive [1,3]-Brook rearrangement has been used in other systems as a dominant direct path to vinylsilane,[10] formation of the unstable oxiranyl anion **7** would render path b rather unfavorable here. On the other hand, for the potential stereoselectivity in [1,2]-Brook path a, we anticipated the sterically hindered $SiMe_3$ group might have some key impacts on the conformation of siloxy carbanion **4**, thus providing reasonable configurational control during formation of the double bond. Herein, we report the realization of this sequential addition/[1,2]-Brook rearrangement/epoxide-opening process.

Table 1. Screening of Reaction Conditions



entry[a]	acylsilane (R_3Si)	epoxide	solvent	product	yield[c]
1	**1a** (Et_3Si)	**2a** (*Si* = Me_3Si)	Et_2O	**6a**	18%
2	**1a** (Et_3Si)	**2a** (*Si* = Me_3Si)	pentane	**6a**	63%
3	**1b** (*t*-$BuMe_2Si$)	**2a** (*Si* = Me_3Si)	pentane	**6b**	42%
4	**1c** ($PhMe_2Si$)	**2a** (*Si* = Me_3Si)	pentane	**6c**	23%
5	**1a** (Et_3Si)	**2b** (*Si* = Ph_3Si)	pentane	**6d**	50%

[a] Reaction conditions: acylsilane **1** (1.0 equiv), epoxide **2** (2.0 equiv), *t*-BuLi (2.0 equiv), TMEDA (2.4 equiv); 0.12 M at −98 °C. [b] The stereoselectivity was determined by ^1H NMR spectroscopy, and the configuration was determined by NOE experiments of **6a**. [c] Isolated yield after purification by silica gel column chromatography.

To establish feasibility, the reaction of acylsilane **1a**[11] with epoxide **2a** was examined initially. Deprotonation of **2a** by *t*-BuLi/TMEDA complex in Et_2O at −98 °C and the following addition to **1a** afforded the desired silyl enol ether **6a**, although in 18% yield, as a single *Z*-diastereomer (Table 1, entry 1). To our delight, using *nonpolar* solvents such as pentane then led to a much higher yield (63%, entry 2). The alkoxide intermediate **5** showed good stability even at room temperature for several hours, and no further 1,3-C_{sp^2} to O silyl migration occurred.[12] The result is consistent with Takeda's observation that such silyl migrations are not active in less polar solvents due to the covalent character of the Li−O bond.[13] Acylsilanes containing the more hindered *t*-$BuMe_2Si$ and $PhMe_2Si$ group proved to

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(11) Xin, L. H.; David, A. N.; Johnson, J. S. *Org. Lett.* **2002**, *4*, 2957.

(12) Further 1,3-C_{sp^2} to O silyl migration of **6a** or **6b** and the following alkylation with alkyl halides would potentially generate various tetrasubstituted silyl enol ethers. Investigations on this transformation are still ongoing. For recent studies on C_{sp2} to O silyl migration, see: (a) Moser, W. H.; Endsley, K. E.; Colyer, J. T. *Org. Lett.* **2000**, *2*, 718. (b) Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *Org. Lett.* **2001**, *3*, 3811. (c) Moser, W. H.; Zhang, J.; Lecher, C. S.; Frazier, T. L.; Pink, M. *Org. Lett.* **2002**, *4*, 1981. (d) Tsubouchi, A.; Itoh, M.; Onishi, K.; Takeda, T. *Synthesis* **2004**, *9*, 1504. (e) Taguchi, H.; Takami, K.; Tsubouchi, A.; Takeda, T. *Tetrahedron Lett.* **2004**, *45*, 429. (f) Devarie-Baez, N. O.; Shuhler, B. J.; Wang, H.; Xian, M. *Org. Lett.* **2007**, *9*, 4655. (g) Smith, A. B., III; Kim, W. S.; Wuest, W. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7082. (h) Devarie-Baez, N. O.; Kim, W. S.; Smith, A. B., III; Xian, M. *Org. Lett.* **2009**, *11*, 1861. (i) Smith, A. B., III; Kim, W. S.; Tong, R. B. *Org. Lett.* **2010**, *12*, 588.

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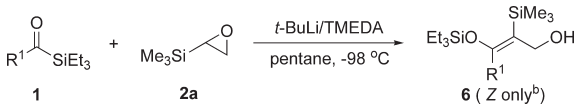
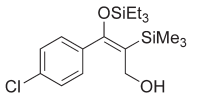
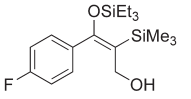
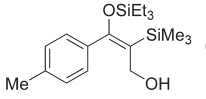
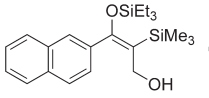
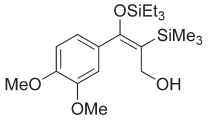
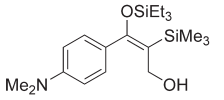
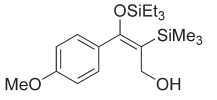
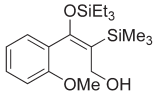
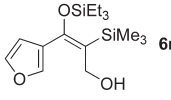
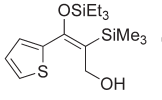
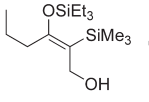
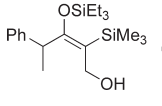
Table 2. Scope of Acylsilanes



entry[a]	acylsilane (R^1)	product		yield[c]
1	**1d** (*p*-Cl-C_6H_4)		**6e**	63%
2	**1e** (*p*-F-C_6H_4)		**6f**	48%
3	**1f** (*p*-Me-C_6H_4)		**6g**	62%
4	**1g** (2-Np)		**6h**	80%
5	**1h** (*m*, *p*-$(MeO)_2$-C_6H_3)		**6i**	90%
6	**1i** (*p*-Me_2N-C_6H_4)		**6j**	92%
7	**1j** (*p*-MeO-C_6H_4)		**6k**	70%
8	**1k** (*o*-MeO-C_6H_4)		**6l**	55%
9	**1l** (3-Furyl)		**6m**	51%
10	**1m** (2-Thienyl)		**6n**	71%
11	**1n** (*n*-C_3H_7)		**6o**	—
12	**1o** (PhMeCH)		**6p**	50%

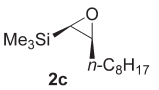
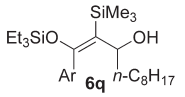
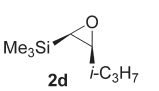
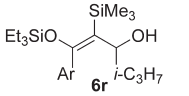
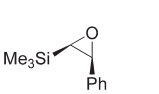
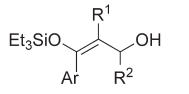
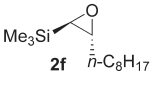
[a] Reaction conditions: acylsilane **1** (1.0 equiv), epoxide **2a** (2.0 equiv), *t*-BuLi (2.0 equiv), TMEDA (2.4 equiv); 0.12 M in pentane at −98 °C. [b] The stereoselectivity was determined by ^{1}H NMR spectroscopy. [c] Isolated yield after purification by silica gel column chromatography.

be poor substrates in giving **6b** and **6c**, respectively, in 42% and 23% yield (entries 3 and 4). Additionally, although the electron-deficient triphenylsilyl group is expected to make the oxiranyl anion of **2b** more stable than that of **2a**, its bulkiness appears to prohibit further addition partially with giving **6d** in the moderate 50% yield.

With the optimal conditions identified, the scope of this approach was examined. As summarized in Table 2, the reaction is suitable for a wide range of aryl acylsilanes (entries 1−8). Compared to the one bearing an electron-deficient phenyl group (entry 1 and 2), electron-rich phenyl acylsilanes appear to undergo the process more efficiently with higher yields (entries 5−7). Probably, the lower stability of siloxy carbanion **4** attached to an electron-rich phenyl group might accelerate the epoxide-opening step and thus make the overall process more facile. The steric effects of an aryl ring also present certain impacts on the efficiency, as reaction of *para*-methoxy phenyl acylsilane **1j** gave a higher yield (70%, entry 7) than that of *ortho*-methoxy-substituted one **1k** (55%, entry 8). The process is tolerant of heterocyclic acysilanes **1l** and **1m** as well (entries 9 and 10). The potential deprotonation of a heterocycle ring by an oxiranyl anion appeared not to interfere with the course. However, reaction of unbranched alkyl acylsilane **1n** suffered a lot from the deprotonation at the α-position of the carbonyl group and led to a very complex mixture (entry 11). A successful example was achieved when **1o** containing a sterically more hindered PhMeCH group was employed (50%, entry 12). This success also implies that relief of epoxide ring strain, to a large extent, drives the [1,2]-Brook rearrangement since the C_{sp^2}-stabilization of a silyloxy carbanion does not exist in this case.[9b]

With acylsilane **1j**, multisubstituted epoxides were further evaluated under the same condition. For *cis*-disubstituted epoxide **2c**[5c] bearing an unbranched chain and **2d**[14] bearing a more bulky isopropyl group, reactions proceeded quite smoothly to give the desired silyl enol ether **6q** and **6r**, respectively, in 92% and 64% yield (Table 3, entries 1 and 2). Poor regioselectivity of deprotonation of

Table 3. Scope of TMS-Substituted Epoxides

entry	epoxide	product[c]	yield[d]
1[a]	 **2c**	 **6q**	92%
2[a]	 **2d**	 **6r**	64%
3[a]	 **2e**	 **6s** (R^1 = $SiMe_3$, R^2 = Ph) **6t** (R^1 = Ph, R^2 = $SiMe_3$)	50% (**6s**:**6t** = 1:1)
4[b]	 **2f**	—	N.R.

[a] Reaction conditions: acylsilane **1j** (1.0 equiv), epoxide **2c**−**2e** (2.0 equiv), *t*-BuLi (2.0 equiv), TMEDA (2.4 equiv); 0.12 M in pentane at −98 °C. [b] Deprotonation was performed at −116 °C for 3.0 h. [c] The stereoselectivity was determined by ^{1}H NMR spectroscopy. Ar = *p*-MeOPh. [d] Isolated yield after purification by silica gel column chromatography.

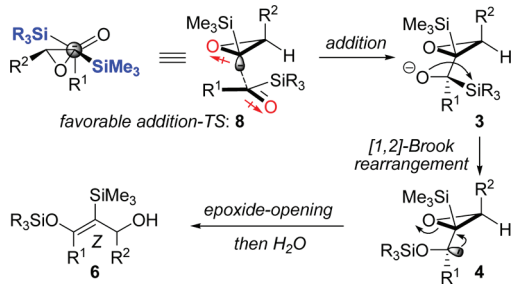


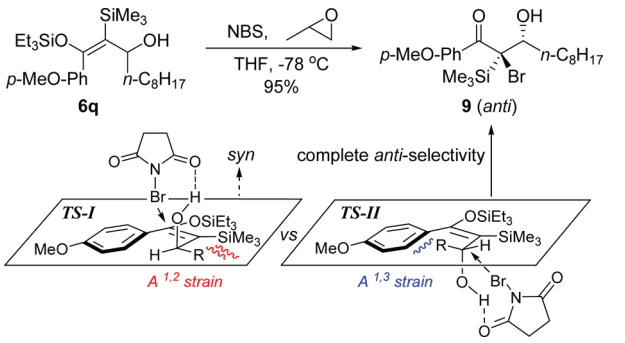
Figure 1. Model analysis for the high *Z*/*E*-stereoselectivity.

epoxide **2e**[14] containing a *cis*-phenyl group was found to give **6s** and **6t** as an inseparable mixture and in 50% yield (entry 3). Additionally, no reaction occurred when *trans*-disubstituted epoxide **2f**[5c] was employed. Imaginably, the formed *trans*-oxiranyl anion increases the difficulty of its approach to bulky acylsilane (entry 4).[15]

Rationalization for the high *Z*/*E* selectivity is proposed as follows. The initial addition is expected to proceed through the favorable transition state **8**, in which the two bulky silyl groups are oriented *anti* to each other to avoid the potential steric interaction, and the two oxygen atoms are also oriented in such a setup to minimize the dipole moment in the nonpolar solvent (Figure 1). Thus, alkoxide **3** would be formed diastereoselectively and further transformed via C to O-silyl migration to siloxy carbanion **4** with retention of the stereochemistry. Due to the fact that the sp^3 hybridized orbital containing a negative charge is aligned antiperiplanar to the cleaved C−O bond, **4** could undergo smooth epoxide opening to provide the observed (*Z*)-silyl enol ether **6** predominantly.[16]

The stereochemical course of the electrophilic addition of silyl enol ether **6q** was further examined with NBS (Scheme 2). Based on the proposed formation of a hydrogen bond between the hydroxyl group and NBS,

Scheme 2



two transition states **TS-I** and **TS-II** involving conflicting $A^{1,2}$ strain (between *n*-C_8H_{17} and $SiMe_3$ groups) and $A^{1,3}$ strain (between *n*-C_8H_{17} and aryl groups) would be expected to give different facial selectivities. In fact, we found that only the *anti*-isomer of *β*-hydroxy ketone **9**[17] containing a quaternary carbon center was formed in 95% yield. This result suggests that $A^{1,2}$ strain in **TS-I** is much stronger than $A^{1,3}$ strain in **TS-II**; thus **TS-II** would be more favorable in leading to the complete *anti*-selectivity.

In conclusion we have described a sequential addition/[1,2]-Brook rearrangement/epoxide-opening process of TMS-substituted oxiranyl anions with acylsilanes. This route provides a direct and stereoselective entry to novel tetrasubsitituted (*Z*)-*β*-hydroxy-α-TMS silyl enol ethers. Further applications of these useful building blocks are ongoing in our group.

Acknowledgment. This research was supported by the NSFC (20802044, 21021001), the National Basic Research Program of China (973 Program, 2010CB833200), and RFDP (200806101091). The authors also thank Prof. Richard P Hsung (UW, Madison) for invaluable discussions.

Supporting Information Available. Experimental procedures and spectra data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) (a) Burford, C.; Cooke, F.; Roy, G.; Magnus, P. *Tetrahedron* **1983**, *39*, 867. (b) Burford, C.; Cooke, F.; Ehlinger, E.; Magnus, P. *J. Am. Chem. Soc.* **1977**, *99*, 4536.

(15) Similar sluggish reactivity was also found in the reaction of trisubstituted epoxide $Me_3SiCHOC(CH_2)_5$, in which only the reduced product of acylsilane **1j** was obtained via a proposed successive SET process.

(16) The authors thank referees' helpful suggestions on proposing this mechanism. In addition, despite formation of the corresponding *β*-silyloxy ketone being possible for the *E*-isomer via O to O silyl transfer, no such compounds were observed after isolation.

(17) The stereochemistry of **9** was determined by NOE experiments of α-bromo enone **10**, which was obtained in 79% yield through a Peterson olefination protocol of **9** with NaH in DMF.