Stereospecific Synthesis of Chiral α-Sulfinylhydrazones

Luca Banfi, Lino Colombo, Cesare Gennari

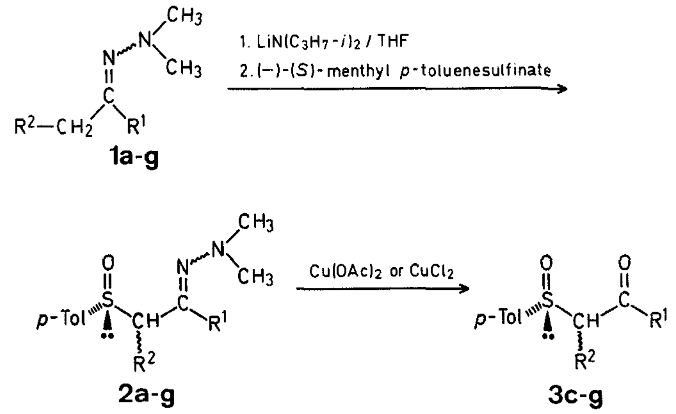
Istituto di Chimica Organica dell'Università, Via Venezian 21, I-20133 Milano, Italy

Rita Annunziata, Franco Cozzi

Centro CNR *and* Istituto di Chimica Industriale dell'Università, Via Golgi 19, I-20133 Milano, Italy

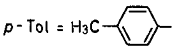
The wide applicability[1] of *N,N*-dimethylhydrazones in organic synthesis, in particular in C—C bond formation, is known. A synthesis of chiral hydrazones has therefore aroused considerable interest. Both enantiomers of 1-amino-2-methoxymethylpyrrolidine were prepared[2] and they were condensed with aldehydes and ketones to give chiral hydrazones which proved to be effective reagents in asymmetric synthesis[3]. In this class of compounds, the source of chirality is an asymmetric C-atom in the pyrrolidine moiety.

A more straightforward approach to optically active hydrazones is the reaction of α-lithio-*N,N*-dimethylhydrazones with (–)-(*S*)-menthyl *p*-toluenesulfinate[4]; this method avoids the multistep synthesis of the chiral hydrazine[2]. Thus, we have now investigated the reaction of 2 equivalents of easily available[1,5] dimethylhydrazones (**1a-g**) with 2 equivalents of lithium diisopropylamide in tetrahydrofuran and then with 1 equivalent of (–)-(*S*)-menthyl *p*-toluenesulfinate at –78 °C which affords the optically active *α-sulfinylhydrazones* [(*R*)-**2a-g**] in high yields (Table 1). Attempts to use 2 equivalents of lithium diisopropylamide and only 1 equivalent of *N,N*-dimethylhydrazone resulted in the isolation of considerable amounts of *N,N*-diisopropyl-*p*-toluenesulfinamide. The absolute configuration at the S-atom was assigned as *R* on the basis of the reasonable assumption that also this reaction, like many other Andersen-type syntheses, proceeds with inversion of chirality at sulfur[6]. In the cases of **2c**, **2d**, and **2f**, this inversion was confirmed by conversion into the known optically active 2-oxoalkyl sulfoxides (**3**).

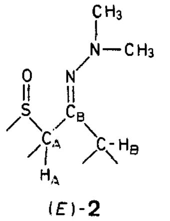


1a-g **2a-g** **3c-g**

	R^1	R^2
a	H	H
b	H	CH_3
c	CH_3	H
d	C_2H_5	H
e	$-(CH_2)_4-$	
f	C_6H_5	H
g	CH_3	C_6H_5

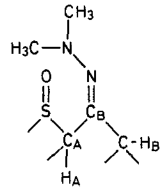


The (E/Z)-ratios reported in Table 1 were determined by ^{1}H- *and* ^{13}C-N.M.R. spectrometry after the solutions of compounds **2** in $CDCl_3$ had been allowed to stand overnight, the configuration at the C=N double bond being tentatively assigned either on the basis of the ^{1}H chemical shift values reported for aldehyde[5,7] and ketone[5] dimethylhydrazones or by empirical correlation of the influence of the position of the dimethylamino group on the ^{1}H- and ^{13}C chemical shifts.



(*E*)-**2**

H_A, H_B, C_B upfield shift
C_A downfield shift



(*Z*)-**2**

H_A, H_B, C_B downfield shift
C_A upfield shift

The α-sulfinylhydrazones obtained by the described procedure were found to be enantiomerically pure at the S-atom. For compounds **2a** and **2f**, this was demonstrated by ^{1}H-N.M.R. spectrometry using the chiral shift reagents Eu(tfc)$_3$ and Eu(hfc)$_3$, respectively, under the conditions pre-established on racemic samples (molar ratio substrate: shift reagent = 5 : 1). Further, compounds **2c** and **2d** were converted into the corresponding enantiomerically pure (*R*)-2-oxoalkyl sulfoxides (**3c** and **3d**, Table 2) by reaction with copper(II)

0039-7881/82/1032-0829 $ 03.00

Table 1. Synthesis of α-Sulfinyldimethylhydrazones (**2**)

2	Yield [%]	m.p. [°C]	$[\alpha]_D^{23}$ (c 1, acetone)	Molecular formula[a]	C=N (E/Z)-ratio[b]	CH—R² Epimer ratio[b]
a	94	[c]	$+183.2^{\circ}$	$C_{11}H_{16}N_2OS$ (224.3)	100/0	—
b	80	[c]	$-1.05^{\circ d,e}$	$C_{12}H_{18}N_2OS$ (238.3)	95/5	55/45
c	85	[c]	$+150.5^{\circ e}$	$C_{12}H_{18}N_2OS$ (238.3)	75/25	—
d	85	[c]	$+131.9^{\circ e}$	$C_{13}H_{20}N_2OS$ (252.4)	45/55	—
e	60	41–43°	$+155.1^{\circ e}$	$C_{15}H_{22}N_2OS$ (278.4)	90/10	60/40
f	90	122–123°	$-65.2^{\circ e}$	$C_{17}H_{20}N_2OS$ (300.4)	15/85	—
g	80	[c]	-39.3°	$C_{18}H_{22}N_2OS$ (314.4)	100/0	100/0

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.20; H, ±0.21; N, ±0.21.

[b] As determined by ¹H-N.M.R. spectrometry.

[c] Low-melting material.

[d] c 5, acetone.

[e] Rotation of (E/Z)-mixtures.

Table 2. 2-Oxoalkyl Sulfoxides (**3**) obtained from α-Sulfinylhydrazones (**2**) by Hydrolysis

3	Yield [%]	m.p. [°C]	$[\alpha]_D^{23}$ (c 1, acetone)	e.e. value (enantiomeric excess) [%]	Molecular formula or m.p. [°C] reported
c	95	38°	$+255.0^{\circ a}$	100[b]	low°[9]
d	95	69–70°	$+260.0^{\circ}$	100[c]	69–70°[10,13]
e	90	$77–94^{\circ d}$	$+151.8^{\circ d}$	—	100–101.5°[12]
f	90	81–83°	$+227.7^{\circ}$	85[c]	82–83.5°[10]
g	90	$104–112^{\circ d}$	$+87.3^{\circ d}$	—	$C_{16}H_{16}O_2S$ (272.4)[e]

[a] $[\alpha]_D^{23}$: +243.3° (c 1, methanol).

[b] Determined by ¹H-N.M.R. spectrometry using $Eu(tfc)_3$ as shift reagent under the conditions pre-established with a racemic sample; molar ratio $Eu(tfc)_3$: substrate = 5 : 1.

[c] Determined by comparison with previously reported[10] values.

[d] Mixture of diastereoisomers.

[e]

	C	H
calc.	70.56	5.92
found	70.49	5.97

acetate[8]. It must be noted that the maximum optical rotation value reported[9] for compound **3c** corresponds to 81% optical purity. The 2-oxoalkyl sulfoxides **3e**, **f**, **g** were obtained in high yield using copper(II) chloride[8] but with partial loss of enantiomeric purity, probably because of the slight acidity (pH 4) of the reaction medium. Attempts to hydrolyze the α-sulfinylhydrazones **2a**, **b** to the corresponding aldehydes **3a**, **b** were unsuccessful under a variety of conditions; this is very likely due to the instability of α-sulfinylaldehydes.

α-Sulfinylhydrazones (2a–g); General Procedure:

A stirred suspension of the α-lithio-N,N-dimethylhydrazone[1] (15.24 mmol) in tetrahydrofuran (57 ml) is cooled in a dry, oxygen-free argon atmosphere to −78 °C. A solution of (−)-(S)-menthyl p-toluenesulfinate[4] (2.254 g, 7.62 mmol) in tetrahydrofuran (35 ml) is slowly added during 20 min. After a further 30 min at −78 °C, the pale yellow, clear solution is quenched with saturated ammonium chloride solution (40 ml), and extracted with ether (3 × 20 ml). The organic extract is dried with sodium sulfate and evaporated in vacuo. The residual product is purified by flash chromatography[11] using ethyl acetate or diethyl ether containing 1–6% of triethylamine as eluent. [In the absence of triethylamine, compounds **2c**, **d**, **e**, **g** are cleaved to some extent by the silica gel to give the corresponding ketones].

Table 3. I.R. Data and Selected[a] ¹H- and ¹³C-N.M.R. Data of Compounds **2** and **3**

Compound	I.R. ($CHCl_3$) ν [cm⁻¹]	¹H-N.M.R. ($CDCl_3/TMS_{int}$) δ [ppm]	¹³C-N.M.R. ($CDCl_3/TMS_{int}$) δ [ppm]
2a	1578 (C=N); 1100–1000 (S=O)	$C\underline{H}_2$: 3.66 (d, J = 6.4 Hz); $C\underline{H}$=N: 6.24 (t, J = 6.4 Hz)	SO—$\underline{C}H_2$: 60.4; $\underline{C}$=N: 121.6
2b	1575 (C=N); 1100–1000 (S=O)	$C\underline{H}$—C=N: 3.2–3.9 (m); (E) $C\underline{H}$=N: 6.02 (d, J = 6.0 Hz); 6.14 (d, J = 6.0 Hz)	(E) SO—$\underline{C}H$: 61.5, 63.2; $\underline{C}$=N: 127.5, 127.7 (Z) SO—$\underline{C}H$: 65.5, 67.1
2c	1625 (C=N); 1100–1000 (S=O)	(E) $C\underline{H}_2$: 3.60, 3.69 (AB system, J = 14 Hz); $\underline{H}_3C$—C=N (s, 1.94) (Z) $C\underline{H}_2$: 3.90, 3.99 (AB system, J = 14 Hz); $\underline{H}_3C$—C=N: (s, 1.98)	(E) SO—$\underline{C}H_2$: 65.5; $\underline{C}$=N: 157.4 (Z) SO—$\underline{C}H_2$: 58.7; $\underline{C}$=N: 160.8
2d	1620 (C=N); 1100–1000 (S=O)	(E) SO—$C\underline{H}_2$: 3.70, 3.82 (AB system, J = 14 Hz) (Z) SO—$C\underline{H}_2$: 3.97 (s)	(E) SO—$\underline{C}H_2$: 62.4; $\underline{C}$=N: 163.4 (Z) SO—$\underline{C}H_2$: 58.1; $\underline{C}$=N: 164.8
2e	1620 (C=N); 1100–1000 (S=O)	(E) $C\underline{H}$: 3.35 (t); Ar—$C\underline{H}_3$: 2.20 (s) (Z) $C\underline{H}$: 3.40 (t); Ar—$C\underline{H}_3$: 2.22 (s)	(E) SO—$\underline{C}H$: 68.9, 71.5; $\underline{C}$=N: 162.7, 163.3 (Z) SO—$\underline{C}H$: 61.5, 64.3; $\underline{C}$=N: 166.3, 166.7
2f	1665 (C=N); 1100–1000 (S=O)	(E) $C\underline{H}_2$: 3.94, 3.75 (AB system, J = 14 Hz); $N(C\underline{H}_3)_2$: 2.34 (s) (Z) $C\underline{H}_2$: 4.35, 4.28 (AB system, J = 12 Hz); $N(C\underline{H}_3)_2$: 2.36 (s)	(E) $\underline{C}H_2$: 67.2; $N(\underline{C}H_3)_2$: 47.0 (Z) $\underline{C}H_2$: 57.4; $N(\underline{C}H_3)_2$: 47.4
2g	1630 (C=N); 1100–1000 (S=O)	SO—$C\underline{H}$: 4.33 (s); $\underline{H}_3C$—C=N: 2.00 (s)	SO—$\underline{C}H$: 79.9; $\underline{C}$=N: 161.0
3c	1710 (C=O); 1100–1000 (S=O)	$C\underline{H}_2$: 3.85 (s); CO—$C\underline{H}_3$: 2.25 (s)	
3d	1710 (C=O); 1100–1000 (S=O)	S$\underline{O}$—$C\underline{H}_2$; 3.75, 3.86 (AB system, J = 13.5 Hz)	
3e	1710 (C=O); 1100–1000 (S=O)	$C\underline{H}$: 3.25–3.7 (m); Ar—$C\underline{H}_3$: 2.42 (s)	
3f	1710 (C=O); 1100–1000 (S=O)	$C\underline{H}_2$: 4.23, 4.50 (AB system, J = 13.5 Hz); Ar—$C\underline{H}_3$: 2.40 (s)	
3g	1710 (C=O); 1100–1000 (S=O)	$C\underline{H}$: 4.55 (s), 4.62 (s); CO—$C\underline{H}_3$: 2.00 (s), 2.30 (s)	

[a] Only those chemical shifts are listed which are significant for structure and/or isomer ratio determinations.

2-Oxoalkyl Sulfoxides (3c-g) from α-Sulfinylhydrazones (2); General Procedure (cf. Ref.[8]):

To a solution of the α-sulfinylhydrazone (**2**; 1.0 mmol) in tetrahydrofuran (20 ml) is added copper(II) acetate (for **2c, d**; 0.4 g, 2.0 mmol) in water (20 ml) or copper(II) chloride (for **2e, f, g**; 0.188 g, 1.1 mmol) in 0.02 normal phosphate buffer (8 ml; pH 7). The mixture is stirred at 25 °C for the appropriate time and is then worked up as described previously. The crude product **3** is purified by flash chromatography[11] on silica gel using ether containing 5-22% ethyl acetate as eluent.

Received: April 8, 1982

---

[1] E. J. Corey, D. Enders, *Chem. Ber.* **111**, 1337, 1362 (1978); and references cited therein.

[2] D. Enders, H. Eichenauer, R. Pieter, *Chem. Ber.* **112**, 3703 (1979).

[3] D. Enders, H. Eichenauer, *Angew. Chem.* **88**, 579 (1976); *Angew. Chem. Int. Ed. Engl.* **15**, 549 (1976); *Tetrahedron Lett.* **1977**, 191.
H. Eichenauer, E. Friedrich, W. Lutz, D. Enders, *Angew. Chem.* **90**, 219 (1978); *Angew. Chem. Int. Ed. Engl.* **17**, 206 (1978).
D. Enders, H. Eichenauer, *Angew. Chem.* **91**, 425 (1979); *Angew. Chem. Int. Ed. Engl.* **18**, 397 (1979); *Chem. Ber.* **112**, 2933 (1979).

[4] G. Solladié, *Synthesis* **1981**, 185; and references cited therein.

[5] G. J. Karabatsos, R. A. Taller, *Tetrahedron* **24**, 3923 (1968).

[6] S. Colonna, R. Annunziata, M. Cinquini, *Phosphorus Sulfur* **10**, 197 (1981); and references cited therein.

[7] K. G. Davenport et al., *J. Am. Chem. Soc.* **101**, 5654 (1979).

[8] E. J. Corey, S. Knapp, *Tetrahedron Lett.* **1976**, 3667.

[9] S. Iriuchijima, N. Kojima, *Agric. Biol. Chem.* **42**, 451 (1978).

[10] R. Annunziata, M. Cinquini, F. Cozzi, *J. Chem. Soc. Perkin Trans. 1* **1979**, 1687.

[11] W. C. Still, H. Kanh, A. Mitra, *J. Org. Chem.* **43**, 2923 (1978).

[12] R. M. Coates, H. D. Pigott, *Synthesis* **1975**, 319.

[13] N. Kunieda, H. Motoki, M. Kinoshita, *Chem. Lett.* **1978**, 713.

0039-7881/82/1032-0831 $ 03.00