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Practical Synthesis of Precursors of Cyclohexyne and 1,2-Cyclohexadiene

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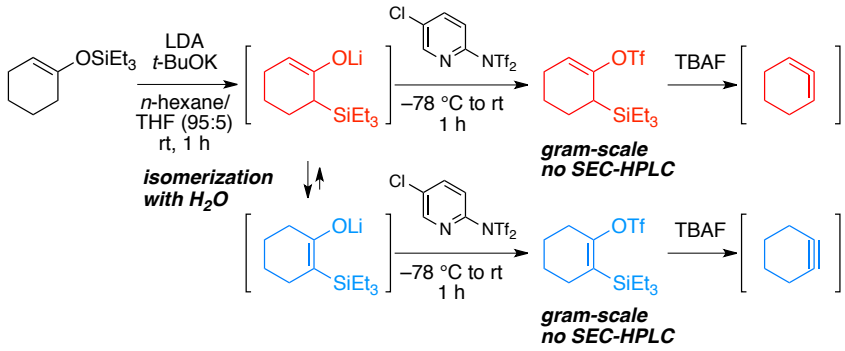

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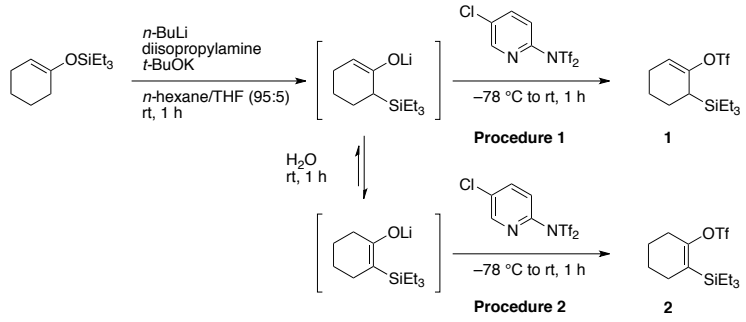
Abstract
This study investigated a practical method for regiocontrolled synthesis of precursors of strained cyclohexynes and 1,2-cyclohexadienes, which is a one-pot procedure consisting of a rearrangement of silyl enol ether and subsequent formation of the enol triflates. Triethylsilyl enol ether, derived from cyclohexanone, was treated with a combination of LDA and *t*-BuOK in *n*-hexane/THF to encourage the migration of the silyl group to generate an α-silyl enolate. Subsequently, the α-silyl enolate was reacted with Comins' reagent to yield the corresponding enol triflate. Finally, the α-silylated trisubstituted lithium enolate for precursor of 1,2-cyclohexadiene was isomerized in the presence of a stoichiometric amount of water for one hour at room temperature to exclusively provide tetrasubstituted lithium enolate for precursor of cyclohexyne in one pot.

Key words strained molecules, allenes, alkynes, enolate, isomerization, lithiation, rearrangement, and solvent effects.

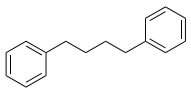
Strained cycloalkynes and cycloallenes have attracted attention as reactive intermediates in a variety of reactions such as cycloaddition and nucleophilic addition.[1] However, synthetic application of cyclohexynes[2] and 1,2-cyclohexadienes[3] lag far behind those of cyclooctynes,[4] dibenzocyclooctyne derivatives,[5] and 4,8-diazacyclononynes,[6] because the latter can be isolated as stable organic compounds. Therefore, various methods to generate cyclohexyne and 1,2-cyclohexadiene *in situ* have been reported.[7] Roberts[8] and Wittig[9] reported seminal work on the generation of cyclohexyne and 1,2-cyclohexadiene, respectively. In addition, Guitián and co-workers reported a fluoride ion-promoted generation of cyclohexynes and 1,2-cyclohexadienes from silyl enol triflates.[10] Recently, we reported a short-step synthesis of the silyl enol triflates from cyclohexanone using a two-pot process based on a modification of Corey's rearrangement reaction[11] of silyl enol ether.[12] However, this method involves tedious purification process that employs SEC (size-exclusion chromatography)-HPLC to separate the desired products from low polarity-compounds. Herein, we describe a detailed modification of reaction conditions and achieve a gram-scale synthesis of silyl enol triflates **1** and **2** without using SEC-HPLC separation.



Scheme 1

In our previous study,[12] a combination of *t*-BuOK and commercially available lithium diisopropylamide (LDA) in tetrahydrofuran (THF)/ethylbenzene/heptane (purchased from Tokyo Chemical Industries (TCI): Product Number L0171) was used for the migration of a silyl group. It was found to be difficult to separate the desired compounds **1** and **2** from low polarity-compounds by silica gel column chromatography. One compound that was obtained by SEC–HPLC separation was

identified to be 1,4-diphenylbutane (**3**) after careful analysis (Figure 1). At first, it was assumed that this compound was generated under the basic conditions from ethylbenzene that was involved in the commercial LDA solution.[13] However, it was found that the LDA solution itself contained compound **3**, because treatment of the LDA solution with water and the extraction of the mixture provided compound **3**.

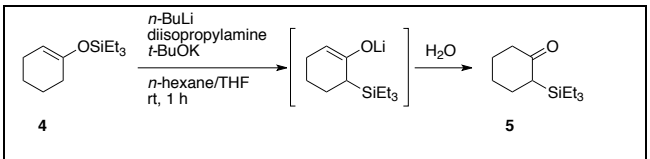


3

Figure 1 Identified compound obtained by SEC-HPLC separation

In order to avoid the tedious SEC–HPLC separation, a readily prepared LDA that did not contain the low polar compound **3** was used. In preliminary experiments, we found that the migration of a silyl group was significantly affected by the solvent ratio. We first examined the solvent ratio between *n*-hexane/THF to establish a robust procedure (Table 1). When only *n*-hexane was used as a solvent, the desired α-silyl ketone **5** was obtained with a 93% recovery of the starting silyl enol ether **4** (entry 1). The reaction was then repeated with an *n*-hexane/THF ratio of 95:5, which is close to the ratio used with the commercially available LDA in the authors' previous work.[12] In this case, the migration of the silyl group smoothly took place to give α-silyl ketone **5** in 84% isolated yield (entry 2). The yield of **5** slightly decreased in *n*-hexane/THF (90:10) (entry 3). The α-silyl ketone **5** was not obtained in *n*-hexane/THF (85:15) with detection of 4% cyclohexanone (entry 4). These results indicated that the silyl group was removed by the nucleophilic attack of LDA. By increasing the solvent ratio, the recovery of the starting silyl enol ether **4** decreased and the formation of cyclohexanone became preferable (entries 5–7). These drastic solvent effects suggest that the aggregation state of LDA is important for the selective formation of α-silyl ketone **5** over cyclohexanone.[14]

Table 1 Effects of solvent on the migration of silyl group



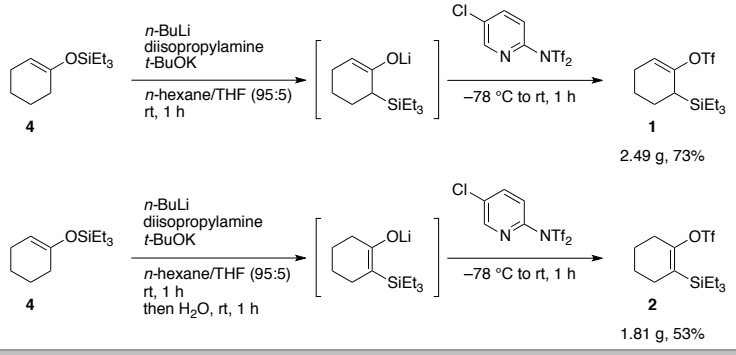
4 **5**

Entry	*n*-hexane/THF (v:v)	Recovered silyl enol ether **4** (%)	Silylketone **5** (%)	Cyclohexanone (%)
1	100:0	93[a]	7[a]	–[b]
2	95:5	–[b]	99[a] (84[c])	–[b]
3	90:10	15[a]	85[a]	–[b]
4	85:15	71[a]	–[b]	4[a]
5	80:20	76[a]	–[b]	11[a]
6	70:30	67[a]	–[b]	2[a]
7	17:83	27[a]	–[b]	65[a]

[a] The yield was determined by ^{1}H NMR spectrum of the crude material with 1,1,2,2-tetrachloroethane as an internal standard.
[b] Not detected in the ^{1}H NMR spectrum of the crude material.
[c] Isolated yield.

Having established the optimal conditions for the migration of the silyl group, we then focused on investigating the one-pot rearrangement of silyl enol ether, followed by triflation without/with isomerization, giving precursors of 1,2-cyclohexadiene and cyclohexyne on multi-gram scales without SEC-HPLC separation (Scheme 2). Thus, the migration proceeded smoothly with *in situ*-generated LDA in *n*-hexane/THF (95:5) at room temperature. The resulting enolate was then trapped with Comins' reagent[15] to provide silyl enol triflate **1** in 73% yield. The trisubstituted enolate was isomerized with water, and the resulting tetrasubstituted enolate was subjected to triflation to give silyl enol triflate **2** in 53% yield.

In summary, we have achieved one-pot gram-scale syntheses of precursors of cyclohexyne and 1,2-cyclohexadiene from the same silyl enol ether. The synthetic method developed in this work could be applied to the synthesis of both cycloalkyne precursor and cycloallene precursor. These results would promote the research on using these reactive and strained synthetic intermediates for bioactive natural products, drugs, and functional organic molecules.



Scheme 2 One-pot gram-scale syntheses of precursors of cyclohexyne and 1,2-cyclohexadiene

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Analytical thin layer chromatography (TLC) was performed on Merck 60 F254 aluminum sheets precoated with a 0.25 mm thickness of silica gel. Infrared (IR) spectra were recorded on a Bruker Alpha with an ATR attachment (Ge) and are reported in wave numbers (cm^{-1}). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and ^{19}F NMR (376 MHz) spectra were measured on a JEOL ECZ400 spectrometer. Chemical shifts for ^{1}H NMR are reported in parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.26 ppm) and coupling constants are in Hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Chemical shifts for ^{13}C NMR are reported in ppm from tetramethylsilane with the

solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm). High-resolution mass spectra (HRMS) were performed on a JEOL JMS-T100LP AccuTOF LC-Plus (ESI) with a JEOL MS-5414DART attachment (DART). All work-up and purification procedures were carried out with reagent solvents in air. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Flash column chromatography was performed on Wakogel® C-300 (45–75 μm, Wako Pure Chemical Industries, Ltd.). Recycling preparative SEC-HPLC was performed with LC-9201 (Japan Analytical Industry Co., Ltd.) equipped with preparative SEC columns (JAI-GEL-1H and JAI-GEL-2H). Anhydrous THF and *n*-BuLi (1.6 M in *n*-hexane) were purchased from Kanto Chemical Co., Inc. THF was further dried by passing through a solvent purification system (Grass Contour) prior to use. Anhydrous *n*-hexane (water content <30 ppm) was purchased from Nacalai Tesque, Inc. LDA (ca. 1.5 M in THF/ethylbenzene/heptane) and *tert*-BuOK (>95.0%) was purchased from Tokyo Chemical Industry Co., Ltd. Diisopropylamine was purchased from FUJIFILM Wako Pure Chemical Co., Ltd. and distilled over CaH_2 prior to use.

Procedures

2-(Triethylsilyl)cyclohexan-1-one (5).

A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with diisopropylamine (0.176 mL, 1.25 mmol, 2.5 equiv) and anhydrous THF (0.20 mL). After the resulting solution was cooled to –78 °C, *n*-BuLi (1.57 M in *n*-hexane, 0.796 mL, 1.25 mmol, 2.5 equiv) was added to the tube. The mixture was then warmed to 0 °C and stirred for 30 min. The resulting LDA solution was warmed to room temperature. To the solution were added anhydrous *n*-hexane (3.11 mL) and *tert*-BuOK (0.139 g, 1.24 mmol, 2.5 equiv). After stirring at room temperature for 30 min, the reaction mixture was treated with silyl enol ether **4** (0.107 g, 0.504 mmol, 1.0 equiv), and the resulting mixture was stirred at room temperature for 1 h, at which time TLC (*n*-hexane/methyl acetate = 9:1) indicated complete consumption of the starting silyl enol ether. The resulting mixture was treated with water (3 mL). After partitioned, the aqueous layer was extracted with diethyl ether (2 mL) three times. The organic extracts were washed with brine (4 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (*n*-hexane/methyl acetate = 20:1) to provide the title compound (90.1 mg, 0.424 mmol, 84%) as a colorless oil, whose spectroscopic data were identical to those reported in the literature.[12]

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.40–2.30 (m, 2H), 2.28–2.16 (m, 1H), 2.00–1.86 (m, 3H), 1.79–1.62 (m, 3H), 0.96 (t, 9H, *J* = 7.8 Hz), 0.65 (q, 6H, *J* = 7.9 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 213.0, 42.0, 41.5, 26.6, 25.2, 23.8, 7.4, 3.3.

1,4-Diphenylbutane (3) from the commercially available LDA.

A flame-dried 500-mL two-necked flask equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with *tert*-BuOK (2.81 g, 25.0 mmol, 2.5 equiv) and anhydrous *n*-hexane (40.0 mL). To the solution was added LDA (1.5 M in THF/ethylbenzene/heptane, 16.7 mL, 25.0 mmol, 2.5 equiv) dropwise and the mixture was stirred at room temperature for 30 min. To the reaction mixture was added silyl enol ether **4** (2.13 g, 10.0 mmol, 1.0 equiv), and the resulting mixture was stirred at room temperature for 1 h, at which time TLC (*n*-hexane/diethyl ether = 9:1) indicated complete consumption of the starting silyl enol ether. To the reaction mixture was added anhydrous THF (40.0 mL). After cooling to –78 °C, the resulting mixture was treated with Comins' reagent (7.86 g, 20.0 mmol, 2.0 equiv) in THF (24.0 mL) dropwise. The reaction mixture was warmed to room temperature. After stirring for 1 h at room temperature, the resulting mixture was treated with water (40 mL). After partitioned, the aqueous layer was extracted with diethyl ether (40 mL) three times, washed with brine (80 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (*n*-hexane) followed by preparative SEC-HPLC to provide 6-(triethylsilyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (**1**)[12] (2.24 g, 6.50 mmol, 65%) as a colorless oil and 1,4-diphenylbutane (**3**)[16] (62.0 mg, 0.316 mmol) as a colorless oil, whose spectroscopic data were identical to those reported in the literatures.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31–7.23 (m, 4H), 7.21–7.11 (m, 6H), 2.68–2.57 (m, 4H), 1.74–1.61 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 142.7, 128.5, 128.4, 125.8, 35.9, 31.2.

6-(Triethylsilyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (1).

A flame-dried 500-mL two-necked flask equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with diisopropylamine (3.52 mL, 25.0 mmol, 2.5 equiv) and anhydrous THF (4.0 mL). After the resulting solution was cooled to –78 °C, *n*-BuLi (1.57 M in *n*-hexane, 15.9 mL, 25.0 mmol, 2.5 equiv) was added to the flask. The mixture was then warmed to 0 °C and stirred for 30 min. The resulting LDA solution was warmed to room temperature. To the solution were added anhydrous *n*-hexane (62.2 mL) and *tert*-BuOK (2.80 g, 25.0 mmol, 2.5 equiv). After stirring at room temperature for 30 min, the reaction mixture was treated with silyl enol ether **4** (2.11 g, 9.93 mmol, 1.0 equiv), and the resulting mixture was stirred at room temperature for 1 h, at which time TLC (*n*-hexane/methyl acetate = 9:1) indicated complete consumption of the starting silyl enol ether. To the reaction mixture was added anhydrous THF (40 mL). After cooling to –78 °C, the resulting mixture was treated with Comins' reagent (7.86 g, 20.0 mmol, 2.0 equiv) in THF (30 mL) dropwise. The reaction mixture was warmed to room temperature. After stirring for 1 h at room temperature, the resulting mixture was treated with water (60 mL). After partitioned, the aqueous layer was extracted with *n*-hexane (40 mL) three times. The organic extracts were washed with brine (80 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (*n*-hexane) to provide the title compound (2.49 g, 7.24 mmol, 73%) as a colorless oil, whose spectroscopic data were identical to those reported in the literature.[12]

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.68–5.60 (m, 1H), 2.27–2.16 (m, 1H), 2.15–2.01 (m, 2H), 2.00–1.90 (m, 1H), 1.72–1.60 (m, 2H), 1.56–1.41 (m, 1H), 0.97 (t, 9H, *J* = 7.8 Hz), 0.66 (q, 6H, *J* = 7.8 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.2, 118.7 (q, $^1J_{C\text{-}F}$ = 319 Hz), 115.2, 26.1, 25.6, 24.3, 21.4, 7.5, 3.0.

2-(Triethylsilyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (2).

A flame-dried 500-mL two-necked flask equipped with a Teflon-coated magnetic stirring bar, a rubber septum, and a three-way stopcock was charged with diisopropylamine (3.52 mL, 25.0 mmol, 2.5 equiv) and anhydrous THF (4.0 mL). After the resulting solution was cooled to –78 °C, *n*-BuLi (1.57 M in *n*-hexane, 15.9 mL, 25.0 mmol, 2.5 equiv) was added to the flask. The mixture was then warmed to 0 °C and stirred for 30 min. The resulting LDA solution was warmed to room temperature. To the solution were added anhydrous *n*-hexane (62.2 mL) and *tert*-BuOK (2.80 g, 25.0 mmol, 2.5 equiv). After stirring at room temperature for 30 min, the reaction mixture was treated with silyl enol ether **4** (2.11 g, 9.93 mmol, 1.0 equiv), and the resulting mixture was stirred at room temperature for 1 h, at which time TLC (*n*-hexane/methyl acetate = 9:1) indicated complete consumption of the starting silyl enol ether. To the reaction mixture was added distilled water (0.270 mL) and anhydrous THF (40.0 mL). After stirring at room temperature for 1 h, the reaction mixture was cooled to –78 °C. To the solution was added Comins' reagent (7.85 g, 20.0 mmol, 2.0 equiv) in THF (30 mL) dropwise. After stirring for 1 h at room temperature, the resulting mixture was treated with water (60 mL). After partitioned, the aqueous layer was extracted with *n*-hexane (40 mL) three times. The combined organic extracts were washed with brine (80 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (*n*-hexane/diethyl ether = 19:1) to provide the title compound (1.81 g, 5.25 mmol, 53%) as a colorless oil, whose spectroscopic data were identical to those reported in the literature.[12]

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.48–2.37 (m, 2H), 2.23–2.13 (m, 2H), 1.80–1.70 (m, 2H), 1.61–1.51 (m, 2H), 0.94 (t, 9H, *J* = 7.8 Hz), 0.72 (q, 6H, *J* = 7.8 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.3, 125.7, 118.5 (q, $^1J_{C-F}$ = 318 Hz), 29.0, 28.5, 23.2, 21.9, 7.4, 3.0.

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Supporting Information

YES

Primary Data

No

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