of special interest in a number of stereoselective processes\textsuperscript{1,2}. Two approaches have been devised for their preparation, involving either carbon-sulfur or carbon-carbon bond formation. The latter route implies the reaction of an optically active $\alpha$-sulfinylcarbanion with electrophiles such as carboxylates, sulfinites, nitriles, carbonyl derivatives, or Schiff bases\textsuperscript{1,2}.

Surprisingly, no example of optically active $\alpha$-functionalized sulfoxides derived by reaction of $\alpha$-metallated sulfoxides with 1,3-dipoles has been reported so far\textsuperscript{1}. We here describe the first example of such a process, namely the formation of optically active $\beta$-oximino sulfoxides 3 from nitrile oxides\textsuperscript{2} 2 and methyl tolyl sulfoxide (1).

\[ \text{H} \text{C} \text{S} \text{Tol-p} \quad + \quad \text{Ar} \quad \text{C} \equiv \text{N} \equiv \text{O} \quad \xrightarrow{\text{base}} \quad \text{Ar} \quad \text{N} \equiv \text{O} \quad \text{CH}_2 \text{S} \text{Tol-p} \]

\[ \text{(+)-(R)-} 1 \quad 2\text{a-c} \quad \xrightarrow{\text{base}} \quad \text{(+)-(R)-} 3\text{a-c} \]

\[
\begin{array}{ccc}
\text{2} & \text{3} & \text{a} \\
\text{b} & & \\
\text{c} & & \\
\end{array}
\]

\[
\begin{array}{cccc}
\text{Ar} & \text{H}_2\text{C} & \text{Cl} & \text{H}_2\text{C} \\
\text{H}_2\text{C} & \text{Cl} & \text{H}_2\text{C} & \text{Cl} \\
\end{array}
\]

Reaction of enantiomerically pure (+)-(R)-p-tolyl methyl sulfoxide (1)\textsuperscript{1,2} with lithium disopropylamide and subsequent addition of the appropriate nitrile oxide 2 afforded optically active products 3 in good to excellent yield (Method A). Alternatively, the nitrile oxides 2 were prepared in situ by reaction of easily available benzohydroximinoyl chlorides\textsuperscript{4} 4 and lithium disopropylamide (Method B). By this route, which constitutes a method for the sulfurization of oximes, compounds 3a, c, and d (Ar = C\textsubscript{6}H\textsubscript{5}) could be prepared in 70–80% yield (Table 1).

\[
\begin{array}{ccc}
\text{H} \text{C} \text{S} \text{Tol-p} \quad + \quad \text{Ar} \quad \text{C} \equiv \text{N} \equiv \text{O} \quad \xrightarrow{\text{base}} \quad \text{Ar} \quad \text{N} \equiv \text{O} \quad \text{CH}_2 \text{S} \text{Tol-p} \\
\text{(+)-(R)-} 1 \quad 4\text{a-c} \\
\end{array}
\]

\[ \xrightarrow{\text{base}} \quad \text{(+)-(R)-} 3\text{a-c} \]

\[
\begin{array}{cccc}
\text{Ar} & \text{H}_2\text{C} & \text{Cl} & \text{H}_2\text{C} \\
\text{H}_2\text{C} & \text{Cl} & \text{H}_2\text{C} & \text{Cl} \\
\end{array}
\]

The optically active $\beta$-oximino sulfoxides (3) obtained are enantiomerically pure, as shown by $^1$H-N.M.R. spectroscopy with the aid of the chiral shift reagent Eu(hfc), in the case of compound 3d. Moreover, since the ligands at sulfur are not involved in the reaction, the absolute configuration, (+)-(R), can be directly assigned to compounds 3a–d on the basis of the (+)-(R) absolute configuration of 1. This stereoselective reaction is also stereospecific, only one of the two possible (E/Z)-stereoisomers being generally formed. In our opinion the preferred one is the (Z)-isomer because of the possibility of hydrogen bond formation between the oximino and the sulfoxide groups to give a seven-membered cyclic structure for compounds 3. The conformational rigidity of the system is clearly shown by the short relaxation times for both the methylene and the oximino carbons (0.4 and 6.9 sec, respectively), in agreement with previous reports\textsuperscript{5,6}.

Only in the case of 3b could minor amounts of the (E)-isomer be detected and no clear-cut evidence has been obtained to account for this behaviour. $\beta$-Oximino sulfoxides (Z)-3b and (E)-3b showed for the methylene carbons and protons (AB system) two different signals at $\delta = 60.2$ ppm and 3.8 ppm, and $\delta = 64.8$ ppm and 4.0 ppm, respectively (in 20:1 chloroform-d/pyridine).
The assignment of the structure was supported by alkylation experiments carried out on compounds 3 to afford the $O$-benzylated products 5a-d (Table 2).

\[
\begin{align*}
&\text{Ar} \quad \text{CH}_2 \quad \text{C}_6\text{H}_5 \\
&\text{S} \quad \text{N} \quad \text{O} \\
&\text{CH}_2 \quad \text{NH} \quad \text{C}_6\text{H}_5 \\
&\text{Tol} \quad \text{p} \\
\end{align*}
\]

It has been shown\(^{11}\) that alkylation of oximes depends on their configuration: $O$-alkylation is predominant for the (Z)-form, while $N$-alkylation is more likely for the (E)-form. Namely, in compounds such as 6, alkylation at oxygen prevails. Indeed, when we reacted $\beta$-oximino sulfoxides 3a-d with benzyl bromide under phase transfer conditions, $O$-benzyl derivatives 5 were isolated in 49–83% yield, the yield being higher in the case of less sterically hindered substrates.

The reactions of $\alpha$-sulfinylcarbanions derived from 1 with nitrones 7 afford optically active hydroxylamines 8a-c (Table 3).

Also in this case the absolute configuration (R) at sulfur can be directly assigned to compounds 8, since the reaction does not affect the chiral sulfoxide moiety in the conversion 1–8. A new chiral center is formed and the reaction is definitely stereoselective, one of the two epimers being predominant. The diastereomeric ratio, as determined by $^1$H-N.M.R. is 75:25, 82:18, and 100:0, in the case of 8a, 8b, and 8c, respectively. Thus, chiral discrimination is very high, and increases with increasing bulkiness of the R residue of the nitron. The enantiomeric purity at sulfur in compounds 5a-c could not be determined directly by $^1$H-N.M.R. spectroscopy with the aid of various chiral shift reagents. However, it is very likely that also in this reaction the chirality at the sulfoxide group is totally retained. The isolation of a diastereomerically homogeneous product, i.e. 8c, strongly sustains this hypothesis.

The high degree of $\beta$-stereoselectivity observed in the reaction leading to 8a–c prompted us to examine the reaction of a sulfoxide which could also give rise to $\alpha$-asymmetric induction. Therefore we reacted optically active ethyl $\beta$-tolyl sulfoxide (+)-(R)-9 with N-butylnitritolone (7c) to give the hydroxylamino sulfoxide 10 (mixture of two epimers in a 6:1 ratio) in 60% yield.

\[
\begin{align*}
&\text{C}_2\text{H}_5 \quad \text{H} \\
&\text{O} \quad \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \\
&\text{CH} \quad \text{C}_6\text{H}_5 \quad \text{CH} \\
&\text{Tol} \quad \text{p} \\
\end{align*}
\]

\[
\begin{align*}
&\text{C}_2\text{H}_5 \quad \text{H} \\
&\text{O} \quad \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \quad + \quad \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \quad \text{O} \\
&\text{CH} \quad \text{C}_6\text{H}_5 \quad \text{CH} \\
&\text{Tol} \quad \text{p} \\
\end{align*}
\]

\[
\begin{align*}
&\text{C}_2\text{H}_5 \quad \text{H} \\
&\text{O} \quad \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \quad + \quad \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \quad \text{O} \\
&\text{CH} \quad \text{C}_6\text{H}_5 \quad \text{CH} \\
&\text{Tol} \quad \text{p} \\
\end{align*}
\]

\[
\begin{align*}
&\text{C}_2\text{H}_5 \quad \text{H} \\
&\text{O} \quad \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \quad + \quad \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \quad \text{O} \\
&\text{CH} \quad \text{C}_6\text{H}_5 \quad \text{CH} \\
&\text{Tol} \quad \text{p} \\
\end{align*}
\]

\[
\begin{align*}
&\text{C}_2\text{H}_5 \quad \text{H} \\
&\text{O} \quad \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \quad + \quad \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \quad \text{O} \\
&\text{CH} \quad \text{C}_6\text{H}_5 \quad \text{CH} \\
&\text{Tol} \quad \text{p} \\
\end{align*}
\]

\[
\begin{align*}
&\text{C}_2\text{H}_5 \quad \text{H} \\
&\text{O} \quad \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \quad + \quad \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \quad \text{O} \\
&\text{CH} \quad \text{C}_6\text{H}_5 \quad \text{CH} \\
&\text{Tol} \quad \text{p} \\
\end{align*}
\]

\[
\begin{align*}
&\text{C}_2\text{H}_5 \quad \text{H} \\
&\text{O} \quad \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \quad + \quad \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \quad \text{O} \\
&\text{CH} \quad \text{C}_6\text{H}_5 \quad \text{CH} \\
&\text{Tol} \quad \text{p} \\
\end{align*}
\]

\[
\begin{align*}
&\text{C}_2\text{H}_5 \quad \text{H} \\
&\text{O} \quad \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \quad + \quad \text{C}_6\text{H}_5 \quad \text{C}_6\text{H}_5 \quad \text{O} \\
&\text{CH} \quad \text{C}_6\text{H}_5 \quad \text{CH} \\
&\text{Tol} \quad \text{p} \\
\end{align*}
\]
larger difference can be expected [see above, in the case of 3b]. Thus, also in the case of sulfoxide 11 a high degree of stereoselection is achieved.

The optically active sulfoxides 1 and 9 were prepared according to Ref. 2:

\[ (+)-(R): 1; [\alpha]_D^{25} = +189^\circ \quad (c = 1, \text{CHCl}_3); \quad \text{Ref. 11};\]

\[ (+)-(S): 9; [\alpha]_D^{25} = -189^\circ \quad (c = 1, \text{acetone}); \quad \text{Ref. 12};\]

Racemic 1: m.p. 42-43 °C; Ref. 13; m.p. 42-43 °C;

Racemic 9: b.p. 104 °C/0.4 torr; Ref. 14; b.p. 105-105.5 °C/0.4 torr.

Nitrile oxides 2, benzohydroximinoxy chloride 4, and nitrone 7 were prepared according to Refs. 8-10. 4-Methoxyphenyl nitrile oxide (2e) was previously unknown; m.p. 64-65 °C (from ethanol).

C$_7$H$_7$NO$_2$ calc. C 64.43 H 4.70 N 9.40

(149.2) found 64.46 4.60 9.35

Optically Active β-Oximino Sulfonlides 3; Typical Procedures:

Method A: (+)-(R)-p-Tolyl methyl sulfonl (1; 0.368 g, 2.0 mmol) in anhydrous tetrahydrofuran (5 ml) is added dropwise to a cooled (−78 °C), stirred solution of lithium diisopropylamide, prepared from diisopropylamine (0.58 ml, 4.0 mmol) and n-butyl lithium (2.66 ml of a 1.5 normal solution in hexane, 4.0 mmol) in tetrahydrofuran (5 ml). The mixture is allowed to reach −20 °C, cooled again to −78 °C, and treated with the nitrile oxide 2 (2.0 mmol) in tetrahydrofuran (10 ml). After 30 min stirring at −78 °C, the reaction is quenched with saturated ammonia chloride solution (5 ml) and the mixture warmed up to room temperature. The organic phase is separated, dried with sodium sulfate, filtered, and evaporated. The crude material is then chromatographed (silica gel; ether: light petroleum; 7:3) to give the pure products.

Method B: (+)-(R)-p-Tolyl methyl sulfonl (1; 0.308 g, 2.0 mmol) in anhydrous tetrahydrofuran (5 ml) is added dropwise to a cooled (−78 °C) stirred solution of lithium diisopropylamide, prepared from diisopropylamine (0.86 ml, 6.0 mmol) and n-butyl lithium (4.0 ml of a 1.5 normal solution in hexane, 6.0 mmol) in tetrahydrofuran (5 ml). The mixture is allowed to reach −20 °C, cooled again to −78 °C, and reacted with the benzohydroximinoxy chloride 4 (2.0 mmol) at −78 °C; the reaction is quenched and worked-up as described above.

Alkylation of β-Oximino Sulfonlides 3; Typical Procedure:

To a stirred mixture of the β-oxidino sulfonl (3 mmol), dichloromethane (5 ml), 10% sodium hydroxide (1 ml), and benzyl bromide (0.48 g, 4 mmol), kept at room temperature, benzylthiethylammonium bromide (0.045 g, 0.2 mmol) is added. After 1 h stirring (48 h in the case of 3b), water (15 ml) and dichloromethane (15 ml) are added to the mixture, the phases are separated, the organic phase is dried with sodium sulfate, and filtered. The crude mixture is purified by column chromatography (silica gel, ether) to give the products.

β-Hydroxyalamino Sulfonlides 8 or 10: Typical Procedure:

(+)-(R)-Sulfonl 1 or 9 (2.0 mmol) in anhydrous tetrahydrofuran (5 ml) is added dropwise to a cooled (−78 °C), stirred solution of lithium diisopropylamide, prepared from diisopropylamine (0.58 ml, 4.0 mmol) and n-butyl lithium (2.66 ml of a 1.5 normal solution in hexane, 4.0 mmol) in tetrahydrofuran (5 ml). The mixture is allowed to reach −20 °C, cooled again to −78 °C, and treated with the nitronate 7 (2.0 mmol) in tetrahydrofuran (10 ml). The mixture is stirred for 30 min at −78 °C, quenched, and worked-up as described for the synthesis of compounds 3. The products are purified by column chromatography (silica gel, ether).

C$_7$H$_7$NO$_2$S calc. C 69.52 H 7.87 N 4.05

(345.5) found 69.50 7.89 4.02

Racemic β-Oximino and β-Hydroxyalamino Sulfonlides:

Racemic compounds were prepared as described above, but starting from racemic sulfoxides 1 and 9.

Racemic 3d; yield: 75%; m.p. 123-124 °C.

Received: May 3, 1982


3. Only recently, racemic 3 have been prepared by oxidation of the corresponding sulfides. Furthermore the formation of an intermediate β-oximino sulfonl has been postulated in the formation of isoxazole derivatives.


6. A few reports on the reaction of nitrile oxides with carbamions have been published.


