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

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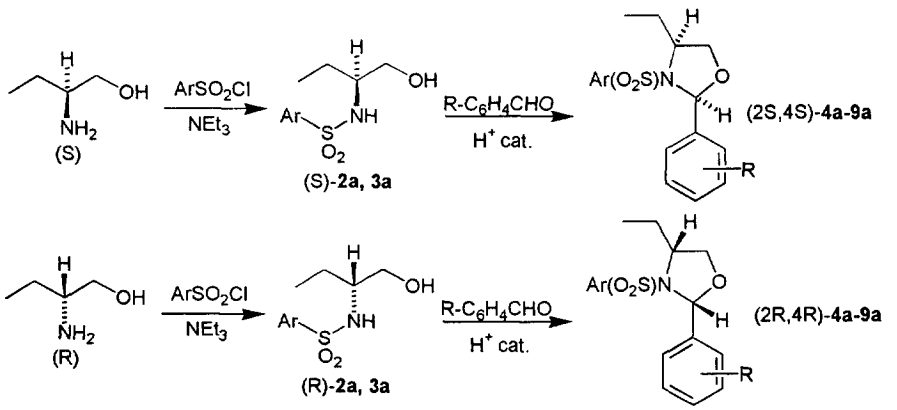
Abstract : N-Arylsulfonamides of *(R)*- and *(S)*-2-amino-1-butanol, on condensation with aromatic aldehydes produced diastereomerically pure 2-aryl-3-arenesulfonyl 4-ethyl-1,3-oxazolidines. The absolute configurations of one enantiomeric pair have been determined from two fully refined X-ray structures,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

3-(p-Toluene sulfonyl)-1,3-oxazolidines derived from enantiomerically pure β-amino alcohols have been recognized as valuable chiral templates in asymmetric synthesis[1]. 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 ^{1}H 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.

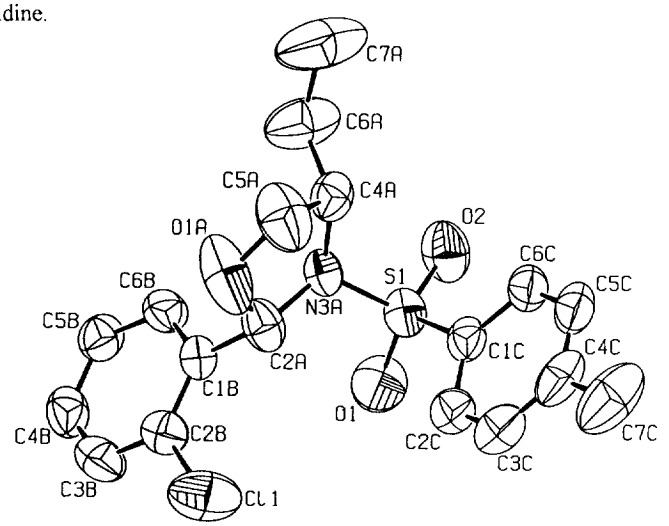
Results and Discussion

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).



Scheme 1: **2,4,5,6** Ar = Ph; **3,7,8,9** Ar = p-Tol; **4,7** R = 3-NO_2; **5,8** R = 2-Cl; **6,9** R = 4-Cl

Conclusive evidence for the formation of 1,3-oxazolidines 4a-8a and 4b-8b was obtained from the ^{1}H 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 ion[5]. The 2,4-*cis* diastereoselectivity observed during the formation of the 1,3-oxazolidines 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)*-2-amino-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 ^{1}H 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

^{1}H 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. $C_{18}H_{20}ClNO_3S$, *M* 365.86. crystal size 0.3 x 0.2 x 0.2 mm. T 293(2) K., Crystal system - orthorhombic, space group $P2_12_12_1$,. *a*=9.113 A°, *b*=13.833A°, *c*=14.196 A°. *U* = 1789.5 A^3, Z=4; D_c 1.358 mg/m^3. μ= 0.346mm^{-1}, F(000)=768, λ(Mo-K_α) = 0.71073A°

Crystal data for 8b. $C_{18}H_{20}ClNO_3S$, *M* 365.86. crystal size 0.3 x 0.2 x 0.2 mm. T 293(2) K. Crystal system - orthorhombic, space group $P2_12_12_1$,. *a*=9.233 A°, *b*=14.017A°, *c*=14.241 A° . *U* = 1866 A^3, Z=4, D_c 1.302 mg/m^3. 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 <=h<=10, -16 <= k <=16, -17<=l<=17.

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 ≤ h ≤ 10, -16 ≤ k≤ 16, -17≤ l ≤ 17.

The structures were solved[6] 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 F^2. Goodness of fit on F^2 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 F^2 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 $CHCl_3$); δ ppm ($CDCl_3$) - 0.75 (3H, t,-CH_3), 1.5 (3H,m,-CH_2-CH), 3.2 (1H,m,-NH), 3.6 (2H,d,-CH_2-O) 7.7, 8.0 (5H, m,-C_6H_5); √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 (*c*1.0 in $CHCl_3$); δ ppm ($CDCl_3$) - 0.75 (3H,t,-CH_3), 1.5(3H,m,-CH_2-CH), 3.1 (1H, m, -NH), 3.6 (2H,d,-CH_2-O), 7.9-8.0 (5H,m,-C_6H_5); √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; $[\alpha]_D$ 70.8 (*c*1.0 in $CHCl_3$); δppm ($CDCl_3$) - 0.8 (3H,t,-CH_3), 1.4 (2H,m,-CH_2), 1.7 (1H,S,-CH), 2.2 (1H, s,-OH), 2.4 (3H,s,-CH_3 on ring), 3.2 (1H, s, -NH), 3.5 (2H,d,-CH_2-O), 7.3,7.8 (2H,2H,d,d, - C_6H_4); √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 (*c*1.0 in $CHCl_3$); δppm ($CDCl_3$) - 0.8 (3H,t,-CH_3), 1.4 (2H,m,-CH_2), 1.7 (1H, m, -CH), 2.2 (1H,s,-OH), 2.4 (3H,s,-CH_3 on ring), 3.2 (1H,s,-NH), 3.5 (2H, d,-CH_2O), 7.3,7.8 (2H, 2H, d,d,-C_6H_4); √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.

***(2S*,4S*)* 2-(3-nitrophenyl)-3-benzenesulfonyl-4-ethyl-1,3-oxazolidine 4a**

Yield 89%; m.p. 124°C; $[\alpha]_D$ -355.7 (*c*1.0 in $CHCl_3$); δppm ($CDCl_3$) - 0.88 (3H,t,-CH_3), 1.38, 1.6 (m,m, 2H, -CH_2), 3.6, 3.8 (3H,m,-CH-CH_2), 6.2 (1H,s,-N-CH-O), 7.56, 8.3 (9H,m,-C_6H_4, - C_6H_5); √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 $CHCl_3$); δppm ($CDCl_3$)-0.9 (3H,t,-CH_3), 1.38, 1.5 (1H,1H,m,m,-CH_2), 3.5,3.9 (3H,m,-CH-CH_2), 6.2 (1H, s, -N-CH-O), 7.6, 8.4 (9H, m, -C_6H_4, - C_6H_5); √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 (*c*1.0 in $CHCl_3$); δppm ($CDCl_3$) - 1.0 (3H,t,-CH_3), 1.8, (2H,m,-CH_2), 3.7 (3H,m,-CH-CH_2), 6.35 (1H,s,-N-CH-O), 7.4, 7.9 (9H,m,-C_6H_5, - C_6H_4); √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 $CHCl_3$); δ ppm ($CDCl_3$)-1.0(3H,t,-CH_3), 1.8 (2H,m,-CH_2), 3.7 (3H, m,-CH-CH_2), 6.35 (1H,s,-N-CH-O), 7.5, 7.8 (9H,m,-C_6H_5,-C_6H_4), √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 $CHCl_3$); δppm ($CDCl_3$) - 0.95 (3H,t,-CH_3), 1.5, 2H,m, -CH_2), 3.7 (3H, m,-CH-CH_2), 6.2 (1H,s,-N-CH-O), 7.5, 7.9 (9H,m,-C_6H_5, - C_6H_4); √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 $CHCl_3$); δ ppm ($CDCl_3$)-0.98 (3H,t,-CH_3), 1.5 (2H,m,-CH_2), 3.7 (3H, m,-CH-CH_2), 6.2 (1H,s,-N-CH-O), 7.6, 7.9 (9H,m,-C_6H_5,-C_6H_4), √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 $CHCl_3$); δppm ($CDCl_3$) - 0.9 (3H,t,-CH_3), 1.6, (2H,m, -CH_2), 2.4, (3H, s,-CH_3 on ring), 3.6 (1H,m,-CH), 3.8 (2H,d,-CH_2,-O), 6.2 (1H,s,-N-CH-O), 7.2, 7,7 (8H, m, -C_6H_4, -C_6H_4); √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 $CHCl_3$); δppm ($CDCl_3$) - 0.9 (3H,t,-CH_3), 1.6, (2H,m, -CH_2), 2.4, (3H, s,-CH_3 on ring), 3.6 (1H,m,-CH), 3.8 (2H,d,-CH_2,-O), 6.2 (1H,s,-N-CH-O), 7.2, 7,7 (8H, m, -C_6H_4, -C_6H_4); √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 $CHCl_3$); δppm ($CDCl_3$) - 1.0 (3H,t,-CH_3), 1.6, 2.1 (2H,m, -CH_2), 2.4, (3H,S,-CH_3 on ring), 3.5 (1H, m,-CH), 3.7 (2H,d,-CH_2,-), 6.2 (1H,s,-N-CH-O), 7.3, 7.9 (8H, m, -C_6H_4, -C_6H_4); √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 $CHCl_3$); δ ppm ($CDCl_3$) - 1.0 (3H,t,-CH_3), 1.6, 2.1 (2H,m, -CH_2), 2.4, (3H,s,-CH_3 on ring), 3.5 (1H, m,-CH), 3.7 (2H,d,-CH_2), 6.2 (1H,s,-N-CH-O), 7.3, 7.9 (8H, m, -C_6H_4, -C_6H_4); √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 $CHCl_3$); δ ppm ($CDCl_3$) - 0.8 (3H,t,-CH_3), 1.4, 1.6 (2H,m, -CH_2), 2.5, (3H,s,-CH_3 on ring), 3.5 (1H, m,-CH), 3.7 (2H,d,-CH_2), 6.2 (1H,s,-N-CH-O), 7.3, 7.6 (8H,

m, $-C_6H_4$, $-C_6H_4$); √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 $CHCl_3$); δ ppm ($CDCl_3$) - 0.8 (3H,t,$-CH_3$), 1.4, 1.6 (2H,m, $-CH_2$), 2.5 (3H,s,$-CH_3$ on ring), 3.5 (1H, m,-CH), 3.7 (2H,d,$-CH_2$), 6.2 (1H,s,-N-CH-O), 7.3, 7.6 (8H, m, $-C_6H_4$, $-C_6H_4$); √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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