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ASYMMETRIC SYNTHESIS V[1]. ENANTIOSPECIFIC SYNTHESIS OF β-AMINOALCOHOLS IN THE PIPERIDINE SERIES : (+)-β-CONHYDRINE

Virginie RATOVELOMANANA, Jacques ROYER and Henri-Philippe HUSSON*

Institut de Chimie des Substances Naturelles du CNRS, 91190 Gif-sur-Yvette (France)

Abstract

The first enantiospecific synthesis of the piperidine derivative (+)-β-conhydrine 4 has been achieved from the chiral 2-cyano-6-oxazolopiperidine synthon 1.

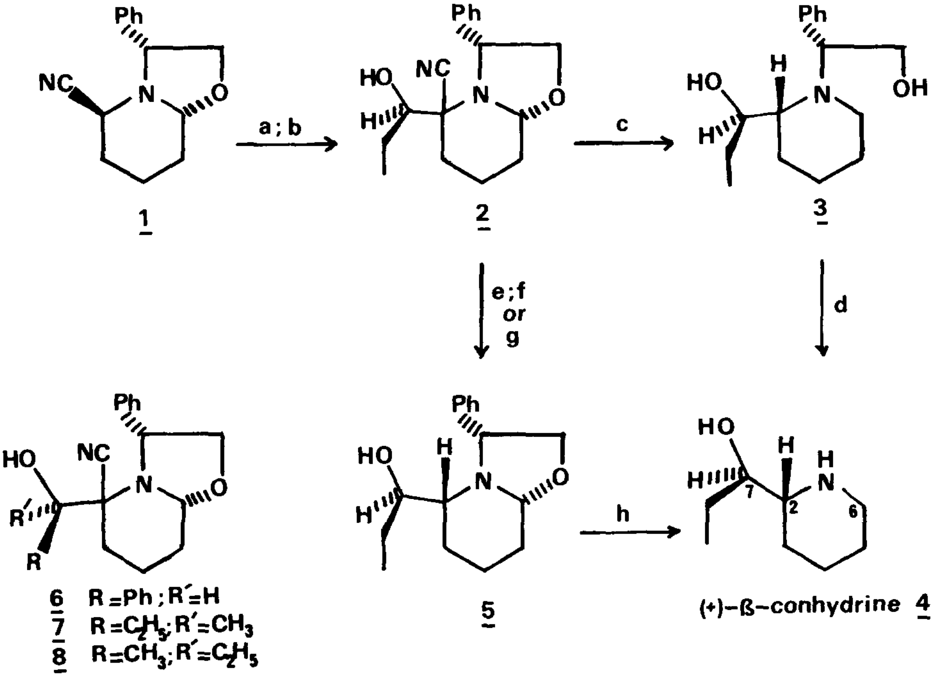
Reaction of anions derived from chiral α-aminonitriles with aldehydes or ketones has not received very much attention. The recent work of Enders, Mazaleyrat and co-workers[2] deals with the reactivity of aldehydes with aminonitriles (Strecker type derivatives) derived from ephedrine or prolinol. These metalated aminonitriles used as latent carbonyl anions led after hydrolysis to chiral α-hydroxyketones in poor to excellent enantiomeric excesses (5 to 97%).

In a recent series of papers[3-5] we have described the preparation and chemistry of 2-cyano-6-oxazolopiperidine 1, a new type of chiral synthon which shows considerable value for the asymmetric synthesis of alkaloids. Of particular interest is the masked iminium reactivity of the anion derived from 1 with alkyl halides. In continuation of our work we wish to report here the reaction of this carbanion with aldehydes and ketones. Although piperidine synthons with a negative charge at the position α to the nitrogen atom have been reacted with aldehydes[6,7] no attention has been paid to asymmetric synthesis of the resultant β-aminoalcohols whose biological interest is known.

The potential of our method will be illustrated by the enantiospecific synthesis of (+)-β-conhydrine representing the first asymmetric synthesis in this series of alkaloids[8].

Preparation of the anion of 1 (LDA, THF, -78°C) and its reaction with propionaldehyde led to the formation of a single product 2[9] (Y : 44%, + 55% of recovered 1). The complete reduction of 2 ($NaBH_4$ in EtOH) was stereospecific giving the aminoalcohol 3[9] (Y : 78%) which was cleanly debenzylated (Pd/C, H_2, MeOH, 15h) to (+)-β-conhydrine 4[10] (Y : 70%).

An alternative route to 4 was the chemiospecific decyanation[3] of aminonitrile 2. We first investigated the reaction of 2 with $Zn(BH_4)_2$ at -60°C in THF after complexation of the cyano group with $AgBF_4$ giving oxazolidine 5[9] (Y : 82%). The same product was also obtained using Na/NH_3 liq. (1 h, -78°C ; Y : 74%). Finally, hydrogenolytic cleavage ($Pd(OH)_2$, H_2, MeOH, 4 days) of the N-benzyl and aminoether groups gave (+)-β-conhydrine 4 (Y : 62%).



Reagents :

a) LDA, THF, -78°C, 30 min ; b) C_2H_5CHO, THF, -78°C, 5 min ; c) $NaBH_4$, EtOH, reflux, 5h ; d) H_2, Pd/C 5%; MeOH, 15h ; e) $AgBF_4$, THF, r.t., 10 min ; f) $Zn(BH_4)_2$, THF, -60°C, 1h ; g) Na, NH_3 liq. -78°C, 1h ; h) H_2, $Pd(OH)_2$, MeOH, 4 days.

The threo stereochemistry of 4 was established by comparison of ^1H, ^{13}C NMR and mass spectra of the (±)-β-conhydrine[11]. Thus the two asymmetric centres of 4 were successively formed in a stereospecific manner. As the absolute configuration at C-2 of 3, 4 or 5 is known as R on the basis of our previous results[3], we postulate that the absolute configuration of (+)-β-conhydrine is 2R, 7R[12].

It should be noted that decyanation with Na/NH$_3$ liq. can efficiently replace borohydrides an important consideration if the molecule is sensitive to such reductive reagents[14]. The same stereochemical outcome of these reactions is consistent with the stereoelectronic control[4,5] of hydride reduction of the intermediate iminium salt and axial protonation of the anion formed by two electron transfer reactions with Na/NH$_3$[13].

Racemic erythro and threo conhydrine alkaloids have been stereospecifically synthesized[11] ; however using a piperidine synthon the threo isomer could not be obtained[7] or was isolated as a minor derivative[6].

Interesting complementary results were obtained upon alkylation of the anion derived from 1 with benzaldehyde, compound 6 (Y : 24%) being formed exclusively whereas with 2-butanone two products 7 and 8 (Y : 22% ; 7 : 8 = 73 : 27) were observed[15]. The difference in the stereoselectivity of reaction between propionaldehyde, benzaldehyde and bulkier ketone reagents indicates that the difference in steric requirements between an hydrogen and an alkyl group plays an important role in the transition state.

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References and Notes

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9 All new compounds have been fully characterized and their spectral data are in accord with the proposed structures.

10 **4** : mp 72°C (hexane) ; $[\alpha]_D^{20}$ 8.6 (EtOH, c 1) MS m/z 143 ($M^{+\cdot}$), 114 (15), 84 (100) ; ^1H NMR ($CDCl_3$, 400 MHz) : 3.15 (m, J = 8 Hz, J' = 7.5 Hz, J" = 3 Hz, 1H. H-7), 3.01 (d, J = 12 Hz, H-6e), 2.5 (m, J = 12 Hz, J' = 12 Hz, J" = 3 Hz, 1H, H-6a), 2.23 (m, J = 12 Hz, J' = 7.5 Hz, J" = 3 Hz, 1H, H-2a) ; ^{13}C NMR ($CDCl_3$, 50 MHz) : 10.2, 24.5, 26.3, 26.4, 29.1, 46.6, 61.1, 75.4.

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12 As β-conhydrine is the unnatural diastereomer no specific rotation is known which does not allow a correlation.

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15 Decyanation of **6** ($NaBH_4$, MeOH) also led to the threo isomer according to the ^1H NMR spectrum (J_{2-7} = 10 Hz).

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