

Synthesis of Aminoalcohols via Perihydro-1,3-oxazin-2-ones and
Absolute Configuration Assignment through MM2 Calculations

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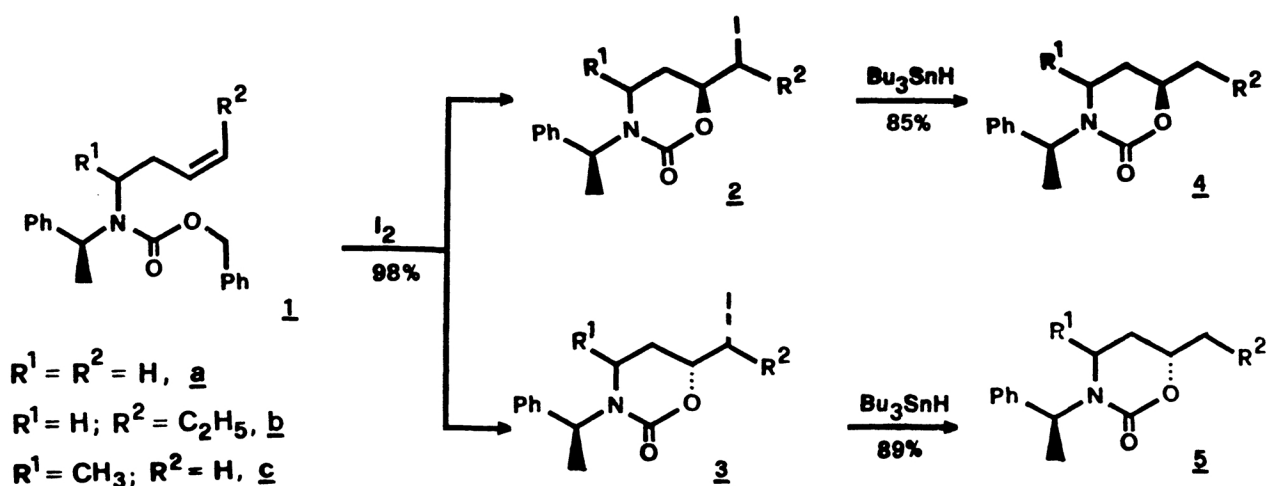
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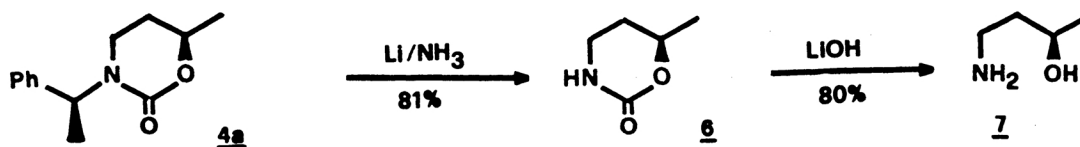
Diastereomeric perihydro-1,3-oxazin-2-ones are useful intermediates to enantiomerically pure aminoalcohols: their absolute configuration is assigned from ^1H NMR data and supported by MM2 calculations.

The products of halocyclofunctionalization of homoallylic carbamates are versatile intermediates in synthesis, since the hydrolytic cleavage of the heterocyclic ring provides the aminoalcohols frequently found in biologically active compounds. The utility of this strategy is greatly enhanced when the starting homoallylamine can be readily prepared in the optically active form. The use of commercially available (S)-1-phenylethylamine for this purpose has been previously investigated.¹⁾ We report now that the halocyclization of homoallylic carbamates affords diastereomeric mixtures of perihydro-1,3-oxazin-2-ones easily resolved by chromatography, that are useful to synthesize enantiomerically pure compounds. Moreover, on comparison of ^1H NMR and ^{13}C NMR spectra of diastereomers, we have elaborated a method¹⁾ to assign the absolute configuration of the newly introduced stereogenic centers.

Our results indicate that a preferred conformation of the heterocyclic ring is favoured and computational models support these conclusions. The carbamate 1a, ($[\alpha]_D -72.9^\circ$ (c 2.2; CHCl_3)), obtained from the corresponding amine and benzyloxycarbonyl chloride, is cyclized with iodine in CHCl_3 to give in a quantitative yield a 1:1 mixture of cyclic iodocarbamates 2a ($[\alpha]_D -19.5^\circ$ (c 1.1; CHCl_3)), and 3a ($[\alpha]_D -68.1^\circ$ (c 1.1; CHCl_3)), as determined by ^{13}C NMR. Separation of the diastereomers is accomplished by flash chromatography and successive reduction of pure 2a and 3a with Bu_3SnH produces 4a ($[\alpha]_D -29^\circ$ (c 2.23; CHCl_3)) and 5a ($[\alpha]_D -132.1^\circ$ (c 2.2; CHCl_3)), respectively. The iodocyclization of carbamate 1b ($[\alpha]_D -65.3^\circ$ (c 1.96; CHCl_3)) gives 2b ($[\alpha]_D -19.9^\circ$ (c 1.45; CHCl_3)) and 3b ($[\alpha]_D -57.1^\circ$ (c 1.32; CHCl_3)). Structural assignment of these pairs is made on the basis of the non-equivalence of H_a and H_b chemical shifts in the ^1H NMR spectra.

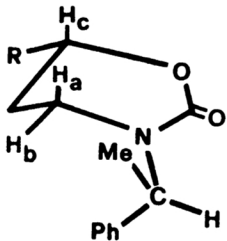
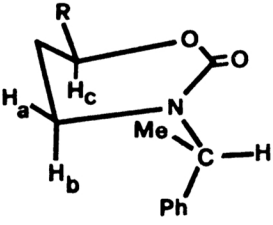


Assuming that the resonance of hydrogen at upfield strongly depends on the shielding of the phenyl ring on the stereogenic center, a preferred A conformation is envisaged. In fact the 1H NMR spectroscopy of the pairs of 6-substituted perihydro-1,3-oxazin-2-ones shows that the substituent at C-6 displays a strong tendency to occupy the equatorial position in both the isomers, as proven by the coupling constants of the heterocyclic ring. The H_c chemical shifts and the values of the coupling constants ($J_{aa} = 9.6$ Hz, $J_{ae} = 3$ Hz) show that H_c is in an axial position, independently from the absolute configuration of the stereogenic center at C-6. Since this result, we propose a unique model for each diastereomer of the perihydro-1,3-oxazin-2-ones. In such envelope of the oxazin-2-one ring, the phenyl group always shields the H_b resonating upfield, that occupies the axial position in a diastereomer and the equatorial in the other one. On the basis of the chemical shifts and the values of the coupling constants of H_a and H_b , it is possible to establish the absolute configuration of the molecule. Selected chemical shifts and coupling constants from 1H NMR spectra are collected in Table 1. To confirm these results, 4a has been treated with Li/NH_3 to give 6 and successive basic treatment with $LiOH/H_2O/MeOH$ at reflux affords the (R)-1-amino-3-hydroxybutane 7 ($[\alpha]_D +13.1^\circ$ (c 1.39; H_2O)).²⁾



To explain the 1H NMR spectra of both the diastereomers, the most stable conformations are calculated by molecular mechanics method.³⁾ By a full rotation around the $N-C_7$ bond, both diastereomers exhibit a very similar conformational energetic profile and only two minima are found. In the calculated geometries of

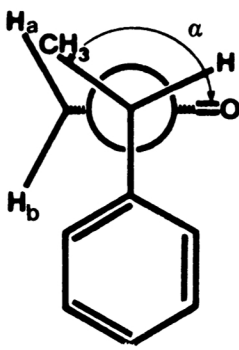
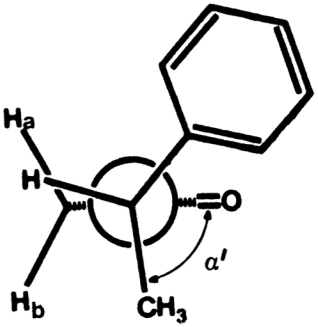
Table 1 . Selected ^1H NMR data for some perihydro-1,3-oxazin-2-ones

| |  | | | | | | |  | | | | | |
|-----------------|---|----------------------|------------------|-------------------|------------------|-------------------|-----------------|---|----------------------|------------------|-------------------|------------------|-------------------|
| | δ_{Ha} | δ_{Hb} | $J_{\text{a,5}}$ | $J_{\text{a,5'}}$ | $J_{\text{b,5}}$ | $J_{\text{b,5'}}$ | | δ_{Ha} | δ_{Hb} | $J_{\text{a,5}}$ | $J_{\text{a,5'}}$ | $J_{\text{b,5}}$ | $J_{\text{b,5'}}$ |
| (6R)- <u>3a</u> | 3.1 | 2.8 | 11.4 | 4.7 | 5.4 | 3.0 | (6S)- <u>2a</u> | 3.1 | 2.75 | 5.6 | 3.5 | 10.8 | 5.0 |
| (6S)- <u>4a</u> | 3.1 | 2.8 | 11.4 | 4.8 | 5.4 | 3.0 | (6R)- <u>5a</u> | 3.1 | 2.70 | 5.7 | 3.0 | 10.2 | 5.4 |
| (6S)- <u>4c</u> | 1.2 ^{a)} | 3.2 | — | — | 4.5 | 5.0 | (6R)- <u>5c</u> | 3.6 | 0.7 ^{a)} | 4.5 | 5.0 | — | — |

a) Chemical shift of the C-4 methyl.

the most stable conformers, C-6, O-1, C-2, N-3, C-4 atoms are almost coplanar, while the C-5 is about 20° out of the plane, the methyl group being in the most favoured equatorial position. From this conformation, corresponding to the absolute minimum in the energetic profile, it results that the H_b experiences the phenyl shielding more than H_a . This result confirms the proposed model used to explain the observed ^1H NMR pattern. The geometries of the minima can be rationalized on the basis of the interactions between the C=O group and both phenyl and methyl groups. In fact, in the conformations relative to the minima, the two interactions are mutually minimized and the conformer A, which shows the

Table 2 . Energy and population for conformers A and B

| |  | | | |  | | |
|-------|---|------------------------|--------------------|--|--|-------------------------|--------------------|
| (6S): | $\alpha = 133^\circ$ | Energy = 17.2 kcal/mol | population = 78% | | $\alpha' = 73^\circ$ | Energy = 17.95 kcal/mol | population = 22% |
| (6R): | $\alpha = 119^\circ$ | Energy = 17.2 kcal/mol | population = 62.4% | | $\alpha' = 70^\circ$ | Energy = 17.5 kcal/mol | population = 37.6% |

greater distances among the interacting groups, is the favoured one (Table 2). In order to test the usefulness of our method,¹⁾ we have synthesized the perihydro-1,3-oxazin-2-ones 4c and 5c through the cyclization of 1c and successive dehalogenation. Of the four possible isomers, only those in the trans configuration are formed, the more stable for this kind of compounds.⁴⁾ The analysis of the coupling constants (Table 1) for H-6 and H-4 shows that for both the isomers the substituent on C-6 is in equatorial position and the methyl on C-4 is in the axial position, probably since methyl on C-4 is forbidden to lie in the equatorial position by steric hindrance with the bulky substituent on N. We can now assign the absolute configuration of these two isomers following the method of preferential shielding previously described. In the isomer 3c, because the methyl on C-4 is more deshielded and H-4 is more shielded, the methyl lies in the place of H_a. Further support for this result arises from the ¹³C spectrum, where we found C-8 and C-10 more deshielded in these isomers, following the synaxial effect present in this conformation (17.7 and 21.7 δ vs. 16.4 and 20.6 δ). The other, of course, is the isomer where the methyl lies in the place of H_b.

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