## Synthesis of Enantiomerically Enriched α-Sulfenylated Ketones and Aldehydes

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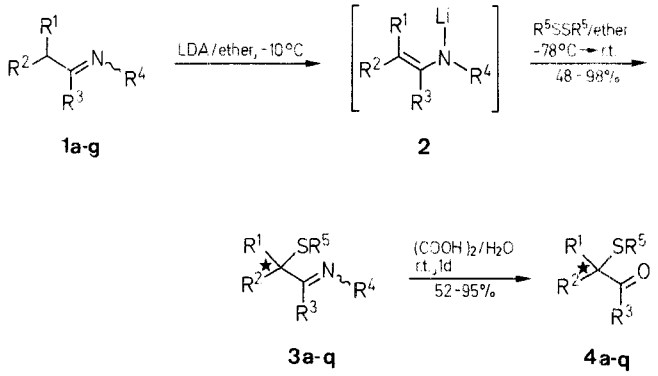
α-Sulfenylated carbonyl compounds are prepared by the reaction of imines of aldehydes and ketones containing α-hydrogens with disulfides *via* the metalloenamines. With (*R*)-α-phenylethylamine as chiral auxiliary, enantiomeric excesses of 13–51% are observed.

Chiral sulfoxides have found widespread use in organic synthesis, particularly for the synthesis of natural products.[1-3] α-Sulfinylketones are compounds of special interest in this respect.[4-6] However. no practical procedure for the preparation of optically active α-sulfinylaldehydes has been reported up to now. In this publication, we wish to present a synthesis of potential precursors of these compounds, α-sulfenylated aldehydes and ketones. In contrast to the α-sulfinylaldehydes,[4] they are stable and easy to handle, and may be oxidized to the corresponding sulfoxides. The chemistry of achiral and racemic α-sulfenylated carbonyl compounds has been reviewed,[7] their preparation *via* metalloenolates and their applications in organic synthesis have been reported.[8] However, this preparation, as well as others already known, e.g. the direct thiolation of ketones,[9] the substitution reactions of α-halogenated carbonyl compounds,[10] and the reaction of aldehydes with special phosphonium ylids,[11] can probably not be extended to obtain enantiomerically enriched compounds.

In analogy to the well-known α-alkylations of imines *via* the metalloenamines,[12] which lead to optically active carbonyl compounds if chiral amines are used for the formation of the imines,[13-15], we studied transformations of the type given below:




1a-g 2 3a-q 4a-q

As only one example for such a reaction sequence has been found in the literature,[16] we first studied the feasibility of the method by preparing achiral or racemic α-sulfenylated aldehydes and ketones (Table 1).

Treatment of an imine **1** with lithium diisopropylamide (LDA) gave the metalloenamine **2** which reacted cleanly with a disulfide to give a α-sulfenylimine **3**. Hydrolysis by dilute oxalic acid afforded the α-sulfenylated carbonyl compound **4**. The introduction of steric hinderance by bulky substituents at the nitrogen atom is essential for high yields, the methyl imine **1c** gave product **4b** in only 25% overall yield, while the *t*-butyl imine **1b** leads to 91% of **4b**. A comparison with procedures for the preparation of α-sulfenylated carbonyl compounds *via*

**Table 1.** α-Sulfenylimines **3** and α-Sulfenylated Carbonyl Compounds **4** from Imines **1** and Disulfides

| Starting Imine | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Imine | Yield (%) | b.p. (°C/torr) | Molecular Formula[b] | Product No. | Yield[a] (%) | b.p. (°C/torr) | Molecular Formula[b] Lit. p.p. (°C)/torr |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1a** | $CH_3$ | $CH_3$ | H | *t*-$C_4H_9$ | 4-$CH_3C_6H_4$ | **3a** | 98 | 86/0.4 | $C_{13}H_{23}NS$ (249.4) | **4a** | 94 | 82/0.6 | $C_{11}H_{14}OS$ (194.3) |
| **1b** | H | *i*-$C_3H_7$ | H | *t*-$C_4H_9$ | 4-$CH_3C_6H_4$ | **3b** | 98 | 95/0.3 | $C_{16}H_{25}NS$ (263.4) | **4b** | 93 | 96/0.6 | $C_{12}H_{16}OS$ (208.3) |
| **1c** | H | *i*-$C_3H_7$ | H | $CH_3$ | 4-$CH_3C_6H_4$ | **3c** | 48 | 80/0.4 | $C_{13}H_{19}NS$ (221.4) | **4b** | 52 | 96/0.6 | $C_{12}H_{16}OS$ (208.3) |
| **1d** | H | $-(CH_2)_4-$ | | *c*-$C_6H_{11}$ | $CH_3$ | **3d** | 97 | 83/0.2 | $C_{13}H_{23}NS$ (225.4) | **4d** | 93 | 62/0.6 | 83–84/6.8[8] |
| **1d** | H | $-(CH_2)_4-$ | | *c*-$C_6H_{11}$ | $C_6H_5$ | **3e** | 98 | 112/0.4 | $C_{18}H_{25}NS$ (287.5) | **4e** | 87 | 106/0.6 | 118/0.04[8] |

[a] Yield of isolated product.

[b] All new compounds gave satisfactory microanalytical data: C ±0.29, H ±0.17, N ±0.18 and consistent mass spectra.

**Table 2.** Optically Active α-Sulfenylated Aldehydes and Ketones 4 from Imines 1 and Disulfides[a]

| Imine | $R^1$ | $R^2$ | $R^3$ | $R^5$ | Product No. | Yield[b] (%) | m.p. (°C) or b.p. (°C/torr) | $[\alpha]_D^{20}$[c] | Molecular Formula[d] or Lit. b.p. (°C/torr) |
|---|---|---|---|---|---|---|---|---|---|
| **1e** | H | $i$-$C_3H_7$ | H | $CH_3$ | **4f** | 88 | 32/1.8 | −19.0 | $C_6H_{12}OS$ (132.2) |
| **1e** | H | $i$-$C_3H_7$ | H | $C_6H_5$ | **4g** | 92 | 93/1.5 | − 8.5 | 93/0.1[11,e] |
| **1e** | H | $i$-$C_3H_7$ | H | 4-$CH_3C_6H_4$ | **4h** | 89 | 86/0.4 | − 5.5 | $C_{12}H_{16}OS$[f] (208.3) |
| **1f** | $C_6H_5$ | $CH_3$ | H | $CH_3$ | **4i** | 93 | 58/0.1 | +12.5 | $C_{10}H_{12}OS$ (180.3) |
| **1f** | $C_6H_5$ | $CH_3$ | H | $i$-$C_3H_7$ | **4j** | 91 | 70/0.1 | +10.0[g] | $C_{12}H_{16}OS$ (208.3) |
| **1f** | $C_6H_5$ | $CH_3$ | H | $CH_2C_6H_5$ | **4k** | 79 | 120/0.3 | +13.5 | $C_{16}H_{16}OS$ (256.4) |
| **1f** | $C_6H_5$ | $CH_3$ | H | $C_6H_5$ | **4l** | 95 | 74[h] | +57.0[i] | $C_{15}H_{14}OS$ (242.3) |
| **1f** | $C_6H_5$ | $CH_3$ | H | 4-$CH_3C_6H_4$ | **4m** | 94 | 73[h] | +63.5[j] | $C_{16}H_{16}OS$ (256.4) |
| **1g** | H | $-(CH_2)_4-$ | | $CH_3$ | **4n** | 92 | 62/0.6 | −15.5 | $C_7H_{12}OS$[k] (144.2) |
| **1g** | H | $-(CH_2)_4-$ | | $i$-$C_3H_7$ | **4o** | 87 | 72/0.6 | +11.5 | 59.5/0.5[26,e] |
| **1g** | H | $-(CH_2)_4-$ | | $C_6H_5$ | **4p** | 92 | 98/0.3 | − 2.0 | $C_{12}H_{14}OS$[l] (206.3) |
| **1g** | H | $-(CH_2)_4-$ | | 4-$CH_3C_6H_4$ | **4q** | 91 | 103/0.3 | − 1.5 | 154/0.8[27,e] |

[a] $R^4N$ = = (*R*)-α-phenylethylimino. Compounds **3f–g** were not isolated.
[b] Yield of isolated product based on **1**.
[c] $c = 1$, Chloroform.
[d] All new compounds gave satisfactory microanalytical data (C ±0.28, H ±0.27) and consistent mass spectra.
[e] Literature data for racemic product.
[f] Racemic product = **4b**.
[g] e.e. = 13%.
[h] Recrystallized from hexane.
[i] e.e. = 42%.
[j] e.e. = 51%.
[k] Racemic product = **4d**.
[l] Racemic product = **4e**.

enamines[17–20] reveals that most of these reactions need highly reactive sulfenylating agents, e.g. sulfenyl chlorides, which are less convenient than the disulfides. The yields of the compounds **4** are in most cases lower than those obtained with the imine method. We therefore considered the imine procedure to be most promising.

For the preparation of enantiomerically enriched α-sulfenylated carbonyl compounds, we used (*R*)-(+)-α-phenylethylamine as chiral auxiliary. The imines of this amine, when treated as above, gave the desired compounds **4** in good overall yield (Tables 2 and 3).

As the optical rotations of the enantiomerically pure compounds **4** are not known, a direct determination of the enantiomeric excesses by polarimetry is not possible. However, the chiral shift reagent tris-(heptafluoropropyl-camphorato)-europium(III) [Eu(hfc)$_3$] splits up the signals of the aldehyde groups in the $^1$H-NMR specta of the aldehydes **4j, l** and **m** and allows the determination of the enantiomeric excesses (e.e.). The results (maximum e.e. = 51%) compare well with those of the asymmetric alkylation of imines.[13] The use of chelating amines as chiral auxiliaries[14,15] can be expected to improve the optical purities.

An interesting dependence of the enantiomeric excesses on the substituent R of the disulfide is observed. In the case of the imine **1f**, aromatic disulfides give much higher enantiomeric excesses than the aliphatic counterparts. On the other hand, the optical rotations of the α-sulfenylcyclohexanones **4n–q** suggest an inverse effect in the case of the imine **1g**. This leads to the conclusion that the interactions of the substituents R of the disulfide with the substituents of the metalloenamine **2** are mainly responsible for the asymmetric inductions observed.

Preliminary experiments show that the oxidation of the α-sulfenylated carbonyl compounds to the corresponding chiral sulfoxides is possible, thus giving an alternative to present syntheses of this important class of compounds.

The imines **1** used as starting materials have been prepared from the corresponding aldehydes or ketones and amines by standard methods; **1a**,[21] **1b**,[22] **1c**,[23] **1d**,[24] **1e**,[25] **1g**.[13]

The new imine **1f** has been prepared analogously,[25] yield: 92%, b.p. 94°C/0.6 torr, $[\alpha]_D^{20} = -64.5$ ($c = 1$, chloroform).

$C_{17}H_{19}N$ (237.3) calc. C 86.03 H 8.07 N 5.90
found 86.20 8.15 5.70

$^1$H-NMR ($CDCl_3$/TMS): $\delta = 1.41$ (d, 3H, $J = 7$ Hz); 1.73 (d, 3H, $J = 9$ Hz); 3.61 (m, 1H); 4.23 (q, 1H, $J = 7$ Hz); 7.30 (m, 10H); 7.70 ppm (d, 1H, $J = 5$ Hz).

**α-Sulfenylated Imines 3; General Procedure:**
To a solution of diisopropylamine (4.04 g, 40 mmol, distilled over calcium hydride) in dry ether (20 ml), a 1.5 molar solution of *n*-butyllithium in hexane (42 mmol, 28.0 ml) is added at −10°C with stirring. After 30 min at this temperature, the imine **1** (40 mmol) in dry diethyl ether (10 ml) is added dropwise with stirring. After stirring for 30 minutes still at −10°C, the mixture is cooled to −78°C and a solution of the disulfide (40 mmol) in dry diethyl ether (20 ml) is added dropwise. Stirring is continued for 2 h at −78°C and for 12 h at room temperature. The mixture is then poured into 10% aqueous sodium hydroxide solution (200 ml) and stirred vigorously for 10 min. The phases are separated and the aqueous phase is extracted with ether (2 × 150 ml). The combined organic phases are washed with water (3 × 150 ml) and dried with sodium sulfate. The solvent is evaporated in vacuum and the residue is either distilled (compounds **3a–e**) or used directly for hydrolysis.

**α-Sulfenylated Carbonyl compounds 4; General Procedure:**
The imine **3** (30 mmol) is stirred for one day at room temperature with a solution of oxalic acid (3.2 g, 35 mmol) in water (150 ml). The mixture is extracted with ether (1 × 200 ml, 3 × 70 ml) and the combined organic solution is washed with saturated aqueous solution of sodium hydrogen

**Table 3.** Spectroscopic Data of Isolated New Compounds **3** and **4**.

| Compound | $^1$H-NMR ($CDCl_3$/TMS) $\delta$ (ppm)[a] | | | | | IR (Film)[b] $\nu$ ($cm^{-1}$) | MS (70 eV)[c] $m/e$ ($M^+$) |
|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | | |
| **3a** | 1.40 (s, 6H) | | 7.53 (s, 1H) | 1.10 (s, 9H) | 2.30 (s, 3H); 7.02, 7.35 (4H, AA'BB') | 1650 | 249 |
| **3b**[d] | 3.52 (t, 1H, $J$ = 8 Hz) | 1.00 (m, 6H); 2.10 (m, 1H) | 7.30 (m, 1H) | 1.10 (s, 9H) | 2.25 (s, 3H); 7.17 (m, 4H) | 1640 | 263 |
| **3c**[d] | 3.43 (dd, 1H, $J_1$ = 6 Hz, $J_2$ = 12 Hz) | 1.03 (m, 6H); 2.67 (m, 1H) | 7.30 (m, 1H) | 2.36 (s, 3H) | 2.36 (s, 3H); 7.45 (m, 4H) | 1640 | 221 |
| **3d**[d] | 2.57 (m, 1H) | 0.90 | ... | 2.37 (m, 16H) 3.40 (m, 1H) | 1.90 (s); 2.00 (s); (3H)[d] | 1620 | 225 |
| **3e** | 4.70 (m, 1H) | 0.76 | ... 2.26 (m, 2H) | 2.12 (m, 16H) 3.10 (m, 1H) | 7.23 (m, 5H) | 1610 | 287 |
| **4a** | 1.23 (s, 6H) | | 9.30 (s, 1H) | – | 2.28 (s, 3H); 7.03, 7.28 (4H, AA'BB') | 1710 | 194 |
| **4b**[e] | 3.18 (dd, 1H, $J_1$ = 5 Hz, $J_2$ = 8 Hz) | 1.11 (t, 6H, $J$ = 8 Hz) 2.13 (m, 1H) | 9.33 (d, 1H, $J$ = 5 Hz) | – | 2.28 (s, 3H); 7.03, 7.30 (4H, AA'BB') | 1715 | 208 |
| **4f** | 2.73 (dd, 1H, $J_1$ = 5 Hz, $J_2$ = 9 Hz) | 1.00, 1.15 (2d, 6H, $J$ = 3 Hz); 2.03 (m, 1H) | 9.20 (d, 1H, $J$ = 5 Hz) | – | 1.95 (s, 3H) | 1710 | 132 |
| **4i** | 7.43 (m, 5H) | 1.66 (s, 3H) | 9.33 (s, 1H) | – | 1.93 (s, 3H) | 1710 | 180 |
| **4j** | 7.40 (m, 5H) | 1.73 (s, 3H) | 9.46 (s, 1H) | – | 1.33 (d, 6H, $J$ = 7 Hz); 2.86 (sept, 1H) | 1710 | 208 |
| **4k** | 7.30 (m, 5H) | 1.66 (s, 3H) | 9.33 (s, 1H) | – | 3.50 (s, 2H); 7.30 (m, 5H) | 1705 | 256 |
| **4l** | 7.36 (m, 5H) | 1.56 (s, 3H) | 9.63 (s, 1H) | – | 7.36 (m, 5H) | 1710 | 242 |
| **4m** | 7.43 (m, 5H) | 1.56 (s, 3H) | 9.67 (s, 1H) | – | 2.36 (s, 3H); 7.08 (d, 2H); 7.33 (d, 2H, $J$ = 8 Hz) | 1710 | 256 |

[a] Recorded on a Jeol PMX 60 spectrometer.
[b] Recorded on a Perkin-Elmer 177 spectrophotometer. Compounds **4l** and **4m** were recorded in KBr.
[c] Recorded on a Varian CH5 instrument.
[d] *E*/*Z*-isomers.
[e] Spectra identical with **4h**.

carbonate (200 ml) and saturated brine (200 ml). After drying with sodium sulfate, the solvent is evaporated in vacuum and the residue either distilled or recrystallized from hexane (compounds **4l** and **4m**).

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*Dedicated to Professor Burchard Franck on the occasion of his 60th birthday.*

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(1) Colonna, S., Annunziata, R., Cinquini, M. *Phosphorus Sulfur* **1981**, *10*, 197.
(2) Solladié, G. *Chimia* **1984**, *38*, 233.
(3) Solladié, G. *Chem. Scr.* **1985**, *25*, 149.
(4) Banfi, L., Colombo, L., Gennari, C., Annunziata, R., Cozzi, F. *Synthesis* **1982**, 829.
(5) Annunziata, R., Cozzi, F., Cinquini, M., Colombo, L., Gennari, C., Poli, G., Scolastico, C. *J. Chem. Soc., Perkin Trans. 1* **1985**, 251.
(6) Annunziata, R., Cinquini, M., Cozzi, F., Gilardi, A., Cardani, S., Poli, G., Scolastico, C. *J. Chem. Soc., Perkin Trans. 1* **1985**, 255.
(7) Trost, B.M. *Chem. Rev.* **1978**, *78*, 363.
(8) Seebach, D., Teschner, M. *Chem. Ber.* **1976**, *109*, 1601.
(9) Scholz, D. *Liebigs Ann. Chem.* **1984**, 239.
(10) Duhamel, P., Duhamel, L., Chauvin, J. *C. R. Acad. Sci. Ser. C* **1972**, *274*, 1233.
(11) Bestmann, H.J., Angerer, J. *Justus Liebigs Ann. Chem.* **1974**, 2085.
(12) Stork, G., Dowd, S.R. *J. Am. Chem. Soc.* **1963**, *85*, 2187.
(13) Kitamoto, M., Hiroi, K., Terashima, S., Yamada, S.-I. *Chem. Pharm. Bull.* **1974**, *22*, 459.
(14) Meyers, A.I., Williams, D.R., Erickson, G.W., White, S., Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081.
(15) Meyers, A.I., Williams, D.R., White, S., Erickson, G.W. *J. Am. Chem. Soc.* **1981**, *103*, 3088.
(16) Coates, R.M., Pigott, H.D., Ollinger, J. *Tetrahedron Lett.* **1974**, 3955.
(17) Kuehne, M.E. *J. Org. Chem.* **1963**, *28*, 2124.
(18) Kumamoto, T., Kobayashi, S., Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 866.
(19) Furukawa, M., Kojima, Y., Tsuji, S., Hayashi, S. *Chem. Pharm. Bull.* **1972**, *20*, 2738.
(20) Scholz, D. *Monatsh. Chem.* **1984**, *115*, 655.
(21) House, H.O., Liang, W.C., Weeks, P.D. *J. Org. Chem.* **1974**, *39*, 3102.
(22) Martin, H., Herrmann, R. *Z. Naturforsch.* **1986**, *41B*, 1260.
(23) Tiollais, R., Guillerm, H. *Bull. Soc. Chim. Fr.* **1947**, 937.
(24) Pfau, M., Ribière, C. *Bull. Soc. Chim. Fr.* **1971**, 2584.
(25) Patel, M.S., Worsley, M. *Can. J. Chem.* **1970**, *48*, 1881.
(26) Gasteiger, J., Herzig, C. *Angew. Chem.* **1981**, *93*, 993; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 868.
(27) Jílek, J.C., Holubek, J., Pomikáček, J., Protiva, M. *Coll. Czech. Chem. Commun.* **1971**, *36*, 2824.