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A new and facile route for the synthesis of chiral 1,2-diamines and 2,3-diamino acids

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Abstract—The synthesis of chiral diamines and diamino acids has been achieved from the corresponding *N*-arylsulfonyl aziridines through reaction with a chiral isocyanate and subsequent hydrolysis of 2-imidazolidinones. The method appears to be general and of wide applicability.

1,2-Diamines are important[1] since they are constituents of several natural products of biological significance and are key materials in the preparation of compounds, which are of value in the field of diagnostic nuclear medicine. They are also useful precursors of azamacrocycles and heterocyclic compounds and are being used increasingly in asymmetric synthesis as chiral auxiliaries and as ligands for catalysts.[1,2] Chiral ethylenediamine derivatives are of interest in the preparation of *cis*-platin analogues, which have been employed in cancer therapy.

2,3-Diaminocarboxylic acids are constituents of several antibiotics, natural products and biologically active molecules.[1,3] They are also used as building blocks for peptidomimetics in medicinal chemistry due to their protease resistance and potential conformational constraints. Their metal complexing abilities have been well documented.

Chiral diamines can be obtained by resolution of racemates using optically active dicarboxylic acids such as mandelic[4a] or tartaric[4b] or the recently reported dehydroabietic acid.[4c] Chiral diamines and diamino acids have been prepared by a variety of other methods. Most are based on the chirality of amino acids and related amino alcohols.[5a–d] Procedures based on chiral diols,[6a–c] mandelic[6d] and tartaric acids,[6e] cyanohydrins,[6f] amines,[6g] hydrazones,[6h,i] imines[6j] and bisimines,[6k,l] aziridines,[6m] oxazolines[6n] and oxazolidinones[6o] and sulfilimines[6p] are also known. Syntheses in which the chirality originates from the catalyst have also been reported.[7a,b]

Although several methods for preparing chiral diamines and diamino acids are known, most of them suffer from one or more drawbacks including lack of generality, inaccessibility of starting materials and cumbersome procedures.[8] There is thus a need for developing improved and more general procedures.

In our ongoing programme of studying the ring opening reactions of *N*-arylsulfonylaziridines,[9] we have investigated their reaction with isocyanates in the presence of iodide ions to give 2-imidazolidinones.[10a] The regio- and stereochemical course of these reactions has been clearly delineated.[10b] In the present communication we report the use of this reaction for obtaining chiral diamines and diamino acids. The synthetic rationale is depicted in Scheme 1.

It was proposed that the reaction of aziridines with commercially available *R*-(+)-α-methylbenzyl isocyanate **2** would give a mixture of diastereomeric 2-imidazolidinones, which on subsequent reduction and treatment with acid would yield both enantiomers of the diamines. The question of regiochemistry had already been settled since 2-alkylaziridines have been shown to undergo iodide attack at the unsubstituted carbon whereas with 2-phenylaziridines the nucleophile opened the ring at C-2.[10b]

Accordingly, aziridines **1a**,**b** were prepared as previously reported[11] and reacted with isocyanate **2**. The two

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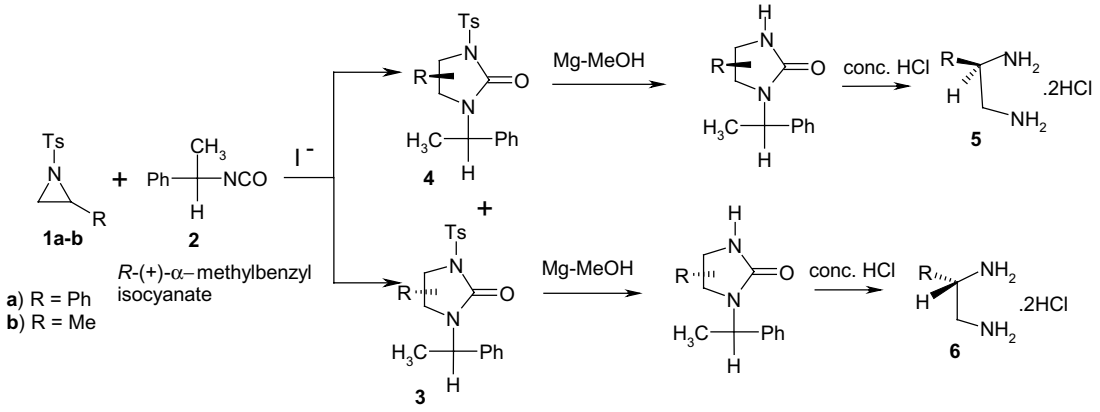
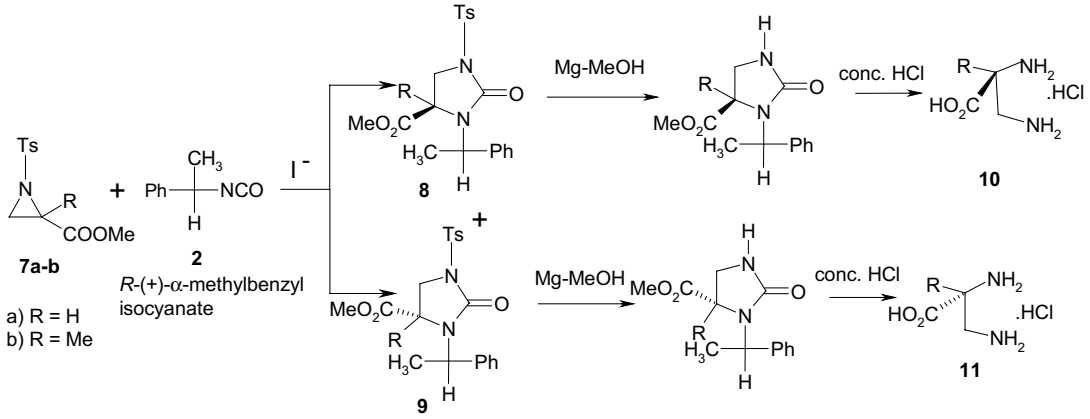


Scheme 1. Synthesis of diamines via hydrolysis of 2-imidazolidinones.



Scheme 2. Synthesis of diamino acids via hydrolysis of 2-imidazolidinones.

Table 1. Synthesis of diastereomeric 2-imidazolidinones from *N*-arylsulfonylaziridines

Entry	Aziridines	Diastereomeric mixture of 2-imidazolidinones	Yield (%) mixture of diastereomers	Diastereomeric ratio[a]
1	**1a**	**3a**, **4a**	90	60:40
2	**1b**	**3b**, **4b**	88	50:50
3	**7a**	**8a**, **9a**	85	65:35
4	**7b**	**8b**, **9b**	87	54:46

[a] The diastereomeric ratios were not always 50:50. This aspect is being investigated.

diastereoisomers **3** and **4**[12a,b] were obtained in excellent yields (ratio of **3**:**4** with R = Ph was 60:40 and with R = Me; 50:50 as determined by ^{1}H NMR), see Table 1. Only one regioisomer was obtained in both cases; with **1a**, the phenyl group was found to be adjacent to the *N*-methylbenzyl group whereas for **1b**, the methyl group was adjacent to the N–Ts group. The regio-and stereochemistry was further confirmed by single crystal X-ray diffraction data of compound **3a** (Fig. 1). The diastereomers could be separated by crystallization and/or column chromatography and on treatment individually with Mg–MeOH[13] followed by conc. HCl furnished both enantiomers **5a**,**b** and **6a**,**b**.[12c,e] The dihydrochloride salts of **5a** and **6a** were converted into their ditosyl

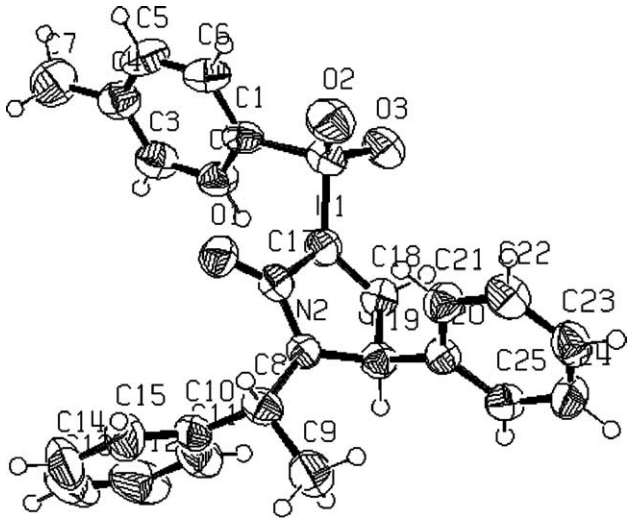


Figure 1. X-ray structure of compound **3a**.

derivatives to compare their optical rotations[12c] with those already reported.[12d]

The same protocol was used to synthesize diamino acids (Scheme 2). Aziridine **7a** was prepared using our recently reported[14] method and on treatment with **2**

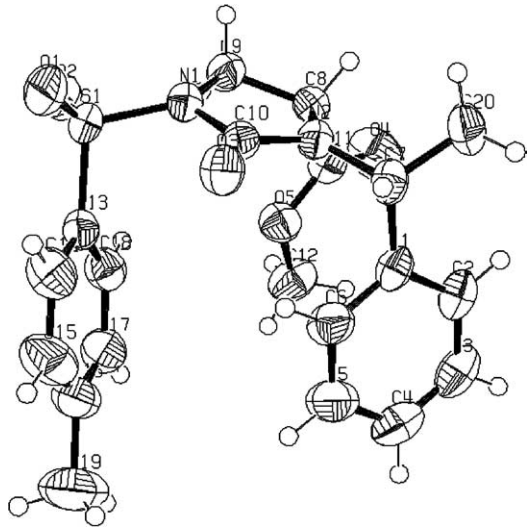


Figure 2. X-ray structure of compound **8a**.

furnished the diastereomeric 2-imidazolidinones **8a**[15a] and **9a**[15b] (65:35 diastereomeric ratio as determined by ^{1}H NMR), Table 1. These were separated by column chromatography and characterized. In this case also only one regioisomer was obtained. The regio- and stereochemistry was further confirmed by single crystal X-ray diffraction data of compound **8a**[16] (Fig. 2). Successive treatment with Mg–MeOH and conc. HCl then furnished the corresponding diamino acids **10a** and **11a**[15c,d] in 85% overall yield. In the case of **7b**, the imidazolidinones **8b** and **9b** could not be separated. However, after reduction with Mg–MeOH, the detosylated imidazolidinones could be separated by column chromatography and these, on hydrolysis with conc. HCl, give the dihydrochloride salts of amino acids **10b** and **11b**. The resulting dihydrochlorides were heated with propene oxide to give pure monohydrochlorides **10b** and **11b** and their optical rotations were then compared.[15c,e]

In conclusion we have developed a new methodology for the synthesis of 1,2-diamines and diamino acids, which is general and has potential for wide structural variation.

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12. (a) Spectral data for compound **3a**: colourless crystalline solid: mp 155–157 °C; IR ν_{max} (KBr) 1716, 1350, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96–6.98 (m, 14H), 4.46 (m, 2H), 4.10 (t, 1H, J = 9.36 Hz), 3.59 (dd, 1H, J = 9.49, 6.87 Hz), 2.48 (s, 3H), 1.63 (d, 3H, J = 7.23 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.82, 144.69, 140.35, 138.30, 134.82, 129.63–126.97 (aromatic), 56.74, 53.68, 50.66, 21.67, 17.85; FAB MS (*m*/*z*) 422 (M^++2, 100%). Anal. Calcd for $C_{24}H_{24}N_2O_3S$: C, 68.57; H, 5.71; N, 6.66. Found: C, 68.36; H, 5.60; N, 6.48; (b) Spectral data for compound **4a**: colourless crystalline solid: mp 135–137 °C; IR ν_{max} (KBr) 1716, 1350, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16–7.01 (m, 14H), 5.23 (q, 1H, J = 7.2 Hz), 4.12 (dd, 1H, J = 9.12, 5.18 Hz), 3.99 (t, 1H, J = 9.3 Hz), 3.61 (dd, 1H, J = 9.4, 5.2 Hz), 2.49 (s, 3H), 1.04 (d, 3H, J = 7.26 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.87, 144.63, 140.18, 138.63, 134.68, 129.47–126.72 (aromatic), 54.58, 52.16, 50.77, 21.48, 17.50; FAB MS (*m*/*z*) 421 (M^++1, 100%). Anal. Calcd for $C_{24}H_{24}N_2O_3S$: C, 68.57; H, 5.71; N, 6.66. Found: C, 68.23; H, 5.94; N,

6.52; (c) Optical rotation $[\alpha]_D^{25}$ of the ditosyl derivative of compound **5a**: *S*-(+)-ditoluene-*p*-sulfonyl-phenylethyl-enediamine: +19.48 (*c*, 0.77 in DMF) [lit.[12d] +19.8 (*c*, 0.77 in DMF)]; optical rotation $[\alpha]_D^{25}$ of the ditosyl derivative of compound **6a**: *R*-(−)-ditoluene-*p*-sulfonyl-phenylethylenediamine: −19.56 (*c*, 0.77 in DMF) [lit.[12d] −19.8 (*c*, 0.77 in DMF)]; optical rotation $[\alpha]_D^{25}$ of *S*-(+)-1,2-propanediamine **5b**: +35 (*c*, 0.97 in benzene) [lit.[12e] +34.8 (*c*, 0.97 in benzene)]; optical rotation $[\alpha]_D^{25}$ of *R*-(−)-1,2-propanediamine **6b**: −34.7 (*c*, 0.97 in benzene) [lit.[12e] −34.8 (*c*, 0.97 in benzene)]; (d) Douglas, G. N.; David, F. E. *J. Chem. Soc. (C)* **1966**, 396; (e) Dwyer, F. P.; Garvan, F. L.; Shulman, A. *J. Am. Chem. Soc.* **1959**, *81*, 290.

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15. (a) Spectral data for compound **8a**: colourless crystalline solid: mp 134–136 °C; IR ν_{max} (KBr) 1750, 1720, 1350, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, 2H, J = 8.4), 7.4–7.2 (m, 7H), 5.1 (q, 1H, J = 7.0 Hz), 4.1 (dd, 1H, J = 3.7, 2.5 Hz), 3.85 (m, 2H), 3.18 (s, 3H), 2.45 (s, 3H), 1.57 (d, 3H, J = 7.07 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.74, 144.82, 138.51, 134.79, 129.57, 128.70, 127.99, 127.74, 53.28, 52.29, 52.07, 45.46, 21.57, 16.66; FAB MS (*m*/*z*) 403 (M^++1, 100%). Anal. Calcd for $C_{20}H_{22}N_2O_5S$: C, 59.69; H, 5.51; N, 6.96. Found: C, 59.67; H, 5.65; N, 6.91; (b) Spectral data for compound **9a**: colourless crystalline solid: mp 108–109 °C; IR ν_{max} (KBr) 1747, 1718, 1350, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, 2H, J = 6.8), 7.39–7.17 (m, 7H), 5.2 (q, 1H, J = 6.7 Hz), 3.8 (m, 3H), 3.75 (s, 3H), 2.49 (s, 3H), 1.48 (d, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.08, 144.91, 138.67, 134.68, 129.62, 128.72, 128.13, 127.14, 52.85, 52.26, 52.09, 45.95, 21.65, 16.79; FAB MS (*m*/*z*) 403 (M^++1, 100%). Anal. Calcd for $C_{20}H_{22}N_2O_5S$: C, 59.69; H, 5.51; N, 6.96. Found: C, 59.61; H, 5.55; N, 6.98; (c) Optical rotation $[\alpha]_D^{25}$ of *S*-(+)-2,3-diaminopropanoic acid hydrochloride **10a**: +24.8 (*c* 0.5 in 1 N HCl) [lit.[15d] +25.0 (*c* 0.5 in 1 N HCl)]; optical rotation $[\alpha]_D^{25}$ of *R*-(−)-2,3-diaminopropanoic acid hydrochloride **11a**: −24.5 (*c* 0.5 in 1 N HCl) [lit.[15d] −25.0 (*c* 0.5 in 1 N HCl)]; optical rotation $[\alpha]_D^{25}$ of *R*-(−)-2,3-diamino-2-methylpropanoic acid monohydrochloride **10b**: −3.2 (*c* 0.7 in H_2O) [lit.[15e] −3.5 (*c* 0.7 in H_2O)]; optical rotation $[\alpha]_D^{25}$ of *S*-(+)-2,3-diamino-2-methylpropanoic acid monohydrochloride **11b**: +3.0 (*c* 0.7 in H_2O) [lit.[15e] +3.5 (*c* 0.7 in H_2O)]; (d) Cardillo, G.; Orena, M.; Penna, M.; Sandri, S.; Tomasini, C. *Tetrahedron* **1991**, *47*, 2263; (e) Hartwig, W.; Mittendorf, J. *Synthesis* **1991**, 939.
16. X-ray data for compounds **3a** and **8a** were collected on a Bruker AXS SMART apex diffractometer, with a CCD area detector (MoKα radiation, graphite monochromator, λ = 0.71073 Å). Cell parameters were retrieved using SMART software and refined using SAINTPLUS software. Absorption correction was applied using SADABS. Structures were solved by direct methods and refined by least square methods as F^2, using the SHEXTL programme package. The non-hydrogen atoms were refined anisotropically. Data for **3a**: $C_{24}H_{24}N_2O_3S$, MW = 422, colourless crystal, crystal system: triclinic, space group: P 1, cell parameters: a = 6.1897(6) Å, b = 10.4578(10) Å, c = 16.6567(17) Å, V = 1064.85(18) $Å^3$, Z = 2, D_c = 1.312 g cm^{-3}, $F(000)$ = 444, total number of 1s parameters = 545, final R indices [$I > 2\sigma(I)$] R_1 = 0.0394, wR_2 = 0.0950, R indices (all data) R_1 = 0.0429, wR_2 = 0.0976, GOF = 1.039, restrained GOF = 1.039 for all data. ORTEP diagram is given in Figure 1. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 253421). Data for **8a**: $C_{20}H_{22}N_2O_5S$, MW = 402, colourless crystal, crystal system: orthorhombic, space group: P2(1)2(1)2(1), cell parameters: a = 7.592(9) Å, b = 13.110(15) Å, c = 19.385(2) Å, V = 1929.7(4) $Å^3$, Z = 4, D_c = 1.615 g cm^{-3}, $F(000)$ = 950, total number of 1s parameters = 256, final R indices [$I > 2\ \sigma(I)$] R_1 = 0.0356, wR_2 = 0.0949, R indices (all data) R_1 = 0.0375, wR_2 = 0.0968, GOF = 1.044, restrained GOF = 1.044 for all data. ORTEP diagram is given in Figure 2. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 253420).