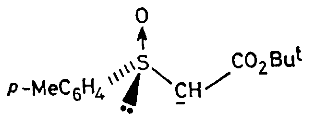
Asymmetric Synthesis of β-Hydroxy-acids Using Chiral α-Sulphinylester Enolate Ions

By Charles Mioskowski and Guy Solladié*

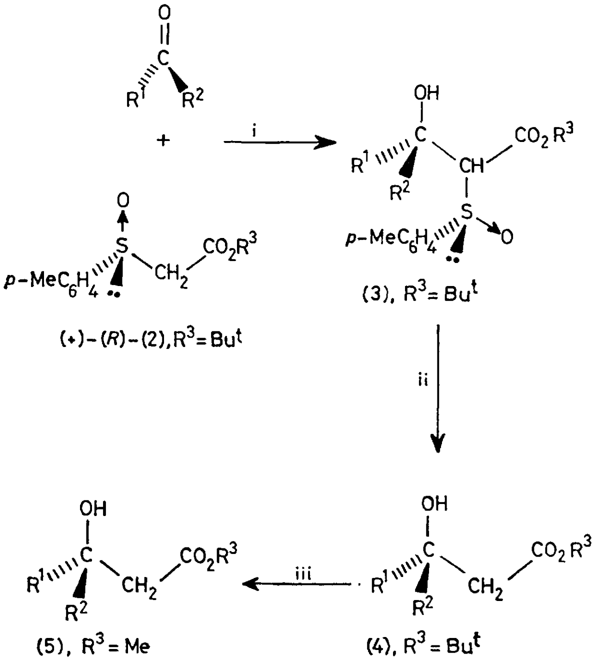
(*Laboratoire de Chimie Organique de l'Ecole Nationale Supérieure de Chimie, Université L. Pasteur, B.P.* 296/*R*8, 67008 *Strasbourg, France*)

Summary Condensation of chiral α-sulphinylester enolate ions with aldehydes and ketones leads to β-hydroxy-acids with high chemical and optical yields.

We have recently developed a stereospecific synthesis of optically active α-sulphinylesters such as (**2**).[1] The corresponding enolate anion (**1**) is comparable with the ethylmalonate anion and is believed to be a powerful nucleophile.



(1)



Scheme. i, Bu^{t}MgBr, THF, −78 °C; ii, Al–Hg; iii, (a) HONa, (b) CH_2N_2.

It has been shown[2] that (**1**) reacts under specific conditions with carbonyl compounds leading to the corresponding addition products. We report that, by using the chirality of (**1**), it is possible to develop an asymmetric synthesis of β-hydroxy-acids from aldehydes and ketones.

To the anion (**1**), prepared by treating (+)-(*R*)-(**2**) with Bu^{t}MgBr in tetrahydrofuran (THF) at −78 °C, were added ketones or aldehydes. After 15 h at −78 °C, the usual work-up gave high yields of (**3**) (Table). The sulphoxide group was removed by treating (**3**) with aluminium amalgam[3] in water–THF, the temperature being maintained between 15 and 20 °C. However, before desulphurization, it is necessary to remove small amounts of the starting aldehyde or ketone by rapid filtration on silica gel (to avoid pinacolic coupling with Al–Hg[4]). That the diastereoisomeric ratio did not change during this operation was shown by the fact that the chemical yield was unchanged (within 5% error) before† and after‡ purification. The resulting t-butyl ester (**4**) was then transformed in nearly quantitative yield into the methyl ester (**5**) of known absolute configuration (Scheme). The optical yields were determined from the optical rotation of (**5**) and were checked by n.m.r. spectroscopy using tris(trifluoromethylhydroxymethylene)-3-(+)-camphorato-europium(III) complex.[5]

The Table shows that the chemical and optical yields in the cases of benzaldehyde, n-octanal, and methyl cyclohexyl ketone have the highest values ever reported for an aldol type condensation.[6–8] Acetophenone did not give good results; 68% asymmetric synthesis is only 10% higher

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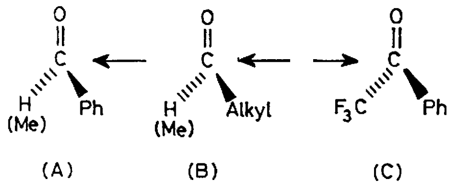
† This was established by n.m.r. spectroscopy [Bu^t protons in crude (**3**) have different chemical shifts from those in (**2**)].

‡ This was established from the amount of recovered (**4**) purified by column chromatography, a technique which does not alter the enantioisomeric ratio (ref. 6), desulphurization being quantitative.

TABLE

R^1	R^2	Yield of (**3**,R^3= Bu^t)/%	$[\alpha]_D$ (EtOH) of (**5**; R^3 = Me)	$[\alpha]_D$ (EtOH) of (**5**; R^3 = H)	Asymmetric synth./%	Absolute configuration of (**5**; R^3 = Me)
H	Ph	85	−16·6° *c* 54·5	−16·4° *c* 4·67	91	(−)-(*S*)[a]
Me	Ph	75	−5·8° *c* 3·59	+7·2° *c* 3·23	68	(−)-(*S*)[b]
Ph	CF_3	75	+1·15° *c* 2·25	−3·57°[f] *c* 2·05	20	(+)-(*R*)[c]
H	n-C_7H_{15}	80	−15·7[f] *c* 2·06	+2·7° *c* 1·65	86	(−)-(*R*)[d]
Me	Cyclohexyl	88	−7·93° *c* 2·65		95[g]	(−)-(*S*)[e]

[a] C. Schopf and W. Wudt, *Annalen*, 1959, **626**, 150. [b] S. Mitsui, K. Kona, I. Onuma, and K. Shimizu, *Nippon Kagaku Zasshi*, 1964, **85**, 440. [c] C. Mioskowski and G. Solladié, *Tetrahedron*, 1973, **29**, 3669. [d] W. L. Parker and M. L. Rathnum, *J. Antibiotics*, 1975, 379 [e] Ref. 7. [f] $CHCl_3$ solvent. [g] Only one enantiomer could be detected by n.m.r. spectroscopy with a chiral shift reagent.



than the value we reported from the condensation of menthyl acetate and Et_2NMgBr.[6] It appears that, in these four cases, the major stereoisomer is formed as a result of the approach of the entering group from the same side of the carbonyl double bond (structures A and B). However, in the case of trifluoromethyl phenyl ketone the nucleophile approaches the carbonyl carbon from the opposite direction (structure C). This, as well as the low optical yield, could be due to the electronic effects of the trifluoromethyl group.[9]

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