Optically Active 4-Substituted (*S*)-2-Phenyl-2-oxazolines

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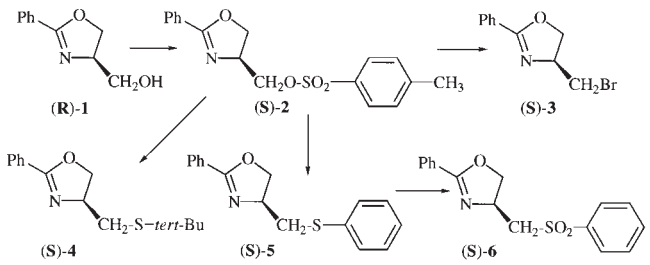
Abstract. (*R*)-4-Hydroxymethyl-2-phenyl-2-oxazoline (*R*)-**1**) was prepared from (L)-serine. The respective tosylate ((*S*)-**2**) was converted into sulfides (*S*)-**4** and (*S*)-**5**, and sulfone (*S*)-**6**, useful starting materials for the elaboration of additional chiral centers. A previously reported $[\alpha]_D^{25}$ value for (*R*)-**4** is corrected.

In a previous publication, we showed that sulfoxides and sulfones derived from (*R*)-4(*tert*-butylthiomethyl)-2-phenyl-2-oxazoline (*R*)-**4**) can be alkylated highly stereoselectively under chelate control giving two consecutive stereogenic centers [1]. Reductive removal of the *tert*-butylmercato group turned out to be difficult. We report here on extensions to the (*S*)-series and on the introduction of the phenylthio group which is known to be more easily removable.



Scheme 1 Preparation of (*S*)-2-phenyl-4-(tosyloxymethyl)-2-oxazoline((*S*)-**2**), (*S*)-4-(*tert*-butylthiomethyl)-2-phenyl-2-oxazoline((*S*)-**4**), (*S*)-2-phenyl-4-(phenylthiomethyl)-2-oxazoline((*S*)-**5**), and phenyl(*S*)-(2-phenyl-2-oxazolin-4-ylmethyl)sulfone((*S*)-**6**)

Earlier, compound (*R*)-**4** was prepared from (*R*)-cysteine. As (*S*)-cysteine is more than a hundred times as expensive and as a *S*-phenylation cannot be executed preparatively, (L)-serine methylester hydrochloride was selected as starting material. This was transformed into (*R*)-**1** by reacting it first with ethyl benzimidate and reducing the obtained ester with $LiAlH_4$ following Paton and coworkers [2]. A. I. Meyers *et al.* [3] showed how (*R*)-**1** can be inverted by a simple three step sequence: a) The oxazoline ring is opened under acid catalysis, b) the benzoate formed is transformed with ethyl benzimidate into -what is now- (*S*)-4-benzoylmethyloxazoline, and c) basic saponification furnishes (*S*)-**1**. In this way both stereoisomers of **1** become principally available.

Hitherto, the bromide **3** has been obtained from optically active **1** with $SOCl_2$ only as the racemate. A mechanism for the (acid catalyzed) racemization has been suggested. [2] Tosylation of (*R*)-**1**, however, gave optically active (*S*)-**2**. There should not be any difficulty in transforming this into (*S*)-**3** by a Finkelstein reaction under neutral conditions. In our hands, tosylate (*S*)-**2** was reacted with sodium *tert*-butylthiolate and with sodium thiophenolate in DMF to give compounds (*S*)-**4** and (*S*)-**5**, respectively. Oxidation of the last mentioned compound led to sulfone (*S*)-**6** finally.

(*S*)-**4** had IR and NMR data which were identical to the ones described by us previously for (*R*)-**4**. The $[\alpha]_D^{25}$ value was –4.2° (c = 5, EtOH), however, whereas $[\alpha]_D^{25} = -1.2$ (c = 1.7, EtOH) was reported for (*R*)-**4** [1]. For comparison and evaluation therefore, (*R*)-**4** was resynthesized by our described method from L-cysteine [1]. Again the spectral data matched, but now $[\alpha]_D^{25}$ was found to be + 3.7° (c = 4.8, EtOH) instead of the previously recorded value. These reasonably similar absolute rotations seemed to underline that the two stereoisomers were actually present. Indeed, HPLC on an optically active column of the two compounds and their mixture showed that both stereoisomers where >90% optically pure previous to further purification. We should like to correct the low negative specific rotation given in our original work [1]. In it, HPLC on an optically active column was not employed. It must be assumed that the very small measured α was mimicked by the presence of an unknown impurity with relatively high negative specific rotation.

Compounds (*S*)-**4** to (*S*)-**6** are useful starting materials for further syntheses along lines outlined before [1].

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Experimental

Boiling points: air bath temperatures of a Kugelrohr distillation apparatus. – NMR spectra: AC 250-P (Bruker) in $CDCl_3$ with TMS as an internal standard. – Rotations: DIP-360 (Jasco). – Chiral HPLC: Chirasep (DNPBG, 5 µm) of Merck A.G., hexane/2-propanol 499:1, flow rate 0.4 ml/min., optical detection at 254 nm.

(S)-2-Phenyl-4-(tosyloxymethyl)-2-oxazoline ((*S*)-**2**)

A solution of 6.9 g (36 mmol) of *p*-toluenesulfonyl chloride in 10 ml of chloroform was dropped into a solution of 5.9 g (33 mmol) of (*R*)-**1** [2] and 7.3 g (72 mmol) of triethylamine in 50 ml of chloroform at 0 °C within 1 h. The mixture was

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stirred at r.t. for 20 h, thereafter washed twice with 10 ml water each time and then with 10 ml of aq. $NaHCO_3$ and again with water. After drying (Na_2SO_4), the solvent was removed *in vacuo*, and the residue was recrystallized from 2-propanol. 8.76 g (80%) yield; *m.p.* 112–116 °C; $[\alpha]_D^{25} = +34°$ (c = 1.0, EtOH). – IR (NaCl): ν/cm^{-1} = 3068, 2978, 1648, 1356, 1175, 969, 836. – ^{1}H NMR: δ/ppm = 2.42 (s, 3H), 4.01–4.07 (m, 1H, -S–CH_2), 4.24–4.33 (m, 1H, -S–CH_2), 4.41–4.50 (m, 3H, heterocycle), 7.26–7.51 (m, 5H), 7.75–7.87 (m, 4H).

$C_{17}H_{17}NO_3S$	Calcd.: C 61.62	H 5.17	N 4.23
(331.39)	Found: C 61.78	H 5.00	N 4.17.

(S)-4-(tert-Butylthiomethyl)-2-phenyl-2-oxazoline ((*S*)-**4**)

1.0 g (3.02 mmol) of (*S*)-**2** in 10 ml of DMF were dropped at 0 °C to a mixture prepared from 0.22 g (5.5 mmol) of NaH (60% in paraffin) and 0.40 g (4.4 mmol) of *tert*-butylmercaptane in 10 ml of DMF. The mixture was stirred for 14 h at r.t., then poured onto ice and extracted with dichloromethane. The organic layer was washed twice with water, then with aq. $NaHCO_3$ and again with water. After drying (Na_2SO_4), the solvent was removed *in vacuo*, and the residue was distilled into a Kugelrohr. Yield 0.62 g (74%), *b.p.* 125–130 °C/2 Torr. – $[\alpha]_D^{25} = -4.2°$ (c = 4.8, EtOH). – IR: ν/cm^{-1} = 3230, 1630, 1440, 1350, 1320, 1150, 1050, 1040, 690 (lit.[1]: identical). – ^{1}H NMR: δ/ppm = 1.34 (s, 9H), 2.54–3.09 (m, 2H), 4.21–4.52 (m, 3H), 7.34–7.48 (m, 3H), 7.93–8.00 (m, 2H) (practically identical to lit.[1]).

(R)-4-(tert-Butylthiomethyl)-2-phenyl-2-oxazoline ((*R*)-**4**)

Prepared as described in lit. [1], yield 90%, *b.p.* 130–135 °C/2 Torr (lit.: 110–115 °C/0.5 Torr); $[\alpha]_D^{25} = +3.7°$ (c = 5.0, EtOH) (lit.: $[\alpha]_D^{25} = -1.2°$ (c = 1.7, EtOH). Spectral data identical to the ones of (*S*)-**4** and lit.[1].

(S)-2-Phenyl-4-(phenylthiomethyl)-2-oxazoline ((*S*)-**5**)

Prepared analogously to (*S*)-**4**, yield 74% , *m.p.* 62–66 °C. – $[\alpha]_D^{25} = -8.6°$ (c = 1.0, EtOH). – IR (NaCl): ν/cm^{-1} = 3059, 3048, 2961, 2917, 1645, 1480, 1270, 1083, 889. – ^{1}H NMR: δ/ppm = 2.86–2.94 (m, 1H), 3.43–3.50 (m, 1H), 4.42–4.51 (m, 3 H 9, 7.15–7.50 (m, 8 H), 7.89–7.94 (m, 2 H).

$C_{16}H_{15}NOS$	Calcd.: C 71.34	H 5.61	N 5.20
(269.36)	Found: C 71.19	H 5.87	N 5.06.

Phenyl (S)-(2-phenyl-2-oxazolin-4-ylmethyl) sulfone ((*S*)-**6**)

300 mg (1.1 mmol) of (*S*)-**5** and 385 mg (4.9 mmol) of $NaHCO_3$ were suspended in 3 ml of dichloromethane at 0 °C. 0.55 g (2.2 mmol) of *m*-chloroperbenzoic acid in 14 ml of CH_2Cl_2 were dropped in, and the mixture was stirred for 3 h at r.t. Chlorobenzoic acid crystallized partially. The mixture was transferred to a separatory funnel containing 1 1 ml of ammonia. Phases were separated, and the organic layer was extracted twice with dilute ammonia, then with brine. After drying (Na_2SO_4), the solvent was removed, leaving the sulfone which was recrystallized from ethanol. Yield 0.27 g (81%); *m.p.* 112–115 °C. – $[\alpha]_D^{25} = +13.2°$ (c = 1.0, EtOH). – IR (NaCl): ν/cm^{-1} = 3058, 2983, 2913, 1646, 1448, 1229, 1147, 1062, 1062, 748, 694, 588. – ^{1}H NMR: δ/ppm = 3.20–3.30 (m, 1H), 3.66–3.72 (m, 1H), 4.42–4.73 (m, 3 H), 7.34–7.71 (m, 6 H), 7.83–7.98 (m, 4 H).

$C_{16}H_{15}NO_3S$	Calcd.: C 63.78	H 5.02	N 4.65
(301.35)	Found: C 63.62	H 4.85	N 4.61.

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