

SYNTHESIS OF OPTICALLY PURE α -HALO- α' -SULPHINYL-KETONES

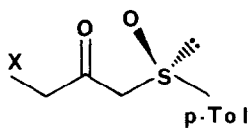
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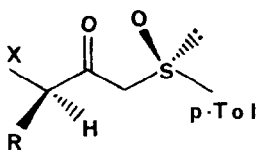
Abstract: when optically pure sulphinyl carbanions are reacted at -75°C with α -chloro or α -bromo carboxylic acid esters addition on the carboxyl group occurs and corresponding α -halo- α' -sulphinyl-ketones are obtained in optically pure form.

When a functional derivative of an α -halogenoacid is treated with a carbanion three main modes of reaction can be followed. Abstraction of the acidic α -proton occurs¹ if the carbanion acts as a base, while displacement of the halogen atom or addition to the carboxyl group can take place alternatively when it behaves as a nucleophile. Stabilized lithium compounds², vinyl copper (I) derivatives³, and alkyl, or aryl, cadmium species⁴ are known to react with α -halo-esters to give alkylation products while Grignard reagents⁵ attack the same halo-esters on the carboxyl group, but α -halogenated tertiary alcohols form normally. Through condensation reactions, α -chloro-ketones can be obtained in good yields only when α -chloro acyl chlorides are reacted with lithium, or magnesium, cuprates^{6,7} or with alkyl cadmium derivatives⁸.

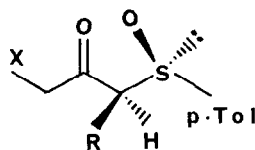
Here we describe how lithium anions obtained from (+)-R-alkyl-p-tolyl sulphoxides (1a-c) condense regioselectively on the carboxyl group of various α -chloro and α -bromo esters (2) to give high yields⁹ of α -halo- α' -sulphinyl ketones which are optically pure only at the sulphur atom (3a-c), at sulphur and α -carbon (3d,e), and at sulphur and α' -carbon (3f-h).



3 a-c



3 d,e



3 f-h

A tetrahydrofuran solution of sulphoxide (1) was added to a slight molar excess of lithium diisopropyl amide in the same solvent maintaining temperature below -75°C . The α -halo-ester (2) was dropped to the yellowish solution of the anion¹⁰ at the same temperature and usual work up gave optically active γ -halo- β -keto-sulphoxides (3a-h) in high yields. Methyl, ethyl, and benzyl esters of both mono-chloro and mono-bromo acids could be employed successfully. Desired products were obtained in low yields, if any, only when we used esters either too sterically hindered (such as *t*-butyl ones) or with very mobile halogens (such as ethyl iodo or tri-bromo acetate). When racemic ethyl α -chloro and α -bromo propionate were employed as nucleophiles R_S -3-chloro (or 3-bromo)-1-(4-methylphenyl)sulphinyl-2-butanones (3d,e) were obtained as a nearly 1:1 mixture of epimers at the halogenated carbon atom and the two diastereoisomers could be easily resolved into single pure compounds through flash chromatography. In order to obtain only the S_C,R_S diastereoisomer from the condensation reaction, we reequilibrated R_C,R_S -3d,e to the thermodynamically stable mixture of epimers at carbon atom through thermal or base catalyzed enolization and proceeded to a new chromatographic separation. Through the application of this sequence our synthesis represents a simple method to convert a racemic α -halo-ester into an α -halo- α' -sulphinyl-ketone enantiomerically pure both at sulphur and at carbon centres. Similarly a mixture of the two compounds epimeric at the α' -carbon was obtained when ethyl and benzyl sulphoxides (1b,c) were condensed with chloro and bromo-acetate. Some preliminary attempts at crystallization resolved the mixture into single compounds in a complete (for 3f) or partial (for 3g, h) manner. Also in these cases the two diastereoisomers can be reequilibrated to the thermodynamically controlled ratio. Structure of obtained products was easily determined through IR and NMR (^1H and ^{13}C) spectroscopies, while circular dichroism was used to determine absolute stereochemistry at the α -carbon atom. In fact α -halo- α' -sulphinyl-ketones (+)-R-(3a-c) which were chiral only at the sulphur atom, showed in acetonitrile solution at room temperature only two absorptions, a positive maximum at 252 nm and a negative one at 220 nm. On the contrary, in spectra of

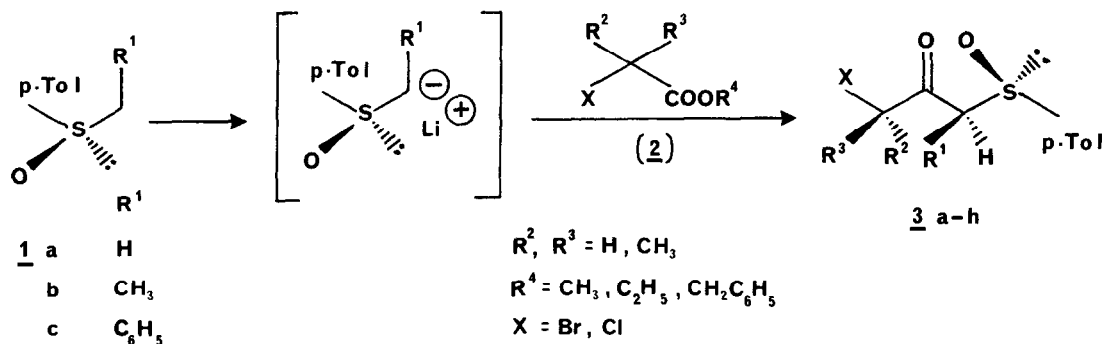


Table - Condensation of lithium sulphinyl carbanions with α -halo-esters ^(a)

Compound	R ¹	R ²	R ³	R ⁴	X	Yield ^(b) %	m.p.(°C) ^(c) (solvent)	$[\alpha]_D^{20}$ (c) ^(d)	¹ H NMR (CDCl ₃) δ_{R^1-C-H} $\delta_{R^2-C-R^3}$
(+)-R-3a ^(e)	H	H	H	C ₂ H ₅	Cl	90	127-129° (AcOEt)	+228 (1.0)	3.96 4.13
(+)-R-3b ^(e)	H	H	H	CH ₃	Br	83 (80,21) ^(f)	125-127° (CHCl ₃ /n-hex.)	+189 (0.7)	4.03 3.97
(+)-R-3c ^(e)	H	CH ₃	CH ₃	C ₂ H ₅	Br	88	82-83° (AcOEt)	+217 (1.0)	4.10 4.43 1.73 1.82
(+)-S _C ,R _S -3d	H	CH ₃	H	C ₂ H ₅	Cl	88 ^(g)	55-57° (AcOEt/n-hex.)	+77 (1.8)	3.95 4.28 1.53 4.33
(+)-R _C ,R _S -3d	H	H	CH ₃	C ₂ H ₅	Cl		liq.	+412 (2.0)	3.95 4.23 1.54 4.34
(-)-S _C ,R _S -3e	H	CH ₃	H	C ₂ H ₅	Br	81 ^(g)	77-79° (AcOEt)	-71 (1.0)	3.51 4.42 1.58 4.46
(+)-R _C ,R _S -3e	H	H	CH ₃	C ₂ H ₅	Br		62-63° (AcOEt/n-hex.)	+382 (1.0)	3.62 4.18 1.71 4.48
(+)-R _S -3f ^(h)	C ₆ H ₅	H	H	C ₂ H ₅	Cl	80	123-125° (CH ₂ Cl ₂ /AcOEt)	+321 (2.0)	5.00 3.88
(+)-(RS) _C ,R _S -3g ⁽ⁱ⁾	C ₆ H ₅	H	H	CH ₃	Br	78	82-90° (AcOEt/n-hex.)	+189 (0.6)	5.07 3.68
(+)-(RS) _C ,R _S -3h ⁽ⁱ⁾	CH ₃	H	H	C ₂ H ₅	Cl	88	44-47° (Et ₂ O/n-pent.)	+104 (1.0)	1.33 4.15

(a) Reported compounds showed expected IR spectra. (b) Values are referred to pure and isolated products. (c) Uncorrected values. (d) All measurements were made in CHCl₃. (e) ¹³C NMR (d₆-DMSO) for (3a): 20.81, 49.91, 64.53, 124.09, 129.80, 139.99, 141.28, 193.77; for (3b): 20.84, 37.25, 64.71, 124.09, 129.80, 140.05, 141.25, 193.27; for (3c): 20.86, 28.42, 28.45, 63.47, 64.59, 124.36, 129.74, 140.75, 141.23, 196.89. (f) Yields in parenthesis are obtained when benzyl and t-butyl esters are used. (g) Yields are referred to the two diastereoisomers. (h) Reported physical data are those of the diastereoisomer obtained in pure form; ¹H NMR resonances for the other are at 4.95 and 4.27 ppm; determination of absolute stereochemistry at carbon atom is being studied. (i) Reported melting points and $[\alpha]_D^{20}$ values refer to a mixture of the two epimers at the carbon atom (approximately 75:25 for 3g and 55:45 for 3h); only ¹H NMR values of the major diastereoisomer are reported.

chlorinated (+)-S_C,R_S-(3d) (mp 55-57°C) and (+)-R_C,R_S-(3d) (liq.) whose absolute stereochemistry was determined through chemical correlation¹¹, a further absorption at longer wavelength was present as a negative maximum (324 nm) and a clear cut positive shoulder (305 nm) respectively. A similar behaviour was observed also in spectra of the two bromine containing diastereoisomers (3e): besides absorptions at 257 and 219 nm a negative maximum at 319 nm was present in the higher R_F compound¹² (mp 77-79°C), while the lower R_F product showed also a positive maximum at 307 nm. The S_C,R_S and R_C,R_S absolute stereochemistry was therefore assigned to them respectively on the assumption that the longer wavelength absorption is due to asymmetric perturbation of ketone chromophore by interaction with the halogenated system.

References and notes

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 9. When we reacted the same lithium anions with lithium bromo acetate (P. Bravo, P. Carrera, G. Resnati, and C. Ticozzi, *Chem. Commun.*, 1984, 19) and lithium bromomethyl acrylate (P. Bravo, G. Resnati, and F. Viani, *Tetrahedron Lett.*, 1985, 2913) the low electrophilicity of the lithium carboxylates disfavoured addition on the carboxyl group and we isolated 3-(4-methylphenyl)sulphinyl carboxylic acids and 4-(4-methylphenyl)sulphinyl-2-methylene-carboxylic acids respectively. A similar reactivity was observed when esters and lithium salts of α -fluoro-carboxylic acids were used as electrophiles.
 10. No differences in chemical yields and reaction times could be observed when the cooled solution of sulphinyl anion was added to the solution of the halo-esters (2) at -75°C.
 11. Condensation of (+)-R-(1a) with (-)-S-methyl-2-chloro-propionate gave a single diastereoisomer (mp 55-57°C) with S_C,R_S absolute stereochemistry.
 12. Silica gel TLC was used and n-hexane/ACoEt = 6/4 was employed as the eluting system.
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