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A Short Conversion of Cyclohexanones to Cycloheptenones

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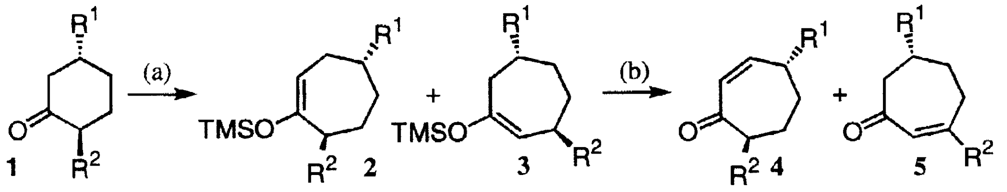
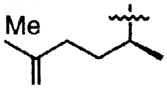
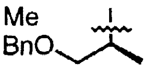
Abstract: Cycloheptenones are efficiently prepared from cyclohexanones *via* organoaluminum-promoted ring enlargement with trimethylsilyldiazomethane and subsequent palladium(II)-catalyzed dehydrosilylation. © 1998 Elsevier Science Ltd. All rights reserved.

Cycloheptenones are suitable building blocks for the hydroazulene skeleton[1] which is an important structural unit found in a variety of natural products with interesting biological activities.[2] In the course of our studies on the total synthesis of defense substances of higher termites,[3] we needed an access to C7-substituted 2-cyclohepten-1-ones. Our attention was drawn to the one-carbon homologation of α-substituted cyclohexanones with insertion of a methylene group predominantly at the less hindered side. A ring enlargement featuring this regioselectivity can be achieved with trimethylsilyldiazomethane (TMSCHN$_2$) in the presence of boron trifluoride etherate[4] or with diazoalkanes promoted by organoaluminum Lewis acids.[5] Since the products initially formed with TMSCHN$_2$ are trimethylsilyl enol ethers, it seemed reasonable that a subsequent palladium(II)-catalyzed dehydrosilylation[6] would directly lead to the desired cycloheptenones. In this communication we report that a combination of homologation and dehydrosilylation indeed provides a short alternative to the established multi-step sequence involving an oxidative ring opening of a cyclohexanone-derived silyloxycyclopropane[1,7] (Table).

Table. Ring Enlargement/Dehydrosilylation of Substituted Cyclohexenones[a]



(a) TMSCHN$_2$, Me$_3$Al; (b) 0.5 eq. Pd(OAc)$_2$, 0.5 eq. benzoquinone

		2	:	3	4	:	5	total yield[b] 2 + 3 (%)	total yield[c] 4 + 5 (%)
a (rac)	R^1 = H R^2 = Me	1.9	:	1.0	2.1	:	1.0	98	90
b	R^1 = Me R^2 = ^{i}Pr	1.1	:	1.0	1.1	:	1.0	99	91
c	R^1 = Me R^2 = 	1.2	:	1.0	1.2	:	1.0	99	80
d	R^1 = Me R^2 = BnO 	1.0	:	2.1	1.0	:	2.3	98	69

[a]Isomeric ratios determined by GC analysis of the crude products. [b]Crude yield. [c]Isolated yield after chromatographic purification.

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Thus, the cyclohexanones **1**[8] listed in the Table were treated with trimethylaluminum and $TMSCHN_2$ in CH_2Cl_2, and the resultant trimethylsilyl enol ethers **2**/**3** were oxidized without prior purification using 0.5 eq. palladium(II)-acetate/0.5 eq. benzoquinone in acetonitrile. As anticipated, this methodology directly provided cycloheptenones **4**/**5**, which were isolated after flash chromatography in good to excellent yields.[9] Whereas a small α-substituent (entry a, R^2 = Me) favored insertion at the less hindered side of the carbonyl group to yield **4a** as the major regioisomer, a bulkier side chain (entries b,c) led to a decreased isomeric ratio. Surprisingly, the presence of an oxygen atom in the side chain (entry d) caused a predominant insertion at the more highly substituted side to give **5d** as the major regioisomer. The isomeric ratio of the cycloheptenones **4** and **5**, which can be readily separated by flash chromatography, correlates very well to the ratio of the corresponding enol ethers **2** and **3**. While the nature of the side chain α to the cyclohexanone carbonyl group can moderately influence the regioselectivity of the homologation step, capillary GC and NMR analyses verified that no epimerization occurred for entries b-d under the conditions used.

In a typical reaction, 1.6 mL of a 2 M solution of Me_3Al in hexanes and 30 ml of dry CH_2Cl_2 were cooled to -78 °C, and 298 mg (2.66 mmol) of **1a** in 10 mL of dry CH_2Cl_2 followed by 1.6 mL of a 2 M solution of $TMSCHN_2$ in hexanes were added. The resulting solution was allowed to warm to room temperature overnight. After diluting with 80 mL of pentane, 8 mL of ice-cooled 2.5 % $NaHCO_3$ were slowly added at 0 °C, and stirring was continued for 5 min. The colorless precipitate was removed by filtration, the aqueous layer was separated, and the cold organic layer was washed rapidly with ice-cooled 0.05 N HCl, ice-cooled 2.5 % $NaHCO_3$, saturated NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. To the residue were added 10 mL of acetonitrile, 295 mg (1.3 mmol) of $Pd(OAc)_2$, and 141 mg (1.3 mmol) of benzoquinone, and the mixture was stirred for 24 h at room temperature. After concentrating *in vacuo*, the residue was extracted thoroughly with diethyl ether (3 × 10 mL), the combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo*, and the crude product was purified by filtration over silica gel (pentane/ethyl acetate, 9:1) to yield 290 mg (88 % from **1a**) of **4a**[10] and **5a**[11] as an isomeric mixture.

In conclusion, we have shown that a combination of organoaluminum-promoted ring enlargement with trimethylsilyldiazomethane and palladium(II)-catalyzed dehydrosilylation constitutes a facile method for a short synthesis of cycloheptenones from readily available cyclohexanones. Presumably, an improved regioselectivity can be achieved by varying the nature of the Lewis acid in the first step. Applications to the synthesis of biologically active natural products are in progress.

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8. The cyclohexanones **1a** and **1b** are commercially available. **1c** was prepared from (-)-isopulegol in 25 % overall yield: a: Ac_2O, pyridine, cat. DMAP, CH_2Cl_2, 20 °C; b: (i) Et_2BH, ether, 20 °C, (ii) Et_2Zn, 0 °C, (iii) CuCN·2 LiBr, THF, -78 °C to 0 °C, (iv) methallyl bromide, -78 °C to 20 °C; c: KOH, MeOH, 20 °C; d: PCC, CH_2Cl_2, 20 °C. **1d**: Schmid, G.; Hofheinz, W. *J. Am. Chem. Soc.* **1983**, *105*, 624-625.
9. All new compounds were completely characterized by appropriate spectroscopic methods and gave satisfactory exact mass molecular weights. The following compounds have been mentioned previously: **4a**: Shono,T.; Hayashi, J.; Omoto, H.; Matsumura, Y. *Tetrahedron Lett.* **1977**, 2667-2670. **5a**: Ilhyong, R.; Matsumoto, K.; Kameyama, Y.; Ando, M.; Kusumoto, N. *J. Am. Chem. Soc.* **1993**, *115*, 12330-12339. **4b**: Murphy, R.; Prager, R.; Rolf, H. *Aust. J. Chem.* **1981**, *34*, 143-150.
10. **4a**: ^1H NMR ($CDCl_3$) δ ppm: 6.0 (m, 1 H), 6.6 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ ppm: 132.6 (CH), 146.0 (CH), 206.2 (C).
11. **5a**: ^1H NMR ($CDCl_3$) δ ppm: 5.9 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ ppm: 129.8 (CH), 158.4 (C), 203.7 (C).