Optically active 2,2-dimethyl-1,3,4-triazabicyclo[4.1.0]heptan-5-one: synthesis, spontaneous resolution and absolute configuration

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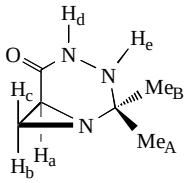
Bicycle (±)-**1** crystallises as a conglomerate (space group $P2_1$) and undergoes spontaneous resolution on crystallisation from chloroform or acetone (16–44% ee). The absolute configuration (*S*)-(–)-**1** was determined by synthesis from (*S*)-Ser-OMe; mutarotation due to the partial conversion of **1** into the corresponding isopropylidene **4** was observed in MeOH solution.

Derivatives of aziridine-2-carboxylic acid (Azy)[1–4] have been studied intensively.[5–7] Some of them (azimexon and leakadine) show high biological activity.[8–10] The asymmetric synthesis of Azy derivatives was reported[3,4,11] and a higher activity of the L-leakadine (amide of aziridine-2-carboxylic acid, Azy-NH_2) with respect to the racemate was observed.[10] The synthesis of these compounds in enantiopure form is of interest from the point of contemporary interest for chiral drugs.[12]



(±)-**1**

The simplest method for obtaining enantiopure materials is their spontaneous resolution by crystallisation, which may occur when the racemate is a conglomerate.[13,14] For the strained aziridine-2-carboxylic acid derivative 2,2-dimethyl-1,3,4-triazabicyclo[4.1.0]heptan-5-one **1**[5] the non-centrosymmetric space group $P2_1$ was determined by X-ray structural analysis.[6] This means that compound **1** forms a conglomerate.

Indeed, on crystallisation (from $CHCl_3$ or acetone) of (±)-**1** prepared by a known procedure,[5] crystalline samples showing (+) or (–) rotation were obtained.†

In order to determine its absolute configuration compound **1** was synthesised from commercial (S)-Ser-OMe hydrochloride {$[\alpha]_D^{23}$ = 3.5° (*c* 5.0 MeOH)} (Scheme 1), eventually giving (*S*)-(–)-**1**.

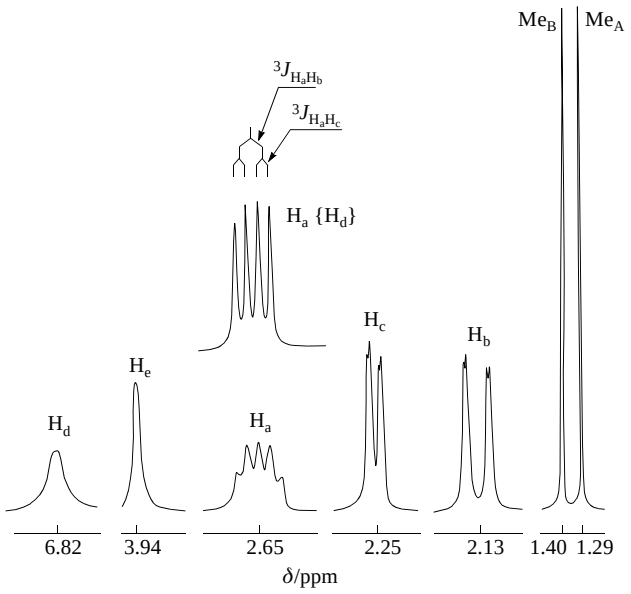
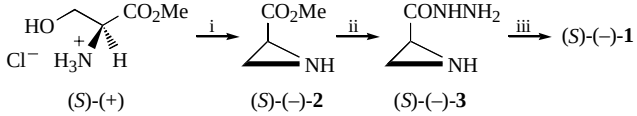


Figure 1 ^{1}H NMR spectrum of (±)-**1** in $CDCl_3$.

Azy-OMe (*S*)-(–)-**2** was prepared under Mitsunobu conditions[15] and was converted into (*S*)-(–)-**1** by a known procedure,[5] the mp of (–)-**2** is higher than that of its racemate: 135–136 °C and 126–127 °C, respectively. The rotation of (*S*)-(–)-**1** in MeOH was found to decrease gradually from –87° to –68.1° (after 1.6 h), –65.7° (after 2.3 h), reaching a constant value of –59.8° after 24 h. According to ^{1}H NMR, the isomerisation of (*S*)-(–)-**1** into isopropylidenehydrazide (*S*)-(–)-**4** to reach equilibrium **1**:**4** ≈ 2 (Scheme 2) is responsible for the observed mutarotation.

All compounds were characterised by spectroscopic data (Figure 1). The ^{1}H NMR spectra of aziridines (*S*)-(–)-**2**–**4** were in line with those obtained from earlier detailed investigations of Azy and their ^{15}N analogues.[16] The ^{1}H NMR signals of **1** (Figure 1) were assigned by selective heteronuclear double resonance. Thus, under the conditions {H_e, δ 3.94 ppm}, the ^{13}C NMR signal for carbon Me_A (qqd, δ 24.14 ppm) transforms



Scheme 1 *Reagents and conditions*: i, NH_3, CH_2Cl_2, then Ph_3P–DIAD, CH_2Cl_2, 1 h, 3–5 °C and 12 h, 20 °C; ii, dry H_2NNH_2, 1.5 h, –10 °C, then 5 h, 20 °C; iii, Me_2CO, 20 h, 55 °C.

† *Characteristics and spectroscopic data*. NMR spectra were recorded on a Bruker WM-400 spectrometer (with TMS as an internal standard) at 400.13 MHz (^{1}H) and 100.62 MHz (^{13}C). Optical rotation was measured on 'Perkin Elmer-141' and 'Polamat A' polarimeters. The CD spectra were taken on a JASCO-J-500A instrument with a DP-500N data processor.

(±)-**1**: obtained by method described in ref. 5, mp 126–127 °C (acetone). ^{1}H NMR ($CDCl_3$) δ: 1.29 (s, 3H, Me_A), 1.40 (s, 3H, Me_B), 2.13 (dd, 1H, H_b, $^3J_{ab}$ 5.9 Hz, $^2J_{bc}$ 1.0 Hz), 2.25 (dd, 1H, H_c, $^3J_{ac}$ 3.0 Hz, $^2J_{bc}$ 1.0 Hz), 2.65 (ddd, 1H, H_a, $^3J_{ab}$ 5.9 Hz, $^3J_{ac}$ 3.0 Hz, $^4J_{ad}$ 2.7 Hz), 3.94 (s, 1H, H_e), 6.82 (s, 1H, H_d). ^{13}C NMR ($CDCl_3$) δ: 24.14 (qqd, Me_A, ^1J 127.9 Hz, $^3J_{CH}$ 4.4 Hz, $^3J_{CH_e}$ 5.0 Hz), 24.98 (qq, Me_B, ^1J 127.9 Hz, $^3J_{CH_c}$ 4.4 Hz), 25.08 (ddd, 7-C, $^1J_{CH_b}$ 181.7 Hz, $^1J_{CH_c}$ 162.8 Hz, $^2J_{CH_a}$ 2.2 Hz), 32.73 (d, 6-C, ^1J 183.8 Hz), 67.80 (s, 2-C), 169.48 (s, 5-C).

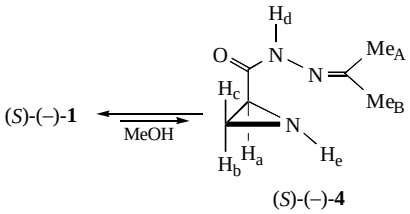
Spontaneous resolution of (±)-**1**: by crystallisation of (±)-**1** (68 mg) from $CHCl_3$ at slow evaporation at 20 °C samples (+)-**1** {2.0 mg, druse, $[\alpha]_D^{20}$ = 14.2° (*c* 0.2, MeOH), ee 16.3%} or (–)-**1** {4.6 mg, small crystals, $[\alpha]_D^{20}$ = –14.8° (*c* 0.5, MeOH), ee 17.0%} were obtained. The crystallisation of (±)-**1** (34 mg) from acetone at 4–6 °C gave one crystal (+)-**1** {1 mg, $[\alpha]_D^{20}$ = 40.9° (*c* 0.1, EtOH), ee 44.3%}.

(*S*)-(–)-**1**: yield 86%, mp 135–136 °C (acetone), $[\alpha]_D^{20}$ = –87° (*c* 2.1, MeOH), $[\alpha]_D^{20}$ = –92.2° (*c* 1.2, EtOH), $[\alpha]_D^{20}$ = –40.8° (*c* 0.9, $CHCl_3$), $\Delta\varepsilon$ = –3.5 (237.5 nm), $\Delta\varepsilon$ = 0 (223 nm), $\Delta\varepsilon$ = +7.7 (212.5 nm) (*c* 0.13 mol l^{-1}, MeOH).

(*S*)-(–)-**2**: yield 36%, bp 72 °C (40 torr), $[\alpha]_D^{20}$ = –23.1° (*c* 1.0, MeOH) (*cf.* ref. 19).

(*S*)-(–)-**3**: yield 50%, oil, $[\alpha]_D^{20}$ = –27.8° (*c* 1.0, MeOH).

(*S*)-(–)-**4**: mp 117–118 °C (C_6H_6) (*cf.* ref. 5); $[\alpha]_D^{20}$ = –6.7° (*c* 0.2, MeOH), calculated from $[\alpha]_D^{20}$ for pure (*S*)-(–)-1 and $[\alpha]_D^{20}$ = –34.3° (*c* 0.2, MeOH) for mixture **4**:**1** = 2. ^{1}H NMR ($CDCl_3$) δ: 1.68 (br. s, 1H, H_e), 1.87 (s, 3H, Me_A), 1.90 (br. m, 1H, H_b), 2.06 (s, 3H, Me_B), 2.09 (br. m, 1H, H_c), 2.83 (br. m, 1H, H_a), 8.51 (br. s, 1H, H_d).



Scheme 2

into qq, and its coupling constant $^3J_{Me_A–H_e}$ 5.0 Hz. At the same time under the conditions {Me_B, δ 1.40 ppm}, the spectrum for carbon Me_B (qq, δ 24.98 ppm) transforms into a pure q. This is in agreement with the molecular structure of **1**:[6] dihedral angles $Me_A–C–N–H_e \approx 0°$, $Me_B–C–N–H_e \approx 90°$. In addition, we observed two features in the ^{1}H NMR spectrum of **1**: large coupling constant $^4J_{H_aCNH_d}$ 2.7 Hz and a strikingly high difference in the coupling constants Δ^1J_{CH} = 18.9 Hz between protons H_b and H_c (usually for aziridine[5] this difference does not exceed 11.6 Hz).[17,18]

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