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ASYMMETRIC ADDITIONS OF α-SULFOXIDE CARBANION ON IMINES

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Abstract

The formation of the anion of methyl *p*-tolyl sulfoxide was studied in various experimental conditions. This allowed to get a very good control of diastereoselectivity during addition of the above carbanion on many imines. Various stereoisomerically pure aminosulfoxides have been prepared by this approach.

Optically active sulfoxides are available by various methods and are useful chiral intermediates in organic synthesis (1,2). Since several years, we have studied the asymmetric oxidation of sulfides into sulfoxides and obtained ee's up to 95% in the case of methyl aryl sulfides with a wide variety of aryl groups (3-5). Because of our current interest for aminosulfoxides as ligands of transition metals, we examined the possibility of stereoselectively condensing sulfoxide carbanions on imines. We wish to present our results.

The only report in the literature of such a reaction is the work of Tsuchihashi et al. (6) in 1972. These authors described the deprotonation of methyl *p*-tolyl sulfoxide by $LiN(Et)_2$ at -10°C to -20°C and the condensation on benzylideneaniline at the same temperature. The aminosulfoxide was reported to be diastereomerically pure, as indicated by nmr on the crude material. We have not been able to reproduce this result, but have always observed a diastereomer ratio of 75:25 (measured by nmr at 250 MHz) (7). However, we tried to improve the diastereoselectivity by a proper choice of experimental conditions.

We found that the diastereomer ratio is very dependent of two temperatures : that used during carbanion formation (T_1) and that maintained during the condensation on the imine (T_2). Some data are listed in

Table 1. The optimum conditions were realized by taking T_1 = 0°C and T_2 = -78°C, in which case (entry 4) the diastereomer ratio is 92:8. The condensation reaction is very fast at -78°C, giving an almost quantitative yield after 10 min. Experimental conditions of entry 1 are similar to the conditions of ref.6. The importance of the temperature during deprotonation, for high diastereoselectivity (compare entries 2 and 4), could be related to a reorganization of the organolithium species occuring at higher temperatures.

Table 1

Condensation of (R)-methyl*p*-tolyl sulfoxide anion on benzylideneaniline

	T_1°C[a]	T_2°C[b]	Reaction time	Diastereomeric ratio[c] RR/RS	Yield (%)[d]
1	-15	-15	10 min	75:25	98
2	-40	-78	1.5 h	77:23	88
3	-15	-78	1.5 h	81:19	98
4	0	-78	10 min	92:8	99
5	0	-110	10 min	87:13	73
6	+10	-78	10 min	84:16	93

a : Temperature during deprotonation of (R)-methyl *p*-tolyl sulfoxide by one mol eq of LDA in THF.
b : Reaction temperature, reaction performed in THF.
c : Measured by ^1H nmr on CH_2 α to sulfinyl group.
d : Isolated yield. The product is recovered after hydrolysis at -15°C (entry 1) or -78°C (entries 2-6) by HCl 6N, CH_2Cl_2 extraction and flash chromatography.

At -40°C, the diisopropylamine remains thightly bound to the lithium cation, while, at 0°C the sulfinyl group is able to displace this amine, giving a chelated anion. This hypothesis is similar to the explanation of Ojima (8) concerning the highly diastereoselective methylation of a β-lactam ester when LDA deprotonation is carried out at 0°C instead of -78°C. Condensations on N-alkyl imines are very slow and the best compromise was to work all the time around -20°C.

The steric course of the reaction (S configuration at C) was established by Tsuchihashi (6) by crystallization of the product and hydrogenolysis into (R) N-phenyl α-phenylethylamine.

Using the optimized conditions of Table 1 (entry 4), we extended the reaction to various kinds of imines. Some results are reported in Table 2.

Table 2

Condensation of the (R)-methyl *p*-tolyl sulfoxide anion on ArCH=N-R[a,b]

	Ar	R	Diastereomer ratio[c]	Yield (%)[d]
1	Ph	Ph	92:8	99
2	Ph	*p*-$OMeC_6H_4$	86:14	32
3	*p*-$OMeC_6H_4$	Ph	86:14	30
4	*p*-$OMeC_6H_4$	*p*-$OMeC_6H_4$	95:5	74
5	*p*-$NO_2C_6H_4$	*p*-$OMeC_6H_4$	76:24	95
6	Ph	Me	82:18	84
7	Ph	*n*-Pr	90:10	76
8	Ph	*i*-Pr	88:12	27
9	Ph	Cyclopropyl	84:16	21
10	Ph	*n*-C_5H_{11}	87:13	52

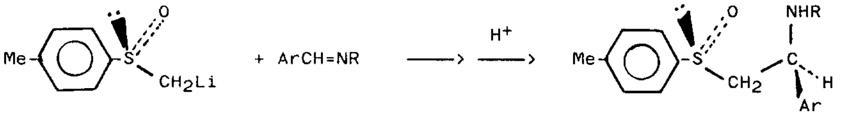
a : Entries 1-5 : Experimental conditions as in Table 1 entry 4. Reaction time is 10 min (entries 1,5), 15 min (entry 2), 20 min (entry 3) or 40 min (entry 4). Hydrolysis at - 78°C by diluted HCl.

b : Entries 6-10 : reaction temperature (deprotonation and condensation) : -20°C. Hydrolysis at - 20°C by diluted HCl.

c : Measured by ^1H nmr.

d : Isolated yield after flash chromatography.

The major diastereomer was always easily purified by crystallization and obtained as a stereochemically pure product. Because of the analogy between the various imines we assumed that the major diastereomer has the configuration R_SS_C (as already established with benzylideneaniline itself (6)). The ^1H nmr similarities between the couple of various compounds is also an argument in favour of the same relative stereochemistry for the major diastereomer.



(R)

1 major
(R=aryl or alkyl)

Table 3

Preparation of stereochemically pure β-amino sulfoxides 1

	Ar	R	Yield (%)[a,b]	mp (°C)	$[\alpha]_D$[c]
1	Ph	Ph	65	217-218	+ 209°
2	*p*-$NO_2C_6H_4$	*p*-$OMeC_6H_4$	60	177-178	- 173°
3	Ph	CH_3	62	102-104	+ 205°
4	Ph	*n*-Pr	53	109-111	+ 196°
5	Ph	*i*-Pr	22	147-149°	+ 207°
6	Ph	Cyclopropyl	25	153-154	+ 264°
7	Ph	*n*-C_5H_{11}	44	87-89	+ 180°

a : Preparation as in Table 2. Recrystallization in cyclohexane.
b : Compounds described have a correct centesimal analysis.
c : In acetone (c=1). For entry 1 $[\alpha]_D$ = +209° in $CHCl_3$ (similar value was given in ref.6).

We are currently looking at the properties of the chiral β-amino sulfoxides as ligands of transition metals. We are also investigating an approach to the stereoselective synthesis of the second diastereomer.

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