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A STEREOSPECIFIC SYNTHESIS OF (±) α-CONHYDRINE AND (±) β-CONHYDRINE.

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(±) α-Conhydrine and (±) β-Conhydrine are easily obtained by an intramolecular regio and stereospecific ring opening of the corresponding trans and cis ω-aminoepoxides.

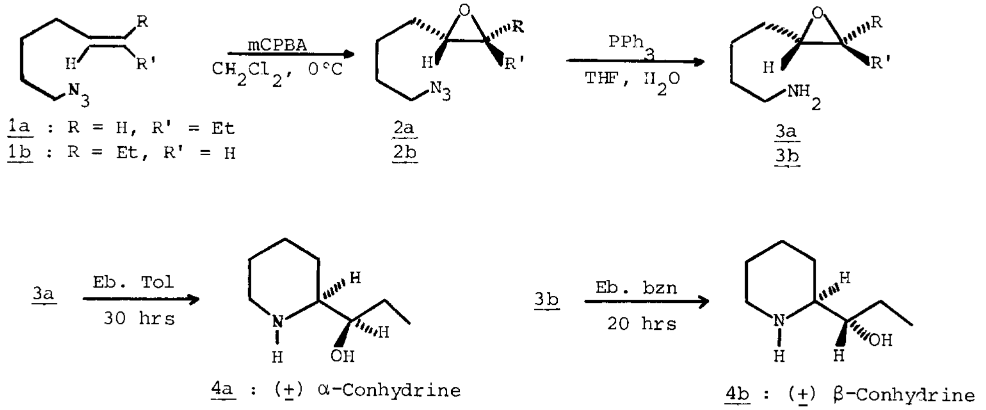
Ethanolamine derivatives are a biologically important class of compounds. Stork (1) has designed a general synthesis of these β-aminoalcohols using the condensation of alpha cyanoamine carbanions with aldehydes as the key step of the sequence. (±) α-Conhydrine 4a is produced stereoselectively in this way. Recently, Shono (2) proposed a stereospecific synthesis of 4a based on the reaction of the carbanion of 2-diphenylphosphinyl-1-methoxycarbonyl piperidine with propionaldehyde, followed by a thermal elimination of the diphenylphosphinyl group and a catalytic hydrogenation of the 2-oxazolone derivative thus obtained. In these two sequences, the stereoselectivity is the result of a reduction by $NaBH_4$ of an iminoderivative in the first case (1) and of a catalytic hydrogenation of a double bond in the second one (2). Furthermore, they do not allow a stereospecific access to the threo derivatives.

We have recently described an easy access to primary amines by a chemoselective reduction of azides (3). Primary epoxyamines are accessible from the corresponding epoxyazides by using this technique. We wish to report here an efficient stereospecific synthesis of (±) α-Conhydrine and its threo diastereomer by a totally different strategy.

Our method is shown in scheme 1.

The epoxidation of the olefins 1a and 1b (4) leads to the corresponding epoxides, respectively 2a and 2b (2a : 82 % after purification by column chromatography on silica gel and bulb to bulb distillation, $Eb_{0.5}$ = 55-60°C (oven temperature) ; 2b : 87 %, same purification). The reaction of 2a and 2b with one equivalent of triphenylphosphine in THF in the presence of water (1.2 eq.) at room temperature for 18 hours gives the primary amines 3a and 3b as isolable oils (bulb to bulb distillation, 3a : 80 %, $Eb_{0.5}$ = 62-65°C, 3b : 85 %, $Eb_{0.1}$ = 45-50°C). The cyclization of 3a by refluxing in toluene for 30 hours leads to (±) α-Conhydrine 4a (90 % (7a,b)).

Scheme 1



In the same way, the threo isomer 4b is obtained by refluxing a benzene solution of the aminoepoxide 3b for 20 hours (4b, 88 % (8)). (±) α-Conhydrine 4a and its diastereomer 4b have melting points identical with those reported in the literature (respectively (7a,b) and (8)). Further confirmation of the structures 4a and 4b was obtained from mass spectrometry (main fragmentation of the molecular ions $4a^{\rceil+\cdot}$ and $4b^{\rceil+\cdot}$: rupture of the 2-2' C-C bond leading to the cation m/e = 84 (100 %) (9)) and NMR (250 MHz : ^{3}J-NH-C$\underline{H}$-C$\underline{H}$OH- = 3.2 Hz and 7.5 Hz for 4a and 4b respectively).

In these two intramolecular cyclizations, the 6-exo mode (10) is exclusive, leading to the piperidines 4a and 4b.

The general problem of the intramolecular ring opening of ω-amino epoxides is under active investigation in this laboratory.

References and notes :

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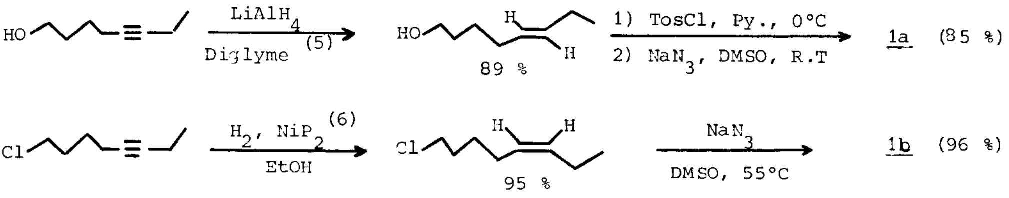
4 - 1a and 1b are obtained according to the following sequences :



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7a - m.p. 99-100°C (ether) ; litt. 99-100°C (7b).

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