## REGIO- AND STEREOSELECTIVE PREPARATION OF SILVL ENOL ETHERS BY ALKYLIDENATION OF SILVL ESTERS

Kazuhiko Takai,\* Yasutaka Kataoka, Takashi Okazoe, and Kiitiro Utimoto Department of Industrial Chemistry, Faculty of Engineering, Kyoto University, Yoshida, Kyoto 606, Japan

Abstract: Treatment of trimethylsilyl esters with a reagent for alkylidenation of carbonyl groups derived from 1,1-dibromoalkane, zinc, TiCl<sub>4</sub>, and TMEDA in THF gives Z-trimethylsilyl enol ethers in a regio- and stereoselective manner.

Silyl enol ethers are one of the most useful synthetic intermediates for introducing a carbon skeleton or a functional group at  $\alpha$ -position of a ketone group in a regiospecific manner.<sup>1</sup> Continued efforts have been devoted to regioselective preparation of the silyl enol ethers.<sup>2</sup> However, it is generally difficult to produce a silyl enol ether regioselectively from a ketone (R<sup>1</sup>COCH<sub>2</sub>R<sup>2</sup>) having a little steric or electronic difference between the two substituents R<sup>1</sup> and R<sup>2</sup>CH<sub>2</sub>. Several methods using prefunctionalized ketones such as  $\alpha$ ,  $\beta$ -unsaturated ones<sup>3</sup> and  $\alpha$ -heterosubstituted ones<sup>4</sup> have been reported.<sup>5</sup> We introduce here a direct access to overcome the difficulty, that is the formation of a carbon-carbon double bond of a silyl enol ether by alkylidenation of a silyl ester (Eq.1).



Alkylidenation of electron-rich carbonyl compounds like esters and amides can not be accomplished with the Wittig reagent.<sup>6</sup> The Tebbe reagent is limited to the methylene transfer to such carbonyl compounds.<sup>7,8</sup> We have recently reported that the reagent derived by reduction of 1,1-dibromoalkanes (RCHBr<sub>2</sub>) by zinc and TiCl<sub>4</sub> in the presence of N,N,N'N'-tetramethylethylenediamine (TMEDA) in THF is effective for the stereoselective transformation of esters to Z-alkenyl ethers.<sup>9</sup> During the investigation of the applicability of the reagent, we have noticed that a trimethylsiloxy group is compatible under the alkylidenation condition.<sup>10,11</sup> This observation prompted us to use trimethylsilyl esters as a substrate of the alkylidenation which would provide a new route for the preparation of trimethylsilyl enol ethers. Treatment of trimethylsilyl benzoate with a reagent prepared from 1,1-dibromoethane, zinc, TiCl<sub>4</sub>, and TMEDA in THF at 25°C for 1.5 h gave l-phenyl-l-trimethylsiloxy-l-propene in 90% yield (Z/E=73/27). The reaction did not proceed without TMEDA. For instance, the same reaction without TMEDA at 25°C for 3 h resulted in recovery of benzoic acid (81%) after acidic workup.

The results of preparation of trimethylsilyl enol ethers from trimethylsilyl esters are shown in Table 1. Similarly to the transformation of alkyl esters,<sup>9</sup> Z-silyl enol ethers were produced in all cases. The stereoselectivity of the alkylidenation depends on the bulkiness of both substituents on carbonyl groups. For example, i) while alkylidenation of trimethylsilyl nonanoate gave Z-silyl enol ethers in 80-95% selectivity, treatment of trimethylsilyl cyclohexanecarboxylate with the reagents afforded the corresponding Z-isomers as a sole product, respectively (runs 9-11). ii) When the substituents on silicon became large from trimethyl to triisopropyl, the Z-selectivity decreased (run 16).

Silyl enol ethers of an unsymmetrical ketone could be prepared regioselectively by using this method (runs 12 and 13, compounds 1 and 2). Trimethylsiloxy-substituted 1,3-butadienes (runs 17-19, compounds 3a-c),<sup>2b</sup> useful building blocks of the Diels-Alder reaction, were prepared stereoselectively from a trimethylsilyl ester of an  $\alpha,\beta$ -unsaturated carboxylic acid.



1 (run 12, ref. 12) 2 (run 13, ref. 13) 3a-c (runs 17-19)

Typical procedure: A solution of TiCl<sub>4</sub> (1.0 M, 4.0 mmol) in dichloromethane was added at 0°C to THF (10 mL) under an argon atmosphere. To the yellow solution at 25°C was added TMEDA (1.2 mL, 8.0 mmol) and the mixture was stirred at 25°C for 10 min. Zinc dust (0.59 g, 9.0 mmol) was added to the mixture and the resulting mixture was stirred at 25°C for 30 min. The color of the suspension turned from brownish yellow to dark greenish blue in a slightly exothermic process. A solution of trimethylsilyl ester (1.0 mmol) and 1,1-dibromoalkane (2.2 mmol) in THF (2 mL) was added to the mixture. The color of the mixture gradually turned dark brown. After being stirred at 25°C for a couple of hours, the reaction mixture was cooled to 0°C and saturated aq.  $K_2CO_3$  solution (1.5 mL) was added to the mixture. After it was stirred at 0°C for another 15 min, the mixture was diluted with ether (10 mL) and then passed rapidly through a short column of silica gel.

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|     | OSiMe <sub>3</sub>                           | Br R <sup>2</sup>                             | Zn, TiCl <sub>4</sub> , TMED/ | A OSiMe <sub>3</sub> | 2                |
|-----|--|---|-------------------------------|----------------------|------------------|
|     | R <sup>1-C≥</sup> 0 +                        | Br—C ~  | THF, 25°C                     |                      |                  |
| Run | R <sup>1</sup>                               | R <sup>2</sup>                                | Time/h                        | Yield/% <sup>b</sup> | Z/E <sup>C</sup> |
| 1   | Ph   | Me  | 1.5                           | 90                   | 73/27            |
| 2   |  | Bu  | 2                             | 84                   | 73/27            |
| 3   |  | PhCH <sub>2</sub> -                           | 2                             | 87                   | 82/18            |
| 4   |  | <sup>с</sup> с <sub>6</sub> н <sub>11</sub> - | 3                             | 74                   | 80/20            |
| 5   | <sup>n</sup> C9 <sup>H</sup> 19 <sup>-</sup> | Me  | 2                             | 77                   | 86/14            |
| 6   | , _,   | Bu  | 2                             | 80                   | 88/12            |
| 7   |  | PhCH <sub>2</sub> -                           | 2                             | 66                   | 95/5             |
| 8   |  | °C6H11-                                       | 2                             | 68                   | 87/13            |
| 9   | °C6H11-                                      | Me  | 2                             | 80                   | 100/0            |
| 10  |  | Bu  | 2                             | 78                   | 100/0            |
| 11  |  | PhCH <sub>2</sub> -                           | 2                             | 84                   | 100/0            |
| 12  | <sup>n</sup> C5H11-                          |   | 2                             | 76                   | 89/11            |
| 13  | PhCH <sub>2</sub> CH <sub>2</sub> -          | Bu  | 2                             | 80                   | 84/16            |
| 14  | Me   | PhCH <sub>2</sub> -                           | 2                             | 79                   | 92/8             |
| 15  |  | _   | 2                             | 78 <sup>d</sup>      | 91/9             |
| 16  |  |   | 1.5                           | 91 <sup>e</sup>      | 77/23            |
| 17  | PhCH=CH-                                     | Me  | 2                             | 65                   | 96/4             |
| 18  |  | Bu  | 1.5                           | 79                   | 100/0            |
| 19  |  | PhCH <sub>2</sub> -                           | 1.5                           | 79                   | 100/0            |

Table 1. Preparation of silyl enol ethers from silyl esters.<sup>a</sup>

a) A trimethylsilyl ester (1.0 mmol) was treated with l,l-dibromoalkane (2.2 mmol), zinc (9.0 mmol), TiCl<sub>4</sub> (4.0 mmol), and TMEDA (8.0 mmol) in THF at 25°C. b) Isolated yields. c) The Z/E ratios were determined by <sup>1</sup>H NMR. d) Instead of a trimethylsilyl group, a tert-butyldimethylsilyl one was used. e) Triisopropylsilyl ester was employed.

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- (10) In contrast to aldol-type condensation mediated by  $TiCl_4$ , silyl enol ethers were remained unchanged under this reaction conditions containing the low-valent titanium generated by  $TiCl_4$ , zinc and TMEDA.
- (11) Under the reaction conditions (preparation of 1-phenyl-1-trimethylsiloxy-1-propene from trimethylsilyl benzoate in 80-90%), compounds were recovered in the following order: 1-dodecanol trimethylsilyl ether (89% recovery); 1-dodecene (92%); 1-iodododecane (93%); dodecanal diethylene acetal (98%).
- (12) Bp 120°C (bath temp, 1.5 Torr); IR (neat): 2954, 2928, 1671, 1454, 1252, 1160, 1004, 844 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>): δ0.19 (s, 9H(E)), 0.20 (s, 9H(Z)), 0.89 (t, J=7 Hz, 3H), 1.19-1.61 (m, 6H), 2.05 (t, J=7 Hz, 2H), 3.35 (d, J=7 Hz, 2H), 4.67 (t, J=7 Hz, 1H(Z)), 4.94 (t, J=7 Hz, 1H(E)), 7.13-7.40 (m, 5H).
- (13) Bp 115°C (bath temp, 1.5 Torr); IR (neat): 2954, 2924, 1674, 1455, 1252, 1178, 987, 843 cm<sup>-1</sup>; NMR (CDCl<sub>3</sub>): δ0.19 (s, 9H(E)), 0.20 (s, 9H(Z)), 0.89 (t, J=7 Hz, 3H), 1.16-1.38 (m, 4H), 1.99 (d, J=7 Hz, 2H), 2.29 (t, J=7 Hz, 2H), 2.78 (t, J=7 Hz, 2H), 4.49 (t, J=7 Hz, 1H(Z)), 4.74 (t, J=7 Hz, 1H(E)), 7.13-7.38 (m, 5H).

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