Tetrahedron Letters, Vol.32, No.48, pp 7127-7130, 1991
Printed in Great Britain

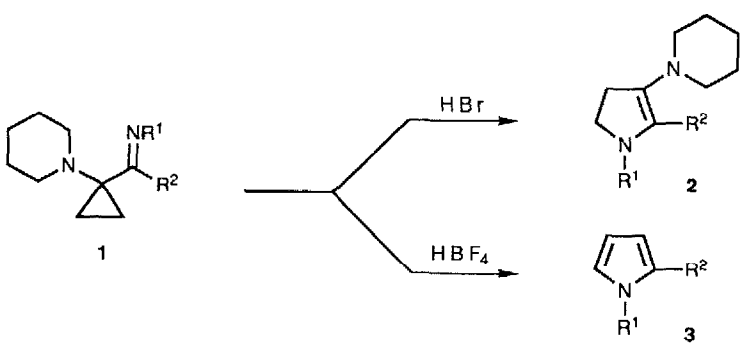
0040-4039/91 $3.00 + .00
Pergamon Press plc

A MECHANISTIC STUDY OF PYRROLE FORMATION IN THE HBF_4-CATALYZED THERMOLYSIS OF CYCLOPROPYL KETIMINES.

Harry H. Wasserman* and James M. Fukuyama†
Department of Chemistry, Yale University, New Haven, CT 06511 USA

Summary: A study of the HBF_4-catalyzed rearrangement of 1-(1-piperidino)cyclopropyl ketimines to 2-substituted pyrroles has been conducted using carbon-13 labeled starting material. The results support the formation of a bicyclic aziridine-containing intermediate.

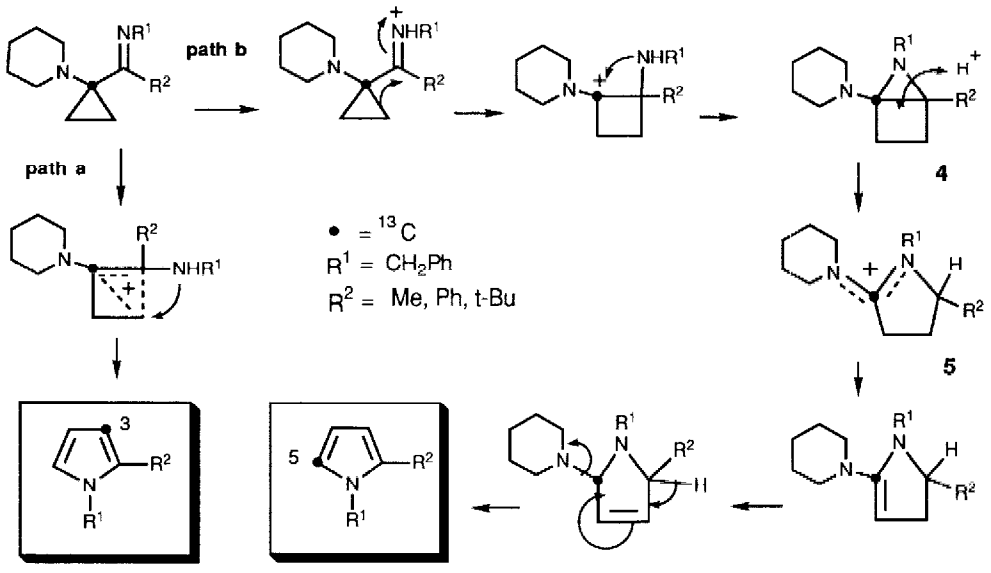
In a previous communication,[1] we reported that the HBF_4-catalyzed rearrangement of 1-(1-piperidino)cyclopropyl ketimines **1** leads to 2-substituted pyrroles **3** (Scheme 1). The reaction is related to the HBr-catalyzed cyclopropyl ketimine rearrangement [2,3] which, with **1** yields 2-pyrroline derivatives **2** in the presence of the nucleophilic (bromide) counterion. When a *non-nucleophilic* counterion (BF_4^-) is used, pyrrole formation (**3**) takes place in both alkyl and aryl cases.[4]



Scheme 1

Two pathways have been considered for this rearrangement.[4] In path **a** (Scheme 2), the bridged ion, formed on protonation, undergoes a bond reorganization analogous to the vinyl cyclopropane rearrangement by attack of the benzylamino group at one of the methylene groups of the cyclopropane. The resulting ring opening would yield a pyrroline which could then be converted to the pyrrole by acid-catalyzed loss of the piperidino group. In path **b**, a cyclopropyl carbinyl cation rearranges to the cyclobutyl ion, stabilized by the adjacent piperidino group. Attack of the neighboring benzylamino group produces a bicyclic intermediate **4** which undergoes ring-opening in acid to form the highly stabilized carbonium ion **5**. Loss of a proton from **5**, double bond shift in acid and loss of piperidine would yield the pyrrole.

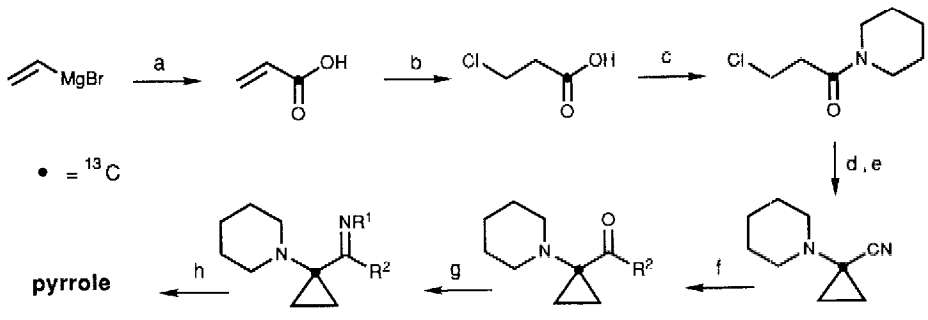
Scheme 2



We sought to distinguish between these two mechanisms using 1-(1-piperidino)cyclopropyl ketimines derived from 1-cyano-1-(1-piperidino)cyclopropane enriched with carbon-13 at the 1-position. Depending upon the pathway followed, the resulting pyrrole product would be ^{13}C-enriched either at the 3-position (path **a**) or the 5 position (path **b**).

The enriched material was prepared using $BaCO_3$ (90%^{13}C) as the carbon-13 source and the pyrrole syntheses carried out as outlined in Scheme 3.[5] An analysis of the 1-cyano-1-(1-piperidino)cyclopropane starting material was consistent with 90% ^{13}C enrichment of the 1-carbon of the cyclopropane ring (39.9ppm).

Scheme 3



a: $Ba^{13}CO_3$, H_2SO_4, -78°C; b: HCl; c: DCC, piperidine; d: Na, Et_2O, TMSCl; e: KCN, AcOH; f: R^2Li, H_3O^+; g: R^1NH_2; h: $HBF_4{\cdot}OMe_2$

Table 1 lists the observed ^{13}C NMR peaks for the three pyrroles formed in this study, and the assignment to the ring carbon atoms 2, 3, 4 and 5. In each case, the ^{13}C absorption corresponding to the 5-position of the substituted pyrrole was strikingly enhanced in accord with 90% isotopic enrichment at that site. The chemical shift assignments were determined by coupled and decoupled ^{13}C spectra and are in agreement with the substituent chemical shift effects proposed by Abraham[6] for substituted pyrroles.

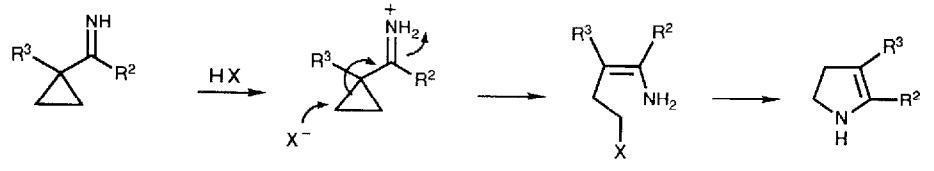
Table 1. Carbon-13 Chemical Shifts

Pyrrole R^2 Substituent	Enhanced Signal (ppm)	C(2)	C(3)	C(4)	C(5)
-t-Bu	115.9	141.8	102.4	107.9	115.9
-Ph	118.9	132.1	105.9	110.0	118.9
-Me	116.2	127.4	105.8	108.3	116.2
-Me[a]	------	128.6	106.4	108.7	115.6

a: values obtained from reference 6

The above results are clearly in accord with mechanism **b** involving the bicyclic intermediate **4** formed by a well-precedented cyclopropyl carbinyl cation rearrangement followed by intramolecular attack by the neighboring secondary amino group. This pathway is thus favored in the absence of a good nucleophilic counterion which can open the cyclopropyl group by the displacement reaction pictured in Stevens' mechanism (Scheme 4).[2]

Scheme 4



Acknowledgment: This work was supported by NIH Grant GM-07874.

References

† From the Ph.D. dissertation of J.M. Fukuyama, Yale University, 1986.

1. Wasserman, H.H. ; Dion, R.P. *Tetrahedron Lett.* **1983**, *24*, 3409.
2. For a review see (a) Stevens, R.V. *Acc. Chem. Res.* **1977**, *10*, 193, and references therein. (b) Boeckman, Jr., R.K.; Jackson, P.F.; Sabatucci, J.P. *J. Am. Chem. Soc.* **1985**, *107*, 2191.
3. For similar rearrangements, see (a) Quast, H. ; von der Saat, W.; Stawitz, J. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 588. (b) Blake, K.W.; Gillies, I.; Denney, R.C. *J. Chem. Soc, Perkin Trans. 1*, **1981**, 700.
4. Wasserman, H.H. ; Dion, R.P.; Fukuyama, J.M. *Heterocycles* **1989**, *28*, 629.
5. (a) Moureu, C.; Chaux, R. *Org. Syn. Coll. Vol. 1*, **1941**, 166. (b) Beck, J.R.; Kwok, R.; Booher, R.N.; Brown, A.C.; Patterson, L.E.; Pranc, P.; Rockey, B.; Pohland, A. *J. Am. Chem. Soc.* **1968**, *90*, 4706. (c) Wasserman, H.H.; Dion, R.P. *Tetrahedron Lett.* **1982**, *23*, 1413. (d) Dion, R.P. Ph.D. Thesis, 1983, Yale University.
6. Abraham, R.J.; Lapper, R.P.; Smith, K.M.; Unsworth, J.F. *J. Chem. Soc. Perkin Trans II*, **1974**, 1004.

(Received in UK 9 October 1991)