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STEREOCHEMISTRY OF THE CARBONATION OF CARBANIONS α TO A CHIRAL SULFOXIDE

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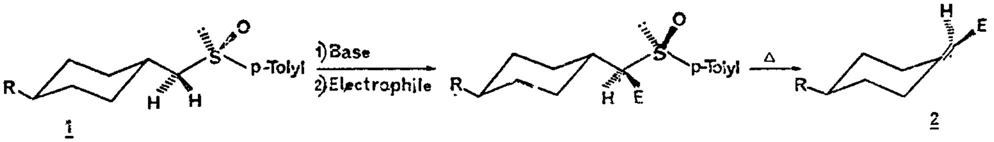
Summary. The carbonation reaction of type 1 sulfoxide anions allowed to synthetize both diastereoisomers of the corresponding sulfinyl esters according to the kinetic or thermodynamic control of the process. Furthermore the stereochemistry of this reaction was shown to be dependent of the amount of lithium salts present in the methylithium used as a base : 90% of asymmetric induction was actually observed under kinetic control by using a low content in lithium salts base, a result consistent with an electrophilic assistance of the lithium cation.

While the ability of sulfur to stabilize negative charges on adjacent carbon atom has been especially important in the development of new ways to form carbon-carbon bonds, the chirality of sulfoxides allowed to extend the synthetic utility of the sulfinylgroup to the field of asymmetric syntheses. However, if asymmetric aldol type condensations of carbanions to chiral sulfoxide have been intensively studied[1] and the results applied to total synthesis of natural products[2,3], alkylation and acylation of such carbanions have mainly been investigated on a fundamental point of view, the application to total synthesis requiring the stereospecific displacement of the sulfoxide moiety on the created asymmetric carbon atom.

Our project (scheme 1) was to introduce stereospecifically an electrophile E^+ in sulfoxide 1 and then to use the cis pyrolytic elimination of the sulfoxide group to obtain, through a chirality transfer, substituted alkylidenecyclohexanes 2, molecules having an axial chirality.



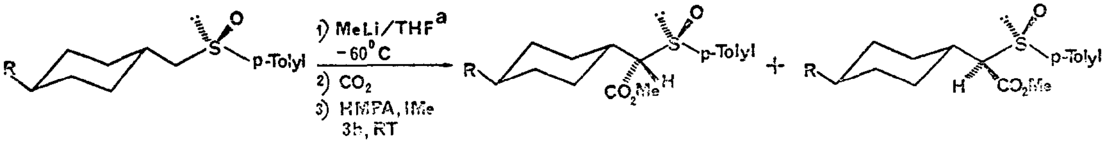
Scheme 1

We report in this communication the study of the stereochemistry of carbonation ($E = CO_2Me$) of type 1 sulfoxide.

Several studies have shown[4-9] that deuteriation and methylation of benzylmethylsulfoxide in presence of methyllithium as a base proceeded, under kinetic control, with a very high degree of stereoselectivity but a reversed stereochemistry which was attributed to the electrophilic assistance of the lithium cation[10]. Furthermore[11] when a low content in lithium salts base is used (methyllithium prepared from methylchloride) the stereoselectivity of the deuteriation of benzylmethylsulfoxide with D_2O is much higher (15:1) than when the base contains one equivalent of lithium salts (methyllithium prepared from methylbromide). Such a salt effect was never observed during the methylation reaction.

Table I

Stereochemistry of carbonation of trans-(+)R-(4-substituted cyclohexyl) methyl p-Tolylsulfoxide



R   SR   RR

R	Solvent	reaction time b)	Yield %	diastereoisomeric ratio SR/RR
CH_3	THF	< 0.5 min.	70	70/30
CH_3	THF	5 min.	90	36/64
CH_3	THF	15 min.	90	30/70
CH_2OMe	THF	< 0.5 min.	89	75/25
CH_2OMe	THF	1 min.	90	65/35
CH_2OMe	THF	2 min.	88	56/44
CH_2OMe	THF	15 min.	87	25/75
CH_2OMe	THF + 8 equi. HMPA	< 0.5 min.	66	57/43
CH_2Cl	THF	< 0.5 min.	70	80/20

a) MeLi Fluka containing 1 mol. equiv. of Li Salt

b) Before quenching with dry ice and including the methyllithium addition.

The only report concerning the carbonation of benzylmethylsulfoxide is due to Nishio[12] who isolated only one diastereoisomer of α-methylsulfinyl phenyl acetic acid but with 30% yield after cristallisation of the crude product. This result cannot be considered as indicative of the reaction stereochemistry and furthermore the described experimental conditions don't indicate if the reaction was under kinetic control.

There is no report in the litterature about any alkylation or carbonation reaction involving aliphatic sulfoxides leading to less stabilized carbanions than benzylsulfoxide.

It is important to recall that methylation of (+)R t-butyl (p-Tolylsulfinyl) acetate proceeded with a very poor stereoselectivity[13] (1:1) probably because of the enolate structure of the anion[14].

We investigated (Table I) the stereochemistry of carbonation of several trans-(+)R-(4-substituted cyclohexyl)-1-methyl p-Tolyl-sulfoxide after metallation with methyllithium Fluka (containing one equivalent of Lithium salts) at -60°C and quenching with carbondioxide (dry ice) followed by esterification with methyl iodide in HMPA.

Yields and diastereoisomeric ratios were determined by ^{1}H NMR from the methyl singlet of the ester group[15]. The absolute configurations were determined by pyrolytic elimination of the sulfoxide moiety, leading to type 2 esters ($E = CO_2Me$) which configuration was known[16] ($R = CH_3$) or deduced from Circular Dichroïsm[17] ($R = CH_2OMe$, CH_2Cl).

Results listed in Table I show that the diastereoisomers ratio, which is around 75/25 under kinetic control, changes to 25/75 under thermodynamic control as the result of the equilibration of the two diastereoisomeric metallated species. When HMPA was added in large excess to the reaction mixture, the stereoselectivity sharply decreased under kinetic control (57/43), a result consistent with an electrophilic assistance of the lithium cation in absence of HMPA.

A salt effect similar to that reported by Durst for the Deuteriation of methylbenzylsulfoxide was shown by using different types of methyllithium (Table II).

TABLE II

Effect of Lithium salt on the stereochemistry of the carbonation of trans (+) R (4-methoxymethylcyclohexyl) methyl p-Tolyl sulfoxide in THF.

type of MeLi	Lithium salt equiv.	reaction time	Yield %	diastereoisomeric ratio SR/RR
Fluka [a]	1	< 0.5 min.	89	75/25
Ventron [b]	7.10^{-2}	< 0.5 min.	79	95/5
Fluka	1	1 min.	90	65/35
Ventron	7.10^{-2}	1 min.	76	80/20
Fluka	1	15 min.	87	25/75
Ventron	7.10^{-2}	15 min.	80	39/61

a) prepared from methylbromide. b) prepared from methylchloride (low content in Lithium salts).

With a low content in lithium salts base (methyllithium Ventron) the stereoselectivity under kinetic control was increased to 90%, the presence of an equimolecular amount of lithium salt decreasing the diastereoisomeric ratio to 75/25. The manner in which the various soluble lithium salts affects the relative amount of each possible species is difficult to rationalize, but these results and those of Durst show that deuteriation and carbonation involve an electrophilic assistance of the lithium cation.

It can be concluded, on a synthetic point of view, that the carbonation reaction of type 1 sulfoxides can be used to prepare both diastereoisomers of the corresponding sulfinyl esters only by performing the reaction under kinetic or thermodynamic control.

The application to the synthesis of optically active substituted alkylidenecyclohexanes will be reported shortly.

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15) ^{1}H-NMR : methyl singlet of the ester group
R = CH_3, 90 MHz, isomer RR $\delta = 3.30$ ppm, RS $\delta = 3.34$ ppm
R = CH_2OCH_3, 200 MHz, RR $\delta = 3.43$ ppm, RS $\delta = 3.46$ ppm.

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