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SYNTHESIS OF SOME NEW CHIRAL SULFONAMIDE LIGANDS

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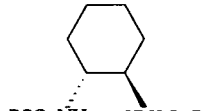
Abstract:
Synthesis of new chiral sulfonamide ligands derived from isatoic anhydride by reaction with *trans*-(*R*,*R*)-1,2-diaminocyclohexane and chiral aminoacid esters.

A plethora of chiral ligands to create chiral Lewis acids have been developed over the years and they have been elegantly used as catalysts to induce asymmetry into achiral molecules[1,2]. Sulfonamides of *trans*-1,2-diaminocyclohexane (1) are one such class of compounds which have been used with titanium as a catalyst to induce high enantioselectivity in many carbon-carbon bond forming reactions[3-9].



(1)

R = 4-C_6H_4-Me; 2,5-C_6H_3-Me_2; 1-Naphtyl; 2,4,5-C_6H_2-Cl_3; 4-C_6H_4-NO_2.

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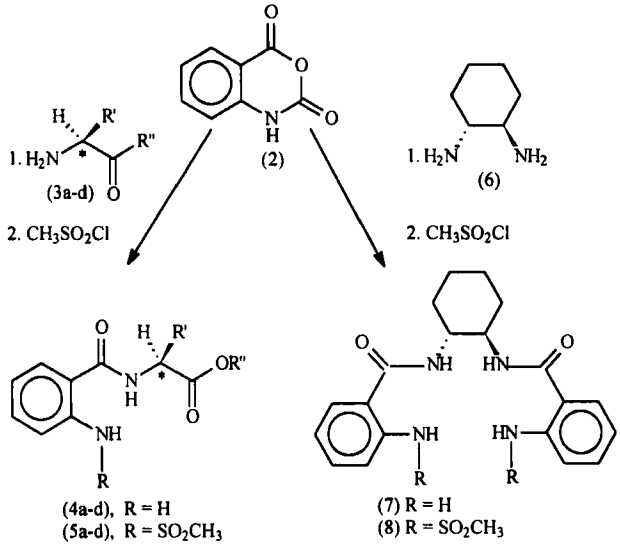
There still appears to be a great demand for metal specific chiral ligands. In our research, we have focused on making such ligands from readily available chiral starting materials. Here we wish to report the synthesis of some novel chiral sulfonamide compounds derived from aminoacid esters and *trans*-1,2-diaminocyclohexane, as potential ligands for early transition metals.



These new compounds were made starting from isatoic anhydride (2), which was reacted either with chiral aminoacid esters (3) or *trans*-(*R*,*R*)-1,2-diaminocyclohexane (6) to give the corresponding amides. Subsequent reaction with methane sulfonyl chloride gave the sulfonamides in good yield. Compounds derived from the aminoacid esters (5a-d) provide useful sources of chiral bidentate or tridentate ligands, for example as shown in the X-ray structure (5a)

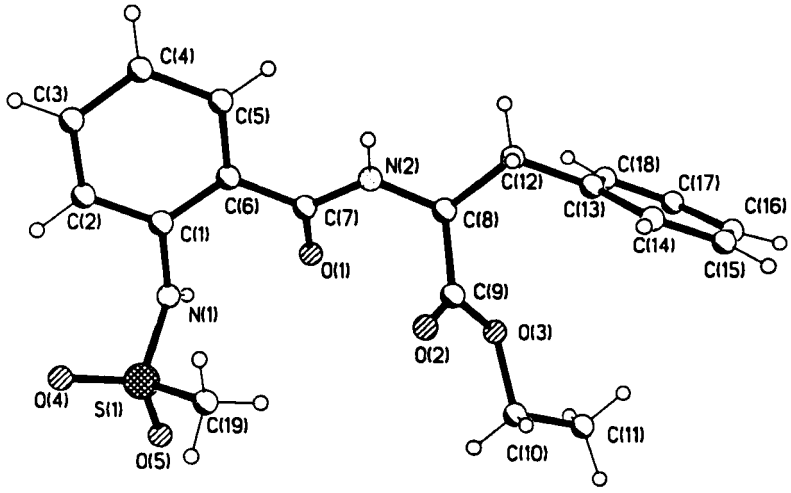


Fig.1. X-ray structure of **5a**.

(Fig. 1.)[10]. Similarly the ligand (8) derived from the chiral *trans*-1,2-diaminocyclohexane could also serve as an excellent tetradentate ligand of the type Trost and others have described [11,12]. Thus our synthesis has used inexpensive chiral molecules to make useful chiral ligands.

EXPERIMENTAL

Melting points were obtained on a Gallenkamp apparatus and are uncorrected. The rotations were obtained on a Rudolph Research Flanders automatic polarimeter. Infrared Spectra were recorded on a Perkin-Elmer FT-IR 1600 Spectrophotometer. The ^{1}H NMR and ^{13}C spectra were recorded on a Varian Gemini 200 Spectrometer at 200 and 50 MHz with TMS as an internal standard. Mass spectra were obtained on a Hewlett Packard MS-Engine 5989A. HRMS were obtained at 70 eV with a VG7070 Spectrometer at the UCR Mass

Spectrometry Facility, Riverside, C.A. The X-ray structure was determined on a Siemens P4, X-ray difractometer.

N-(2-Aminobenzoyl)-*S*-Phenylalanine ethyl ester (4a):

In a typical experiment a 100-mL flask was charged with the phenylalanine ethyl ester hydrocloride (2.29 g, 9.97 mmol) and stirred with triethylamine (2.01 g, 19.94 mmol) in dry DMF(20 mL). To this stirred solution isatoic anhydride (1.63 g, 9.97 mmol) in dry DMF(10 mL) was added dropwise and the temperature was maintained at 50-60 °C. The mixture was stirred for 4h, and then poured into ice water (200 mL) and extracted with dicholoromethane. The organic phase was washed with $NaHCO_3$ (10%) and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave a brown solid (1.57 g, 51%). M.p. 88-90 °C. $[\alpha]^{21}$ = +76.8° (c=2, CH_2Cl_2). IR (KBr): 3475, 3370, 2995, 1713, 1632, 1526, 1268, 751 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.30-7.16(m, 7H, ArH), 6.65(m, 2H, ArH), 6.52(brd, 1H, J=7.1 Hz, O=CNH), 5.45(brs, 2H, Ar-NH_2), 5.00(dt, 1H, J_1=7.4 Hz and J_2=5.8 Hz, CH*), 4.20(c, 2H, J=7.1 Hz, O-CH_2), 3.23(dd, 2H, J_1=5.8 Hz and J_2=2.6 Hz, CH_2-Ar), 1.26(t, 3H, J=7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$): δ 136.13, 129.55, 128.72, 127.55, 127.27, 117.43, 116.83, 61.85, 53.57, 38.29, 14.47; EIMS *m/z* 312 [M^+] (10.4), 239(41), 221(41), 92(21.4), 120(100), 65(8.9); HREIMS *m/z* 312.1462 (calcd. for $C_{18}H_{20}N_2O_3$, 312.1474).

Using the above procedure compounds **(4b-d)** were synthesized.

N-(2-Aminobenzoyl)-*S*-alanine methyl ester, (4b): brown solid (0.9 g, 41%). M.p. 86-89 °C. $[\alpha]^{21}$ = -3.8° (c=2, CH_2Cl_2). IR (KBr): 3441, 3356, 2948, 1747, 1626, 1537, 1219, 761 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40(dd, 1H, J_1=8.3 Hz and

J_2=1.5 Hz, ArH), 7.30(dt, 1H, J_1=7.2 and J_2=1.5 Hz, ArH), 6.69-6.62(m, 3H, ArH and O=CNH), 5.52(brs, 2H, Ar-NH_2), 4.74(q, 1H, J=7.2 Hz, CH*), 3.78 (s, 3H, O-CH_3), 1.50(d, 3H, J=7.2 Hz, CH_3); ^{13}C RMN ($CDCl_3$): δ 173.82, 168.76, 148.91, 132.67, 127.54, 117.41, 116.72, 52.77, 48.39, 18.81; EIMS *m/z* 222 [M^+] (41), 191(1), 163(15), 120(100), 92(19). Anal. Calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.30, Found: C, 59.80; H, 6.62.

N-(2-Aminobenzoyl)-*S*-valine methyl ester, (4c): brown crystals (1.35 g, 54%). M.p. 78-80 °C. $[\alpha]^{21}$= -10° (c=2, CH_2Cl_2). IR (KBr): 3454, 3356, 2954, 1737, 1624, 1526, 1212, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.40(dd, 1H, J_1=8.3 Hz and J_2=1.7 Hz, ArH), 7.24-7.16(m, 1H, ArH), 6.69-6.61(m, 2H, ArH), 6.58(brd, 1H, J=8.2 Hz, O=CNH), 5.46(brs, 2H, Ar-NH_2), 4.72(dd, 1H, J_1=8.5 Hz and J_2=5.0 Hz, CH*), 3.77(s, 3H, O-CH_3), 2.33-2.15(m, 1H, C<u>H</u>(CH_3)$_2$), 1.00(m, 6H, CH(C<u>H</u>$_3$)$_2$); ^{13}C NMR ($CDCl_3$): δ 172.85, 169.14, 132.69, 127.55, 117.47, 116.84, 115.80, 57.37, 52.49, 31.77, 19.34, 18.32; EIMS *m/z* 250 [M^+] (26.5), 191(11), 136(21), 120(100), 92(33.5). Anal. Calcd. for $C_{13}H_{18}N_2O_3$: C, 62.80; H, 7.48, Found: C, 62.40; H, 7.20.

N-(2-Aminobenzoyl)-*S*-leucine methyl ester, (4d): yelow solid (0.84 g, 32%). M.p. 42-46 °C; $[\alpha]^{21}$= -5.9° (c=2, CH_2Cl_2). IR (KBr): 3467, 3357, 2956, 1735, 1638, 1523, 1263, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39(d, 1H, J=7.8 Hz, ArH), 7.26-7.17(m, 1H, ArH), 6.65(m, 2H, ArH), 6.46(brd, 1H, J=7.9 Hz, O=CNH), 5.50(brs, 2H, Ar-NH_2), 4.80(m, 1H, CH*), 3.75(s, 3H, O-CH_3), 1.70 (m, 3H, C<u>H$_2$</u> and C<u>H</u>(CH_3)$_2$, 1.00(m, 6H, CH(C<u>H</u>$_3$)$_2$); ^{13}C NMR ($CDCl_3$): δ 132.77, 127.60, 117.50, 116.83, 51.11, 42.04, 25.33, 23.20, 22.40; EIMS *m/z* 264 [M^+] (19),

208(10), 120(100), 92(15); HREIMS *m/z* 264.1471 (calcd for $C_{14}H_{20}N_2O_3$, 264.1474).

N-[2-N'-Methanesulfonylamino)benzoyl]-*S*-Phenhylalanine ethyl ester (5a): In a typical experiment a 50 mL Schlenk flask was purged with nitrogen and charged with the *S*-N(2-aminobenzoyl)-N-phenylalanine ethyl ester (0.13 g, 1.00 mmol) and stirred in dichloromethane (15 mL). To this stirred solution pyridine (0.7 g, 1.00 mmol) and methanesulfonyl chloride (0.13 g, 1.16 mmol) was added at room temperature. The mixture was stirred for 18 h at room temperature.The stirred mixture was washed with HCl (5%), and the organic phase was dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure gave a brown solid (0.32 g, 83% of yield). M.p. 143-144 °C. IR (KBr): 3361, 2981, 1738, 1636, 1538, 1333, 1208, 759 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.43(brs, 1H, NH-SO_2), 7.69(d, 1H, J=8.2 Hz, ArH), 7.50-7.05(m, 8H, ArH), 6.80(brd, 1H, J=7.2 Hz, O=CNH), 5.00(q, 1H, J=5.9 Hz, CH*), 4.23(c, 2H, J=6.1 Hz, O-CH_2), 3.22(dd, 2H, J_1=13.2 Hz and J_2=6.9 Hz, CH_2), 2.97(s, 3H, SO_2-CH_3), 1.33(t, 3H, J=7.1 Hz, CH_3); EIMS *m/z* 390 [M^+] (3.31), 317(3.91), 214(87.94), 198(100), 120(98.21), HREIMS *m/z* 390.1259 (calcd. for $C_{19}H_{22}N_2O_5S$, 390.1249).

Using the same procedure compounds **(5b-d)** were synthesized.

N-[(2-N'-Methanesulfonylamino)benzoyl]-*S*-alanine methyl ester, (5b): yellow viscous liquid (0.068 g, 50%). IR (film): 3377, 2996, 1738, 1634, 1536, 1334, 1213, 753 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.50(brs, 1H, NH-SO_2), 7.66(d, 2H, J=9.3 Hz, ArH), 7.52-7.43(m, 1H, ArH), 7.23-7.10(m, 1H, ArH), 7.10(brs, 1H, O=CNH), 4.68(q, 1H, J=7.1 Hz, CH*), 3.78(s, 3H, O-CH_3), 2.99(s, 3H, SO_2-

CH_3), 1.52(d, 3H, J=7.2 Hz, CH_3); EIMS *m/z* 300 [M^+] (27.89), 241(56.59), 198 (100), 120 (48.06), 92 (84.30); HREIMS *m/z* 300.0774 (calcd. for $C_{12}H_{16}N_2O_5S$, 300.0779).

N-[(2-N'-Methanesulfonylamino)benzoyl]-*S*-valine-methyl ester, (5c): brown viscous liquid (0.27 g, 82%). IR (film): 3364, 2965, 1738, 1641, 1530, 1334, 1210, 754 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.46(brs, 1H, NH-SO_2), 7.77(d, 2H, J=8.0 Hz, ArH), 7.62-7.47(m, 1H, ArH), 7.26-7.13(m, 1H, ArH), 6.78(brd, 1H, J=8.0 Hz, O=CNH), 4.70(dd, 1H, J_1=8.0 Hz and J_2=4.0 Hz, CH*), 3.80(s, 3H, O-CH_3), 3.02(s, 3H, SO_2-CH_3), 2.38-2.21(m, 1H, C<u>H</u>-$(CH_3)_2$), 1.03-0.98(m, 6H, CH(C<u>H</u>$_3)_2$); EIMS *m/z* 328[M^+] (34.11), 269(49.63), 198(73.33), 120(42.11), 92(38.97), 72(100); HREIMS *m/z* 328.1104 (calcd. for $C_{14}H_{20}N_2O_5S$, 328.1093).

N-[(2-N'-methanesulfonylamino)benzoyl]-*S*-leucine methyl ester, (5d): yellow viscous liquid (0.10 g, 83%). IR (film): 3366, 2951, 1736, 1639, 1520, 1341, 1203, 745 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.43(brs, 1H, NH-SO_2), 7.73(d, 2H, J=8.0 Hz, ArH), 7.60-7.46(m, 1H, ArH), 7.19-7.11(m, 1H, ArH), 6.69(brd, 1H, J= 6.0 Hz, O=CNH), 4.79(m, 1H, CH*), 3.78(s, 3H, O-CH_3), 3.00(s, 3H, SO_2-CH_3), 1.73(m, 3H, C<u>H</u>$_2$ and C<u>H</u>$(CH_3)_2$), 0.99(d, 6H, J=6.0 Hz, CH(C<u>H</u>$_3)_2$); EIMS *m/z* 342[M^+] (22.12), 283(38.66), 198(78.48), 120(53.28), 86(100), 59(19); HREIMS *m/z* 342.1235 (calcd. for $C_{15}H_{22}N_2O_5S$, 342.1249).

Compound **(7)** and **(8)** were synthesized using methods described for **(4a)** and **(5a).**

N,N'-Bis-(2-Aminobenzoyl)-(*R,R*)-1,2-diaminocyclohexane, (7): white solid (2.1 g, 60 %). M.p. 234-235 °C. IR (KBr): 3486, 3380, 1622, 1533, 1261, 1155,

750, 655 cm^{-1}; ^1H NMR ($CDCl_3$) 7.71(d, 2H, J=8.0 Hz, ArH), 7.41(dd, 2H, J_1=8.0 Hz and J_2=1.5 Hz, ArH), 7.11(dt, 2H, J_1=8.0 Hz and J_2=2.0 Hz, ArH), 6.65(dd, 2H, J_1=8.0 Hz and J_2=2.0 Hz, ArH), 6.55(dt, 2H, J_1=8.0 Hz and J_2=2.0 Hz, ArH), 3.88(m, 2H, CyclH), 2.15(m, 2H, CyclH), 1.80(m, 2H, CyclH), 1.42(m, 4H, CyclH). Anal. Calcd. for $C_{20}H_{24}N_4O_2$: C, 68.18; H, 6.81, Found : C, 67.88; H, 6.56.

N,N'-Bis-[(2-N''-Methanesulfonylamino)benzoyl)]-(*R*,*R*)-1,2-diaminocyclohexane, (8): tan solid (0.17 g, 47%). M.p. 238-240 °C. IR (KBr): 3466, 3316, 1647, 1543, 1260, 1155, 983, 905, 861, 761 cm^{-1}; ^1H NMR (DMSO-d_6): δ 10.97(s, 2H, NH, 8.71(d, 2H, J=6.0 Hz, NH), 7.72(d, 2H, J=8.0 Hz, ArH), 7.46(m, 4H, ArH), 7.16(t, 2H, J=8.0 Hz, ArH), 4(m, 2H CyclH), 2.90(s, 6H, SO_2CH_3), 1.85(m, 2H, CyclH), 1.80(m, 2H, CyclH), 1.51(m, 2H, Cycl), 1.25(m, 2H, CyclH). Anal. Calcd. for $C_{22}H_{28}N_4O_6S_2$: C, 51.96; H, 5.51, Found : C, 52.28; H, 5.81.

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10. X-ray analysis of **5a**: empirical formula $C_{19}H_{22}N_2O_5S$, F.W. 390.45, T=294 K, orthorombic, space group $P_2(1)$ 2(1) 2(1), a=7.999(2)Å, b=9.784(2)Å, c= 25.790(4)Å, $\beta=90^\circ$, V=2018.5(7)Å, z=4, D_c=1.285 mg.m^{-3}, F(000)=824, λ=0.71073 Å, μ=0.191 mm^{-1}, $2.23^\circ<2\theta<22.50^\circ$, R_1=0.0511, R_{2w}=0.1317, largest diff. peak 0.225 e. Å^{-3}.

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