Synthesis of the scalemic form of alkaloid (−)-dipthocarpamine

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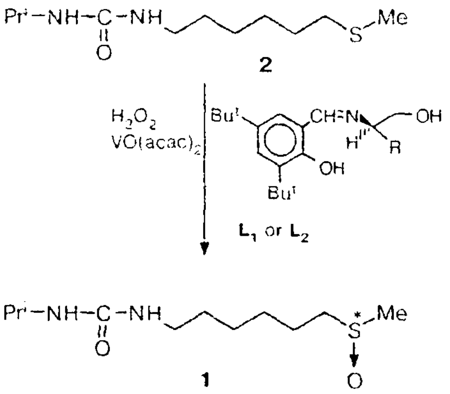
The scalemic form of active alkaloid (−)-dipthocarpamine was synthesized by asymmetric oxidation of *N*-isopropyl-*N*′-(methylthiohexyl)urea with hydrogen peroxide in the presence of vanadium(IV) complexes with chiral Shiff's bases.

Key words: alkaloids, (−)-dipthocarpamine, chiral complexes, dialkyl sulfide, asymmetric oxidation.

As part of continuing studies of catalytic asymmetric oxidation of prochiral sulfides, we directed our attention to the synthesis of optically active alkaloids from the plant *Dipthychocarpus strictus*.[1] The above-mentioned compounds contain the chiral sulfur atom in the sulfoxide fragment and can be prepared by direct oxidation of the corresponding sulfide precursors.[2,3] In this connection, it was of interest to study the behavior of titanium(IV)[4,5] and vanadium(IV)[6–8] complexes in asymmetric oxidation of polyfunctional linear sulfides.

We chose alkaloid (−)-dipthocarpamine (**1**)[9] as the object of investigation and reproduced the synthesis of its deoxy analog, *viz*., *N*-isopropyl-*N*′-(6-methylthiohexyl)urea (**2**).[3] Numerous attempts to oxidize sulfide **2** with Bu^tOOH in the presence of $Ti(OPr^i)_4$ and L-DIPT[4,5] by varying the reaction conditions were unsuccessful. In all cases, racemic alkaloid **1** was isolated along with the starting compound **2**. The chemical yield of the former was no higher than 30—35%. Apparently, the absence of optical induction and the low yield of the target sulfoxide **1** are attributable to competitive complex formation of $Ti(OPr^i)_4$ with the urea fragment of sulfide precursor **2**. At the same time, oxidation of compound **2** with a 35% hydrogen peroxide solution catalyzed by vanadium(IV) complexes with chiral Schiff's bases ($\mathbf{L_1}$ or $\mathbf{L_2}$)[6] afforded specimens of (−)-dipthocarpamine (**1**) of different optical purities (*ee*) in different yields. When the reaction was catalyzed by the complex with Schiff's base ($\mathbf{L_1}$), which was prepared from L-valinol and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde, the *ee* value of the resulting sulfoxide was 25% {$[\alpha]_D^{20}$ −14.5° (*c* 1, MeOH); lit. data[1]: $[\alpha]_D^{20}$ −58.2°}, whereas the *ee* value of (−)-dipthocarpamine (**1**) reached 45% {$[\alpha]_D^{20}$ −23.2° (*c* 1, MeOH)} in the reaction catalyzed by the vanadium complex with Schiff's base ($\mathbf{L_2}$), which was prepared from L-*tert*-leucinol and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde.



$\mathbf{L_1}$: R = Pr^i; $\mathbf{L_2}$: R = Bu^t

The ^1H NMR spectra of both synthetic specimens of alkaloid **1** are identical to those reported in the literature.[3,9]

Therefore, using alkaloid (−)-dipthocarpamine (**1**) as an example, we demonstrated the prospects of the use of vanadium(IV) complexes with chiral Schiff's bases in oxidation of polyfunctional linear sulfides.

Experimental

The ^1H NMR spectra were recorded on a Bruker AC-200 spectrometer in $CDCl_3$ with Me_4Si as the internal standard. The optical rotation was measured on a JASCO DIP-360 polarimeter (Japan). Column chromatography was carried out on SiO_2 (130—270 mesh, Aldrich). TLC was performed on Silufol plates; visualization was carried out with iodine vapor.

***N*-Isopropyl-*N*′-(6-methylsulfinylhexyl)urea, (−)-dipthocarpamine (1).** *N*-Isopropyl-*N*′-(6-methylthiohexyl)urea (**2**)[3] (0.2 g, 760 μmol) was added to a stirred solution of $VO(acac)_2$ (2 mg, 8 μmol) and the $\mathbf{L_1}$ or $\mathbf{L_2}$ ligand[6] (12 μmol) in CH_2Cl_2 (4 mL) at 20 °C and then a 35% H_2O_2 solution (75 μL,

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950 μmol) was added. The reaction mixture was stirred for 2 h (20 °C) and washed with H_2O (2 × 1 mL). The organic layer was separated, dried with $MgSO_4$, and concentrated. The residue was chromatographed (SiO_2, CH_2Cl_2—MeOH, 95 : 5). Oxidation by the complex with the $\mathbf{L_1}$ ligand afforded compound **1** in a yield of 0.19 g (91%), R_f 0.28 ($CHCl_3$—MeOH, 9 : 1), m.p. 87—90 °C (*cf.* Ref. 1: m.p. 100—101 °C for the natural alkaloid). Oxidation by the complex with the $\mathbf{L_2}$ ligand afforded compound **1** in a yield of 0.14 g (66%), m.p. 86—89 °C. Found (%): C, 52.87; H, 9.90; N, 11.01; S, 12.45. $C_{11}H_{24}N_2O_2S$. Calculated (%): C, 53.19; H, 9.74; N, 11.28; S, 12.91.

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Reactivity of functional groups toward H^+ and $SiMe_3^+$ ions

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No correlation was observed between the gas-phase basicities of various functional groups toward H^+ and $SiMe_3^+$ ions. Differences in the reactivity of functional groups studied toward $SiMe_3^+$ ions are smaller than those in the reactivity toward protons.

Key words: mass spectrometry, chemical ionization, trimethylsilyl cation, basicity.

Previously,[1,2] it has been shown that the reactivity of $SiMe_3^+$ ions in reactions with mono-, di-, and trihaloalkanes is determined by the basicity of these molecules, *i.e.*, by their proton affinity.[3] However, studies of compounds with nitrogen-containing functional groups have shown[4] that the basicities of these compounds toward H^+ and $SiMe_3^+$ ions do not correlate (this has been confirmed by quantum-chemical calculations).

This work was carried out in a continuation of comparative studies of the reactivity of various functional groups toward H^+ and $SiMe_3^+$ ions.

Experimental

Mass spectra were recorded on a Kratos MS-30 mass spectrometer (energy of ionizing electrons 200 eV, temperature of the ion source 150 °C). The reagent gas pressure (0.2 Torr) was kept constant with the use of an external manometer mounted on the inlet system. Tetramethylsilane (Merck) of 99.7% purity was used in the experiments. Equimolar mixtures of compounds under study were introduced through a heated direct inlet system.

Results and Discussion

The mass spectra of all compounds in the mixtures studied contain only the peaks of adduct-ions $[M \cdot SiMe_3]^+$. For equimolar mixtures, the ratio of intensities of the ion peaks, $[M^1 \cdot SiMe_3^+]/[M^2 \cdot SiMe_3^+]$, is the equilibrium constant (K_{eq}) of the trimethylsilyl ion transfer reaction.[2]

$$[M^1 \cdot SiMe_3]^+ + M^2 \overset{K_{eq}}{\rightleftharpoons} [M^2 \cdot SiMe_3]^+ + M^1$$

We measured the rate constants for reactions (1)—(11).

The results obtained in this work and in our previous studies[2–4] made it possible to establish the following

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