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Diastereoselective Formation of 2-Aryl-3-arenesulfonyl 4-ethyl-1,3-oxazolidines : An X-Ray Crystallographic and ¹H NMR Study

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Abstract : N-Arylsulfonamides of (R)- and (S)-2-amino-1-butanol, on condensation with aromatic aldehydes produced diastereometrically pure 2-aryl-3-arenesulfonyl 4-ethyl-1,3oxazolidines. The absolute configurations of one enantiometric pair have been determined from two fully refined X-ray structures, supplemented by nmr data. Copyright © 1996 Elsevier Science Ltd

3-(p-Toluene sulfonyl)-1,3-oxazolidines derived from enantiomerically pure β -amino alcohols have been recognized as valuable chiral templates in asymmetric synthesis¹. Previous investigations into the condensation of aldehydes with β -aminoalcohols have shown that the products obtained were found to be an equilibrium mixture of imines and the corresponding 1,3-oxazolidines^{2,3}. Here we wish to report the synthesis of 2-aryl-3-arenesulfonyl-4-ethyl-1,3-oxazolidines derived from N-benzene and N-toluene sulfonamides of (*R*)- and (*S*)-2-amino-1-butanol. The respective sulfonamides, on condensation with a wide variety of aromatic aldehydes furnished single crystalline *cis*-oxazolidines. The enantiomeric excess of the oxazolidines formed were established by ¹H NMR spectroscopic analysis. The absolute configuration of the newly formed stereogenic centre was established by X-ray crystallographic study of the two representative compounds (8a and 8b) making use of the anomalous scattering by the sulfur atom in the molecule by molybdenum radiation.

Results and Discussion

Formation of the oxazolidines was carried out by reaction of the equimolar quantities of the sulfonamides derived from the enantiomerically pure β -aminoalcohols with arylaldehydes in chloroform (Scheme 1).



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Conclusive evidence for the formation of 1,3-oxazolidines 4a-8a and 4b-8b was obtained from the ¹H NMR spectra which show sharp singlets at 6.2 ppm due to -N-CH-O (C-2). The formation of a single diastereomer is confirmed by NMR spectroscopic analysis. The compounds 8a and 8b were subjected to independent X-ray diffraction analyses and were found to have different absolute configurations. The configuration at the newly formed stereogenic center (C-2) is (S) in the case of oxazolidines derived from the sulfonamides of (S)-2-amino-1-butanol and (R) in the case of oxazolidines derived from sulfonamides of (R)-2-amino-1-butanol. The 2,4-relative stereochemistry of hydrogen atoms are found to be cis to each other, in the case of both the diastereomers. These results are in accordance with the cis selectivity observed during the formation of 3-alkyl oxazolidines⁽⁴⁾. Oxazolidine formation occurs by a sequence of reversible steps. The stereodirecting step is the intramolecular addition of the hydroxyl group to the iminium ion, which may produce a mixture of diastereomers, with one in excess. The minor isomer corresponds to the kinetic product of the reaction, which can be isomerised into the major isomer via the intermediate iminium ion⁵. The 2,4-cis diastereoselectivity observed during the formation of the 1,3oxazolidines is due to the arenesulfonyl group at position-3, which prefers to be trans to both the hydrogens at the 2- and 4- positions for steric reasons. The 1,3-oxazolidines obtained from (R) and (S)-2amino-l-butanol showed equal and opposite specific rotations indicating the diastereoselective formation of the 1,3-oxazolidine.



The Figure shows the (2S', 4S') isomer **8a**. Unit cell parameters and basic information about data collection and structure refinement are summarized in the experimental section. The H atom at C-2 and C-4 are *cis* to each other. The X-ray data is consistent with the ¹H NMR data, which shows the exclusive formation of a single diastereoisomer in both the cases. On the basis of the X-ray data the absolute configuration of 8a is assigned as $(2S^*, 4S^*)$ and that of 8b as $(2R^*, 4R^*)$.

In conclusion, the cyclisation of the sulfonamides of (R) and (S)-2-amino-1-butanol with aromatic aldehydes proceeds completely diastereoselectivity, providing a single diastereomer.

Experimental

¹H NMR Spectra were recorded on a Varian EM-390 at 90 MHz or Varian XLAA-400 at 400 MHz. Chemical shifts (δ ppm) are relative to tetramethylsilane. The infrared spectra were recorded on a Shimadzu IR-408 spectrophotometer. Optical rotations were measured on a Jasco-Dip-370 polarimeter. Elemental analyses were carried out on a Coleman instrument. Melting points were obtained on a Gallenkamp-350 micromelting apparatus by open capillary method, and are uncorrected. TLC's were performed on Acme silica gel containing 13% calcium sulfate as binder.

Crystal data and structure refinement

Crystal data for 8a. $C_{18}H_{20}CINO_3S$, *M* 365.86. crystal size 0.3 x 0.2 x 0.2 mm. T 293(2) K., Crystal system - orthorhombic, space group P2₁2₁2₁, *a*=9.113 A°, *b*=13.833A°, *c*=14.196 A°. *U* = 1789.5 A³, Z=4; D_c 1.358 mg/m³. μ = 0.346mm⁻¹, F(000)=768, λ (Mo-K_a) = 0.71073A°

Crystal data for 8b. $C_{18}H_{20}CINO_3S$, *M* 365.86. crystal size 0.3 x 0.2 x 0.2 mm. T 293(2) K. Crystal system - orthorhombic, space group P2₁2₁2₁, *a*=9.233 A°, *b*=14.017A°, *c*=14.241 A°. *U* = 1866 A³, Z=4, D_c 1.302 mg/m³. μ = 0.331 mm⁻¹, F(000)-768, λ (Mo-K_α) = 0.71073A

Crystals of 8a and 8b were mounted on glass fibers, and intensity data were measured on each separately using the small Mar Research image plate scanner and Mo radiation. 95 frames were measured with a 2° rotation and an exposure time of 4 min per frame. Data were processed with the Mar version of the XDS package, to give 9001 reflections for 8a. 3202 were unique with a merging R of 2.37%. θ range for data collection 2.66 to 25.87°, Index ranges $0 \le h \le 10, -16 \le k \le 16, -17 \le 12$.

9367 reflections were collected for 8b of which 3134 were unique with a merging R of 4.2%. θ range for data collection 2.82 to 25.06°. Index Ranges $0 \le h \le 10$, $-16 \le k \le 16$, $-17 \le l \le 17$.

The structures were solved⁶ by direct methods using SHELX-86 and refined with SHELXL. The final conventional R factor is 4.35% for 8a based on 2745 observations for which Fo > 4 σ (Fo) and 5.52% for all 3202 data. The refinement method (for both structures) was full matrix least squares on F². Goodness of fit on F² was 1.114. The absolute structure parameter of Flack as implemented in the package refined to a value of 0.2205(.1054). The largest difference peak and hole in the final map were 0.205 and -0.167e A⁻³;

The final conventional R factor for 8b is 4.27% based on 2743 observations for which Fo > 4 σ (Fo) and 5.23% for all 3134 data. Goodness of fit on F² was 1.070. The absolute structure parameter refined to a final value of -0.0482 (.0975). The largest difference peak and hole in the final map were 0.165 and -0.168 eA⁻³.

The data have been deposited with the Cambridge Crystallographic Data Centre.

General procedure for the preparation of sulfonamides

(R)or(S) 2-amino-1-butanol (5 mmol) was dissolved in dichloromethane (20ml). Triethylamine was added (5 mmol) to the above solution and cooled in an ice bath. A solution of the arene sulfonyl chloride (5 mmol) in dichloromethane was added to the solution, drop by drop by means of a pressure equalising funnel, and kept under constant stirring at 0-3°C for 4 hrs and the reaction mixture was brought to room

temperature. The mixture was washed with 2N aq. H_2SO_4 , and water. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure on a rotary evaporator. The residue was crystallised from diethyl ether, to give the products.

(S)-N-Benzenesulfonyl-2-amino-1-butanol 2a

96% yield; mp 68°C; $[\alpha]_D$ -28.64 (c 1.0 in CHCl₃); δ ppm (CDCl₃) - 0.75 (3H, t,-CH₃), 1.5 (3H,m,-CH₂-CH), 3.2 (1H,m,-NH), 3.6 (2H,d,-CH₂-O) 7.7, 8.0 (5H, m,-C₆H₅); $\sqrt{\max (KBr) / cm^{-1}-3300}$, 2900, 1450, 1320 and 1150; CHN Found (Calculated) C-56.2 (56.3), H-7.01 (7.04), N-6.39(6.57).

(R)-N-Benzene sulfonyl-2-amino-1-butanol 2b

95.7% yield; m.p 69°C; $[\alpha]_D$ + 28.97 (c1.0 in CHCl₃); δ ppm (CDCl₃) - 0.75 (3H,t,-CH₃), 1.5(3H,m,-CH₂-CH), 3.1 (1H, m, -NH), 3.6 (2H,d,-CH₂-O), 7.9-8.0 (5H,m,-C₆H₅); $\sqrt{\max (KBr)/cm^{-1}}$ - 3300, 2900, 1460, 1310 and 1150; CHN Found (Calculated) - C-56.2(56.3), H-7.03 (7.04), N-6.37 (6.57).

(S)-N-Tosyl-2-amino-1-butanol 3a

94.0 yield; m.p. 73°C; [α]_D 70.8 (c1.0 in CHCl₃); δppm (CDCl₃) - 0.8 (3H,t,-CH₃), 1.4 (2H,m,-CH₂), 1.7 (1H,S,-CH), 2.2 (1H, s,-OH), 2.4 (3H,s,-CH₃ on ring), 3.2 (1H, s, -NH), 3.5 (2H,d,-CH₂-O), 7.3,7.8 (2H,2H,d,d, - C₆H₄); $\sqrt{\text{max}}$ (KBr)/cm⁻¹-3540, 3150, 2950, 1600,1315 and 1160; CHN Found (Calculated) - C-54.1 (54.32), H-6.73 (6.99), N-5.67 (5.76).

(R)-N-Tosyl-2-amino-1-butanol 3b

94.6% yield; mp 74°C; $[\alpha]_D$ + 71.2 (c1.0 in CHCl₃); δ ppm (CDCl₃) - 0.8 (3H,t,-CH₃), 1.4 (2H,m,-CH₂), 1.7 (1H, m, -CH), 2.2 (1H,s,-OH), 2.4 (3H,s,-CH₃ on ring), 3.2 (1H,s,-NH), 3.5 (2H, d,-CH₂O), 7.3,7.8 (2H, 2H, d,d,-C₆H₄); \sqrt{max} (KBr)/cm⁻¹-3540,3150, 2950, 1600, 1310 and 1160; CHN Found (Calculated)- C-54.2(54.32), H-6.79 (6.995), N- 5.68 (5.76).

General procedure for the preparation of 1,3-oxozolidines

Compounds 2a,2b,3a,3b (5m.mol) were dissolved separately in 20ml of chloroform, and the aromatic aldehyde (5 m.mol) was added. A drop of concentrated sulfuric acid was also added, and stirred the reaction mixture for 3 hrs at room temperature. The reaction mixture was washed with a 5% solution of sodium bicarbonate, water and then with brine. The organic layer was dried over anhydrous sodium sulfate, and evaporated under reduced pressure on a rotary evaporator. The residue was crystallised from dichloromethane-petroleum ether (60-80) (50:50) to give the 1,3-oxazolidines.

(25',45') 2-(3-nitrophenyl)-3-benzenesulfonyl-4-ethyl-1,3-oxazolidine 4a

Yield 89%; m.p. 124°C; $[\alpha]_D$ -355.7 (c1.0 in CHCl₃); δppm (CDCl₃) - 0.88 (3H,t,-CH₃), 1.38, 1.6 (m,m, 2H, -CH₂), 3.6, 3.8 (3H,m,-CH-CH₂), 6.2 (1H,s,-N-CH-O), 7.56, 8.3 (9H,m,-C₆H₄, - C₆H₅); \sqrt{max} (KBr)/cm⁻¹ 2900, 1530, 1450, and 1360; CHN Found (calculated)-C-58.4 (58.62), H-5.22 (5.17), N-4.0 (4.02).

(2R*,4R*) 2-(3-nitrophenyl)-3-benzenesulfonyl-4-ethyl-1,3 Oxazolidine 4b

Yield 90%; mp 123°C; $[\alpha]_D$ +354.2 (c 1.0 in CHCl₃); δ ppm (CDCl₃)-0.9 (3H,t,-CH₃), 1.38, 1.5 (1H,1H,m,m,-CH₂), 3.5,3.9 (3H,m,-CH-CH₂), 6.2 (1H, s, -N-CH-O), 7.6, 8.4 (9H, m, -C₆H₄, - C₆H₅); $\sqrt{\max (KBr)/cm^{-1}}$ 2900, 1530, 1450 and 1350; CHN Found (Calculated)-C 58.37 (58.62), H 5.281 (5.17), N 4.21 (4.02).

(2S', 4S') 2-(2-chloro phenyl)-3-benzenesulfonyl-4-ethyl-1,3-oxazolidine 5a

Yield 84%; mp. 116-117°C; $[\alpha]_D$ -150.1 (c1.0 in CHCl₃); δppm (CDCl₃) - 1.0 (3H,t,-CH₃), 1.8, (2H,m,-CH₂), 3.7 (3H,m,-CH-CH₂), 6.35 (1H,s,-N-CH-O), 7.4, 7.9 (9H,m,-C₆H₅, - C₆H₄); \sqrt{max} (KBr/cm⁻¹ 2900, 1580, 1450, and 1340; CHN Found (Calculated)-C-58.15 (58.05), H-5.30 (5.12), N-3.81 (3.98).

(2R',4R') 2-(2-chloro phenyl)-3-benzenesulfonyl-4-ethyl-1,3-oxazolidine 5b

Yield 83%; m.p. 116°C; $[\alpha]_D$ + 151.0 (c.1.0 in CHCl₃); δ ppm (CDCl₃)-1.0(3H,t,-CH₃), 1.8 (2H,m,-CH₂), 3.7 (3H, m,-CH-CH₂), 6.35 (1H,s,-N-CH-O), 7.5, 7.8 (9H,m,-C₆H₅,-C₆H₄), $\sqrt{\max (KBr)/cm^{-1}}$ - 2900, 1570, 1480 and 1350. CHN Found (Calculated) -C-58.12 (58.05), H-5.370 (5.12), N-3.88 (3.98).

(2S',4S') 2-(4-chlorophenyl)-3-benzenesulfonyl-4-ethyl-1,3-oxazolidine 6a

Yield 87%; mp. 189°C; $[\alpha]_D$ -7.4 (c.1.0 in CHCl₃); δppm (CDCl₃) - 0.95 (3H,t,-CH₃), 1.5, 2H,m, -CH₂), 3.7 (3H, m,-CH-CH₂), 6.2 (1H,s,-N-CH-O), 7.5, 7.9 (9H,m,-C₆H₅, - C₆H₄); \sqrt{max} (KBr) /cm⁻¹ - 2900, 1450, 1350 and 1170; CHN Found (Calculated)-C-58.1 (58.05), H-5.01 (5.12), N-3.89 (3.98).

(2R', 4R') 2-(4-chlorophenyl)-3-benzenesulfonyl-4-ethyl 1,3-oxazolidine 6b

Yield 85%; m.p. 189°C; $[\alpha]_D$ + 7.66 (c.1.0 in CHCl₃); δ ppm (CDCl₃)-0.98 (3H,t,-CH₃), 1.5 (2H,m,-CH₂), 3.7 (3H, m,-CH-CH₂), 6.2 (1H,s,-N-CH-O), 7.6, 7.9 (9H,m,-C₆H₅,-C₆H₄), $\sqrt{\text{max}}$ (KBr)/cm⁻¹ - 2900, 1450, 1350 and 1160, CHN Found (Calculated) -C-58.18 (58.05), H-5.216 (5.12), N-3.79 (3.98).

(2S^{*},4S^{*}) 2-(3-nitrophenyl)-3-Tosyl-4-ethyl-1,3-oxazolidine 7a

Yield 92%; mp. 157°C; $[\alpha]_D$ -355.8 (c.1.0 in CHCl₃); δ ppm (CDCl₃) - 0.9 (3H,t,-CH₃), 1.6, (2H,m, - CH₂), 2.4, (3H, s,-CH₃ on ring), 3.6 (1H,m,-CH), 3.8 (2H,d,-CH₂,-O), 6.2 (1H,s,-N-CH-O), 7.2, 7,7 (8H, m, -C₆H₄, -C₆H₄); $\sqrt{\max (KBr) / cm^{-1} 2950, 1600, 1525 and 1345}$. CHN Found (Calculated) -C-57.2 (57.44), H-5.21 (5.31), N-7.62 (7.44).

(2R',4R') 2-(3-nitrophenyl)-3-Tosyl-4-ethyl-1,3-oxazolidine 7b

Yield 92%; m.p. 154°C; $[\alpha]_D$ -355.6 (c.1.0 in CHCl₃); δ ppm (CDCl₃) - 0.9 (3H,t,-CH₃), 1.6, (2H,m, - CH₂), 2.4, (3H, s,-CH₃ on ring), 3.6 (1H,m,-CH), 3.8 (2H,d,-CH₂,-O), 6.2 (1H,s,-N-CH-O), 7.2, 7,7 (8H, m, -C₆H₄, -C₆H₄); $\sqrt{\max}$ (KBr) /cm⁻¹ 3040, 2950, 1590, 1525 and 1350; CHN Found (Calculated) -C-57.59 (57.44), H-5.42 (5.31), N-7.62 (7.44).

(2S', 4S') 2-(2-Chlorophenyl)-3-Tosyl-4-ethyl-1,3-oxazolidine 8a

Yield 89%; m.p. 163°C; $[\alpha]_D$ -88.4 (c.1.0 in CHCl₃); δppm (CDCl₃) - 1.0 (3H,t,-CH₃), 1.6, 2.1 (2H,m, - CH₂), 2.4, (3H,S,-CH₃ on ring), 3.5 (1H, m,-CH), 3.7 (2H,d,-CH₂,-), 6.2 (1H,s,-N-CH-O), 7.3, 7.9 (8H, m, -C₆H₄, -C₆H₄); \sqrt{max} (KBr) /cm⁻¹ 2950, 1600, 1160, 1110 and 1090; CHN Found (Calculated) -C-58.95 (59.09), H-5.46 (5.47), N- 3.79 (3.83).

(2R',4R') 2-(2-Chlorophenyl)-3-Tosyl-4-ethyl-1,3-oxazolidine 8b

Yield 91%; mp. 160°C; $[\alpha]_D$ -+89.2, (c 1.0 in CHCl₃); δ ppm (CDCl₃) - 1.0 (3H,t,-CH₃), 1.6, 2.1 (2H,m, -CH₂), 2.4, (3H,s,-CH₃ on ring), 3.5 (1H, m,-CH), 3.7 (2H,d,-CH₂), 6.2 (1H,s,-N-CH-O), 7.3, 7.9 (8H, m, -C₆H₄, -C₆H₄); $\sqrt{\max (KBr) / cm^{-1}}$ 2950, 1600, 1170, 1140 and 1090; CHN Found (Calculated) -C-59.12 (59.09), H 5.20(5.47), N-3.97 (3.83).

(2S', 4S') 2-(4-Chlorophenyl)-3-Tosyl-4-ethyl-1,3-oxazolidine 9a

Yield 87%; mp. 121°C; $[\alpha]_D$ -271.85, (c 1.0 CHCl₃); δ ppm (CDCl₃) - 0.8 (3H,t,-CH₃), 1.4, 1.6 (2H,m, - CH₂), 2.5, (3H,s,-CH₃ on ring), 3.5 (1H, m,-CH), 3.7 (2H,d,-CH₂), 6.2 (1H,s,-N-CH-O), 7.3, 7.6 (8H,

m, $-C_6H_4$, $-C_6H_4$); \sqrt{max} (KBr) /cm⁻¹ 2950, 1600, 1160, 1120 and 1090; CHN Found (Calculated) -C-58.96 (59.09), H-5.34 (5.47), N 4.02 (3.83).

(2R',4R') 2-(4-Chlorophenyl)-3-Tosyl-4-ethyl-1,3-oxazolidine 9b

Yield 88%; mp. 122°C; $[\alpha]_D$ +271.53, (c 1.0 CHCl₃); δ ppm (CDCl₃) - 0.8 (3H,t,-CH₃), 1.4, 1.6 (2H,m, -CH₂), 2.5 (3H,s,-CH₃ on ring), 3.5 (1H, m,-CH), 3.7 (2H,d,-CH₂), 6.2 (1H,s,-N-CH-O), 7.3, 7.6 (8H, m, -C₆H₄, -C₆H₄); $\sqrt{\max (KBr) / cm^{-1} 2950}$, 1600, 1160, 1120 and 1090; CHN Found (Calculated) - C-59.16 (59.09), H-5.26 (5.47), N- 3.77 (3.83).

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