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Unusual Reactivity of 4-Carboxyamido-2-oxazoline Systems: New Synthesis of Optically Active N-Sulphonyl Derivatives.

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Abstract. Optically active 2-alkyl-2-oxazoline-4-carboxyamides, derived from enantiomeric pure α–amino-β-hydroxy acids, react with aryl- and alkyl sulphonyl chlorides in pyridine affording the corresponding optically active 2-alkyl-2-oxazoline-4-carboxyamido-*N*-sulphonyl derivatives without appreciable racemization.

Chiral non-racemic oxazolines derived from amino acids are important precursors in the synthesis of natural products,[1] and biologically active compounds i.e. glycosidase inhibitors,[2] cerebrosides, [3] antibiotics,[4] and antitumorals.[5] Oxazolines derived from optically active aminoalcohols are widely used, especially in asymmetric synthesis. In these examples the chirality of the starting amino alcohol was transferred to the α-exocyclic position of the oxazoline ring.[6]

We have previously described the synthesis of chiral ligands as very efficient chiral catalysts in the enantioselective alkylation of aldehydes with alkylzincs.[7] Developing novel strategies and new synthons for asymmetric synthesis using heterocyclic compounds derived from α-amino acids, we have prepared a series of oxazolines and investigated on their potential in order to obtain optically active ligands for enantioselective processes too.[8]

In this paper we would like to report the unusual reactivity of 4-carboxyamido-2-oxazoline systems and consequently the first synthesis of optically active 2-alkyl-4-carboxyamido-*N*-arylsulphonyl or *N*-alkylsulphonyl-2-oxazolines **1a-e** (Fig. n. 1). These compounds may represent pharmacological agents considering the fact that the racemates of sulphonamides have been extensively used as fungicides, bactericides, and antiphlogistics, and as opposite treatment to *Mycobacterium leprae*, *Mycobacterium tubercolosis* and others.[9,10] To date no examples on the preparation of chiral sulphonamides has been reported.[11]

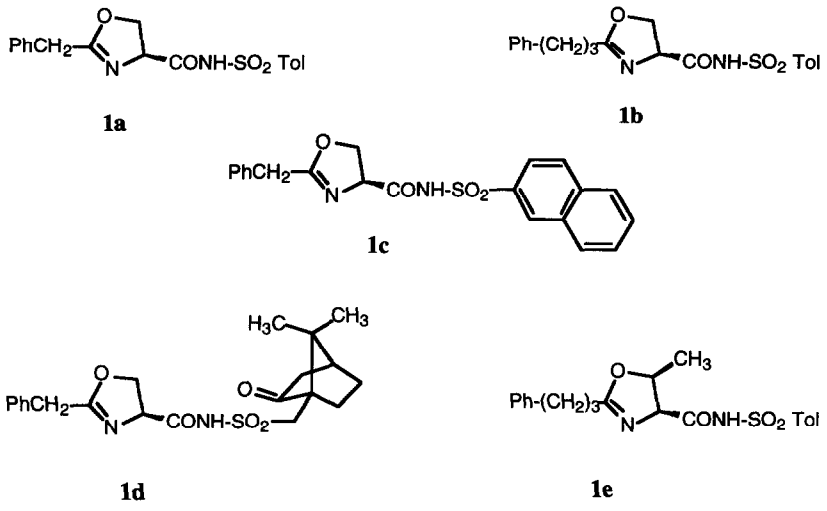
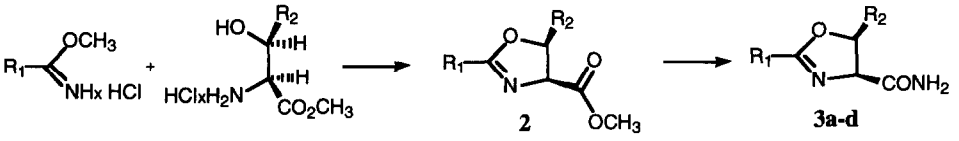


Fig. n. 1

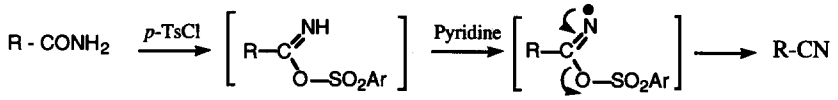
The optically active 2-alkyl-2-oxazoline-4-carboxyamides **3a-d** were prepared by a two-step reaction sequence. The 2-alkyl-4-carbomethoxy-2-oxazolines **2a-d** were first synthesised by treatment of appropriate iminoether hydrochlorides with enantiomerically pure α-amino acid methyl ester hydrochlorides (1:1 molar ratio) in dichloromethane using triethylamine (2:1 mol) as base, without racemization and in good yields.[12] Treatment of these compounds with ammonia in dry methanol, for *ca.* 2 to 6 days, depending upon the substrate, gave compounds **3a-d** (Scheme n. 1).



	R_1	R_2
2a	-Ph	H
2b	$-CH_2$-Ph	H
2c	$-CH_2-CH_2-CH_2$-Ph	H
2d	$-CH_2-CH_2-CH_2$-Ph	CH_3

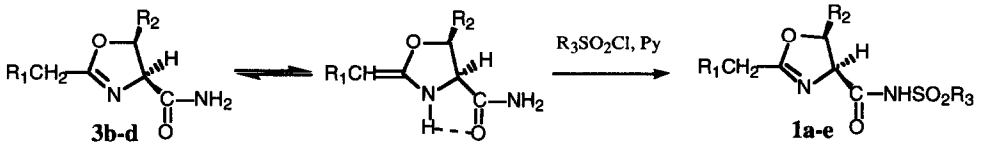
Scheme n.1

It is known that the carboxyamido compounds can be converted into the corresponding nitrile by a facile reaction with *p*-toluenesulphonyl chloride in pyridine. This methodology has been widely employed and several examples have been reported; studies on the dehydration mechanism have indicated that the reaction proceeds *via* an *O*-sulphonylated intermediate (Scheme n. 2).[13]



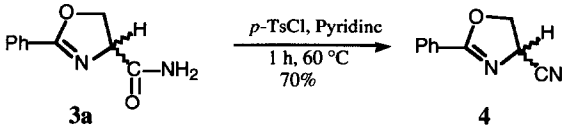
Scheme n. 2

With the aim to obtain the 4-nitrile derivatives, compounds **2b-d** were treated with *p*-toluensulphonyl chloride in pyridine at temperatures ranging from room to reflux. Surprisingly, only the *N*-sulphonylated derivatives were obtained cleanly and in high yield. We assume the presence of an equilibrium between two species, in which a hydrogen bond, between the aminic proton and carbonylic oxygen, may exist, probably due to the presence of protons in exocyclic α-position in compounds **3b-d**. On this basis there is diminished nucleophilic character of the oxygen atom in compounds **3b-d** so that the amidic nitrogen atom reacts with the electrophilic sulphur atom. Furthermore, the same behaviour was observed with sulphonyl chlorides other than *p*-toluensulphonyl chloride, i.e. both commercially available 2-naphthylsulphonyl chloride and (+)-10-camphorsulphonyl chloride, which gave products **1a-e** (Scheme n. 3).



Scheme n. 3

Confirming the role of the protons in the α-exocyclic position, it is noteworthy that racemic 2-phenyl-4-carboxyamido-2-oxazoline **3a** reacts with *p*-toluensulphonyl chloride, affording after 1 h at 60°C only the 4-nitrile derivative **4** (Scheme n. 4).



Scheme n. 4

The reaction sequence depicted in Scheme n. 1 and the sequential *N*-sulphonylation reaction proceed without loss of e.e. at C4, as showed by ^{1}H-NMR experiments on tris[3-(heptafluoropropyl-hydroxymethylene)-*d*-camphorato]europium(III) derivative of compounds **1b** and **1c**, in which no signal due to the presence of the other diastereomer was detected.

From a consideration of selected dipolar interactions, it is possible to assign the H4 and H5 resonances in compound **1e**. Diagnostic interaction was found between H4 and H5 (22% n.O.e. enhancement) and between the methyl group at C5 and H5 (6% n.O.e. enhancement), while no n.O.e. enhancement between the methyl group at C5 and H4 was observed, thus confirming the assignment of the structure.

Furthemore, it should be noted that the oxazolines **1a-e** can be hydrolyzed to the corresponding amminoalcohols. For example, compound **1c** smoothly affords (*S*)-1-amino-2-hydroxypropanamide-N-(2-naphthalenesulphonyl) hydrochloride on treatment with HCl 2N in THF for 12 h at room temperature, without appreciable loss of e.e. (^{1}H NMR, Eu(fod)$_3$).

In conclusion, despite of the difficulty in the preparation of chiral acyl sulphonamides derived from amino acids, this methodology allows us to overcome this problem by virtue of the particular reactivity of the oxazolines presented here. Further studies on the behaviour of oxazoline and thiazoline systems varying the nature of electrophilies species are in progress in our laboratories.

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EXPERIMENTAL

^{1}H and ^{13}C spectra were recorded on Varian VXR 300 spectrometer operating respectively at 300 MHz and 75.4 MHz; chemical shifts are in p.p.m. (δ); tetramethylsilane was used as internal standard (δ_H and δ_C 0.00). Values of optically rotatory powers were obtained on Perkin Elmer 241 polarimeter. IR spectra were performed on Perkin Elmer 983 spectrophotometer. Melting point were determined on a Kofler hot stage apparatus and are uncorrected. Micro analytical determinations were were performed on Perkin Elmer 2400 analyser. Solvents were purified and dried by standard methods. Known compounds used in this research were either purchased from standard chemical suppliers or prepared according to literature procedures and purified to match reported physical and spectral data.

General procedure for the synthesis of (4*S*)-2-aryl- and (4*S*)-2-alkyl-4-carbomethoxy-2-oxazolines

A mixture of iminoether hydrochloride (32.7 mmol), amino acid methyl ester hydrochloride (32.7 mmol) and methylene chloride (120 mL) into a two-neck flask, equipped with dropping funnel and mechanical stirrer was introduced under argon and cooled to 0°C. A solution of triethylamine (9.3 mL) and methylene chloride (50 mL) was added dropwise during two hr at the same temperature. The resulting mixture was stirred for additional 24 hr at room temperature, concentrated at reduced pressure. Toluene (100 mL) was then added and filtered on sintered glass funnel. The solvent was removed under vacuum.

2-phenyl-4-carbomethoxy-2-oxazoline, 2a[12]

40% yield. m.p. 32-34 °C (light petrol). ^{1}H-NMR ($CDCl_3$): 3.80 (s, 3 H), 4.60 (dd, J = 10.7, 8.0 Hz, 1 H), 4.70 (dd, J = 8.7, 8.0 Hz, 1 H), 4.93 (dd, J = 10.5, 8.0 Hz, 1 H), 7.40-7.58 (m, 3 H, Ar), 8.00 (d, J = 7.2 Hz, 2 H). ^{13}C-NMR ($CDCl_3$): 52.40, 68.54, 69.48, 126.85, 128.29, 131.80, 166.22, 171.57. IR (KBr disk) 2960, 1740, 1710, 1640, 1380, 1249, 783, 699 cm^{-1}. Elemental analysis (calcd for $C_{11}H_{11}NO_3$): C 64.13 (64.38); H 5.20 (5.40); N 7.04 (6.83).

(*S*)-2-benzyl-4-carbomethoxy-2-oxazoline, 2b

Oil. 85 % yield. $[\alpha]_D^{25}$ = -14.75 (c = 1.5, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 3.59 (d, 1/2 of AB system, J =

14.7 Hz, 1 H), 3.66 (d, 1/2 of AB system, J = 14.7 Hz, 1 H), 3.74 (s, 3 H, OCH_3), 4.34 (dd, J = 10.5, 8.7 Hz, 1 H), 4.44 (dd, $J_1 = J_2$ = 8.7 Hz, 1 H), 4.70 (dd, J = 10.5, 8.7 Hz, 1 H), 7.10-7.20 (m, 5 H, Ar). IR (neat film) 2954, 1774, 1716, 1389, 1244, 1174, 778, 722 cm^{-1}. Elemental analysis (calcd for $C_{12}H_{13}NO_3$): C 65.53 (65.74); H 5.70 (5.98); N 6.04 (6.39).

(*S*)-2-(3-phenylpropyl)-4-carbomethoxy-2-oxazoline, 2c

Oil. 90 % yield. $[\alpha]_D^{23}$ = + 89.6 (c = 2.1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.94-2.04 (quintet, J = 7.8 Hz, 2 H), 2.30-2.40 (t, J = 7.8 Hz, 2 H), 2.66 (t, J = 7.8 Hz, 2 H), 3.79 (s, 3 H, OCH_3), 4.35 (dd, J = 10.5, 8.7 Hz, 1 H), 4.47 (dd, J_1=J_2 = 8.7 Hz, 1 H), 4.71 (dd, J = 10.5, 8.7 Hz, 1 H), 7.15-7.50 (series of m, 5 H, Ar). Elemental analysis (calcd for $C_{14}H_{17}NO_3$): C 68.25 (68.00); H 7.10 (6.93); N 5.40 (5.66).

(4*S*,5*R*)-2-(3-phenylpropyl)-4-carbomethoxy-5-methyl-2-oxazoline, 2d

Oil. 90 % yield. $[\alpha]_D^{25}$ = -11.3 (c = 3.1, MeOH). ^{1}H-NMR ($CDCl_3$): 1.30 (d, J = 6.3 Hz, 3 H, CH_3), 1.80-1.92 (m, 2 H), 2.17-2.28 (m, 2 H), 2.51-2.59 (m, 2 H),3.67 (s, 3 H, CH_3), 4.13 (d, J = 6.9 Hz, 1 H), 4.66 (m, 1 H), 7.0-7.21 (m, 5 H, Ar). Elemental analysis (calcd for $C_{15}H_{19}NO_3$): C 68.75 (68.94); H 7.20 (7.33); N 5.55 (5.36).

General procedure for the synthesis of (4*S*)-2-aryl- and (4*S*)-2-alkyl-4-carboxyamido-2-oxazoline 3a-d

The following procedure for the conversion of inermediate **2a** into **3a** is representative for the preparation of compounds **3a-d**: an ammonia gas saturated solution of **2a** (64.5 mmol) and dry methanol (250 mL) into a vessel tube was stirred at room temperature. The reaction was monitored by TLC (CH_2Cl_2). Analytically pure compound was recovered by simple concentration at reduced pressure.

2-phenyl-4-carboxyamido-2-oxazoline, 3a

Colourless crystals. 70% yield. ^{1}H-NMR (DMSO-d_6): 4.45-4.60 (m, 2 H), 4.75 (dd, J = 9.0, 8.0 Hz, 1 H), 7.35 (bs, 2 H, NH_2), 7.4-7.6 (m, 3 H, Ar), 7.9 (d, J = 7.2 Hz, 2 H, Ar). ^{13}C-NMR (DMSO-d_6): 68.93, 70.15, 127.37, 128.38, 128.97, 132.15, 164.15, 172.96. Elemental analysis (calcd for $C_{10}H_{10}N_2O_2$): C 63.40 (63.15); H 5.51 (5.30); N 14.90 (14.73).

(*S*)-2-benzyl-4-carboxyamido-2-oxazoline, 3b

80% yield. $[\alpha]_D^{25}$ = +27.2 (c = 0.7, MeOH). ^{1}H-NMR (DMSO-d_6): 3.63 (s, 2 H), 4.29 (quintet, 2 H, J = 9.0 Hz), 4.54 (t, J = 9.0 Hz, 1 H), 7.20-7.40 (m, 7 H, Ar, NH_2); ^{13}C-NMR (DMSO-d_6): 33.69, 68.20, 69.41, 126.77, 128.41, 128.93, 135,30, 166.78, 172.67. Elemental analysis (calcd for $C_{11}H_{12}N_2O_2$): C 64.50 (64.69); H 5.71 (5.92); N 13.90 (13.72).

(*S*)-2-(3-phenylpropyl)-4-carboxyamido-2-oxazoline, 3c

90 % yield. $[\alpha]_D^{28}$ = -22.86 (c = 2.2, $CHCl_3$). m.p. 43-45 °C (AcOEt-light petrol). ^{1}H-NMR ($CDCl_3$): 1.93 (quintet, J = 7.5 Hz, 2 H), 2.29 (t, J = 7.5 Hz, 2 H), 2.63 (t, J = 7.5 Hz, 2 H), 4.36-4.44 (m, 2 H), 4.57 (t, J = 9.9 Hz, 1 H), 5.83 (bs, 1 H, N-H), 6.52 (bs, 1 H, N-H), 7.10-7.30 (m, 5 H, Ar). Elemental analysis (calcd for $C_{13}H_{16}N_2O_2$): C 67.40 (67.22); H 7.12 (6.94); N 12.32 (12.06).

(4*S*,5*R*)-2-(3-phenylpropyl)-4-carboxyamido-5-methyl-2-oxazoline, 3d

Oil. 90 % yield. ^{1}H-NMR ($CDCl_3$, mixture of conformers in 2:1 ratio): 0.45 (m, 2 H, conf. min.), 0.75 (m, 2 H, conf. maj.), 0.95-1.20 (m, 2 H, 2 conf.), 1.26 (d, J = 7.4 Hz, conf. min., 2 H), 1.36 (d, J = 7.4 Hz, conf. maj.), 1.70-2.03, 2.10, 2.30, 2.40-2.75 (series of m, 12 H, 2 conf.), 6.90-7.35 (m, Ar, 2 conf., 5 H), 7.80 (bs , 2 H, NH_2).

General procedure for the reaction of carboxyamides 3b-d with sulphonyl chlorides. Syntheses of 1a-e

The following procedure for the conversion of intermediate **3d** into **1b** is representative for the preparation of compounds **1a-e**: a solution of **3d** (0.45 g, 1.96 mmol), *p*-TsCl (0.4 g, 2.15 mmol) and pyridine (10 mL), was stirred at 75°C, monitoring by TLC (CH_2Cl_2). After 3 h the rection mixture was concentrated at reduced pressure, water (20 mL) was added and the organic phase was extracted with CH_2Cl_2 (70 mL). The organic solution was sequentially washed with water (3 x 50 mL), HCl 10% (3 x 30 mL), water, $NaHCO_3$ (3 x 50 mL) and dried on Na_2SO_4. Evaporation of the solvent at reduced pressure furnishes an oil which was purified by flash-chromatography (CH_2Cl_2-hexane).

1a: colourless crystals. 80 % yield. $[\alpha]_D^{26}$ = - 23.4 (c = 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, mixture of conformers) δ (ppm): 2.35 (bs, 3 H), 3.40-3.80 (m, 2 H), 4.10-4.90 (series of m, 3 H), 6.00, 6.40, 6.45, 6.80 (4 bs, 1 H), 6.97 (bs, 1 H, Ar), 7.15 (m, AA' system, 2 H, Ar), 7.20-7.40 (m, 4 H, Ar), 7.75 (m, AA' system, 2 H, Ar). Elemental analysis (calcd. for $C_{18}H_{18}N_2O_4S$): C 60.70 (60.32); H 5.40 (5.06); N 7.70 (7.82).

1b: oil. 80% yield. $[\alpha]_D^{27}$ = -18.6 (c = 0.8, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.88-2.05 (m, 2 H), 2.20-2.38 (m, 2 H), 2.43 (s, 3 H), 2.60-2.70 (m, 2 H), 3.72 (qd, J = 11.1, 4.8 Hz, 1 H), 4.25 (qd, J = 11.7, 5.4 Hz, 1 H), 4.55 (dt, J = 9.6, 4.8 Hz, 1 H), 6.22 (bs, 1 H, N-H), 7.15-7.40 (series of m, 7 H, Ar), 7.80 (d, AA' system, J = 8.4 Hz, 2 H, Ar). IR (neat film) 3262, 3059, 2945, 1742, 1661, 1596, 1450, 1339, 1163, 815, 748, 702, 668 cm^{-1}. Elemental analysis (calcd. for $C_{20}H_{22}N_2O_4S$): C 62.40 (62.16); H 5.50 (5.74); N 7.43 (7.25).

1c: colourless crystals. 90% yield; $[\alpha]_D^{25}$ = + 32.3 (c = 0.8, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, mixture of rotamers in 1:1 ratio): 3.43 (s, 2 H), 3.96-4.04 (m, 2 H), 4.28-4.38 (m, 1 H), 5.40 (bs, 1/2 H, N-H), 5.80 (d, J = 7.2 Hz, 1 H, Ar), 6.25 (bs, 1/2 H, N-H), 7.05-8.00 (series of m, 10 H, Ar), 8.40 (s, 1 H, Ar). IR (KBr disk) 3200, 1630, 1345, 1160 cm^{-1}. Elemental analysis (calcd. for $C_{21}H_{18}N_2O_4S$): C 63.72 (63.95); H 4.40 (4.60); N 7.10 (7.10).

1d: oil. 85% yield; $[\alpha]_D^{25}$ = +12.8 (c = 1.5, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, mixture of conformers): 0.7-1.24 (series of m, 8 H), 1.26-1.75 (m, 2 H), 1.80-2.20 (m, 5 H), 2.30-2.80 (series of m, 1 H), 3.40-3.70 (m, 4 H), 5.40-5.80 (series of bs, 1 H, N-H), 7.18-7.50 (m, 5 H, Ar). IR (film) 3200, 1630, 1345, 1160. cm^{-1}.

1e: oil. 85% yield; $[\alpha]_D^{26}$ = -14.0 (c = 0.9, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, mixture of conformers): 0.82-0.92 (m, 2 H), 1.17 (d, J = 6.4 Hz, 1 H), 1.27 (s, 3 H), 1.51 (d, J = 6.4 Hz, 1 H), 1.92-2.05 (m, 2 H), 2.10-2.40 (series of s, 3 H), 2.90 (t, J = 7.8 Hz, 2 H), 6.80 (bs, 1 H), 7.10-7.45, 7.50-7.90 (series of m, 10 H, Ar, N-H). IR (neat film) 3334, 1741, 1557, 1457, 1376, 1160, 1085, 808, 722, 699 cm^{-1}. Elemental analysis (calcd. for $C_{21}H_{24}N_2O_4S$): C 62.72 (62.98); H 6.40 (6.04); N 7.10 (6.99).

2-phenyl-4-nitrile-2-oxazoline, 4

The reaction conditions described for the preparation of compounds **1a-e** were employed: 80% yield. m.p. 49-51°C (light petrol-ethyl acetate). ^{1}H-NMR ($CDCl_3$): 4.65 (d, J = 9.7 Hz, 2 H), 5.08 (d, J = 9.7 Hz, 1 H), 7.40-7.49 (m, 2 H, Ar), 7.50-7.60 (m, 1 H, Ar), 7.97 (m, 2 H, Ar). IR (KBr disk) 2220 cm^{-1}. Elemental analysis (calcd. for $C_{10}H_8N_2O$): C 69.62 (69.76); H 4.80 (4.68); N 16.50 (16.27).

(*S*)-1-ammino-2-hydroxy-propanamide-N-(2-naphthalenesulphonyl) hydrochloride.

A solution of THF (10 mL), **1c** (0.1 g, 0.53 mmol) and 2*N* HCl (5 mL) was stirred at room temperature for 12 h. The mixture was extracted with $CHCl_3$ (3 x 50 mL) and dried over Na_2SO_4. Evaporation of the solvent at reduced pressure furnishes 0.08 g (95 % yield) of a colourless solid. $[\alpha]_D^{26}$ = -4.0 (c = 1.4, $CHCl_3$); ^{1}H-NMR (4:1 ratio of a $CDCl_3$:DMSO-d_6 solution of a mixture of conformers): 3.35-3.90 (series of m plus a broad signal, 7 H), 6.65, 6.95, 7.05 (3 s, 1 H, NH), 7.10-7.95 (series of m, 6 H, Ar), 8.25 (bs, 1 H, Ar). IR (KBr disk) 3443, 3304, 2949, 1687, 1589, 1450, 1406, 1320, 1241, 1197, 1158, 1132, 864, 839, 752, 700, 672 cm^{-1}.

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