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## SYNTHESIS OF 5-SUBSTITUTED 4,5,6,7-TETRAHYDROINDOLES FROM CYCLOHEXANONES

Chang Kiu Lee,<sup>a\*</sup> In-Sook Han Lee,<sup>b</sup> and Wayland E. Noland<sup>c</sup>

<sup>a</sup>Department of Chemistry, Kangwon National University, Chuncheon 200-701,  
S. Korea. E-mail: cklee410@kangwon.ac.kr

<sup>b</sup>Department of Science Education, Kangwon National University, Chuncheon  
200-701, S. Korea. E-mail: ishl@kangwon.ac.kr

<sup>c</sup>Department of Chemistry, University of Minnesota, Minneapolis, MN 55455-  
0431, U. S. A. E-mail: nolan001@umn.edu

**Abstract-** 5-Substituted 4,5,6,7-tetrahydroindoles were prepared from 4-substituted cyclohexanones in three steps: conversion to an enol silyl ether, introduction of a formylmethyl group at 2-C, and the Paal-Knorr pyrrole synthesis by reacting the 1,4-dicarbonyl compounds with ammonia. The substituents are H, methyl, ethyl, *tert*-butyl, methoxy, and phenyl.

### INTRODUCTION

4,5,6,7-Tetrahydroindole may be considered as a 4,5-disubstituted pyrrole and any electrophilic substitution or addition should take place at 2-position.<sup>1</sup> Therefore, the synthesis of tetrahydroindoles seems to be worthwhile because the compounds, once converted to indoles, may be a useful intermediates for the synthesis of various natural products with biological activities. However, there are not many reports of general procedures.

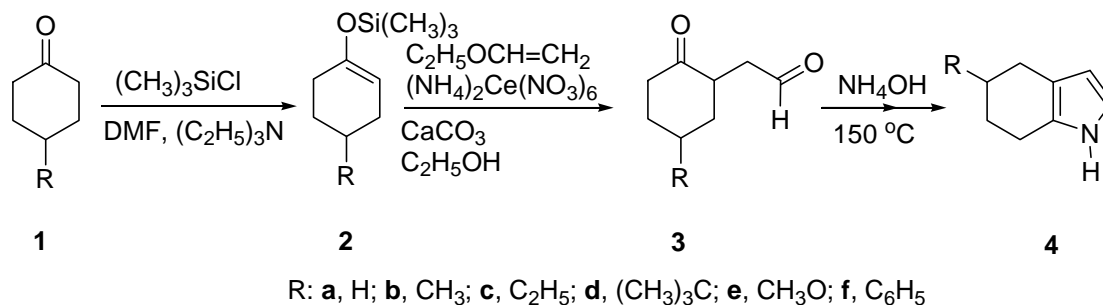
Starting with cyclohexanone dimethylhydrazone Marchetti, *et al.* prepared 1-dimethylamino-4,5,6,7-tetrahydroindole, but the removal of the dimethylamino group was not efficient.<sup>2</sup> Trofimov, *et al.* reported methods by which cyclohexanone oxime was reacted with acetylene or its precursor in KOH and DMSO.<sup>3</sup> However, the methods suffers disadvantage due to the formation of *N*-vinyl derivative of the indole as a side product which needs separation by chromatography. Reaction of cyclohexanone with *O*-(2-hydroxyethyl)hydroxylamine, exchange of the -OH of the oxime with -I using methyltriphenoxyphosphonium iodide, and subsequent cyclization with potassium *tert*-butoxide in *tert*-butyl alcohol seems to work well with unsubstituted cyclohexanone.<sup>4</sup> But it was generally difficult to prepare *O*-(2-hydroxyethyl)hydroxylamine in reasonable yield. Furthermore, purification of the oxime having substituents by distillation under vacuum was difficult due to high boiling points of the products.

Tetrahydroindole can be prepared from 1,3-cyclohexanedione.<sup>5</sup> But the method cannot be applicable for the preparation of 5-substituted compounds because the 4-substituted 1,3-cyclohexanediones may give a mixture of 4- and 6-substituted tetrahydroindoles. 5-Substituted 1,3-cyclohexanedione should give only 6-substituted tetrahydroindole. Therefore, we have investigated a general and efficient synthetic route that may lead to tetrahydroindole. The present paper reports our extensive study on the synthesis of 5-substituted tetrahydroindoles from 4-substituted cyclohexanones.

## RESULTS AND DISCUSSION

Because we were interested in preparing 2,3-unsubstituted 4,5,6,7-tetrahydroindoles, we explored the potential application of the Paar-Knorr synthesis. In order to employ the conventional synthetic method we needed 1,4-dicarbonyl compounds with substituents at suitable positions. Our synthetic approach is illustrated in Scheme 1. The key intermediate is (2-oxocyclohexyl)acetaldehyde (**3**). At first, we attempted the Stork enamine synthesis with 1-pyrrolidinylcyclohexene.<sup>6</sup> To our surprise the yield of the alkylation with bromoacetaldehyde diethyl acetal was less than 10% under a variety of conditions.

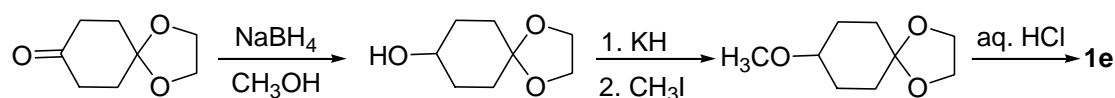
Scheme 1



On the other hand, the Schiff base formed from **1a** and cyclohexylamine did undergo  $\alpha$ -alkylation with the acetal, but the yield was about 50% after distillation under vacuum (lit.<sup>7</sup> 62%). The hydrolysis of both the imine and the acetal to give **3a** was not as effective as reported in the literature. Furthermore, it seems essential to use the imine compound that is purified by distillation under vacuum for LDA-promoted alkylation. Such a purification procedure is a serious disadvantage for the preparation of the imines that have substituents.

The most convenient procedure for the preparation of **3** was the reaction of the enol silyl ether (**2**) with ethyl vinyl ether in the presence of ammonium cerium nitrate (CAN reagent).<sup>8</sup> The procedure was generally applicable for all the ketones employed in the present report. The cyclohexanones (**1**) are commercially available except for **1e**. Compound (**1e**) was prepared from 1,4-cyclohexanedione ethylene glycol monoacetal by modifying the procedure for the synthesis of 4-benzyloxycyclohexanone,<sup>9</sup> as illustrated in Scheme 2.

Scheme 2

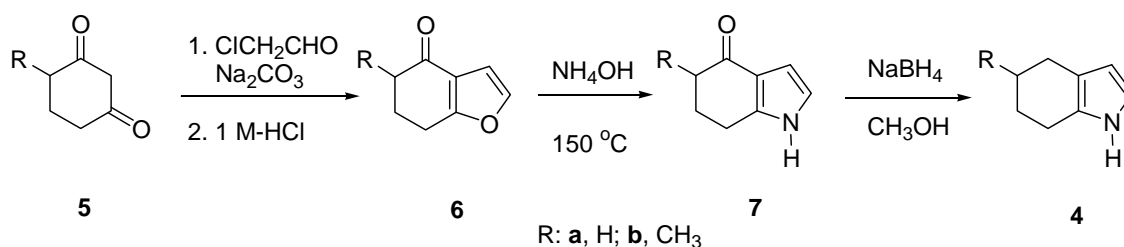


The preparation of the enol silyl ether (**2**) was carried out by using either trimethylsilyl chloride in the presence of triethylamine in DMF for **2a-d**<sup>10</sup> or *N,O*-bis(trimethylsilyl)acetamide<sup>11</sup> in the ionic liquid solution of tetra-*n*-butylammonium bromide. The ionic liquid could be reused for three more times, but it is not recommendable for repeated use because of the contamination by tri-*n*-butylamine which distills out along with **2** during the distillation. The presence of the amine did not cause lowering the yield of the next steps (**2** to **3**, and **3** to **4**), but the impurity was not completely removable by distillation under vacuum without lowering the yield of the final product during the purification.

The Paal-Knorr condensation<sup>12</sup> of the 1,4-dicarbonyl compound (**3**) with ammonia was examined under various conditions. The conventional method<sup>13</sup> of using ammonium carbonate gave only low yield (ca. 10%). Also, there were several compounds in the reaction mixture which seemed to be formed by inter- and intramolecular addition or condensation of **3**, although we have not thoroughly characterized the structures of the side products. The best yield was achieved by heating **3** with 28%-NH<sub>4</sub>OH in a sealed stainless steel tube at 150 °C for 12-15 h.

The unsubstituted tetrahydroindole (**4a**) could be prepared from 1,3-cyclohexanedione in a sequence of transformation as shown in Scheme 3.

Scheme 3



The procedure worked fairly well for the preparation of **4a** (ca. 35% from **5a**). However, 4-substituted 1,3-cyclohexanediones are neither commercially available nor easy to synthesize. There is a report of the methylation of **6a** using LDA and CH<sub>3</sub>I to **6b** in 70% yield,<sup>14</sup> but we were not able to separate **6b** from **6a** in reasonable yield. Furthermore, the separation of **7a** and **7b** to achieve analytically pure material was also difficult. The separation of **4a** and **4b** was virtually impossible because of the reasons described below.

The tetrahydroindoles (**4a-e**) are extremely sensitive to air and they turned dark brown when exposed to air. Therefore, it is necessary to distill the reaction mixtures right after the reaction to ensure the

maximum yield. The product should be kept under N<sub>2</sub> in a freezer. The 5-phenyltetrahydroindole (**4f**) was difficult to purify by distillation. Instead, it was purified by chromatography using a silica gel column and eluting with hexane-ethyl acetate (99:1). It was also sensitive to air and the purified yield was usually low (ca. 20%).

The 1,4-dicarbonyl compounds (**3b-f**) have two chiral carbon atoms. The formation of diastereomers is expected. This is the case only with **3e** and **3f**. Although the diastereomers were not separated, the <sup>13</sup>C NMR spectra of **3e** and **3f** clearly show the presence of two sets of peaks corresponding to each of the diastereomers. The chemical shift values of <sup>1</sup>H and <sup>13</sup>C NMR spectra of **2**, **3**, and **4** are listed in Tables 1, 2, and 3, respectively. All assignment were made by DEPT, COSY, and HETCOR spectroscopy.

The mass spectra of the tetrahydroindoles (**4a-f**) show very characteristic fragmentation pattern. All of them show *m/z* 93 as the base peak. Formation of the base peak can be explained by retro-Diels-Alder cleavage as shown in Scheme 4.

Scheme 4

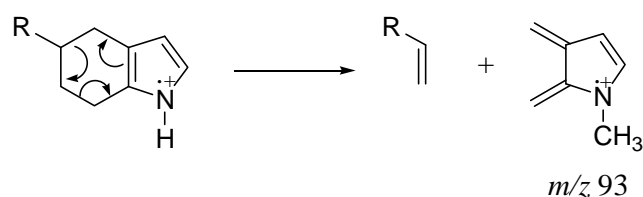


Table 1. <sup>1</sup>H and <sup>13</sup>C NMR Spectral Data of the Enol Silyl Ethers (**2**)

| Position                           | <b>2a</b> (H) | <b>2b</b> (Me)   | <b>2c</b> (Et)              | <b>2d</b> ( <i>t</i> -Bu)                 | <b>2e</b> (OMe)  | <b>2f</b> (Ph)   |
|------------------------------------|---------------|------------------|-----------------------------|---|------------------|------------------|
| OSi(CH <sub>3</sub> ) <sub>3</sub> | 0.17 s        | 0.18 s           | 0.18 s                      | 0.19 s                                    | 0.18 s           | 0.23 s           |
| 2-H                                | 4.88 m        | 4.84 m           | 4.84 t<br>( <i>J</i> = 2.7) | 4.85 dt<br>( <i>J</i> = 5.7,<br>1.8, 2.4) | 4.74 m           | 4.98 m           |
| 3-H                                | 2.0 m         | 1.65 m<br>2.10 m | 1.77 m<br>2.01 m            | 1.82 m                                    | 2.10 m<br>2.18 m | 2.27 m           |
| 4-H                                | 1.85 m        | 1.99 m           | 1.66 m                      | 1.24 m                                    | 3.42 m           | 2.68 m           |
| 5-H                                | 1.52 m        | 1.31 m<br>1.65 m | 1.30 m                      | 1.82 m<br>1.24 m                          | 1.68 m<br>1.95 m | 1.98 m<br>2.10 m |
| 6-H                                |               | 1.65 m           | 2.09 m                      | 2.03 m                                    | 2.10 m           | 1.90 m<br>1.98 m |

|             |            |  |  |  |                               |  |
|-------------|------------|--|--|--|-------------------------------|--|
| Substituent |            | 0.95 d<br>(CH <sub>3</sub> , <i>J</i> = 6.3) | 0.90 t<br>(CH <sub>3</sub> CH <sub>2</sub> , <i>J</i> = 7.2) | 0.88 s<br>(CH <sub>3</sub> ) <sub>3</sub> C  | 3.40 s<br>(OCH <sub>3</sub> ) | 7.2-7.4 m<br>(C <sub>6</sub> H <sub>5</sub> )  |
|             |            |  | 1.30 m<br>(CH <sub>3</sub> CH <sub>2</sub> )                 |  |                               |  |
| 1-C         | 150.37     | 150.15                                       | 150.34   | 150.35                                       | 150.01                        | 150.39   |
| 2-C         | 104.34     | 103.68                                       | 103.70   | 104.11                                       | 100.74                        | 103.76   |
| 3-C         | 23.23      | 32.36  | 29.77  | 25.15  | 29.49                         | 30.25  |
| 4-C         | 23.88      | 31.31  | 35.19  | 44.04  | 75.47                         | 40.04  |
| 5-C         | 22.40      | 28.37  | 28.70  | 24.46  | 29.49                         | 30.21  |
| 6-C         | 29.96      | 29.68  | 30.10  | 32.22  | 28.12                         | 32.03  |
| Substituent | 0.30 (SiC) | 0.34 (SiC)                                   | 0.38 (SiC)   | 0.41 (SiC)                                   | 0.35 (SiC)                    | 0.45 (SiC)   |
|             |            | 21.33<br>(CH <sub>3</sub> )                  | 11.80<br>(CH <sub>3</sub> CH <sub>2</sub> )                  | 27.44<br>(C(CH <sub>3</sub> ) <sub>3</sub> ) | 55.96<br>(OCH <sub>3</sub> )  | 126.12 ( <i>p</i> )<br>127.00 ( <i>m</i> )<br>128.43 ( <i>o</i> )<br>146.76 ( <i>i</i> ) |
|             |            |  | 29.01<br>(CH <sub>3</sub> CH <sub>2</sub> )                  | 31.00<br>(C(CH <sub>3</sub> ) <sub>3</sub> ) |                               |  |

Table 2. <sup>1</sup>H and <sup>13</sup>C NMR Spectral Data of the (2-Oxocyclohexyl)acetaldehydes (**3**)

| Position    | <b>3a</b> (H)               | <b>3b</b> (Me)                              | <b>3c</b> (Et)   | <b>3d</b> ( <i>t</i> -Bu)                     | <b>3e</b> (OMe) <sup>a</sup>             | <b>3f</b> (Ph) <sup>a</sup>               |
|-------------|-----------------------------|---|--|---|--|---|
| 2-H         | 2.40 m                      | 3.01 m                                      | 2.96 m   | 2.98 m  | 2.85 m                                   | 2.56 m                                    |
| 3-H         | 1.44 m, 1.85 m              | 2.42 m                                      | 2.02 m   | 1.22 m<br>2.10 m                              | 1.55 m<br>2.35 m                         | 1.95 m<br>2.25 m                          |
| 4-H         | 2.15 m                      | 2.05 m                                      | 1.74 m   | 1.68 m  | 3.65 m                                   | 3.20 m                                    |
| 5-H         | 1.64 m                      | 1.38 m<br>2.05 m                            | 1.78 m   | 1.40 m<br>2.10 m                              | 1.55 m<br>2.35 m                         | 1.73 m<br>2.25 m                          |
| 6-H         | 2.28 m<br>2.40 m            | 1.21 m<br>2.05 m                            | 2.24 m   | 2.41 m  | 2.35 m                                   | 3.00 m<br>3.20 m                          |
| 7-H         | 2.40 m<br>2.99 m            | 2.20 m<br>2.98 m                            | 2.40 m   | 2.25 m<br>2.98 m                              | 3.65 m                                   | 2.25 m<br>2.56 m                          |
| 8-H         | 9.80 t<br>( <i>J</i> = 5.4) | 9.80 t<br>( <i>J</i> = 1.2)                 | 9.80 t<br>( <i>J</i> = 1.2)                                  | 9.80 t<br>( <i>J</i> = 1.2)                   | 9.80 t <sup>b</sup><br>( <i>J</i> = 1.2) | 9.79 t<br>( <i>J</i> = 0.9)               |
| Substituent |                             | 1.0 d<br>(CH <sub>3</sub> , <i>J</i> = 6.0) | 0.93 t<br>(CH <sub>3</sub> CH <sub>2</sub> , <i>J</i> = 7.5) | 0.91 s<br>(C(CH <sub>3</sub> ) <sub>3</sub> ) | 3.65 s<br>(OCH <sub>3</sub> )            | 7.3 m<br>(C <sub>6</sub> H <sub>5</sub> ) |

|             | 1.33 m<br>(CH <sub>3</sub> CH <sub>2</sub> ) |                             |   |  |                              |                                |
|-------------|--|-----------------------------|---|--|------------------------------|--------------------------------|
| 1-C         | 210.92                                       | 210.00                      | 211.72                                      | 211.25                                       | 210.66<br>(210.55)           | 210.15<br>(211.41)             |
| 2-C         | 43.67  | 44.52                       | 43.67                                       | 44.78  | 36.70<br>(37.92)             | 41.24<br>(36.85)               |
| 3-C         | 27.79  | 41.00                       | 40.92                                       | 35.02  | 39.89<br>(41.41)             | 34.69<br>(31.05)               |
| 4-C         | 24.46  | 31.96                       | 33.28                                       | 47.03  | 73.43<br>(76.66)             | 44.85<br>(43.90)               |
| 5-C         | 25.27  | 35.69                       | 39.75                                       | 28.52  | 30.60<br>(31.44)             | 41.06<br>(36.79)               |
| 6-C         | 41.81  | 42.05                       | 38.44                                       | 41.08  | 36.38<br>(37.53)             | 43.23<br>(38.25)               |
| 7-C         | 45.52  | 43.60                       | 44.53                                       | 43.83  | 43.16<br>(43.46)             | 43.50<br>(41.67)               |
| 8-C         | 200.89                                       | 200.90                      | 200.91                                      | 200.91                                       | 200.17<br>(200.29)           | 200.61<br>(200.43)             |
| Substituent |  | 21.21<br>(CH <sub>3</sub> ) | 11.77<br>(CH <sub>3</sub> CH <sub>2</sub> ) | 27.67<br>(C(CH <sub>3</sub> ) <sub>3</sub> ) | 56.11<br>(OCH <sub>3</sub> ) | 126.83( <i>o</i> )<br>(126.60) |
|             |  |                             | 28.58<br>(CH <sub>3</sub> CH <sub>2</sub> ) | 32.48<br>(C(CH <sub>3</sub> ) <sub>3</sub> ) | (56.53)                      | 128.75( <i>m</i> )<br>(127.64) |
|             |  |                             |   |  |                              | 126.89( <i>p</i> )<br>(126.76) |
|             |  |                             |   |  |                              | 144.29( <i>i</i> )<br>(142.80) |

<sup>a</sup> Values in the parenthesis correspond to a diastereomer present as minor component. <sup>b</sup> 9.78 (t, *J* = 0.9 Hz) corresponding to a diastereomer present as minor component.

Table 3. <sup>1</sup>H and <sup>13</sup>C NMR Spectral Data of the Tetrahydroindoles (**4**)

| Position | <b>4a</b> (H)               | <b>4b</b> (Me)              | <b>4c</b> (Et)              | <b>4d</b> ( <i>t</i> -Bu)   | <b>4e</b> (OMe)             | <b>4f</b> (Ph)              |
|----------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| 1-H      | 7.75 br s                   | 7.80 br s                   | 7.73 br s                   | 7.72 br s                   | 8.20 br s                   | 7.80 br s                   |
| 2-H      | 6.66 t<br>( <i>J</i> = 2.7) | 6.76 t<br>( <i>J</i> = 2.7) | 6.68 t<br>( <i>J</i> = 2.7) | 6.69 t<br>( <i>J</i> = 2.7) | 6.69 t<br>( <i>J</i> = 2.7) | 6.72 t<br>( <i>J</i> = 2.7) |

|             |                         |  |  |  |  |  |
|-------------|-------------------------|--|--|--|--|--|
| 3-H         | 6.03 t<br>( $J = 2.7$ ) | 6.17 t<br>( $J = 2.7$ )  | 6.05 t<br>( $J = 2.7$ )  | 6.07<br>( $J = 2.7$ )  | 6.08 t<br>( $J = 2.7$ )  | 6.08<br>( $J = 2.7$ )  |
| 4-H         | 2.58 m                  | 2.35 m<br>2.80 m   | 2.21 m<br>2.75 m   | 2.36 m<br>2.68 m   | 3.02 dd<br>( $J = 4.8, 15$ )                                       | 2.80 m   |
| 5-H         | 1.80 m                  | 2.02 m   | 1.70 m   | 1.52 m   | 3.77 m   | 3.05 m   |
| 6-H         | 1.80 m                  | 1.67 m<br>2.02 m   | 1.60 m<br>2.00 m   | 1.52 m<br>2.08 m   | 1.98 m<br>2.20 m   | 2.10 m   |
| 7-H         | 2.58 m                  | 2.80 m   | 2.65 m   | 2.68 m   | 2.70 m   | 2.80 m   |
| Substituent |                         | 1.27 d<br>( $\underline{\text{C}}\underline{\text{H}}_3$ , $J = 6.6$ ) | 1.04 t<br>( $\underline{\text{C}}\underline{\text{H}}_3\underline{\text{C}}\underline{\text{H}}_2$ , $J = 7.5$ )<br>1.50 q<br>( $\underline{\text{C}}\underline{\text{H}}_3\underline{\text{C}}\underline{\text{H}}_2$ , $J = 7.5$ ) | 1.03 s<br>( $\text{C}(\underline{\text{C}}\underline{\text{H}}_3)_3$ )   | 3.55 s<br>( $\text{O}\underline{\text{C}}\underline{\text{H}}_3$ ) | 7.3 m<br>( $\text{C}_6\text{H}_5$ )  |
| 2-C         | 115.70                  | 116.20   | 115.99   | 116.14   | 116.91   | 116.28   |
| 3-C         | 107.47                  | 107.40   | 107.47   | 107.66   | 107.56   | 107.39   |
| 3a-C        | 116.93                  | 117.08   | 116.96   | 117.49   | 114.29   | 117.06   |
| 4-C         | 23.96                   | 31.78  | 29.33  | 24.35  | 29.11  | 31.43  |
| 5-C         | 22.86                   | 30.45  | 37.14  | 46.00  | 77.56  | 41.91  |
| 6-C         | 22.99                   | 32.08  | 29.75  | 25.09  | 28.52  | 30.80  |
| 7-C         | 23.55                   | 22.73  | 22.65  | 23.75  | 20.77  | 23.16  |
| 7a-C        | 127.03                  | 126.91   | 127.07   | 127.12   | 125.92   | 126.60   |
| Substituent |                         | 22.13<br>( $\underline{\text{C}}\underline{\text{H}}_3$ )              | 11.90<br>( $\underline{\text{C}}\underline{\text{H}}_3\underline{\text{C}}\underline{\text{H}}_2$ )<br>29.17<br>( $\underline{\text{C}}\underline{\text{H}}_3\underline{\text{C}}\underline{\text{H}}_2$ )                           | 27.70<br>( $\text{C}(\underline{\text{C}}\underline{\text{H}}_3)_3$ )<br>32.68<br>( $\underline{\text{C}}(\underline{\text{C}}\underline{\text{H}}_3)_3$ ) | 56.20<br>( $\text{O}\underline{\text{C}}\underline{\text{H}}_3$ )  | 126.20( <i>p</i> )<br>127.16( <i>o</i> )<br>128.53( <i>m</i> )<br>147.21( <i>i</i> ) |

## EXPERIMENTAL SECTION

IR spectra were obtained using a MIDAC M4000 FT-IR spectrophotometer. NMR spectra were recorded using a Varian 300 MHz FT-NMR spectrometer. Mass spectra were obtained using a MAT 95 mass spectrometer. Elemental analysis was performed by M-H-W Laboratories, Phoenix, Arizona.

**Starting Materials.** Cyclohexanones (**1a-d** and **1f**) were commercial products. Liquid cyclohexanones were dried over Drierite and distilled under vacuum prior to use. All reagents were commercially purchased and used as delivered. The yields and the boiling points of **2-4** are listed in Table 4.

Table 4. Yields and Boiling Points of the Compounds (2-4)

|          | 2                  |             | 3                  |             | 4                  |             |
|----------|--------------------|-------------|--------------------|-------------|--------------------|-------------|
|          | Yield from<br>1, % | Bp, °C/torr | Yield from<br>2, % | Bp, °C/torr | Yield from<br>3, % | Bp, °C/torr |
| <b>a</b> | 60                 | 75-76/20    | 62                 | 55-56/0.1   | 83                 | 64/0.1      |
| <b>b</b> | 55                 | 54-57/4     | 63                 | 74-76/0.2   | 78                 | 72/0.1      |
| <b>c</b> | 67                 | 66-70/0.4   | 59                 | 86/0.15     | 43                 | 65-67/0.1   |
| <b>d</b> | 90                 | 90-94/0.2   | 80                 | 98/0.1      | 64                 | 90-93/0.1   |
| <b>e</b> | 95                 | 38-42/0.5   | 47                 | 92/0.3      | 70                 | 96-97/0.3   |
| <b>f</b> | 92                 | 97-99/0.3   | 60                 | 112-121/0.1 | 20                 | Mp 67-68    |

**4-Methoxycyclohexanone (1e).** A solution of 1,4-cyclohexanedione monoethylene ketal (10.06 g, 64.4 mmol) in MeOH (150 mL) was cooled in an ice-water bath and NaBH<sub>4</sub> (2.58 g, 58.2 mmol) was added in portions. After an exothermic reaction was subdued, the solution was stirred at rt for 3 h. The solution was neutralized with 1.05 M-HCl to pH 7 and then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 200 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. After evaporation of the solvent, 7.31 g of 4-hydroxycyclohexanone ethylene ketal was obtained. The ketal was dissolved in THF (20 mL) and the solution was added to a suspension of KH (9.00 g, 35% in mineral oil before treatment with dried hexane) in THF (120 mL) in an ice salt bath. The mixture was stirred until the evolution of H<sub>2</sub> gas ceased. Iodomethane (4.5 mL, 72.3 mmol) was added. The mixture was stirred at rt for 18 h. Saturated aqueous NH<sub>4</sub>Cl solution (100 mL) was added. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 150 mL). The organic extract was dried over Na<sub>2</sub>SO<sub>4</sub>. After evaporation of the solution, the residual liquid was distilled under reduced pressure to give 4-methoxycyclohexanone ethylene ketal (5.86 g, 75%, bp 56-60 °C/0.3 torr). The ketal was mixed with THF (220 mL) and 1.05 M-HCl (75 mL) and the resulting solution was heated at reflux for 5 h. After cooling the solution was neutralized to pH 7 with a saturated aqueous NaHCO<sub>3</sub> solution (ca. 100 mL). The aqueous solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 × 50 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. After the solvent was evaporated off, the residual liquid was distilled under reduced pressure to give **1e** (4.2 g, 95%, bp 53-55 °C/5 torr; lit.,<sup>15</sup> 86 °C/16 torr).

**An Illustrative Procedure for the Preparation of Enol Silyl Ethers 2. For 2b.** A solution of DMF (distilled at 45-48 °C/20 torr, 170 mL) and triethylamine (distilled over KOH, bp 88-89 °C, 76 mL) was cooled to 0 °C. Trimethylsilyl chloride (35 mL, 0.27 mol) was added followed by the addition of 4-methylcyclohexanone (**1b**, 22.44 g, 0.20 mol). The mixture was gradually brought to rt and then heated at reflux for 3 days. After cooling to rt, the mixture was filtered and the residue was washed with hexane (total 440 mL). The filtrate and the wash were combined and extracted with cold saturated NaHCO<sub>3</sub>



solution (3 × 220 mL), cold 1.5 M-HCl solution (100 mL), and then cold saturated NaHCO<sub>3</sub> solution (100 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>. The dried solution was filtered, concentrated and the residual liquid was distilled under vacuum to give **2b** (26.5 g, 55%, bp 54-57 °C/4 torr).

**An Illustrative Procedure for the Preparation of (2-Oxocyclohexyl)acetaldehyde. For 3b.** Absolute EtOH (200 mL) was cooled to -10 °C and Ce(NH<sub>4</sub>)<sub>2</sub>(NO<sub>3</sub>)<sub>6</sub> (53.1 g, 96.9 mmol) and CaCO<sub>3</sub> (19.5 g, 191 mmol) were added. Ethyl vinyl ether (13 mL) was added while keeping the temperature below -5 °C. A solution of **2a** (12.0 g, 65.3 mmol) in ethyl vinyl ether (53 mL, total 686 mmol) was added dropwise while the temperature was kept at -5 – 0 °C. The mixture was stirred in the cooling bath for 3 h and then filtered through Celite. The filtrate was mixed with EtOH (400 mL) and extracted with CHCl<sub>3</sub> (4 × 100 mL). The solvent was evaporated to dryness. The residual liquid was mixed with 1,4-dioxane (80 mL) and 5%-H<sub>2</sub>SO<sub>4</sub> (80 mL). The mixture was stirred at room temperature for 5 h and then neutralized with saturated aqueous NaHCO<sub>3</sub> solution to pH 7. The aqueous solution was extracted with CHCl<sub>3</sub> (3 × 120 mL) and the organic extract was dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration the solvent was evaporated off. The residual liquid was distilled under vacuum to give **3a** (5.6 g, 63%, bp 74-76 °C/0.2 torr).

**An Illustrative Procedure for the Preparation of 5-Substituted 4,5,6,7-Tetrahydroindoles. For 4b.**

A mixture of **3b** (3.6 g, 23.5 mmol), ethanol (5 mL), and 28%-NH<sub>4</sub>OH (27 mL) was placed in a stainless steel tube and sealed. The tube was placed in an oil bath heated at 150 °C for 12 h. After cooling, the reaction mixture was removed by dilution with EtOH. The EtOH solution was evaporated to dryness using a rotating evaporator under aspirator pressure. The residue was twice coevaporated with absolute EtOH to remove water. The residue was distilled under vacuum to give **4b** (2.47 g, 78%).

**4a.** Mp 53-55 °C (lit.,<sup>16</sup> 53-54 °C); IR, cm<sup>-1</sup>: 3373 s (NH), 3097 w, 2924 vs, 2850 s, 1443 m, 1088 m, 712 m; MS, *m/z* (%): 122 (3), 121 (40, M<sup>+</sup>), 120 (11), 94 (7), 93 (100).

**4b.** IR, cm<sup>-1</sup>: 3359 s (NH), 3098 w, 2954 s, 2925 vs, 2871 s, 2844 m, 1456 w, 1099 m, 711 m; MS, *m/z* (%): 136 (4), 135 (36, M<sup>+</sup>), 120 (4), 94 (8), 93 (100). Anal. Calcd for C<sub>9</sub>H<sub>13</sub>N (135.21): C, 79.95; H, 9.69; N, 10.36. Found: C, 80.06; H, 9.49; N, 10.11.

**4c.** IR, cm<sup>-1</sup>: 3375 vs (NH), 3097 w, 2959 s, 2917 vs, 2851 s, 1462 m, 1444 m, 1090 m, 1062 w, 711 s; MS, *m/z* (%): 150 (4), 149 (34, M<sup>+</sup>), 120 (9), 94 (9), 93 (100). Anal. Calcd for C<sub>10</sub>H<sub>15</sub>N (149.24): C, 80.48; H, 10.13; N, 9.39. Found: C, 80.30; H, 10.20; N, 9.37.

**4d.** IR, cm<sup>-1</sup>: 3379 vs (NH), 3095 w, 2959 vs, 2863 s, 1479 m, 1469 m, 1365 m, 1091 w, 1066 w, 710 m; MS, *m/z* (%): 178 (5), 177 (36, M<sup>+</sup>), 120 (25), 94 (9), 93 (100). Anal. Calcd for C<sub>12</sub>H<sub>19</sub>N (177.29): C, 81.30; H, 10.80; N, 7.90. Found: C, 81.47; H, 10.70; N, 8.00.

**4e.** IR, cm<sup>-1</sup>: 3371 vs, 3096 w, 2954 vs, 2846 s, 1467 m, 1342 m, 1097 vs, 1063 m, 714 s; MS, *m/z* (%): 152 (3), 151 (30, M<sup>+</sup>), 120 (6), 119 (22), 118 (29), 109 (11), 94 (10), 93 (100). Anal. Calcd for C<sub>9</sub>H<sub>13</sub>NO (151.21): C, 71.49; H, 8.67; N, 9.26. Found: C, 71.60; H, 8.82; N, 9.04.

**4f.** IR,  $\text{cm}^{-1}$ : 3475 s, 3085 w, 3063 w, 3029 w, 2920 s, 2850 s, 1675 m, 1594 m, 1493 ms, 1454 m, 1086 w, 702 s; MS,  $m/z$  (%): 198 (6), 197 (36,  $\text{M}^+$ ), 94 (8), 93 (100). Anal. Calcd for  $\text{C}_{14}\text{H}_{15}\text{N}$  (197.28): C, 85.24; H, 7.66; N, 7.10. Found: C, 85.21; H, 7.69; N, 6.80.

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