Tetrahedron Letters,Vol.30,No.41,pp 5655-5658,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

STEREOCONTROLLED SYNTHESIS OF 4- AND 9-ETHYL-2-AZABICYCLO[3.3.1]NONAN-7-ONES VIA 2-CYANOPIPERIDINES[1]

Josep Bonjoch*, Núria Casamitjana, Jordi Gràcia, and Joan Bosch*

Laboratory of Organic Chemistry, Faculty of Pharmacy,
University of Barcelona, 08028-Barcelona, Spain

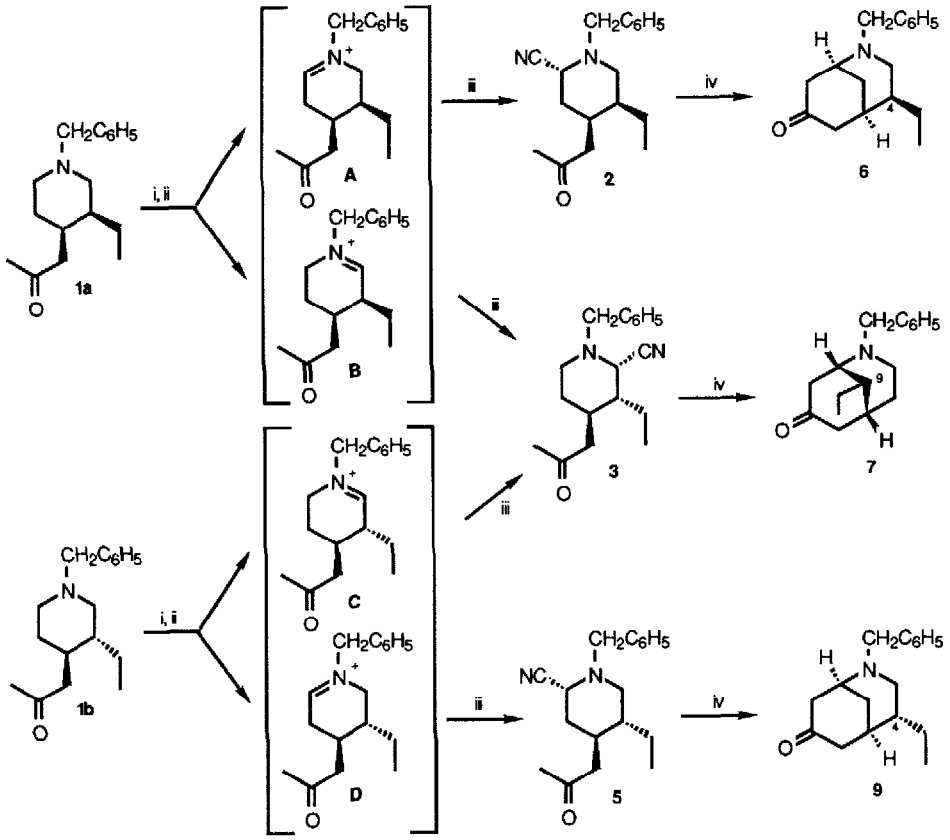
A stereoselective synthesis of 4- and 9-ethyl substituted morphans from 4-acetonyl-3-ethylpiperidines, involving the acidic cyclization of the corresponding 2-cyanopiperidines, is reported.

The intramolecular reactions of 2,3,4,5-tetrahydropyridinium intermediates have proven to be particularly useful for the synthesis of 2-azabicyclo-[3.3.1]nonanes (morphans) when a suitable side chain containing a properly located nucleophilic carbon is attached at C-4 of the piperidine ring. In this context the required iminium salts have generally been obtained by mercuric acetate oxidation of amines[2] or by protonation of enamines,[3] although in the last few years we have most efficiently employed[4] 2-cyanopiperidines for this purpose.[5,6]

Our interest in functionalized morphans lies in the fact that this bicyclic unit is present in the *Strychnos* indole alkaloids.[7] However, these alkaloids bear a two-carbon appendage (usually ethyl, cis with respect to the substituent at C-4 of the piperidine ring) either at the 4- (Strychnan type) or at the 9-position (Aspidospermatan type).

In order to obtain both 4- and 9-ethyl substituted morphans that would allow further access to the above-mentioned alkaloids,[8] we planned to study the preparation and the cyclization of the 2-cyanopiperidines derived from the *cis*-3,4-disubstituted piperidine **1a**, a compound for which we had previously developed a stereoselective synthesis.[9]

cis-Piperidine **1a** was converted in a 79% overall yield[10] into a mixture (5:3 ratio) of the cyanopiperidines **2** and **3**[11,12] by a one-pot, three step reaction sequence consisting of *N*-oxide formation, modified Polonovski reaction,[13] and trapping of the two possible regioisomeric iminium salts **A** and **B** with potassium cyanide[14] (Scheme 1). Not very surprisingly, cyanopiperidine **3** showed a trans-relationship between the substituents at the 3- and 4-positions, thus indicating that an epimerization at carbon 3 had occurred.[15] This epimerization can be rationalized by considering that, at the pH 4-5 required in the cyanation process, the iminium salt **B** is in equilibrium with the corresponding enamine and that the more stable trans 3,4-diequatorial disposition is reached.



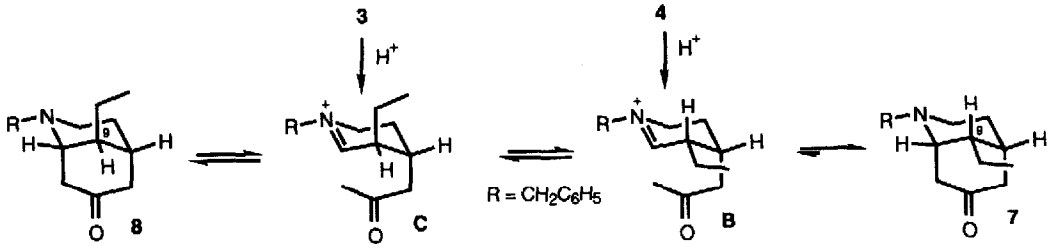
Scheme 1. Reagents: (i) m-CPBA, CH_2Cl_2, 0°C, 1 h; (ii) TFAA, -15°C, 1 h; (iii) aq KCN, NaOAc, pH 4-5, 30 min; (iv) 12N aq HCl-MeOH (1:9), 40 h, rfx.

As could be expected, treatment of cyanopiperidine **2** with hydrogen chloride in refluxing methanol afforded the Strychnan-type morphan **6** in 69% yield. A similar cyclization from cyanopiperidine **3**, having a wrong trans-relationship between the substituents at the 3 and 4 positions, gave bicyclo **7** in 68% yield. This compound possesses the correct Aspidospermatan-type

Table I. ^{13}C-NMR Data of 2-Cyanopiperidines 2-5[a]

Compound	C-2	C-3	C-4	C-5	C-6	CH_2-CO-CH_3			CN	CH_2-CH_3		CH_2Ar[b]
2	52.6	29.9	31.9	38.5	50.9	46.5	207.6	30.2	116.7	17.4	12.1	60.2
3	56.2	44.0	33.8	31.3	48.7	47.0	207.8	30.5	115.0	22.4	11.0	60.4
4	53.8	42.8	31.7	26.9	49.8	47.2	207.5	30.2	116.5	17.3	11.6	60.1
5	51.5	34.1	32.9	41.3	54.1	46.8	207.4	30.3	116.2	23.4	10.8	60.4

[a]Chemical shifts in ppm relative to TMS. Measured in $CDCl_3$ solution at 50.3 MHz. [b] Phenyl ring carbons were found (average values) at 137.0 (ipso-C), 128.8 (o-C), 128.5 (m-C), and 127.6 (p-C) ppm.



Scheme 2. Stereochemical Control in the Cyclization Step

relative stereochemistry at the bridge carbon, thus pointing out that a further epimerization has taken place during the cyclization step.

This unexpected, but desirable epimerization can be rationalized as shown in Scheme 2; cyclization of the trans-iminium salt **C** should necessarily occur through a conformation in which both piperidine substituents adopt an axial disposition. This cyclization would lead to bicyclo **8**, in which the bridge carbon 9 has a relative configuration opposite to that of natural products. However, this cyclization not only probably requires a high activation energy but also is reversible because the resulting product is a ß-amino ketone that can undergo a retro-Mannich reaction. This fact was experimentally proved as a pure sample of **8**, which had been obtained as a minor by-product in the cyclization, was almost completely converted into its more stable epimer **7** under acidic conditions. The iminium salt **C** epimerizes, through the corresponding enamine, to **B**, which cyclizes to the isolated bicyclic amino ketone **7**.

Operating as in the *cis* series, cyanation of *trans*-piperidine **1b** (Scheme 1) gave a mixture of the above 3,4-*trans* 2-cyanopiperidine **3** and its regioisomer **5** (3:5 ratio, 71% overall yield), whose cyclization afforded (61% yield) a separable mixture of morphans **7** and **9**.[16]

Table II. ^{13}C-NMR Data of 2-Azabicyclo[3.3.1]nonan-7-ones 6-9[a]

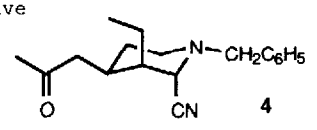
Compound	1-C	3-C	4-C	5-C	6-C	7-C	8-C	9-C	CH_2-CH_3		CH_2Ar[b]
6	53.9	51.2	40.9	32.2	41.9	211.5	40.5	34.2	23.9	11.3	59.1
7	58.0	44.3	32.7	31.8	42.4	211.7	35.9	42.6	23.9	11.7	59.4
8	55.9	44.6	26.4	32.2	48.4	211.8	40.4	43.1	23.3	12.2	59.5
9	54.6	47.3	41.9	33.1	48.5	211.6	40.1	28.7	25.4	12.4	59.5

[a]Chemical shifts in ppm relative to TMS. Measured in $CDCl_3$ solution at 50.3 MHz. [b]Phenyl ring carbons were found (average values) at 139.2 (ipso-C), 128.5 (o-C), 128.2 (m-C), and 126.9 (p-C) ppm.

ACKNOWLEDGMENT. Support for this research was provided by the DGICYT (Spain) through Grant PB 87-0062 and by the CIRIT (Catalonia) through Grant AR-88-100. Thanks are also due to the CIRIT for a fellowship given to one of us (J.G.).

REFERENCES AND NOTES

1. Functionalized 2-azabicyclo|3.3.1|nonanes. Part XII. For part XI in this series, see: Amat, M.; Sanfeliu, E.; Bonjoch, J.; Bosch, J. *Tetrahedron Lett.* **1989**, *30*, 0000.
2. (a) Bonjoch, J.; Casamitjana, N.; Bosch, J. *Tetrahedron* **1982**, *38*, 2883. (b) Bonjoch, J.; Casamitjana, N.; Quirante, J.; Rodríguez, M.; Bosch, J. *J. Org. Chem.* **1987**, *52*, 267. (c) Bonjoch, J.; Casamitjana, N.; Quirante, J.; Torrens, A.; Paniello, A.; Bosch, J. *Tetrahedron* **1987**, *43*, 377.
3. (a) Evans, D. A.; Mitch, C. H.; Thomas, R. C.; Zimmerman, D.; Robey, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 5955. (b) Burke Jr., T. R.; Jacobson, A. E.; Rice, K. C.; Weissman, B. A.; Huang, H.-C.; Silverton, J. V. *J. Med. Chem.* **1986**, *29*, 748.
4. (a) Bonjoch, J.; Casamitjana, N.; Bosch, J. *Tetrahedron* **1988**, *44*, 1735. (b) Bonjoch, J.; Quirante, J.; Rodríguez, M.; Bosch, J. *Tetrahedron* **1988**, *44*, 2087.
5. For other syntheses of functionalized 2-azabicyclo|3.3.1|nonanes also starting from piperidine derivatives, see: (a) by Dieckmann cyclization: Bosch, J.; Bonjoch, J. *J. Org. Chem.* **1981**, *46*, 1538. (b) by reductive rearrangement of enol lactones: Bosch, J.; Bonjoch, J.; Serret, I. *Tetrahedron Lett.* **1982**, *23*, 1297. (c) by α,α'-annelation of 2,5-piperidinediones: Bonjoch, J.; Quirante, J.; Serret, I.; Bosch, J. *Tetrahedron Lett.* **1989**, *30*, 1861. (d) see also reference 1.
6. For other syntheses of bridged azabicyclic compounds by cyclization of 2-cyanopiperidines, see: (a) Gnecco Medina, D. H.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1983**, *24*, 2099. (b) Lounasmaa, M.; Jokela, R.; Tamminen, T. *Tetrahedron Lett.* **1985**, *26*, 801.
7. Bosch, J.; Bonjoch, J. "Studies in Natural Products Chemistry", vol. 1, Atta-ur-Rahman, ed., Elsevier, Amsterdam, **1988**, pp 31-88.
8. For previous work in the deethyl series, see reference 2b.
9. Bonjoch, J.; Linares, A.; Guardià, M.; Bosch, J. *Heterocycles* **1987**, *26*, 2165.
10. This yield is significantly higher than those observed in similar reactions from tetrahydropyridines as in the latter series competing disproportionation processes of the dihydropyridinium intermediates occur: Grierson, D. S.; Vuilhorgne, M.; Husson, H.-P.; Lemoine, G. *J. Org. Chem.* **1982**, *47*, 4439.
11. There are no precedents for the formation of 2-cyanopiperidines starting from 1,3,4-trisubstituted piperidines. For the regiochemistry of this reaction on 1,3-disubstituted piperidines, see: (a) Jokela, R.; Tamminen, T.; Lounasmaa, M. *Heterocycles* **1985**, *23*, 1707. (b) Jokela, R.; Karvinen, E.; Tolvanen, A.; Lounasmaa, M. *Tetrahedron* **1985**, *44*, 2367.
12. For other procedures leading to 1,3,4-trisubstituted 2-cyanopiperidines, see: (a) by controlled reduction of 2-piperidones followed by cyanation : Glass, R. D.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 1324. (b) by nucleophilic addition of a soft carbanion to a 2-cyano-1,2,5,6-tetrahydropyridine followed by reintroduction of cyanide ion: Grierson, D. S.; Harris, M.; Husson, H.-P. *Tetrahedron* **1983**, *39*, 3683 and references therein; Koskinen, A.; Lounasmaa, M. *J. Chem. Soc. Chem. Commun.* **1983**, 821; Chapman, R. F.; Philips, N. I. J.; Ward, R. S. *Tetrahedron* **1985**, *41*, 5229.
13. Lounasmaa, M.; Koskinen, A. *Heterocycles* **1984**, *22*, 1591.
14. (a) Groutas, W. C.; Essawi, M.; Portoghese, P. S. *Synth. Commun.* **1980**, *10*, 495. (b) Grierson, D. S.; Harris, M.; Husson, H.-P. *J. Am. Chem. Soc.* **1980**, *102*, 1064. (c) Lounasmaa, M.; Karvinen, E.; Koskinen, A.; Jokela, R. *Tetrahedron* **1987**, *43*, 2135.
15. The epimeric cyanopiperdine **4**, with retention of the relative configuration at C-3, was formed in a yield lower than 5%.



4

16. (a) The structure assigned to each new compounds is in accord with its infrared, 200-MHz ^{1}H-, and 50-MHz ^{13}C-NMR spectra. (b) In addition, an analytical sample of the new compounds (**2**, **3**, **6-9**) gave satisfactory C, H, and N combustion analyses.

(Received in UK 4 August 1989)