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# Asymmetric Synthesis of β-Hydroxy Esters by Reformatsky Reactions and Amide Base Mediated Condensations

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Chiral lithium dialkylamides have been used as bases in asymmetric condensation reactions between acetates and ketones. Generally, the asymmetric inductions obtained from these chiral bases were low. Under the experimental conditions used, lithium ester enolates generated from amide bases and acetates of chiral alcohols gave higher optical yields of *1*, and in most cases also of *2*, than did the Reformatsky reagents obtained from zinc and bromoacetates of the same chiral alcohols.

In 1973 we reported the asymmetric synthesis of (*S*)-(+)-diethyl citramalate (*1*) by condensation of (−)-menthyl acetate with ethyl pyruvate using sterically hindered amide bases as condensating agents.[1] We now report the results of an extended study of this type of reaction. The purpose of this work was two-fold. Firstly, to introduce a new source of asymmetry into the condensations, namely optically active amide bases, and to study their influence, both alone and in combination with optically active acetates, on the optical yields. Secondly, to make a comparison between the optical yields obtained by the major condensation routes to β-hydroxy esters: the reaction of an aldehyde or ketone with (a) an acetate of a chiral alcohol plus an amide base or with (b) a Reformatsky reagent derived from the bromoacetate of the same alcohol.

Thus, ethyl pyruvate and acetophenone were condensed with the acetates of (−)-menthol (*3*), (−)-borneol (*4*) or 1,2:5,6-diisopropylidene-α-D-glucofuranose (*5*) to give, after hydrolysis and esterification, diethyl citramalate (*1*) and methyl 3-hydroxy-3-phenylbutanoate (*2*) respectively. The amide bases were derived from diisopropylamine (IPA), *N*-isopropylcyclohexylamine (ICA), *N*-isopropyl-(−)-menthylamine (IMA), and *N*-isopropyl-(+)-neomenthylamine (INMA). The two latter bases were conveniently prepared in excellent yields by direct alkylation of the corresponding primary amines with 2-iodopropane; no tertiary amines could be detected in the reaction mixtures.

Compounds *1* and *2* were also the products in the Reformatsky reactions of the bromoacetates (*6*–*8*) of the three chiral alcohols mentioned. Tetrahydrofuran was used as solvent in both these and the amide base mediated reactions. The degree of thermodynamic control in the Reformatsky reactions is not known. It is assumed that the stereochemistry of the amide base mediated condensations is kinetically controlled.

## RESULTS AND DISCUSSION

The results are summarized in Tables 1–3. When optically active amide bases are used in the condensation of ethyl acetate with acetophenone or ethyl pyruvate, the resulting condensation products *1* and *2* are obtained in low (<3 %) optical yields. Although low, these optical yields probably indicate that the secondary amine binds to the lithium ion of the lithium ester enolate and thereby promotes asymmetric induction. In most reactions the results obtained by the simultaneous use of optically active amide base and optically active acetate differ only little from those obtained using optically active acetate as the only chiral component. Substantial differences are, however, noted for the reactions involving *5*.

Despite the fact that the acetates *3* and *4* possess the same chiral order of the $R_{small}$, $R_{medium}$, and $R_{large}$

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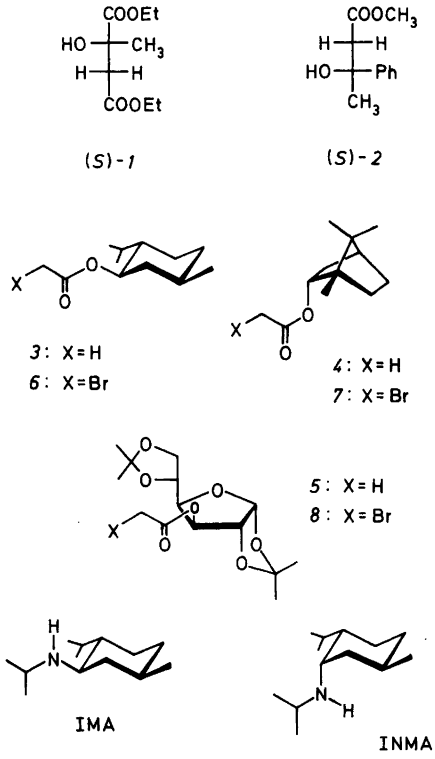


groups bonded to the carbinol carbons, they react with acetophenone by the amide base route to give (*R*)-*2* and (*S*)-*2* respectively in enantiomeric excess (Table 2). Similar results have been obtained in the corresponding Reformatsky reactions with *6* and *7*, both in this work (Table 3) and in other studies,[2] and also in reactions of *3* and *4* mediated by diethylaminomagnesium bromide.[2,3] These anomalous results are not restricted to additions to acetophenone but have also been obtained with other aromatic ketones as well as with benzaldehyde.[2] Our experiments show that this stereochemical effect is unspecific with respect to the nature of the cation; it operates for lithium as well as for zinc or magnesium. A stereochemical control exercized by both α and β chiral centers in *3* and *4* has been proposed in order to account for these results.[2]

On the other hand, we obtained normal stereochemical results in the additions to ethyl pyruvate, both by the amide base (Table 1) and by the Reformatsky route (Table 3). This difference between acetophenone and ethyl pyruvate may possibly be due to the ester group of the latter, which can be expected to associate to the cation of the nucleophilic reagent, thus leading to a higher degree of stereochemical uniformity among the competing transition states than in the case of acetophenone, and hence to normal asymmetric induction.

*Table 1.* Asymmetric synthesis of diethyl citramalate (*1*) by condensation of chiral acetates with ethyl pyruvate. ICA = *N*-isopropyl-cyclohexylamine. IMA = *N*-isopropyl-(−)-menthylamine. INMA = *N*-isopropyl-(+)-neomenthylamine. IPA = diisopropylamine.

| Acetate of | Base | Optical yield/% and configuration of *1* |
|---|---|---|
| (−)-Menthol (*3*) | ICA | 24 *S* |
| | IMA | 25 *S* |
| | INMA | 30 *S* |
| (−)-Borneol (*4*) | ICA | 36 *S* |
| | IMA | 45 *S* |
| | INMA | 30 *S* |
| 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (*5*) | IPA | 35 *S* |
| | IMA | 14 *S* |
| | INMA | 31 *S* |
| Ethanol | IMA | 3 *R* |

The addition of zinc or magnesium salts to solutions of lithium ester enolates strongly affects the steric course of the reactions. In one experiment even a change of predominant enantiomer from (*S*)-*2* to (*R*)-*2* was obtained (Table 2, reactions with *5*). In view of the fact that enolate anions form stronger bonds to halozinc than to lithium counterions, one may expect the addition of zinc bromide to a solution of a lithium ester enolate to lead to the same intermediate as in the Reformatsky reaction. In asymmetric syntheses run under identical conditions, the two techniques should then give identical optical yields. Practically the same optical yields were obtained in syntheses of *2* (14 and 16% enantiomeric excess of (*R*)-*2* respectively), but these results can probably not be compared since different reaction temperatures were used.

In most reactions, the asymmetric inductions obtained from the glucose derivatives *5* and *8* follow those obtained from the bornyl derivatives *4* and *7*, respectively, but one exception is the reaction between *8* and ethyl pyruvate (Table 3). In most reactions, *5* and *8* thus function as though C(4)

*Table 2.* Asymmetric synthesis of methyl 3-hydroxy-3-phenylbutanoate (*2*) by condensation of chiral acetates with acetophenone. Abbreviations: see Table 1.

| Acetate of | Base | Optical yield/%[a] and configuration of *2* |
|---|---|---|
| (−)-Menthol (*3*) | ICA | 1 *R* |
| | IMA | 4 *R* |
| | INMA | 4 *R* |
| | ICA (+$MgCl_2$) | 34 *R* |
| | ICA (+$MgBr_2$) | 29 *R* |
| | ICA (+$ZnBr_2$) | 14 *R* |
| (−)-Borneol (*4*) | ICA | 17 *S* |
| | IMA | 20 *S* |
| | INMA | 21 *S* |
| | ICA(+$MgBr_2$) | 6 *S* |
| 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (*5*) | IPA | 29 *S* |
| | IMA | 49 *S* |
| | INMA | 46 *S* |
| | IPA (+$MgBr_2$) | 8 *R* |
| Ethanol | IMA | 2 *R* |
| | INMA | 1 *S* |

[a] The optical yields are based on a value of $[\alpha]_D$ −8.55° for the pure *S* enantiomer (see Experimental).

were $R_{large}$ and C(2) were $R_{medium}$. This seems to be the natural consequence of the *cis* relationship which exists between substituents on C(3) and C(4) of the furanose ring.

As shown by GLC of the crude reaction mixtures, the low to moderate chemical yields of *1* and *2* are due to incomplete reaction between the starting materials rather than to side reactions of the initially formed reaction products. This means that the optical yields should be reliable despite the fact that only low chemical yields were obtained. In many of the syntheses, a higher optical yield is obtained by the amide base route than by the Reformatsky route. At least part of this difference may be due to the lower reaction temperature used in the former reaction (−70 to 0 °C *vs.* +66 °C).

*Table 3.* Asymmetric synthesis of *1* and *2* by the Reformatsky reaction.

| Bromoacetate of | | Ketone | Optical yield/% and configuration of product |
|---|---|---|---|
| (−)-Menthol | (*6*) | ethyl pyruvate | 8 (*S*)-*1* |
| (−)-Borneol | (*7*) | ethyl pyruvate | 8 (*S*)-*1* |
| 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose | (*8*) | ethyl pyruvate | 6 (*R*)-*1* |
| (−)-Menthol | (*6*) | acetophenone | 16 (*R*)-*2* |
| (−)-Borneol | (*7*) | acetophenone | 14 (*S*)-*2* |
| 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose | (*8*) | acetophenone | 20 (*S*)-*2* |

## EXPERIMENTAL

Melting points are corrected. Spinning band distillations were carried out on a Nester-Faust NFT-51 instrument. Analytical GLC was performed on a Perkin-Elmer 900 chromatograph equipped with a JXR column (3 % on Gas-Chrom Q, 100–120 mesh, 0.2 × 180 cm). Preparative GLC was carried out on an SE-52 column (5 % on Chromosorb AW DMCS, 60–80 mesh, 0.4 × 155 cm) mounted in a Varian Aerograph 1400 instrument. Optical rotations were measured on a Perkin-Elmer 141 polarimeter and NMR spectra were recorded on a Varian XL-100 instrument.

The acetates (*3*,[4] *4*,[5] *5*[6]) of (−)-menthol, (−)-borneol and 1,2:5,6-di-isopropylidene-α-D-glucofuranose, respectively, as well as the bromoacetates (*6*,[7] *7*[7]) of the two first alcohols showed specific rotations and melting points or boiling points close to those given in the literature. The bromoacetate *8* is a new compound which after four recrystallizations from hexane showed m.p. 53.5–55 °C; $[\alpha]_D^{25}$ −30.2° (*c* 1.1, chloroform). Its $^1$H NMR spectrum was in full accord with the assumed structure.

Aldol condensations were carried out in THF starting at −70 to −78 °C as described previously.[1] Reaction mixtures were poured into a solution of the equivalent amount of hydrochloric acid in 0.1 M pH 7.0 phosphate buffer. The mixture was extracted three times with ether and after evaporation of the solvent the residue was treated with potassium hydroxide (1 M) in ethanol–water (1:1, reflux overnight). Most of the ethanol was evaporated and replaced with water. The solution was washed with ether and acidified. In the case of the reactions with acetophenone, the 3-hydroxy-3-phenylbutanoic acid was extracted with ether and weighed to determine the chemical yield (19–69 %). After esterification with diazomethane, the methyl ester was purified by preparative GLC. In the case of the reactions with ethyl pyruvate, the acidic aqueous solution was concentrated and treated as previously described[1] to give diethyl citramalate (*1*). The chemical yield (29–92 %) was determined for the crude diethyl ester and the optical yield on a sample purified by preparative GLC. The yields of 3-hydroxy-3-phenylbutanoic acid and *1* were in some cases checked by $^1$H NMR spectroscopy.

The reactions in which zinc or magnesium salts were used as additives were carried out by adding a solution of the salt (0.9 mol equiv.) in THF to a cold solution of the ester enolate, and then adding the ketone component as usual. The salt solutions were obtained by reaction of the metal with 1,2-dihaloethane in THF.

Reformatsky reactions were carried out by refluxing (18 h) a THF solution (30 ml) of the reaction components (10 mmol each). The products were isolated and analyzed in the same way as those of the reactions mediated by amide bases.

Calculations of optical yields are based on the following specific rotations: $[\alpha]_D^{24}$ +19.4° (*c* 2.2, chloroform) for (*S*)-*1*[1] and $[\alpha]_D^{22}$ −8.55° (*c* 4, ethanol) for (*S*)-*2*.[3] The latter rotation is calculated from $[\alpha]_D$ −4.96° (*c* 3.8, ethanol) which is given[3] for a sample being approximately 58 % optically pure ($^1$H NMR – chiral shift reagent). The corresponding acid showed $[\alpha]_D$ +6.0°, thus indicating a specific rotation of 10.3° for the enantiomerically pure compound.[3] This latter value is somewhat higher than those previously reported: $[\alpha]_D$ +8.92,[7] −8.0,[8] +9.86,[9] or +8.6°[10] (all in ethanol).

*(−)-Menthylamine* was synthesized according to Wallach.[11] However, distillation with steam was omitted and most of the ethanol was evaporated and replaced with water. Extraction three times with ether afforded a crude product which was dissolved in 4M hydrochloric acid. After washing of the acidic solution with ether, the solvent was evaporated and the hydrochloride thus formed was recrystallized three times from water; $[\alpha]_D^{22}$ −31.1° (*c* 2.0, $H_2O$); lit. value:[12] $[\alpha]_D^{17}$ −35.8° (*c* 2, $H_2O$).

N-*isopropyl* (−)-*menthylamine.* A mixture of (−)-menthylamine (8.7 g, 56 mmol), isopropyl iodide (12.4 g, 73 mmol), ethanol (13 g), and anhydrous potassium carbonate (10.0 g, 73 mmol) was refluxed for 4 days. Most of the ethanol was evaporated, water was added and the mixture extracted with ether. Drying ($Na_2SO_4$) and concentration yielded the title amine (10.9 g), approximately 95 % pure (GLC). No impurity with longer retention time could be detected. Spinning-band distillation at 52–54° (0.2 kPa) afforded pure (>99 %, GLC) *N*-isopropyl-(−)-menthylamine, $[\alpha]_D^{23}$ −73.8° (*c* 1.7, chloroform). $^1$H NMR ($CDCl_3$): δ 2.92 (septet, 1H, *J* 5 Hz); δ < 2.44 (26 H).

(+)-*Neomenthylamine* was prepared from (−)-menthyl tosylate, *via* the azide.[13]

N-*isopropyl-(+)-neomenthylamine* was prepared by a method analogous to that for *N*-isopropyl-(−)-menthylamine. The product was distilled on the spinning-band column at 54–56 °C (0.3 kPa); $[\alpha]_D^{22}$ +36.2° (*c.* 2.2, chloroform); purity >99 % (GLC). $^1$H NMR ($CDCl_3$): δ 2.96 (q, 1H, *J* 1.6 Hz); δ 2.82 (septet, 1H, *J* 5.0 Hz); δ < 2.0 (25 H).

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