Note

Synthesis and X-ray analysis of 1-((1S)-phenylethyl)-azetidine-(2R)-piperidinamide

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The crystal and molecular structure of a new azetidine-2-carboxylic amide derivative is described. The structure was solved by direct methods and refined by least squares methods to $R1 = 0.0393$ for 4264 reflections (with $I > 2\sigma(I)$). The structure consists of two independent molecules which are chemically the same with slight differences in geometry. Crystal data: $C_{17}H_{24}N_2O$, monoclinic, space group $P2_1$, $a = 8.3782(4)$, $b = 20.0342(13)$, $c = 9.7769(8)$Å, $\beta = 109.687(6)°$, $V = 1545.1(2)$Å^3, $Z = 4$.

Introduction

Optically active azetidine-2-carboxylic acid is a versatile starting material for chiral auxiliaries[1a,b] and was first synthesized in enantiomerically pure form by

tion.[3b] We now describe an improved route towards two stereoisomers of azetidine-2-carboxylic ester derivatives derived from both enantiomers of the parent acid using optically active (S)-(α)-methyl-benzyl-amine in stoichiometric amounts (Scheme 1).

Scheme 1
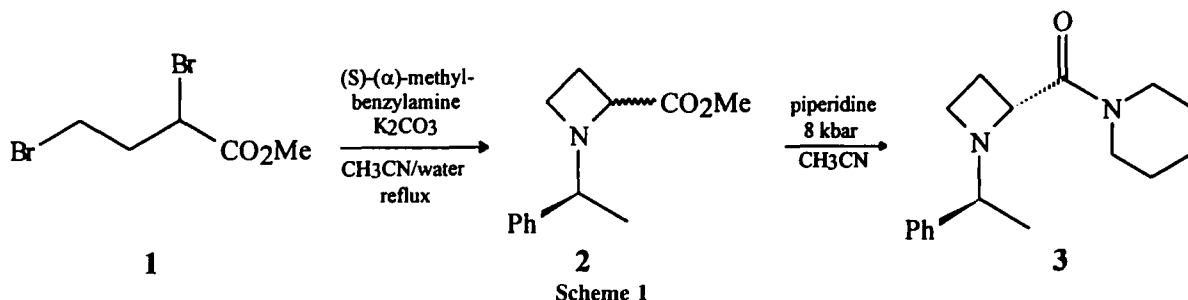
Miyoshi *et al.*[2] An easier route by Rodebaugh *et al.*[3a] afforded racemic azetidine-2-carboxylic acid which still had to be separated into its enantiomers by resolu-

Methyl 2,4-dibromobutyrate **1** was ringclosed with 1.1 equivalent (S)-(α)-methyl-benzylamine and 2 equivalents K_2CO_3 in acetonitrile/water heated at reflux temperature. A 1:1 mixture of diastereomeric methyl 1-((1S)-phenylethyl)azetidine-2-carboxylate **2** was obtained which was separated by flash-column chromatography. The configuration of thus obtained diastereomers could not be determined by spectroscopic methods and therefore one of the diastereomers was transformed into the crystalline piperidinamide **3**.[4] An X-ray diffraction analysis was undertaken to

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Table 1. Crystal data and summary of intensity data collection, structure solution, and refinement

Crystal data	
Compound	$C_{17}H_{24}N_2O$
Color/shape	Colorless/irregular
Crystallization	Hexane
Formula weight	272.38
Crystal system	Monoclinic
Space group	$P\,2_1$
Temperature, K	208(2)
Cell constants[a]	
a, Å	8.3782(4)
b, Å	20.0342(13)
c, Å	9.7769(8)
β,°	109.687(6)
Cell volume; Å^3	1545.1(2)
Formula units/unit cell	4
D-calc, g-cm^{-3}	1.171
Mu-calc, cm^{-1}	0.682
$F(000)$, electrons	592
Intensity data collection	
Diffractometer/scan	Enraf-Nonius CAD-4/ω-scan
Radiation, graphite monochromator	Mo$K\alpha$ (λ = 0.71073Å)
Crystal dimensions, mm	0.65 × 0.51 × 0.18
Scan width,°	1.5
Standard reflections	3, every 7200 seconds exposure time
Decay of standards	1.000 − 0.979
Reflections measured	6473
2θ-range,°	up to 49.94
Range of h,k,l	$-9 \le$ h ≤ 1, $-23 \le k \le 23$, $-11 \le l \le 11$
Corrections	
Decay correction	
Lorentz-polarization	
EMPABS[7] correction	0.988 − 1.013
Reflcns (obs., $I_0 > 2\mathrm{sigma}(I_0)$)	5410(4264)
Rmerge[b]	0.0185
Computer programs[c]	Local programs
Structure solution and refinement	
Structure solution	Direct methods/automatic Fourier extension
Computer programs	CRUNCH[5]
Structure refinement	Full matrix least squares on F^2
Non-H-atoms	anisotropic
H-atoms	isotropic
Computer program	SHELXL[8]
Weights[8]	0.0286 0.1150
Shift/esd	less than 0.001
No. of restraints/parameters	1/553
Goodness-of-fit on F^2	1.103
R index [$I > 2\sigma(I)$]	$R1$ = 0.0393
R indices (all data)	$R1$ = 0.0612, $wR2$ = 0.0798,
Largest diff. peak and hole, e.Å^{-3}	0.12 and -0.14

[a] Least-squares refinement for 25 reflections $11.527 < \theta < 17.844°$.
[b] Rmerge = $\Sigma[Fo - \langle Fo\rangle]/\Sigma Fo]$.
[c] Using neutral scattering factors and anomalous dispersion corrections.[10]

Table 2. Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3) for **3**[a]

	x	y	z	$U_{(eq)}$
Molecule A				
N(1A)	−6335(2)	599(1)	−12213(2)	41(1)
C(2A)	−4557(3)	828(1)	−11920(3)	43(1)
C(3A)	−4642(5)	545(2)	−13402(3)	77(1)
C(4A)	−6576(4)	568(2)	−13784(3)	65(1)
C(5A)	−7467(3)	1063(1)	−11831(3)	40(1)
C(6A)	−9263(4)	783(2)	−12369(4)	59(1)
C(7A)	−6873(3)	1183(1)	−10207(2)	35(1)
C(8A)	−6283(3)	667(1)	−9218(3)	44(1)
C(9A)	−5830(3)	786(2)	−7745(3)	53(1)
C(10A)	−5957(3)	1418(2)	−7238(3)	55(1)
C(11A)	−6524(3)	1931(2)	−8210(3)	52(1)
C(12A)	−6972(3)	1818(1)	−9686(3)	41(1)
C(13A)	−3246(3)	496(1)	−10642(3)	43(1)
O(14A)	−3312(2)	−108(1)	−10481(2)	73(1)
N(15A)	−1963(2)	857(1)	−9767(2)	38(1)
C(16A)	−636(4)	525(1)	−8596(3)	51(1)
C(17A)	−703(4)	740(2)	−7136(3)	54(1)
C(18A)	−523(4)	1487(1)	−6972(3)	51(1)
C(19A)	−1859(4)	1828(1)	−8227(3)	49(1)
C(20A)	−1819(4)	1584(1)	−9677(3)	43(1)
Molecule B				
N(1B)	−7511(2)	−1608(1)	−9573(2)	31(1)
C(2B)	−5706(3)	−1406(1)	−8987(2)	34(1)
C(3B)	−5685(3)	−1395(2)	−10556(3)	46(1)
C(4B)	−7593(3)	−1323(1)	−10997(2)	38(1)
C(5B)	−8626(3)	−1320(1)	−8862(2)	37(1)
C(6B)	−10457(3)	−1499(2)	−9739(3)	50(1)
C(7B)	−8099(3)	−1565(1)	−7312(2)	38(1)
C(8B)	−8038(3)	−2239(1)	−7005(3)	47(1)
C(9B)	−7499(4)	−2463(2)	−5587(3)	56(1)
C(10B)	−7046(3)	−2018(2)	−4459(3)	55(1)
C(11B)	−7108(4)	−1348(2)	−4733(3)	55(1)
C(12B)	−7628(3)	−1122(1)	−6154(3)	44(1)
C(13B)	−4523(3)	−1882(1)	−7912(2)	33(1)
O(14B)	−4854(2)	−2478(1)	−7940(2)	49(1)
N(15B)	−3077(2)	−1631(1)	−6971(2)	39(1)
C(16B)	−2017(4)	−2041(1)	−5761(3)	48(1)
C(17B)	−2160(4)	−1785(1)	−4351(3)	50(1)
C(18B)	−1720(4)	−1045(1)	−4136(3)	51(1)
C(19B)	−2757(3)	−642(1)	−5458(3)	42(1)
C(20B)	−2565(3)	−929(1)	−6820(3)	38(1)

[a] $U_{(eq)}$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 3. Bond lengths (Å) and angles (°) for **3**

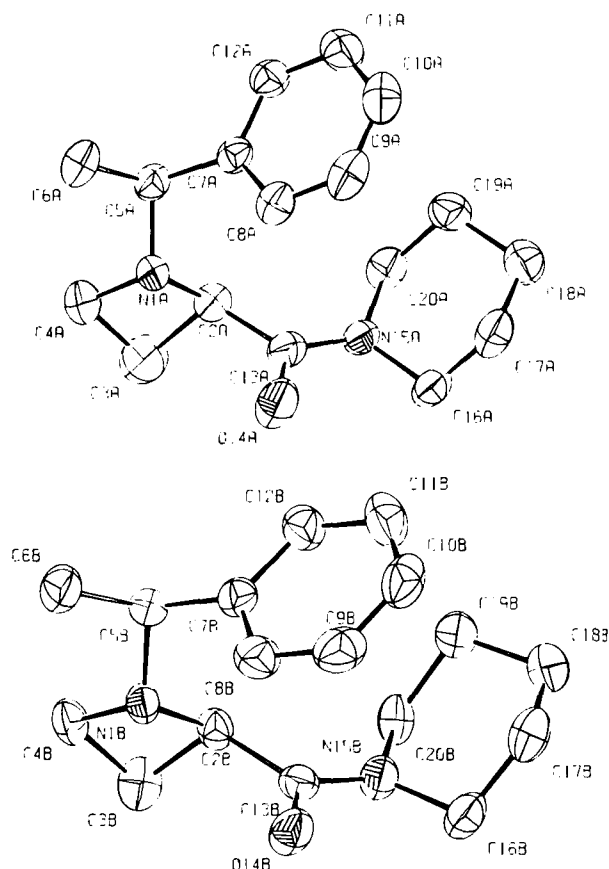| Molecule A		Molecule B	
N(1A)−C(2A)	1.491(3)	N(1B)−C(2B)	1.481(3)
N(1A)−C(4A)	1.481(3)	N(1B)−C(4B)	1.485(3)
N(1A)−C(5A)	1.463(3)	N(1B)−C(5B)	1.458(3)
C(2A)−C(3A)	1.534(4)	C(2B)−C(3B)	1.540(3)
C(2A)−C(13A)	1.512(3)	C(2B)−C(13B)	1.515(3)
C(3A)−C(4A)	1.536(5)	C(3B)−C(4B)	1.516(3)
C(5A)−C(6A)	1.523(4)	C(5B)−C(6B)	1.527(4)
C(5A)−C(7A)	1.514(3)	C(5B)−C(7B)	1.510(3)
C(7A)−C(8A)	1.388(3)	C(7B)−C(8B)	1.382(3)
C(7A)−C(12A)	1.384(3)	C(7B)−C(12B)	1.387(3)
C(8A)−C(9A)	1.381(4)	C(8B)−C(9B)	1.379(3)
C(9A)−C(10A)	1.377(4)	C(9B)−C(10B)	1.369(4)
C(10A)−C(11A)	1.372(4)	C(10B)−C(11B)	1.365(4)
C(11A)−C(12A)	1.382(4)	C(11B)−C(12B)	1.385(4)
O(13A)−C(14A)	1.225(3)	O(13B)−C(14B)	1.225(3)
N(13A)−C(15A)	1.338(3)	N(13B)−C(15B)	1.348(3)
N(15A)−C(16A)	1.461(3)	N(15B)−C(16B)	1.468(3)
N(15A)−C(20A)	1.461(3)	N(15B)−C(20B)	1.462(3)
C(16A)−C(17A)	1.510(4)	C(16B)−C(17B)	1.513(4)
C(17A)−C(18A)	1.507(4)	C(17B)−C(18B)	1.525(4)
C(18A)−C(19A)	1.516(4)	C(18B)−C(19B)	1.523(3)
C(19A)−C(20A)	1.510(4)	C(19B)−C(20B)	1.508(3)
N(1A)−C(2A)−C(3A)	88.9(2)	N(1B)−C(2B)−C(3B)	88.3(2)
N(1A)−C(2A)−C(13A)	115.1(2)	N(1B)−C(2B)−C(13B)	116.1(2)
N(1A)−C(4A)−C(3A)	89.1(2)	N(1B)−C(4B)−C(3B)	89.1(2)
N(1A)−C(5A)−C(6A)	109.2(2)	N(1B)−C(5B)−C(6B)	108.9(2)
N(1A)−C(5A)−C(7A)	110.9(2)	N(1B)−C(5B)−C(7B)	109.4(2)
C(2A)−N(1A)−C(4A)	89.5(2)	C(2B)−N(1B)−C(4B)	88.7(2)
C(2A)−N(1A)−C(5A)	116.6(2)	C(2B)−N(1B)−C(5B)	116.2(2)
C(2A)−C(3A)−C(4A)	85.9(2)	C(2B)−C(3B)−C(4B)	85.4(2)
C(2A)−C(13A)−O(14A)	119.2(2)	C(2B)−C(13B)−O(14B)	120.6(2)
C(2A)−C(13A)−N(15A)	119.6(2)	C(2B)−C(13B)−N(15B)	117.8(2)
C(3A)−C(2A)−C(13A)	114.1(2)	C(3B)−C(2B)−C(13B)	118.4(2)
C(4A)−N(1A)−C(5A)	114.7(2)	C(4B)−N(1B)−C(5B)	117.4(2)
C(5A)−C(7A)−C(8A)	121.7(2)	C(5B)−C(7B)−C(8B)	120.8(2)
C(5A)−C(7A)−C(12A)	119.5(2)	C(5B)−C(7B)−C(12B)	121.2(2)
C(6A)−C(5A)−C(7A)	111.0(2)	C(6B)−C(5B)−C(7B)	112.7(2)
C(7A)−C(8A)−C(9A)	120.4(3)	C(7B)−C(8B)−C(9B)	120.8(3)
C(7A)−C(12A)−C(11A)	120.4(2)	C(7B)−C(12B)−C(11B)	121.1(3)
C(8A)−C(7A)−C(12A)	118.7(2)	C(8B)−C(7B)−C(12B)	117.9(2)
C(8A)−C(9A)−C(10A)	120.5(3)	C(8B)−C(9B)−C(10B)	120.4(3)
C(9A)−C(10A)−C(11A)	119.4(3)	C(9B)−C(10B)−C(11B)	120.0(3)
C(10A)−C(11A)−C(12A)	120.6(3)	C(10B)−C(11B)−C(12B)	119.8(3)
C(13A)−N(15A)−C(16A)	119.3(2)	C(13B)−N(15B)−C(16B)	120.2(2)
C(13A)−N(15A)−C(20A)	127.5(2)	C(13B)−N(15B)−C(20B)	126.4(2)
O(14A)−C(13A)−N(15A)	120.9(2)	O(14B)−C(13B)−N(15B)	121.6(2)
N(15A)−C(16A)−C(17A)	110.5(2)	N(15B)−C(16B)−C(17B)	109.5(2)
N(15A)−C(20A)−C(19A)	110.6(2)	N(15B)−C(20B)−C(19B)	109.9(2)
C(16A)−N(15A)−C(20A)	112.5(2)	C(16B)−N(15B)−C(20B)	111.4(2)
C(16A)−C(17A)−C(18A)	110.5(2)	C(16B)−C(17B)−C(18B)	111.4(2)
C(17A)−C(18A)−C(19A)	109.9(2)	C(17B)−C(18B)−C(19B)	110.8(2)
C(18A)−C(19A)−C(20A)	111.7(2)	C(18B)−C(19B)−C(20B)	110.3(2)

Fig. 1. ORTEP[11] drawing of the molecule with atomic numbering for the two independent molecules. Thermal ellipsoids are at 50% probability.

Table 4. Selected torsion angles (°)

	Molecule A	Molecule B
C(3)−C(2)−C(13)−O(14)	−57.04(0.38)	−76.91(0.29)
C(2)−C(13)−N(15)−C(20)	14.58(0.39)	3.81(0.33)
O(14)−C(13)−N(15)−C(16)	−0.72(0.38)	−12.25(0.34)
C(2)−N(1)−C(5)−C(6)	173.24(0.22)	171.72(0.20)
C(2)−N(1)−C(5)−C(7)	−64.17(0.25)	−64.66(0.23)
N(1)−C(5)−C(7)−C(8)	−41.88(0.29)	−57.46(0.28)

3. The crystal structure consists of two independent molecules which are chemically the same with slight differences in geometry. In Table 4 selected torsion angles are given which illustrate the geometrical differences between both molecules. Geometrical calculations revealed neither unusual geometric features, nor unusual short intermolecular contacts. Calculations with PLATON[6] revealed no higher symmetry and no solvent accessible areas.

establish the configuration at C-2 relative to the (1S)-phenylethyl group. It was found that the analyzed compound had the *R*-configuration at C-2.

Experimental

The crystal data and a summary of the data collection, the structure solution and refinement are given in Table 1. The atomic positional and vibrational parameters are given in Table 2. The structure was solved by the program CRUNCH.[5] The hydrogen atoms were placed at calculated positions and were freely refined subsequently.

Discussion

The structure and atomic numbering are presented in Fig. 1. Bond distances and angles are given in Table

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