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# DIASTEREOSELECTIVE REDUCTIONS OF CYCLOHEXANONES WITH DIISOBUTYLALUMINUM 2,6-DI-*t*-BUTYL-4-METHYLPHENOXIDE

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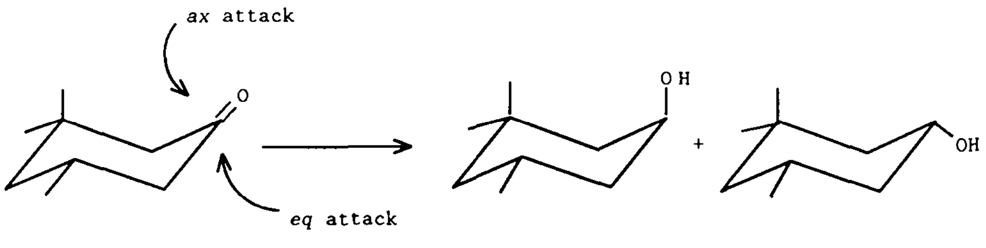
Abstract: Isomerization of aluminum alcoholates occurs in the reduction of cyclohexanones with diisobutylaluminum 2,6-di-*t*-butyl-4-methylphenoxide **1** in the presence of excess ketone. Factors affecting the diastereoselectivity of reduction of cyclohexanones with **1** were investigated.

Diisobutylaluminum 2,6-di-*t*-butyl-4-methylphenoxide **1** has been shown to be a useful reagent for the diastereoselective reduction of ketone intermediates in prostaglandin syntheses[1-4]. To our knowledge few reports have appeared on the utility of this reagent for stereoselective reductions of cyclohexanones. We have explored reductions of 3,3,5-trimethylcyclohexanone **2** (Scheme 1) and 4-*t*-butylcyclohexanone **3** with **1** and show that several experimental factors strongly affect diastereoselectivity with these cyclohexanone substrates. Furthermore, under certain conditions the more stable cyclohexanol epimer becomes the major product as the result of isomerization of aluminum alcoholates. The results obtained are consistent with a proposed mechanism for reductions of ketones with **1**[2].

The substrates chosen for this study have different steric environments about the carbonyl groups. While **3** is relatively unhindered, **2** has an *axial* methyl group which partially shields the carbonyl group from *axial* attack.

SCHEME 1



2 *TRANS* *CIS*

Table 1 shows the results of reductions with **1** and with diisobutylaluminum 2,4,6-tri-*t*-butylphenoxide **4** and diisobutylaluminum hydride, DIBAH for comparison. Reduction of **2** with **1** is highly diastereoselective at -80°C using a large excess (10:1 molar ratio) of **1**, affording almost entirely *trans*-3,3,5-trimethylcyclohexanol. High selectivity could be achieved at 0°C with a large excess of reagent. On the other hand, with a moderate excess of reagent (2:1 molar ratio) at 0°C no selectivity could be obtained in the reduction of **2**. These dramatic differences in selectivity emphasize the crucial effect of reagent excess. Possibly more than one molecule of **1** is involved in the reduction process under these conditions. The presence of excess reagent would also be expected to favor a kinetically-controlled product by precluding isomerization promoted by the presence of ketone (see below).

Table 1 Reduction of **2** and **3** with Diisobutylaluminum Aryloxides[a]

| ketone | reagent | reagent/ketone molar ratio | t, °C | time, h | mol% products[b] ketone | *axial* alc |
|---|---|---|---|---|---|---|
| **2** | **1** | 2:1 | 0 | 2 | 3 | 52 |
| **2** | **1** | 11:1 | 0 | 2 | 1 | 91 |
| **2** | **1** | 10:1 | -80 | 2 | <1 | 99 |
| **2** | **4**[c] | 11:1 | -80 | 2 | <1 | 94 |
| **2** | DIBAH | 10:1 | -80 | 2 | 0 | 65 |
| **3** | **1** | 10:1 | -80 | 2 | 2 | 53 |

[a] Reductions were carried out in toluene. [b] Analyses by GC. 3,3,5,5-tetramethylcyclohexanone was used as internal standard. Alcohols are normalized to 100%. Products accounted for 95% or more of the initial substrate **2**. [c] **4** is diisobutylaluminum 2,4,6-tri-*t*-butylphenoxide.

Reduction of **2** with DIBAH, under optimal conditions of reagent excess and low temperature showed much lower diastereoselectivity and afforded only 65% of the *axial* epimer. Reduction of **2** with reagent **4** was highly diastereoselective. This is contrary to reductions of acyclic enones with **4**[2]. Reduction of **3** with **1** showed no stereoselectivity[5]. Selectivity is sensitive to the steric environment of the carbonyl group. Isomerization of initially formed *axial* alcoholate species occurs in the presence of excess ketone. This was demonstrated in an experiment in which excess **2** was added to a reaction mixture following initial reduction of **2** with **1** (Table 2).

Table 2 Time Dependence of Product Isomer Ratio for Reduction of **2** with **1**[a]

| time, h | alcohol composition, mol%[b] | | recovered **2** |
|---|---|---|---|
| | *axial* | *equatorial* | mol% |
| 0.08 | 51 | 49 | 16 |
| 2.23 | 44 | 56 | 7 |
| 26.82 | 19 | 81 | 33[c] |

[a] 5 Mmol of **2** was initially reduced with ca. 10 mmol **1** at 0°C in toluene. [b] Normalized to 100%. [c] An additional 7 mmol **2** was added to the reaction mixture after 3.27 h after which the reaction mixture was allowed to warm to room temperature.

A control experiment was carried out in which **2** was reduced with **1** at -80°C (molar ratio **1**/**2** =12) and the reaction mixture allowed to warm to room temperature. After 66 h there was no change in product composition (94% *axial* alcohol, 1% recovered **2**). Isomerization therefore requires the presence of ketone. In a related experiment 20 mmol **2** were reduced with an equivalent quantity of **1** at 0°C. The reaction mixture was sampled (aliquot 1) and 20 mmol of 4-methylcyclohexanone **5** then added (Table 3). The observed increase in **2** (aliquot 2) corresponds to an oxidation of initially formed alcoholate by **5**[6]. These results are in accord with and support a Meerwein- Ponndorf-Verley type mechanism which has been proposed[2] for reductions with **1**.

Table 3 Reduction of **2** with **1** with Subsequent Addition of **5**

| aliquot | time,h[a] | product composition, mol%[b] | | | |
|---|---|---|---|---|---|
| | | **2** | **6**[c] | **5** | **7**[c] |
| 1 | 0 | 27 | 77 | - | - |
| 2 | 0.3 | 53 | 66 | 64 | 90 |
| 3 | 3.2 | 56 | 72 | 57 | 89 |
| 4 | 14.7 | 49 | 79 | 34 | 92 |
| 5 | 20.9 | 40 | 84 | 23 | 92 |
| 6 | 90 | 27 | 94 | 18 | 92 |

[a] After addition of **5**. Aliquot 1 taken immediately before addition of **5**. [b] Corresponding ketones and alcohols are normalized to 100%. Alcohol isomer ratios are normalized to 100% with values for *equatorial* isomers shown. [c] **6** is *cis*-3,3,5-trimethylcyclohexanol. **7** is *trans*-4-methylcyclohexanol.

## Experimental Section

DIBAH solutions in toluene were obtained from Aldrich Chemical Co. Toluene was refluxed over calcium hydride and distilled and stored under dry nitrogen. 2,6-Di-*t*-butyl-4-methylphenol was obtained from Aldrich (99+%). 2,4,6-Tri-*t*-butylphenol was recrystallized from hexane and from ethanol, m.p. 130-132°C. Ketone **2** was prepared by the oxidation of the commercial alcohol[7]. GC analyses were performed on a HP 7880A gas chromatograph equipped with a flame ionization detector. Retention times of products were compared with those of known compounds on 6' and 24' Carbowax 20M and 6' 10% DEGS columns. *Trans*-3,3,5-trimethylcyclohexanol was prepared by the reduction of **2** with L-selectride[8]. The *cis*-isomer was obtained from Pfalz and Bauer Inc. (97% *cis*). 4-*t*-Butylcyclohexanol isomers were obtained by $LiAlH_4$ reduction of **3**. Other compounds were obtained from Aldrich. Apparatus were flame-dried under dry nitrogen. Manipulations were carried out using syringe techniques.

Reduction of **2** with Diisobutylaluminum 2,6-di-*t*-butyl-4-methylphenoxide **1** at -80°C. A toluene solution of DIBAH (10 mL of 1M DIBAH, 10 mmol) was transferred to a reaction flask (Ace reactor) equipped with a mechanical stirrer, equilibrated addition funnel, septa, and containing a thermocouple well for measuring reaction mixture temperature. A solution of 2,6-di-*t*-butyl-4-methylphenol (2.61g, 11.8 mmol) in 5 mL of toluene was added at ice-water temperature. After 1 h the temperature was lowered with a dry ice-acetone bath. A solution of **2** (0.1420g, 1.0 mmol) in 5 mL of toluene was added dropwise with no marked exothermic effect. The temperature of the reaction mixture was maintained at -80°C for 2 h and then allowed to warm to -9°C over 1 h. The reaction mixture was hydrolyzed with 10% HCl and diluted with ether. The separated aqueous layer was extracted several times with ether and the combined organic solution was washed with sat'd. $NaHCO_3$, sat'd. NaCl and dried over anhyd. $MgSO_4$. The yield determined by quantitative GC analysis with 3,3,5,5-tetramethylcyclohexanone added as internal standard was 95%. The normalized alcohol composition was 98.7% *trans*-isomer and 1.3% *cis*-isomer. Less than 1% of **2** was detected.

## References and Notes

1. Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H. *J. Org. Chem.* **1979**, *44*,1363.
2. Iguchi, S.; Nakai, H.; Hayashi, M.; Yamamoto, H.; Maruoka, K. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3033.
3. Bartmann, W.; Beck, G.; Jahne, G.; Lerch, U.; Wess, G. *Liebigs Ann. Chem.* **1987**, 321.
4. Corey, E. J.; Ohuchida, S.; Hahl, R. *J. Am. Chem. Soc.* **1984**, *106*, 3875.
5. The reduction of **3** with **1** at -78°C was reported to give 72% *equatorial* isomer, ref. 2.
6. Later aliquots showed a decrease in the $C_7/C_9$ molar ratio, probably resulting from preferential condensation reactions of **5**.
7. Eliel, E. L.; Haubenstock, H. *J. Org. Chem.* **1961**, *26*, 3504.
8. Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.