Pergamon

Tetrahedron Letters 42 (2001) 369–372

TETRAHEDRON
LETTERS

# A facile generation of enolates from silyl enol ethers by potassium ethoxide

Wensheng Yu and Zhendong Jin*

*Division of Medicinal and Natural Products Chemistry, College of Pharmacy, The University of Iowa, Iowa City, IA 52242, USA*

Received 31 October 2000; accepted 6 November 2000

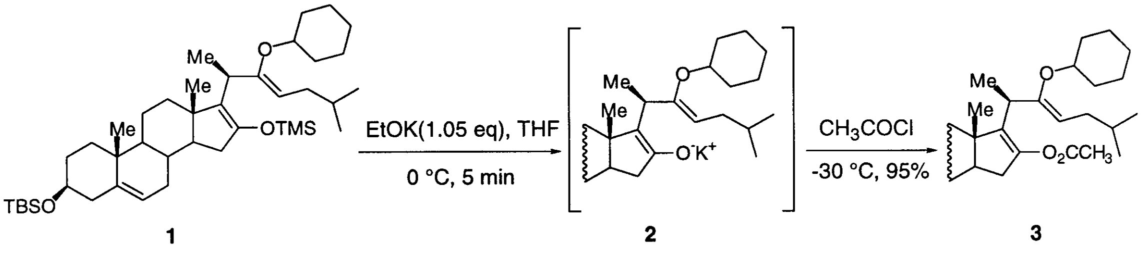
---

**Abstract**—Cyclic silyl enol ethers were successfully cleaved by EtOK to generate the corresponding enolates. Reactions with EtOK were faster and the corresponding enolates could be trapped by electrophiles and oxidants to give the kinetic products exclusively. © 2001 Elsevier Science Ltd. All rights reserved.

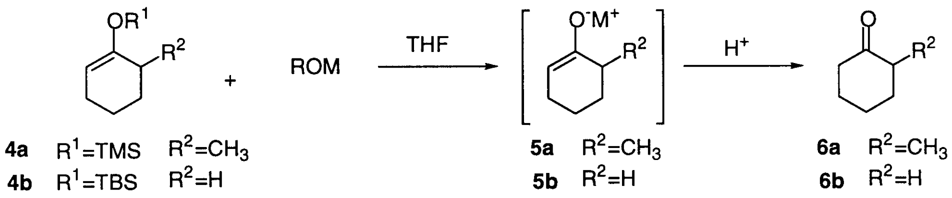
---

Generation of enolates from trimethylsilyl enol ethers via nucleophilic cleavage is an important transformation in organic synthesis.[1] Methyl lithium,[2] lithium amide in ammonia,[3] and fluoride salts[4] have been used in this purpose. However, limitations about these procedures still exist. The reactions employing methyl lithium require relatively high temperature (0°C) at which very few functionalities can tolerate its strong nucleophilicity and basicity. The lithium amide procedure requires dry ammonia which sometimes is not convenient. 'Dry' fluoride salts are either not readily available or relatively expensive.[4a]

In connection with a project in our laboratories, we needed to convert silyl enol ether **1** to vinyl acetate **3** (Scheme 1). Applying the methyl lithium protocol, it took 5 equiv. of MeLi for 8 hours at 25°C to completely convert compound **1** to its enolate **2**. Several fluoride salts were investigated, but none of them gave satisfactory results. Therefore, we decided to develop a new method which can easily cleave silyl enol ethers with readily available and inexpensive reagents.



**Scheme 1.**



**Scheme 2.**

---

*Keywords*: silyl enol ether; potassium alkyloxide; kinetic enolate; oxidation.

* Corresponding author. E-mail: zhendong-jin@uiowa.edu

PII: S0040-4039(00)01970-5

We found that the commercially available potassium ethoxide (EtOK) is a very good reagent for this purpose. The reaction of silyl enol ether **1** with 1.05 equiv. of EtOK at 0°C afforded enolate **2** in less than 5 minutes. The enolate **2** reacted with acetyl chloride to give the desired vinyl acetate **3** in 95% yield (Scheme 1).

The fast reaction between silyl enol ether **1** and EtOK prompted us to investigate the rates of the reactions between various alkyloxide salts and silyl enol ethers (Scheme 2). The results are summarized in Table 1. Although both *t*-BuOK[5] and EtOK converted silyl enol ether **4a** to enolate **5a** at 0°C in 5 minutes (Table 1, entries 1 and 2), the reaction with *t*-BuOK at −78°C was much slower than that with EtOK (Table 1, entries 3 and 4). As expected, MeONa reacted very slowly with silyl enol ether **4a** (Table 1, entry 5). Surprisingly, the reaction with MeOK was much slower than that with EtOK (Table 1, entry 6). We believe that this is primarily due to the very poor solubility of MeOK in THF. In addition, EtOK completely cleaved *t*-butyldimethylsilyl enol ether **4b** in 10 hours at 25°C, whereas the reaction between *t*-BuOK and **4b** reached only 45% completion after 24 hours (Table 1, entries 7 and 8).

When both kinetic and thermodynamic enolates can be generated, the distinct advantage for using EtOK over *t*-BuOK becomes more obvious. The majority of the enolate was the thermodynamic enolate after compound **4a** was treated with 1 equiv. of *t*-BuOK[6] at 0°C for only 5 minutes (Table 2, entry 1). Lowering the temperature to −50°C increased the proportion of the kinetic enolate, but the reaction could not go to completion, and about 50% of the starting material **4a** was recovered (Table 2, entry 2). In addition, a large amount of thermodynamic enolate was still formed even if the reaction was kept at −78°C for 10 hours (Table 2, entry 3). The formation of the thermodynamic product is presumably due to the slower reaction rate of the cleavage of silyl enol ether by *t*-BuOK and the presence of the trace amount of *t*-BuOH in *t*-BuOK which is difficult to eliminate. We were delighted to observe that by employing EtOK,[7] the kinetic enolate could be successfully trapped at low temperature and the yields and ratio were excellent (Table 2, entries 4 and 5).

The reactions between various trimethylsilyl enol ethers with EtOK followed by in situ trapping the enolates

**Table 1.** Rates of reactions of various alkyloxide salts with cyclic silyl enol ethers[a]

| Entry | Substrates | ROM | *T* (°C) | Reaction time | Results |
|---|---|---|---|---|---|
| 1 | **4a** | *t*-BuOK | 0 | 5 minutes | Complete conversion |
| 2 | **4a** | EtOK | 0 | 5 minutes | Complete conversion |
| 3 | **4a** | *t*-BuOK | −78 | 24 hours | 5% Starting material left |
| 4 | **4a** | EtOK | −78 | 2.5 hours | Complete conversion |
| 5 | **4a** | MeONa | 25 | 10 hours | Complete conversion |
| 6 | **4a** | MeOK | 25 | 3 hours | Complete conversion |
| 7 | **4b** | *t*-BuOK | 25 | 24 hours | 45% Conversion |
| 8 | **4b** | EtOK | 25 | 10 hours | Complete conversion |

[a] 1.05 equiv. of alkyloxide was used and freshly distilled THF was the reaction solvent.

**Table 2.** Trapping the cyclic kinetic enolate generated by *t*-BuOk or EtOK

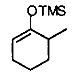
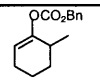
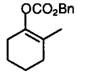
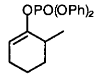
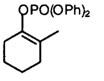
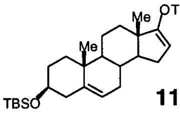
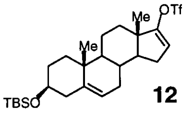
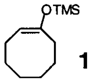
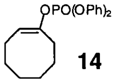
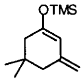
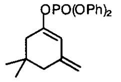
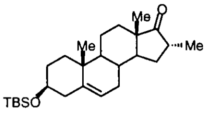
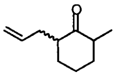
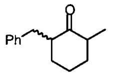
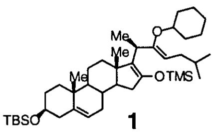
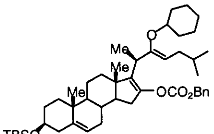
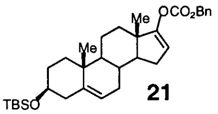
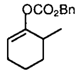
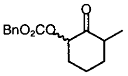
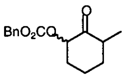
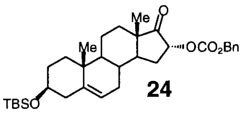
| Entry | Substrates | Reaction Conditions | Products | Yield |
|---|---|---|---|---|
| 1 | <br>**4a** | i. 1 equiv. *t*-BuOK, 0 °C, 5 min<br>ii. BnO2CCl, 0 °C, 30 min | <br>**7**<br><br>**8**<br>20 : 80 | 88% |
| 2 | **4a** | i. 1 equiv. *t*-BuOK, -50 °C, 20 min<br>ii. BnO2CCl, -50 °C, 30 min | **7** + **8**<br>70 : 30 | 43% |
| 3 | **4a** | i. 1 equiv. *t*-BuOK, -78 °C, 10 h<br>ii. BnO2CCl, -78 °C, 30 min | **7** + **8**<br>56 : 44 | 77% |
| 4 | **4a** | i. 1 equiv. EtOK, 78 °C, 2.5 h<br>ii. BnO2CCl, -78 °C, 30 min | **7** + **8**<br>95 : 5 | 87% |
| 5 | **4a** | i. 1 equiv. EtOK, 78 °C, 2.5 h<br>ii. (PhO)2POCl, -78 °C, 30 min | <br>**9**<br><br>**10**<br>95 : 5 | 95% |

**Table 3.** Reactions of enolates generated from cyclic trimethylsilyl enol ethers by EtOK

| Entry | Substrates | Reaction Conditions | Product(s) | Yield |
|---|---|---|---|---|
| 1 |  **11** | i. Method B<br>ii. $Ph_2NTf$ |  **12** | 93% |
| 2 |  **13** | i. Method B<br>ii. $(PhO)_2POCl$, -78-0 °C, 30 min |  **14** | 82% |
| 3 |  **15** | i. Method A<br>ii. $(PhO)_2POCl$, -78-0 °C, 30 min |  **16** | 87% |
| 4 | **11** | i. Method B<br>ii. MeI, 0 °C, 1h |  **17** | 85% |
| 5 | **4a** | i. Method A<br>ii. *n*-BuLi (0.05 equiv.),[9] LiBr (5 equiv.), HMPA, Allyl Iodide, -78 °C, 12 h |  **18** | 61% |
| 6 | **4a** | i. Method A<br>ii. *n*-BuLi (0.05 equiv.),[9] LiBr (5equiv.), HMPA, Benzyl bromide, -78 °C, 24 h |  **19** | 53% |
| 7 |  **1** | i. Method B<br>ii. $(BnOCO_2)_2$, -78 °C,15 min |  **20** | 88% |
| 8 | **11** | i. Method B<br>ii. $(BnOCO_2)_2$, -78 °C, 15 min |  **21** | 91% |
| 9 | **4a** | i. Method A<br>ii. $(BnOCO_2)_2$, -78 °C, 15 min |  **22** +  **23**<br>27:73 | 78% |
| 10 | **4a** | i. Method A; ii. LiBr (5 equiv.)<br>iii. $(BnOCO_2)_2$, -78 °C, 15 min |  **23** | 66% |
| 11 | **11** | i. Method B<br>ii. LiBr (5 equiv.)<br>iii. $(BnOCO_2)_2$, -78 °C,15 min |  **24** | 84% |

Method A: EtOK (1.05 equiv.), −78°C, 2.5 h; Method B: EtOK (1.0 equiv.), 0°C, 10 minutes.

with different electrophiles are summarized in Table 3.[8] Under our conditions, compound **11** was converted to the enolate which reacted with $Ph_2NTf$ to give vinyl triflate **12** in 93% yield (Table 3, entry 1). Both silyl enol ethers **13** and **15** were successfully converted to vinyl phosphates in excellent yields (Table 3, entries 2 and 3). The enolates generated by our method were also suitable for alkylation. Methylation of the enolate generated from **11** afforded monomethylated product **17** in 85% yield (Table 3, entry 4). Alkylation of the kinetic enolate generated from **4a** with allyl iodide and benzyl bromide at low temperature provided monoalkylated products **18** and **19** with the retention of the regiochemistry (Table 3, entries 5 and 6).[9]

Because the potassium enolates were prepared in the absence of amines,[10] the enolates generated by our method were particularly suitable for the oxidation by dibenzyl peroxydicarbonate developed by Vederas and his co-workers.[10a,11] We found that oxidation of the potassium enolates by dibenzyl peroxydicarbonate provided vinyl carbonates exclusively (Table 3, entries 7 and 8) or partially (Table 3, entry 9). However, we found that the reactions could afford the carbonates of α-hydroxy ketones exclusively simply by addition of 5 equiv. of LiBr to the potassium enolates prior to the addition of the oxidant (Table 3, entries 10 and 11).

A typical procedure for the preparation of enolates by EtOK from silyl enol ethers follows: 51 mg (0.61 mmol) of EtOK was placed in a 10 mL flame dried flask under argon. Freshly distilled THF (2 mL) was added and then the suspension was cooled to 0°C (or −78°C for the generation of kinetic enolate). Silyl enol ether **4a** (112 mg, 0.61 mmol) was dissolved in 0.5 mL of freshly distilled THF and the solution was cannulated to the EtOK solution. The reaction was monitored by TLC. Once silyl enol ether **4a** disappeared, an electrophile or dibenzyl peroxydicarbonate was added.

In conclusion, we have discovered that cyclic silyl enol ethers can be readily cleaved by EtOK to generate the corresponding enolates. Compared to the other methodologies, our conditions are milder and faster. Furthermore, it is also possible to trap the kinetic enolates exclusively by electrophiles and oxidants under our conditions.

## Acknowledgements

This work was supported by Grant #IN-122S from the American Cancer Society, administered through The University of Iowa Cancer Center, a Research Project Grant RPG-00-030-01-CDD from the American Cancer Society, and the Central Investment Fund for Research Enhancement (CIFRE) at The University of Iowa. Special thanks are due to The Center for Biocatalysis and Bioprocessing at The University of Iowa for providing a fellowship to W.Yu.

## References

1. Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181 and references cited therein.
2. Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464.
3. Binkley, E. S.; Heathcock, C. H. *J. Org. Chem.* **1975**, *40*, 2156.
4. (a) Busch-Petersen, J.; Bo, Y.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 2065 and references cited therein; (b) Seppelt, K. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 292; (c) Schwesinger, R.; Link, R.; Thiele, G.; Rotter, H.; Honert, D.; Limbach, H.-H.; Mannle, F. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1372; (d) Gingras, M. *Tetrahedron Lett.* **1991**, *33*, 7381; (e) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901; (f) Middleton, W. J. US Patent 3,940,402, 1976; (g) Noyori, R.; Nishida, I.; Sakata, J.; Nishizawa, W. *J. Am. Chem. Soc.* **1980**, *102*, 1223; (h) Kuwajima, I.; Nakamura, E. *J. Am. Chem. Soc.* **1975**, *97*, 3257; (i) Nakamura, E.; Shimizu, M.; Kuwajima, I. *Tetrahedron Lett.* **1976**, 1699; (j) Noyori, R.; Yokoyama, K.; Sakata, J.; Kuwajima, I.; Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1977**, *99*, 1265; (k) Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 1025; (l) Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181.
5. (a) Duhamel, P.; Cahard, D.; Poirier, J. M. *J. Chem. Soc., Perkin Trans. 1* **1993**, *21*, 2509; (b) Quesnel, Y.; Bidois-Sery, L.; Poirier, J.-M.; Duhamel, L. *Synlett* **1998**, 413.
6. Solid *t*-BuOK, purchased from Aldrich, was vacuumed for 12 hours before it was used in the reactions. 1.0 M solution of *t*-BuOK in THF which was also purchased from Aldrich gave the same results.
7. EtOK was purchased from Aldrich and was used directly without further purification.
8. All compounds were fully characterized.
9. Morita, Y.; Suzuki, M.; Noyori, R. *J. Org. Chem.* **1989**, 54, 1785. The potassium enolate was converted to the lithium enolate by addition of 5 equiv. of lithium bromide prior to addition of alkyl halide. To eliminate the trace amount of proton in the reaction solution, 0.05 equiv. of *n*-BuLi was added before the addition of lithium bromide and HMPA.
10. The presence of amines often leads to low yields in the oxidation of enolates (a) Gore, M. P.; Vederas, J. C. *J. Org. Chem.* **1986**, *51*, 3700; (b) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M. *J. Org. Chem.* **1984**, *49*, 3243.
11. One of the advantages of employing dibenzyl peroxydicarbonate in the oxidation of enolates is that it can avoid the formation of the dimer of α-hydroxy ketone which sometimes occurs in the oxidation of silyl enol ethers.