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Novel Phenomenon of Oxygen-to-oxygen Silyl Migration in Directed Aldol Reaction

Zhi Quan ZHAO[1], Li Zeng PENG[1]*, Yu Lin LI[2]*

[1]Lunan Pharmaceutical Co., Ltd., Linyi, Shandong 276003
[2]National Laboratory of Applied Organic Chemistry, Institute of Organic Chemistry, Lanzhou University, Lanzhou 730000

Abstract: The phenomenon of migration of the silyl groups from *α*-oxygen to *β*-oxygen in sodium aldol reaction was observed for the first time in this paper.

Keywords: Silyl migration, *α*-silyloxy ketone, aldol reaction.

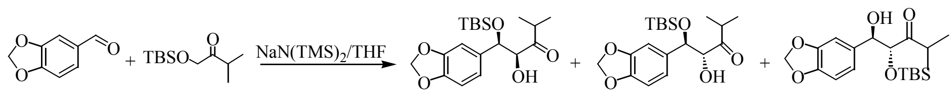
The migration of trialkylsilyl protecting groups (TBS, TBDPS, TIPS, TMS *etc.*) from oxygen to oxygen is a well-known phenomenon in organic chemistry. Usually, these rearrangements occur in a 1, 4 or 1, 5 fashion, and 1, *n* (n=6–11 *etc.*) type silyl migration has also been observed[1].

We are interested in this process during our studies on the directed aldol reactions of *α*-silyloxy ketone **2a** with heliotropin **1a** (**Scheme 1**). The aldehyde **1a** was used in the aldol reaction with the sodium enolate of *α*-siloxy ketone **2a**. When the aldol reaction mixture was maintained at –78°C for 0.5 h and allowed to warm up to 0°C, then the reaction was quenched with dilute hydrochloric acid, the *anti* isomer **4aa** with its *syn* isomer **3aa** and the other *anti* isomer **5aa**[2] in the ratio of 88:10:2 were obtained in the total yield of 85%. The ratio was determined by HPLC and ^{1}H NMR (entry 7). When the aldol reaction mixture was maintained below –78°C for 2 h, to ensure complete reaction, and quenched with dilute hydrochloric acid at this temperature under these conditions (kinetic), the *syn* isomer **3aa** along with its *anti* isomers **4aa** and **5aa** was obtained in 85% yield in the ratio of 85:12:3 (entry 1). HPLC, TLC, and NMR indicate that each adduct to be a single *racemic* isomer. The MS indicates that **3aa** and **4aa** are *β*-silyloxy products, and **5aa** is *α*-silyloxy product. Aldol **4aa** was desilylated by treatment with TBAF in THF to give the corresponding diol**,** which showed identical spectral data with that obtained from the aldol **5aa**.

The aldol reactions[3] of sodium enolates of other *α*-silyloxy ketones with aldehydes (alkyl, allyl, aryl) were also investigated. The results were consistent with the above observations (see **Scheme 2, Table 1**).

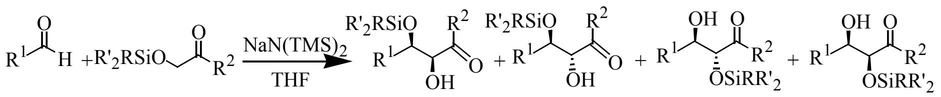
* E-mail: penglizeng@163.net; lily@lzu.edu.cn

Scheme 1

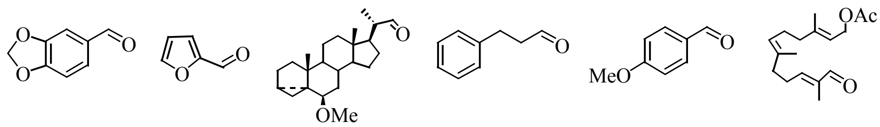


1a **2a** **3aa** **4aa** **5aa**

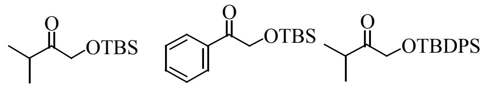
Scheme 2 Aldol condensation of α-siloxy ketone **2** with aldehyde **1**



1 **2** **3** **4** **5** **6**



1a **1b** **1c** **1d** **1e** **1f**



2a **2b** **2c**

Table 1 Aldol condensation of α-siloxy ketone **2** with aldehyde **1**

Entry	**1** + **2**	Conditions [a]	**3: 4: 5: 6** [b]	Isolated Yield %
1	**1a** + **2a**	A	85: 12: 3: 0	85
2	**1b** + **2a**	A	45: 10: 10: 35	85
3	**1c** + **2a**	A	95: 5: 0: 0 [c]	80
4	**1d** + **2a**	A	86: 12: 2: 0	75
5	**1e** + **2a**	A	85: 15: 0: 0	80
6	**1f** + **2a**	A	100: 0: 0: 0 [c]	75
7	**1a** + **2a**	B	10: 88: 2: 0	85
8	**1c** + **2a**	B	15: 85: 0: 0 [c]	70
9	**1e** + **2b**	B	85: 13: 2: 0	90
10	**1a** + **2c**	A	75: 20: 5: 0	90

[a]Conditions A: 3.0 equiv of NaN(TMS)$_2$, 2.2 equiv of **2**, 1.0 equiv of **1**, –78°C, 2 h; B: 3.0 equiv of NaN(TMS)$_2$, 2.2 equiv of **2**, 1.0 equiv of **1**, –78–0°C; C: 1.1 equiv of NaN(TMS)$_2$, 1.0 equiv of **2**, 1.0 equiv of **1**, –78–0°C; [b]The ratio of **3, 4, 5** and **6** in the product mixture was determined by 400 MHz ^{1}H NMR spectra of the crude products before chromatography; [c]See ref. 2 and ref. 4.

In summary, a novel phenomenon that the silyl groups (TBS and TBDPS) migrated from α-oxygen to β-oxygen (1, 4 fashion) in directed aldol reaction was described[4].

Acknowledgments

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References and Notes

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2. Spectral data: **3aa,** IR (film): 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): –0.10 (s, 3 H, Me), 0.06 (s, 3 H, Me), 0.90 (s, 9 H, $C(CH_3)_3$), 1.00 (d, 3 H, *J* = 6.6 Hz, Me), 1.11 (d, 3 H, *J* = 6.6 Hz, Me), 3.09 (m, 1H, C*H*$(Me)_2$), 3.48 (d, 1 H, *J* = 7.2 Hz, OH), 4.38 (dd, 1 H, *J* = 7.2, 3.6 Hz, C*H*OH), 4.91 (d, 1 H, *J* = 3.6 Hz, C*H*OTBS), 5.91 (s, 2 H, CH_2), 6.72 (m, 2 H, 2×CH), 6.80 (s, 1 H, CH); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): –5.4, –4.9, 16.6, 17.9, 19.1, 25.6, 37.5, 75.3, 78.6, 100.8, 106.7, 107.6, 119.3, 128.5, 133.8, 147.2, 213.9; EIMS *m/z*: 265 (M^+–101, 65); Anal. Calcd. for $C_{19}H_{30}O_5Si$: C, 62.26; H, 8.25. Found: C, 62.34; H, 8.24. **4aa,** IR (film): 1720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): –0.09 (s, 3 H, Me), 0.05 (s, 3 H, Me), 0.89 (s, 9 H, $C(CH_3)_3$), 0.90 (d, 3 H, *J* = 6.6 Hz, Me), 1.01 (d, 3 H, *J* = 6.6 Hz, Me), 2.50 (m, 1H, C*H*$(Me)_2$), 3.51 (d, 1 H, *J* = 5.8 Hz, OH), 4.45 (dd, 1 H, *J* = 5.8, 4.0 Hz, C*H*OH), 4.85 (d, 1 H, *J* = 4.0 Hz, C*H*OTBS), 5.98 (s, 2 H, CH_2), 6.80 (m, 2 H, 2×CH), 6.90 (s, 1 H, CH); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): –5.1, –4.8, 16.5, 18.0, 18.8, 25.6, 38.3, 77.2, 79.8, 101.0, 106.9, 107.8, 119.5, 147.0, 147.6, 214.1; EIMS *m/z*: 265 (M^+–101, 42); Anal. Calcd. for $C_{19}H_{30}O_5Si$: C, 62.26; H, 8.25. Found: C, 62.30; H, 8.26. **5aa**, IR (film): 1726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): –0.24 (s, 3 H, Me), –0.02 (s, 3 H, Me), 0.87 (s, 9 H, $C(CH_3)_3$), 0.99 (d, 3 H, *J* = 6.6 Hz, Me), 1.02 (d, 3 H, *J* = 6.6 Hz, Me), 2.98 (m, 1H, C*H*$(Me)_2$), 4.18 (d, 1 H, *J* = 6.8 Hz, CH), 4.73 (d, 1 H, *J* = 6.8 Hz, CH), 5.96 (s, 2 H, CH_2), 6.79 (m, 2 H, 2×CH), 6.90 (s, 1 H, CH); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): –5.4, –5.0, 18.0, 18.6, 25.7, 36.3, 75.8, 81.2, 101.0 (CH_2), 107.6, 107.9, 120.8, 134.1, 147.5, 147.6, 215.9; EIMS *m/z*: 349 (M^+-17, 0.2), 265 (M^+–101, 0.02), 151 (M^+-215, 40); Anal. Calcd. for $C_{19}H_{30}O_5Si$: C, 62.26; H, 8.25. Found: C, 62.30; H, 8.28. **3fa,** IR (film): 1700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): –0.01 (s, 3 H, Me), 0.03 (s, 3 H, Me), 0.89 (s, 9 H, $C(CH_3)_3$), 1.08 (d, 3 H, *J* = 6.6 Hz, Me), 1.11 (d, 3 H, *J* = 6.6 Hz, Me), 1.57 (s, 3 H, Me), 1.59 (s, 3 H, Me), 1.69 (s, 3 H, Me), 2.05 (s, 3 H, Me), 1.98-2.20 (m, 8 H), 3.10 (m, 1H, C*H*$(Me)_2$), 3.25 (d, 1 H, *J* = 7.3 Hz, OH), 4.18 (dd, 1 H, *J* = 7.3, 3.4 Hz, C*H*OH), 4.32 (d, 1 H, *J* = 3.4 Hz, C*H*OTBS), 4.59 (d, 2 H, *J* = 6.8 Hz, CH_2OAc), 5.10 (d, 1 H, *J* = 6.8 Hz, CH=), 5.34 (d, 1 H, *J* = 6.8 Hz, CH=), 5.42 (d, 1 H, *J* = 6.8 Hz, CH=); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): –5.4, –4.8, 12.8, 15.8, 16.3, 17.1, 17.6, 18.0, 18.4, 18.8, 20.9, 25.7, 26.1, 37.3, 39.0, 39.4, 61.3, 76.3, 118.2, 123.9, 127.7, 133.8, 134.9, 142.0, 170.9, 215.2; EIMS *m/z*: 393 (M^+–101, 15); Anal. Calcd. for $C_{28}H_{50}O_5Si$: C, 68.04; H, 10.19. Found: C, 68.00; H, 10.20.
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