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2-CYANO Δ^3 PIPERIDINES IV[1] : SPIROANNELATION IN THE PIPERIDINE SERIES

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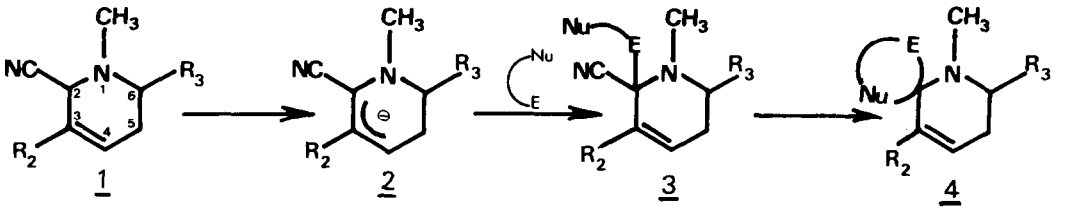
Summary : The preparation of piperidines 7 and 11 spirosubstituted at C-2 from the 2-cyano Δ^3 piperidine 5 is described. The mechanism of their formation is discussed.

We have shown[2] that aminonitriles of type 1 undergo nucleophilic substitutions regioselectively at C-2 or C-4. On the other hand, regioselective electrophilic substitutions at these carbon centers can be achieved via the ambident anion 2. The stepwise substitution of 1 with a molecule containing an electrophile and a nucleophile in a protected form could allow the possibility of the formation of a spirocyclic piperidine of type 4 (scheme 1).



Scheme 1

A great deal of interest has been shown in the preparation of piperidines containing a spiro cyclohexane substituent, this system occurring in the potent frog toxin histrionicotoxin which, with its equally active perhydroderivative 12, has been the subject of numerous synthetic approaches[3].

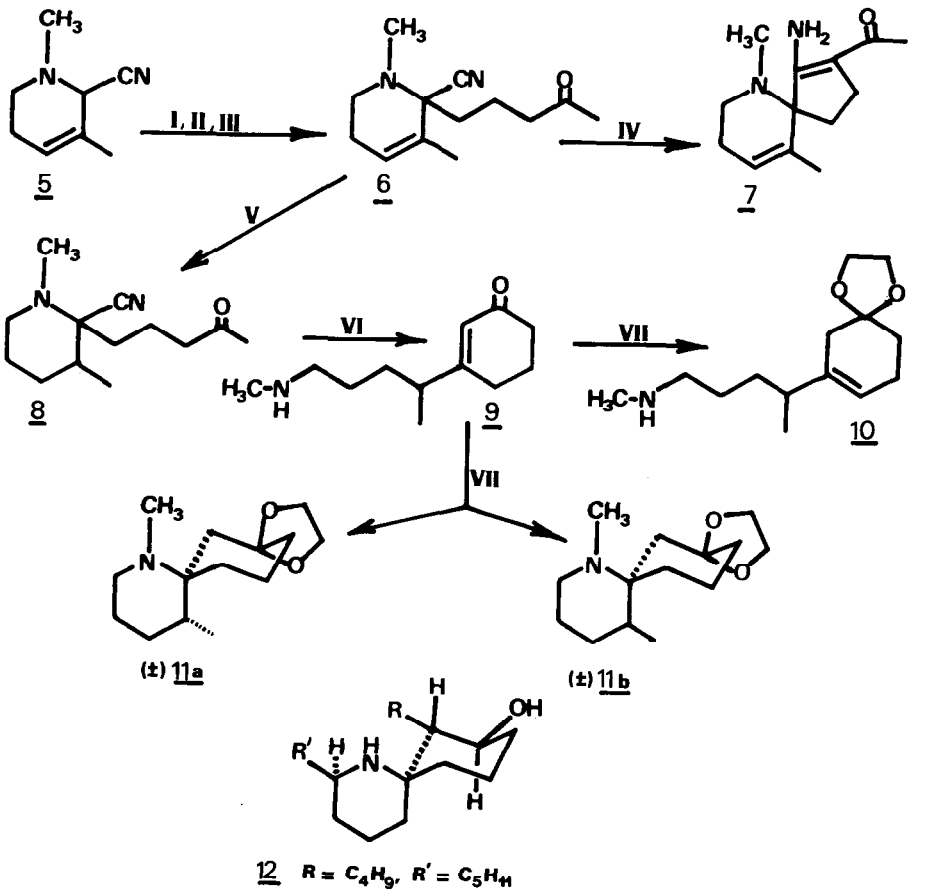
In this paper we describe the results of studies on the experimental validification of the strategy outlined in scheme 1. It was decided to use a cyano-Δ^3 piperidine 5 substituted at C-3 as starting material because of its greater stability relative to 1 ($R_2 = R_3 = H$)[2].

The condensation of the ambident anion derived from 5[2] with 5-iodo-pentanone ethylene ketal gave the ketone 6[4] (Y = 83 %), after deprotection with aqueous HCl. We initially approached the cyclisation of the iminium equivalent 6 via the ketone enolate[2]. Treatment of 6 with bases such as LDA under various conditions led to the recovery of starting material, despite proof that the kinetic enolate was being formed, by its trapping as its t-butyl dimethylsilyl ether.

When t-BuOK was employed as base, the compound 7[5] was obtained (Y = 69 %) via the thermodynamic enolate. We believe that the cyclisation in the case of the thermodynamic enolate is promoted by chelation between the heteroatoms and the cation which disfavours the retro-reaction probably occurring in the case of the kinetic enolate.

Cyclisation under acidic conditions was then attempted in spite of the failure of Mannich type spiro cyclisation reactions previously reported on a piperideinium salt[6]. Initially, 6 was hydrogenated into 8[7] in order to avoid disproportionation reactions of the intermediate 5,6-dihydropyridinium salt[2]. Refluxing 8 with TsOH in C_6H_6 afforded 9[8] (Y = 61 %), the product resulting from a retro-Michael reaction of the initially cyclised product 14 (scheme 3). The compound 9 was treated in refluxing benzene in the presence of TsOH and glycol in order to trap the products in the cyclic form and avoid the retro-reaction[9,10].

Under these conditions the spirocyclic products 11a and 11b[11] were isolated together with the product 10[12] of ketalisation of the α, β unsaturated ketone 9 with concomitant double bond migration[13]. The spirocyclic structure of 11a and 11b was ascertained on consideration of the spectral data in particular the ^{13}C NMR[11].



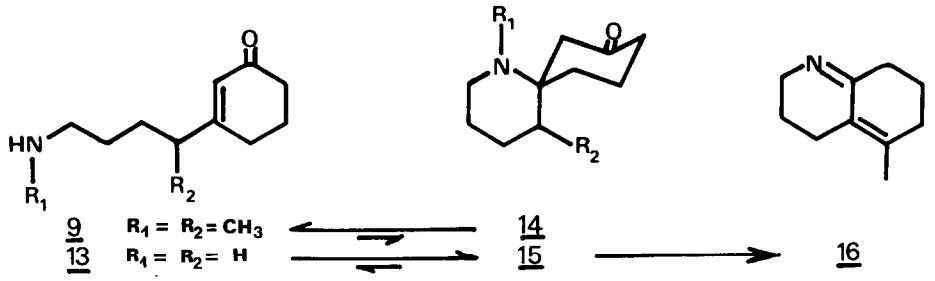
Reagents : I, n Buli, THF, − 30° ; II, I-$(CH_2)_3$ $-C(OCH_2CH_2O)-$ CH_3, 20°, 2 h ; III, H_3O^+ ; IV, THF, 20°, t-BuOK, 2.5 h ; V, H_2, C/Pd .10%, EtOH ; IV, C_6H_6, TsOH, Δ, 21 h ; VII, C_6H_6, TsOH, $HOCH_2$-CH_2OH.

Scheme 2

Some points of note arise from these results. Firstly, all attempts to cyclise 9 under acidic conditions led to recovery of starting material unless the cyclised products were trapped as 11, indicating that the equilibrium 9 ⇆ 14 (scheme 3) lies to the left, in contrast with previous results on 13[6,14]. A hydrogen bond could explain the stabilisation of 15 (R_1 = H) not possible for 14 (R_1 = CH_3).

Furthermore, no attack of the enamine derived from 8 on the keto group which was observed for similar system where R_2 = H[6,14] (e.g. 15 ⟶ 16) occurred.

It is evident that the substituents R_1 and R_2 on the enamine system play a determinant rôle in the direction of the reactions outlined in scheme 3.



Scheme 3

In conclusion, we have demonstrated that 2-cyano piperidines of type 1 are potential synthons for the preparation of piperidines spirosubstituted at C-2 as represented by compounds 7 and 11.

Aknowledgements : The authors would like to thank M. VUILHORGNE for fruitful discussions concerning ^{13}C NMR.

References and Notes

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4. 6 : oil ; MS m/e (relative intensity) : $M^{+\cdot}$ 220 (20), 205 (5), 177 (8), 136 (90), 135 (100), 43 (65) ; ^1H NMR ($CDCl_3$, 60 MHz, TMS δ = 0) : 1.80 (3H, broad s, H_3C-C = C), 2.10 (3H, s, CH_3C = O), 2.42 (3H, s, CH_3N), 5.79 (1H, m, HC = C) ; ^{13}C NMR ($CDCl_3$, 15.08 MHz, TMS δ = 0) : 16.1 (t), 19.4 (q), 25.3 (t), 30.1 (q), 32.4 (t), 40.1 (q), 42.8 (t), 49.2 (t), 64.7 (s), 118.2 (s), 127.9 (d), 129.9 (s), 208.5 (s).

5. 7 : oil, MS m/e (relative intensity) : $M^{+\cdot}$ 220 (28), 203 (20), 189 (100) ; UV λ_{max}^{EtoH} qualitative 317 nm ; IR neat 3480 s, 3340 m, 1650 s, 1590, 1510 cm^{-1} ; ^1H NMR ($CDCl_3$, 60 MHz, TMS δ = 0) : 1.55 (3H, broad s, H_3C-C = C), 2.06 (3H, s, CH_3C = O), 2.12 (3H, s, CH_3N), 5.5 (1H, m, HC = C), 6.5 (2H, broad NH_2) ; ^{13}C NMR ($CDCl_3$, 22.63 MHz, TMS δ = 0) : 18.9 (q), 23.9, 25.9, 28.3, 28.9, 38.7(q), 47.5 (q), 74.9 (s), 107.0 (s), 121.5 (d), 137.1 (s), 162.9 (s), 195.9 (s).

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7. 8 : obtained as a single isomer (Y : 98 %) - oil ; MS m/e (relative intensity) : $M^{+\cdot}$ 222 (5), 207 (3), 195 (10), 137 (100) ; ^1H NMR ($CDCl_3$, 60 MHz, TMS δ = 0) : 1.05 (3H, d, J : 6 Hz, H_3C-CH), 2.19 (3H, s, CH_3-CO), 2.40 (3H, s, CH_3N).

8. 9 : oil ; MS m/e (relative intensity) : $M^{+\cdot}$ 195 (100), 180 (14), 152 (50), 139 (50), 110 (80), 44 (100). UV $\lambda_{max.}^{EtOH}$ qualitative 236 nm ; ^1H NMR ($CDCl_3$, 60 MHz, TMS δ = 0) : 5.95 (1H, broad s, HC = C).

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10. The same kind of reaction was carried out in a recent synthetic approach to histrionicotoxin :
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11. 11 : oily products obtained as epimers (Y : 22 %, ratio 1 : 2.6).
major : MS m/e (relative intensity) : $M^{+\cdot}$ 239 (80), 209 (20), 196 (100), 194 (80) - ^{13}C NMR ($CDCl_3$, 15.08 MHz, TMS δ = 0) : 16.1 (q), 18.6, 20.1, 26.5 (q), 28.0, 29.6, 35.4, 36.5, 50.1, 59.4 (s), 64.2, 64.5, 110.2 (s)
minor : MS m/e (relative intensity) : $M^{+\cdot}$ 239 (100), 209 (30), 196 (50), 194 (10) - ^{13}C NMR : 14.6 (q), 18.1, 20.4, 27.9, 28.9, 30.5, 32.2 (q), 35.6, 37.2, 50.3, 59.0 (s), 63.8, 64.5, 110.6 (s).

12. 10 : oil (Y : 39 %), MS m/e (relative intensity) : 239 (100), 196 (100), 99 (50) - ^1H NMR ($CDCl_3$, 60 MHz, TMS δ = 0) : 1.0 (3H, d, J = 6Hz, H_3C-CH), 2.4 (3H, s, NCH_3), 4.00 (4H, s, OCH_2CH_2O), 5.4 (1H, m, H-C = C) ; ^{13}C NMR ($CDCl_3$, 22.63 MHz, TMS δ = 0) : 19.3 (q), 24.0, 27.7, 30.9, 32.4, 35.2, 36.5 (q), 40.5, 52.3, 64.3, 108.7 (s), 119.3 (d), 139.5 (s).

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