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Synthesis of (2*R*,3*S*)-(−)-2-phenyl-3-methylaziridine

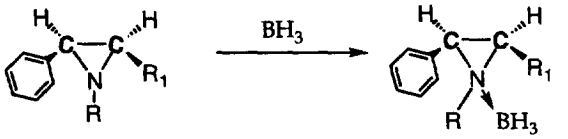
Alberto Galindo*,[a,*] Laura Orea F.,[a] Dino Gnecco*,[a] Raúl G. Enríquez,[b] R. Alfredo Toscano[b] and William F. Reynolds[c]

[a] Centro de Química, Instituto de Ciencias, BUAP, Puebla 72000, Mexico
[b] Instituto de Química, UNAM, Cd. Universitaria, Mexico, D. F. 04510, Mexico
[c] University of Toronto, 80 St. George St. Toronto, Ont. M5S 1A1, Canada

Abstract: We report the total synthesis of aziridine **3**, carried out in a two-step method involving double Walden inversion at the carbon atom bearing the hydroxy group of (1*R*,2*S*)-(−)-norephedrine, **1**, which was used as starting material. Compound **3** was obtained for the first time as a solid therefore allowing its unambiguous X-ray structure determination. © 1997 Elsevier Science Ltd

The aziridines are an attractive class of compounds available enantiomerically pure by a variety of procedures. For example, synthetic procedures have been developed for the single-step, stereoselective/stereospecific conversions of suitable precursors (e.g. 1,2-amino alcohols, 1,2-azido alcohols epoxides, etc.) into chiral aziridines using a variety of cyclodehydrating reagents.[1]

On the other hand, since amino boranes are known to be good reducing agents for carbonyl compounds,[2] we were interested in exploring the synthesis of enantiomerically pure aziridines from ephedrine derivatives in order to obtain the corresponding borane complexes[3,4] (Scheme 1) necessary for the enantioselective reduction of prochiral aldehydes and ketones.



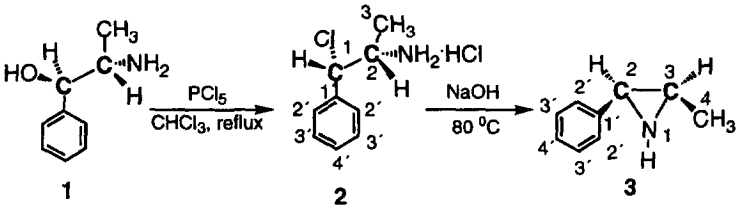
Scheme 1.

In this work, we report a simplified method for the preparation of the aziridine **3**, as a pure enantiomer. This was achieved in a two step procedure in good yield. Firstly, (1*R*,2*S*)-(−)-norephedrine, **1**, was chlorinated with PCl_5,[5] after refluxing in dry chloroform, to yield (1*S*,2*S*)-(+)-1-chloro-1-phenyl-2-propylamine hydrochloride, **2**,[6] in good yield. This involved inversion of configuration at the carbon bearing the hydroxyl group.[7,8] The second step involves the cyclization, via nucleophilic substitution, of the chlorine atom which occurs by an internal S_N2 Walden inversion[9] to yield **3**. This was achieved by treatment of **2** with a sodium hydroxide solution (Scheme 2). The resulting (2*R*,3*S*)-(−)-2-phenyl-3-methyl-1-aziridine, **3**, could be purified by high vacuum distillation, using a Kugelrohr apparatus. This represents the first report of **3** as a pure, crystalline solid.

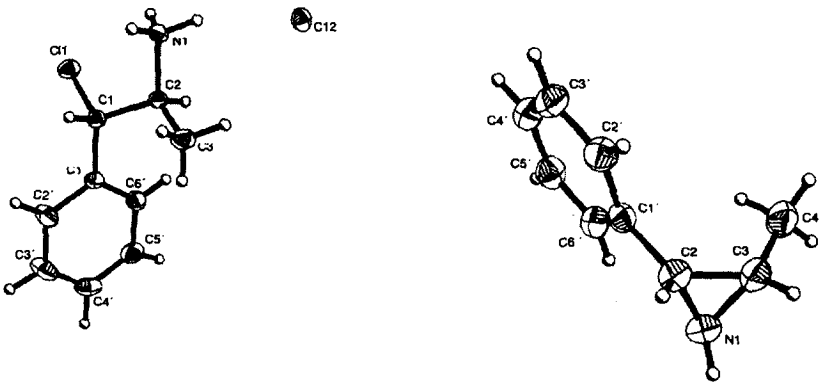
The absolute configuration of **2**, could be established by Roger's method[10] (η=0.95 (13)) and such data were used as prior reference for the X-ray determination of structure **3**.

While (1*R*,2*S*)-(−)-norephedrine, **1**, was the only compound used as a starting material, the described synthetic method is at least potentially useful for obtaining other enantiomerically pure aziridines.

* Corresponding author.



Scheme 2.



X-ray structure of 2: *Crystal data* $C_9H_{13}Cl_2N$, M_w=206.17, monoclinic, space group $P2_1$, Z=2, a=5.434 (1) Å, b=8.261 (1) Å, c=11.661 (1) Å, β=95.283 (8)°, V=521.26 (12) Å^3, d_c=1.313 Mg/m^3, F (000)=216, λ (MoKα)=0.71073 Å, μ=0.571 mm^{-1}; 3518 measured intensities, 3050 unique. Intensity data were measured on a Siemens P4-PC diffractometer using the θ–2θ scan technique up to 2θ=60°. 2802 intensities with F>4.0 σ (F) were considered as observed and kept in refinement calculations, σ (F) being derived from counting statistics. The structure was solved by the direct method and refined by full matrix least-squares treatment using SHELXTL PLUS (PC Version),[11] minimizing the function $\sum w (F_o-F_c)$.[2] Final discrepancy factors: R=3.23, wR=4.16%.

Preparation of 3. To a solution of 12 ml of NaOH (20%) was added 2.9 mmol of **2**. The reaction was stirred for 2 h at 80°C. The reaction was extracted with CH_2Cl_2 (3×25 ml), the organic layer was dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. The viscous oil obtained was distilled in a Kugelrohr apparatus at 70°C (5 mm), obtaining the crystalline aziridine, **3**. Yield 65%. **3**: m.p. 68°C (Lit.[9] 43–44.5°C), $[\alpha]_D^{25}$=−74 (c=3, EtOH); IR (KBr) 3218, 1600 cm^{-1}; ^{1}H and ^{13}C NMR: $CDCl_3$ (δ, ppm): 0.9 (3H, d, J=7.6 Hz), 2.38 (m, 1H, J=7.6 Hz and J=8.8 Hz), 3.22 (d, 1H, J=6.2 Hz) 3.7C (s, 1H, NH), 7.2–7.3 (m, 5H, Ph); ^{13}C: 137.6 (C-1′), 127.9 (C-2′) 127.8 (C-3′), 126.6 (C-4′), 37.1 (C-2), 32.1 (C-3), 13.6 (C-4).

X-ray structure of 3: *Crystal data:* $C_9H_{11}N$, M_w=133.2, orthorhombic, space group $P2_12_12_1$, Z=4, a=5.693 (1) Å, b=8.145 (1) Å, c=17.309 (4) Å, V=802.6 (2) Å^3, d_c=1.102 Mg/m^3, F (000)=288, λ (CuKα)=1.54178 Å, μ=0.493 mm^{-1}; 660 unique reflections were measured on a Siemens P4-PC diffractometer using the θ–2θ scan technique up to 2θ=113.5°. Decay (17.3%) correction based on standards was applied in addition to the normal Lp correction. 549 intensities with F>4.0, σ (F) were considered as observed and kept in refinement calculations, σ (F) being derived from counting statistics. The structure was solved by direct methods and refined by full matrix least-squares using SHELXTL PLUS (PC Version),[11] minimizing the function $\Sigma w (F_o-F_c)$.[2] Final discrepancy factors; R=4.22, wR=5.27%.

Acknowledgements

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5. The utilization of PCl_5 is more convenient that the $SOCl_2$ for reasons of cost and facility of manipulation.
6. Preparation of **2** is typical. To 25 ml of dry $CHCl_3$ solution of (6.6 mmol) of **1** was added 8.6 mmol of PCl_5 The mixture was stirred and refluxed for 1 h. The reaction was allowed to stand at room temperature for one additional hour and then the excess PCl_5 was decomposed with 5 ml of methanol. Finally the solvent was removed *in vacuo* and a white crystalline hydrochloride, **2**, was obtained. The latter was recrystallized from ethanol–diethylether. Yield 75%. **2**: m.p. 167°C (Lit[8] 198–203°C); [α]=+76 (c=6, EtOH); IR (KBr) 3300–2600, 712 cm^{-1}; ^1H and ^{13}C NMR: D_2O (δ, ppm): 1.2 (d, 3H, J=7 Hz), 3.98 (m, 1H, J=7 Hz, J=9 Hz), 5.1 (d, 1H, J=9 Hz), 7.27 (m, 5H, Ph). ^{13}C: 137.0 (C-1′), 130 (C-2′), 129.6 (C-3′), 127.9 (C-4′), 64.3 (C-1), 53.6 (C-2), 16 (C-3). If the compound **2** is left for several weeks in the NMR (D_2O) tube, the resultant spectrum shows peaks that correspond to a mixture of diastereoisomers in a relationship 2:1=(1*S*,2*S*):(1*R*,2*S*).
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