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REGIOSELECTIVE TRANSFORMATION OF UNSYMMETRICAL BIS(*N*-NITROSOSULFONAMIDES) LEADING TO OPTICALLY ACTIVE CYCLIC IMINO ACID DERIVATIVES FROM L-LYSINE AND L-ORNITHINE

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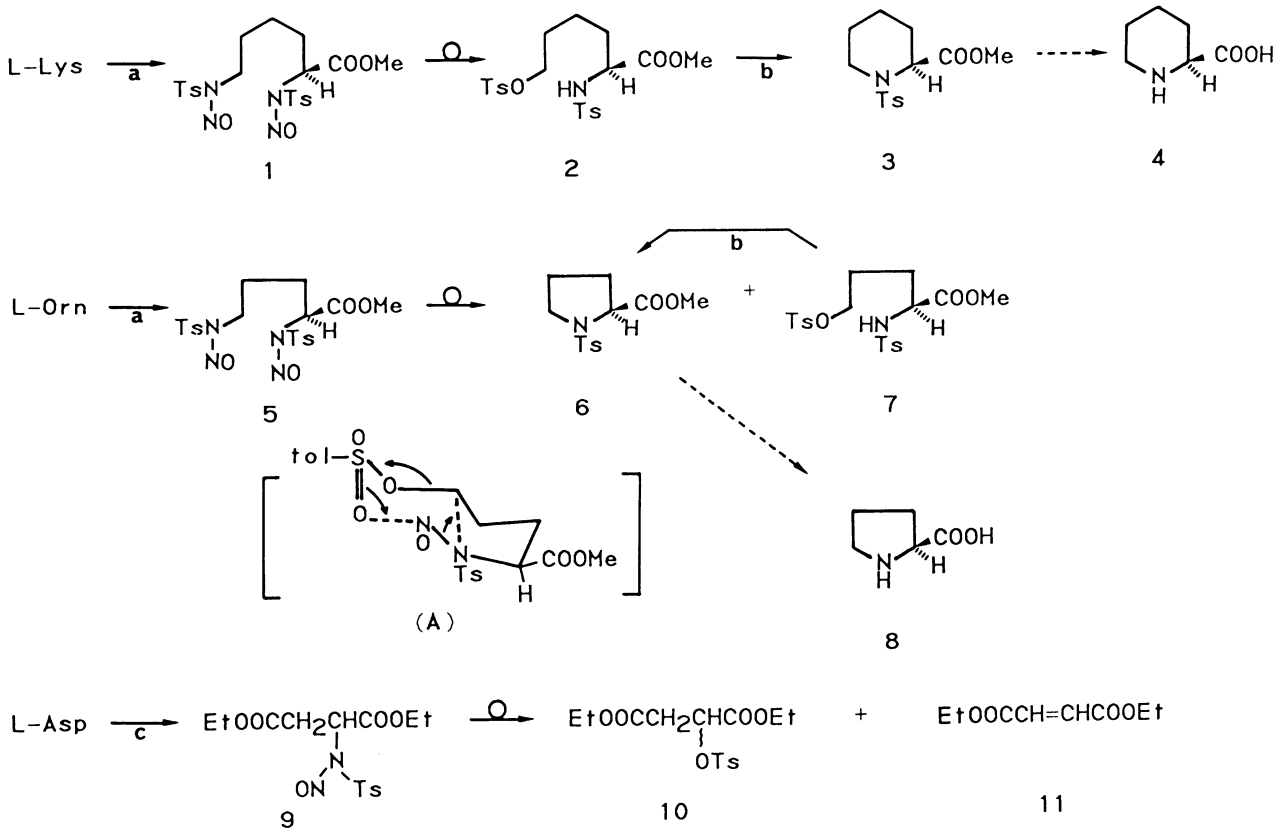
Chiral cyclic imino acid derivatives were prepared from unsymmetrical bis(*N*-nitrososulfonamides) of diaminocarboxylic acids, L-lysine and L-ornithine, in good yields through kinetically controlled regioselective *N*-nitrososulfonamide-sulfonate rearrangement.

The finding of kinetically controlled bifunctionalization of symmetrical α,ω-bis(*N*-nitrososulfonamides)[1] encouraged us to examine its feasibility for the stereospecific synthesis of L-pipecolic acid (4) and L-proline (8) from the corresponding *N*-nitrososulfonamides, 1 and 5, of diaminocarboxylic acids, L-lysine and L-ornithine. The designed route to the naturally occurring cyclic imino acids from open-chain amino acids would be achieved if the transformation occurs exclusively at one *N*-terminal remote from the asymmetric center.

When $N^{\alpha},N^{\varepsilon}$-dinitroso-$N^{\alpha},N^{\varepsilon}$-ditosyl-L-lysine methyl ester (1) was heated at *ca.* 80 °C in benzene for 24 h, methyl 2-tosylamino-6-tosyloxycaproate (2) was obtained in 28% yield as main product. Treatment of 2 with K_2CO_3 in *N*,*N*-dimethylformaide gave methyl *N*-tosyl-L-pipecolate (3) ($[\alpha]_D$ -37.2° (c 0.62, MeOH)) in 90% yield. Surprisingly, when N^{α},N^{δ}-dinitroso-N^{α},N^{δ}-ditosyl-L-ornithine methyl ester (5) ($[\alpha]_D$ +38.5° (c 0.65, $CHCl_3$)) was heated as described above, *N*-tosyl-L-proline methyl ester (6) ($[\alpha]_D$ -79.1° (c 0.69, MeOH)) was directly obtained in 49% yield, accompanied by methyl 2-tosylamino-5-tosyloxyvalerate (7) (7%). These observations clearly indicate that the *N*-nitrososulfonamide-sulfonate rearrangement reaction occurs exclusively at ω-*N*-nitrosotosylamino group attached to the methylene group. The direct formation of 6 could be explainable by the intramolecular pericyclic transition state (A) as proposed in the previous report.[1] Further support for the intermediacy of the δ-tosyloxy group instead of that in the α-position was provided by the reaction of L-aspartate derivative (9). This gave optically inactive diethyl 2-*O*-tosylmalate (10) (26%), diethyl fumalate (11) (5%), and optically active denitrosated product (52%) ($[\alpha]_D$ +33.3° (c 1.56, $CHCl_3$)). Loss of optical activity of 10 indicates that the rearrangement at the chiral center results in complete racemization, Therefore, the direct formation of 6 should proceed

through intramolecular reaction of the δ-tosylate group with α-*N*-nitrososulfonamide *via* the transition state (A).

Preparations of L-pipecolic acid from L-lysine and L-proline from L-ornithine have been reported by use of a conventional method[2] and the double Walden inversion method,[3] respectively. The present approach is characterized by (i) short-cut synthesis of optically active useful intermediate 3 leading to expensive L-pipecolic acid from cheap L-lysine, (ii) direct intramolecular cyclization *via* the transition state (A) with retention of configuration, and (iii) kinetically controlled regioselective rearrangement of unsymmetrical bis(*N*-nitrososulfonamides). Optically active cyclic imino acid derivatives, 3 and 6, will be useful intermediates in stereospecific synthesis of alkaloids and in general organic synthesis.



Scheme 1. a: i) HCl/MeOH, ii) TsCl/pyridine, iii) $NaNO_2/Ac_2O/AcOH$. b: K_2CO_3/DMF. c: i) HCl/EtOH, ii) TsCL/pyridine, iii) $NaNO_2/Ac_2O/AcOH$. The circles on the arrow denote rearrangement in benzene.

References

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