

ASYMMETRIC ALKYLATION OF AN α -KETO ESTER WITH CHIRAL LITHIUM ALKOXY-TRIBUTYLALUMINATES

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Abstract : Lithium tetrabutylaluminate modified by either (-)-N-methylephedrine or Darvon alcohol [(+)-(2S, 3R)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol] readily reacts with phenylglyoxylic acid methyl ester to give the expected α -butyl α -hydroxy ester with a good chemical yield and an optical yield of 43% when Darvon alcohol is used.

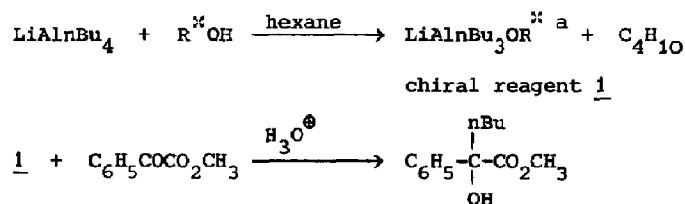
The reaction of an achiral organometallic compound with a chiral α -keto ester to produce chiral α -hydroxyacids has been well studied, and has led to Prelog's generalisation (1).

In a previous report we have shown that aluminium-ate complexes modified by chiral aminoalcohols react with carbonyl compounds to produce chiral alcohols with optical yields up to 44% (2,3).

In the present work we describe a new method of synthesis of chiral α -alkyl α -hydroxy-esters by the reaction of such modified ate complexes with achiral α -keto esters.

The sequence of reactions may be formulated as in scheme 1 :

Scheme 1



^{**} R OH : (-)-N-methylephedrine [α]_D²⁰ 29.5° (methanol c = 4.5)

Darvon alcohol : (+)-(2S, 3R)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol [α]_D²⁵ = + 8.1°
 (ethanol c = 9.55) (4,5,6)

The results obtained are reported in Table 1

^athis formulation only indicates the combining ratio for the reagents used.

Table 1^a

| R ^{**} OH | Solvent | t°C | [α] _D ²⁰ | optical purity % |
|-----------------------|------------------------------|----------|--|------------------|
| (-)-N-methylephedrine | hexane + benzene | 0 | - 3.45° CHCl ₃ c = 11.01 | 9 ^c |
| Darvon alcohol | hexane + THF ^d | 0 | - 0.60° CHCl ₃ c = 12.1 | 1.6 ^c |
| " | hexane + THF ^c | 0 | 0° | 0 |
| " | hexane | 0 | + 16.2° CHCl ₃ c = 12.8 | 43 ^b |
| " | hexane | -78 to 0 | + 15.8° CHCl ₃ c = 9.42 | 40 ^c |

a : chemical yield in α-hydroxy ester (based on α-keto ester) : 80-85%

b : evaluated by NMR with the aid of chiral shift reagent Eu (t.fac.Cam.)₃ (7) after transformation of ester group into methyl group (8)

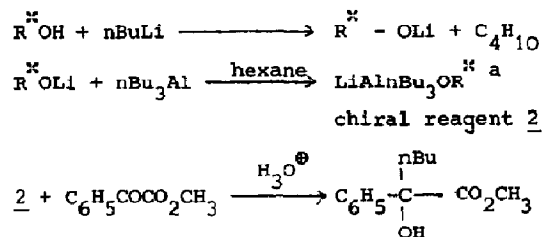
c : Based on [α]_D²⁰ = 16.2° (CHCl₃, c = 12.8)

d : ratio $\frac{\text{THF}}{\text{LiAlnBu}_3\text{OR}^*} = 2$

e : Solvent : 50 ml hexane + 50 ml THF

However, these asymmetric alkylating reagents were also prepared by causing trialkylaluminium to react with lithium alcoholate of aminoalcohol, as reported in Scheme 2.

Scheme 2



a : this formulation only indicates the combining ratio for the reagents used.

Results obtained with chiral reagent 2 are reported in table 2

Table 2 ^a

| R ^x OH | Solvent | t°c | $[\alpha]_D^{20}$ | optical purity % |
|-----------------------|---------|-----|---------------------------------------|------------------|
| (-)-N-methylephedrine | hexane | 0 | - 7.3° CHCl ₃ c = 10.7 | 19 ^b |
| Darvon alcohol | hexane | 0 | + 15.9° CHCl ₃ c = 17.2 | 42 ^b |

a : chemical yield in α -alkyl, α -hydroxy ester : 80 - 85%

b : based on $[\alpha]_D^{20} = + 16.2$ (CHCl₃ c = 12.8)

Typical procedure.

28.6 mmoles (8.09 g) of Darvon alcohol dissolved in 100 ml of hexane were slowly added to 28.6 mmoles of LiAlnBu₄ prepared at 0° under argon by mixing equimolecular amounts of nBu₃Al (0.84 M in hexane) and nBuLi (1.6 M in hexane). Next, 27.1 mmoles (3.85 ml) of phenylglyoxylic acid methyl ester were added. the mixture was stirred for 2 h. at 0°, then hydrolyzed with 75 ml of HCl 2N. The organic layer was washed three times with 20 ml HCl 2 N to completely extract the aminoalcohol which can be recovered almost totally by treating the aqueous layer with K₂CO₃ 2 M followed by ether extraction. After the usual work up of the organic layer and evaporation of the solvent 5.1 g (80%) of crude product was obtained. Analysis by NMR and G.C. showed a purity in α -alkyl, α -hydroxy ester of at least 95%. The α -alkyl, α -hydroxy ester was then purified by preparative G.C. for determination of $[\alpha]_D$. The enantiomeric excess was evaluated as follows : methyl, 2-phenyl, 2-hydroxy hexanoate was reduced into 2-phenyl-1,2-hexane-diol with LiAlH₄. The diol was then transformed into monotosylate (8) which was reduced with LiAlH₄ to give 2-phenyl-2-hexanol. The enantiomeric excess was then evaluated by NMR by means of chiral shift reagent Eu (t.fac.cam.)₃ using the protons of the -2 methyl group.

Results and discussion.

Chiral reagents 1 and 2 readily react at 0° with the α -keto ester to give the expected α -alkyl, α -hydroxy ester with a good chemical yield. It should be noted that using Darvon alcohol chiral reagents 1 or 2 leads to the same optical yield (40-43%), whereas using (-)-N-methylephedrine, chiral reagents 1 gives a 9% optical yield and chiral reagent 2 a 19% optical yield. The results could be related to a difference in structure between reagents 1 and 2 when (-)-N-methylephedrine was used as we suggested before studying the reactivity of reagents 1 and 2 with acetophenone; we found that reagent 2 was far less reactive than reagent 1 and was not able to alkylate acetophenone (3).

Even more interesting is the fact that reagent 2, which reacts with α -keto ester is readily accessible since various trialkylaluminiums are now commercially available.

Owing to the higher reactivity of α -keto esters, the reaction occurs in THF (table 1) whereas we do not observe any reaction in this solvent with ketones. This fact can be very useful in synthesis since it is possible to prepare in THF a great variety of aluminium-ate complexes by hydroalumination with LiAlH_4 of terminal C-C double bonds (9, 10). Unfortunately, in this solvent, no asymmetric induction was observed.

Conclusion.

In this paper, we describe a simple "one pot" synthesis of an optically active α -alkyl, α -hydroxy ester from an achiral α -keto ester. We will now extend our studies in the field of asymmetric alkylation, with the purpose of preparing chiral α -alkyl α -hydroxy ester with high optical purity since a wide range of tetraalkylaluminates or trialkylaluminiums, α -keto esters and aminoalcohols can be tested.

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