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# Thermal Conversion of Phorone into Isophorone via (Trimethylsilyl)oxyhexatriene (SOH) Cyclization

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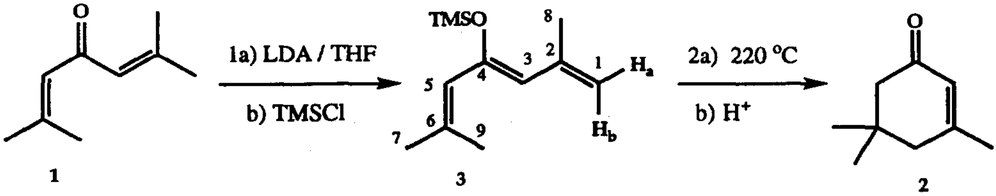
**Summary:** Heating of 3-Z-4-(trimethylsilyl)oxy-2,6-dimethylhepta-1,3,5-triene, readily available from phorone (LDA; TMSCl), at 220 °C caused isomerization and cyclization to afford isophorone after deprotection.

The development of methods for the synthesis of cyclohexenones remains one of the most important endeavors of the synthetic organic chemist.[3-5] Based on earlier findings of Scanio[6] and Yoshikoshi,[7] Magnus proposed a general approach to the annulation of cyclohexenones involving the thermal conversion of enolates derived from acyclic dienones.[8] It was not until recently that we[9] and Fehr[10] were able to demonstrate the viability of Magnus' proposal. We reported[9] that at 110 °C the all-cis[11] enolate of a fully conjugated dienone undergoes a hexatriene-like cyclization[12] at a very slow rate. The silyl enol ether is also resistant to cyclization at 110 °C.[9] The electronic bias against thermal cyclization of these electron-rich hexatrienes could be overcome using palladium catalysts.[9] The palladium-mediated cyclization of silyl enol ethers of dienones is especially interesting because the all-cis geometry is not required. With *trans*-(trimethylsilyl)oxyhexatrienes[11] (*trans*-SOHs), cis/trans isomerization occurs under the reaction conditions and cyclization was shown to proceed, albeit in low to moderate yields. Shortly thereafter, Fehr showed that all-cis SOHs undergo thermal cyclization in the absence of palladium catalysts using flash pyrolytic conditions (0.8 mL/min, 365 °C),but apparently the trans isomers were returned unchanged.[10]

The cyclization of *cis*-(trimethylsilyl)oxyhexatrienes has been developed into a general approach to cyclohexenone annulation. However, the unreliability of the cyclization of *trans*-SOHs severely limits its usefulness. Herein we report that the *trans*-SOH derived from phorone will undergo thermal cis/trans isomerization followed by cyclization at 220 °C in xylenes to afford isophorone in good yield after deprotection.

## RESULTS AND DISCUSSION:

Phorone (*1*) was chosen as the model dienone for optimization of the *trans*-SOH cyclization both because *1* and isophorone (*2*), the product of the cyclization, are readily available, and because the synthesis of *2* from *1* is a problem of continuing interest.[13-16] Treatment of phorone with LDA in THF at -78 °C followed by quenching of the resulting enolate with TMSCl afforded SOH *3* as a single isomer (84% yield). The NOESY spectrum of SOH *3* showed correlations



between the C-8 methyl (δ 1.91) and the silyl methyls (δ 0.11), as well as the vinylidene protons at 4.69 ($H_a$) and 4.93 ($H_b$) ppm. Similarly, difference NOE enhancements were observed for protons at 5.80 (C-5), 1.91 (C-8) and 1.77 (C-9) ppm on irradiation at 5.00 (C-3) ppm, and for protons at 5.00 (C-3), 4.69 ($H_b$) and 0.11 (TMS) on irradiation at 1.91 ppm. Deprotonation of phorone with LDA in THF must be chelation controlled via the *s*-cis conformer.

Treatment of *trans*-SOH *3*under our previous conditions ($Pd(PFu_3)_2Cl_2$, tol, 110 °C; then $H^+$, $H_2O$, THF) afforded a 1:7 mixture of isophorone and phorone. Attempts to improve the cyclization by varying the stabilizing ligand either had little effect ($PPh_3$, $P(o\text{-tol})_3$, dppe, $P(OPh)_3$) or lowered the yield of isophorone to the trace level ($PBu_3$, dppp, dppf, $P(OMe)_3$, $P(Oi\text{-}Pr)_3$, bipy, ethylenediamine). Varying the solvent at 110 °C (sealed tube) also either had little effect (THF, $CH_2Cl_2$) or lessened the yield of isophorone (HMPA, 1,2-dichloroethane, $CCl_4$). Reaction in the presence of Wilkinson's catalyst ($Rh(PPh_3)_3Cl$) in toluene at 110 °C afforded only traces of cyclized product, and $Ru(PPh_3)_3Cl_2$ gave 2 and *1* in a 1:3.3 ratio.

As the reaction temperature is increased, the proportion of cyclized product changes dramatically (Table 1). At 140 °C the reaction in the presence of a Pd(II) catalyst affords a 3:2 mixture of 2 and *1* (entry 2). At 140 °C palladium clearly mediates the cyclization, as indicated by the observation of only trace levels of phorone after thermolysis in the absence of a palladium catalyst (entry 4).

Cyclization of *3* at 220 °C in the presence of 5 mol% $Pd(PFu_3)_2Cl_2$ ($Pd(CH_3CN)_2Cl_2/2\ PFu_3$) caused the ratio of isophorone to phorone to increase to 54:1 (entry 3). To our surprise, this effect was also observed in the absence of a catalyst. On heating the non-catalyzed reaction mixture at 220 °C ($NH_4OH$ washed sealed tube) three isomeric silyl enol ethers were observed by GC/MS, which upon treatment with 10% HCl afforded isophorone as the only product observed (53% isolated yield, entry 5). The highest yield of isophorone could be obtained by heating Z-SOH 3 at 220 °C in the presence of 10% Pd/C (5 mol% based on Pd, entry 8). In this case, the majority of the initial product was deprotected during the reaction and brief treatment with acid afforded isophorone. As before, lower temperatures led to diminished yields of 2. Interestingly, use of toluene or benzene at 220 °C (sealed tube) also caused the ratio of cyclised product to acyclic dienone to drop (compare entries 8-10).

The cross-over in the requirement for palladium catalysts between 140 and 220 °C suggests a change from a palladium-mediated mechanism to a thermal isomerism/cyclization mechanism. Thermal isomerizations are well precedented, with carbon-substituted hexatrienes reported to undergo cis/trans equilibration at 200-300 °C.[17]

**Table 1.** Catalyzed and Uncatalyzed Thermal Cyclizations of SOH **3** [a]

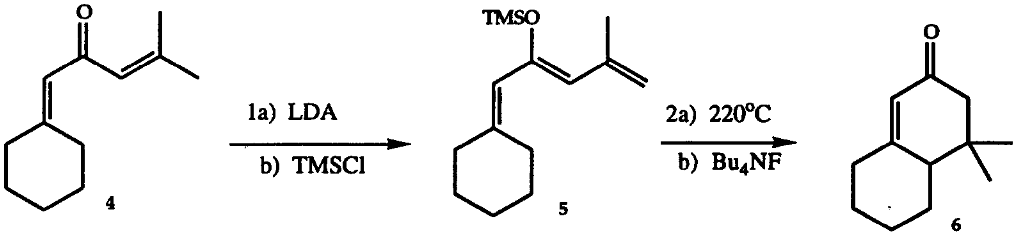
| Entry | Catalyst | Solvent | Reaction Temperature (°C) | Ratio of **2** : **1**[c] | |
|---|---|---|---|---|---|
| 1 | $Pd(CH_3CN)_2Cl_2$ / 2 $PFu_3$ | toluene | 110[b] | 1.0 : 6.7 | |
| 2 | $Pd(CH_3CN)_2Cl_2$ / 2 $PFu_3$ | xylenes | 140[b] | 1.5: 1.0 | |
| 3 | $Pd(CH_3CN)_2Cl_2$ / 2 $PFu_3$ | xylenes | 220 | 54 : 1.0 | |
| 4 | none | xylenes | 140[b] | 1.0 : 49 | |
| 5 | none | xylenes | 220 | >50 : <1 | (53) |
| 6 | $PdCl_2$ | xylenes | 220 | >50 : <1 | |
| 7 | 10% Pd/C | xylenes | 140[b] | 1.3 : 1.0 | |
| 8 | 10% Pd/C | xylenes | 220 | >50 : <1 | (70) |
| 9 | 10% Pd/C | toluene | 220 | 4.3 : 1.0 | |
| 10 | 10% Pd/C | benzene | 220 | 1.6 : 1.0 | |

a) Reaction of Z-SOH **3** with 5 mol% catalyst in a sealed tube at the temperature indicated for 36 h, followed by 10% HCl. Product ratios determined by gas chromatography.

b) Reaction run in indicated solvent at the reflux temperature.

c) Number in parenthesis refers to isolated yield.

To test the relative rates of SOH cyclization versus 1,7-hydride shift/SOH cyclization, dienone **4**, an unsymettrical phorone analogue, was synthesized from cyclohexanone [a. $(EtO)_2P(O)CH_2CO_2ET$, NaH; b. LiOH; c. $(COCl)_2$; $Bu_3SnCH{=}C(CH_3)_2$, $Pd(AsPh_3)_4$] and treated with LDA in THF at -78 °C, followed by quenching with TMSCl/$Et_3N$ to give SOH **5** as the only isomer observed (99% isolated yield). Heating of a xylenes solution of SOH **5** to 220 °C in the absence of a palladium catalyst, followed by deprotection ($Bu_4F$) afforded bicyclic enone **6** (53% isolated yield). The result of a tandem isomerization/1,7-hydride shift/SOH cyclization, as the only cyclized product observed.



In conclusion, we have found thermal conditions for the cyclization of (trimethylsilyl)oxyhexatrienes derived from phorone. Where relevant, a 1,7-hydride shift may occur, resulting in a change or mixture of products. Studies on the scope and limitations of this process, as well as the application of the reaction to the total synthesis of (+)-adrenosterone will be reported in due course.

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