

SYNTHESIS OF 3-AZABICYCLO (4.1.0.) HEPTANES VIA RADICAL CYCLISATION
OF N-CHLORO β -METHYLENENCYCLOPROPYL AMINE

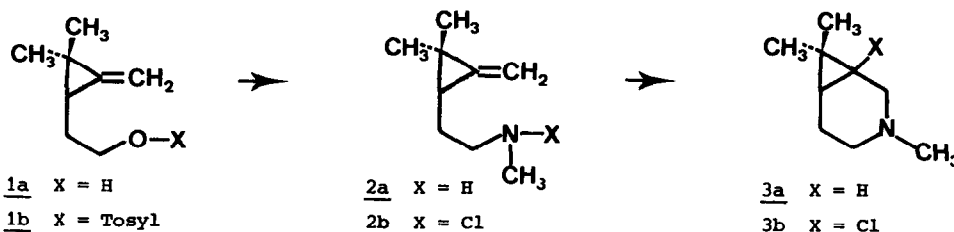
Jean-Louis STEIN, Lucien STELLA, Jean-Marie SURZUR*

Laboratoire de Chimie Organique B, associé au CNRS (LA 109)
Faculté des Sciences (St Jérôme) - 13397 Marseille Cedex 4 - France

Summary : The N-chloro β -methylenecyclopropyl amine leads to 1-aza 3-chloro bicyclo (4.1.0) heptane by an unusual regioselective radical cyclisation.

The use of N-chloroamines in the synthesis of azaheterocyclic compounds related to alkaloids (pyrrolizidine, indolizidine, benzomorphone) ⁽¹⁾ has been described in recent years. The key step, the intramolecular addition of an aminyl radical to an olefinic double bond, is highly regioselective towards the *exo*-product. Such a regioselectivity is in agreement with Baldwin's rules ⁽²⁾ and with the general behaviour of oxygen- and unstabilized carbon-centered radicals, which add irreversibly ⁽³⁾.

We wish to report now an example of intramolecular addition to a methylenecyclopropyl group leading exclusively, by *endo*-cyclisation, to bicyclic (4.1.0) products 3.



The tosylate 1b ⁽⁴⁾ of the β -methylenecyclopropanic alcohol 1a ⁽⁵⁾ is converted into the secondary amine 2a ⁽⁶⁾ on standing for 4 days at 100° in a methanolic solution of methylamine {60%, bp 64°/15 Torr, δ (CDCl₃) 0.76 ppm (s, 1, NH), 1.08 ppm (s, 3, CH₃), 1.16 ppm (s, 3, CH₃), 0.9-1.25 ppm (m, 1), 1.3-1.7 ppm (m, 2), 2.34 ppm (s, 3, NCH₃), 2.60 ppm (t, 2, NCH₂), 5.20 ppm (s, 2, =CH₂)}. N-chlorination ⁽⁷⁾ gives 2b {98%, bp 26°/0.15 Torr, λ_{\max} (C₆H₁₂) 275 nm}.

Slow addition of 15% aqueous titanium trichloride solution (9 mmole, -5°, nitrogen stream) to a 1:1 acetic acid-water solution of N-chloroamine 2b (46 mmole) leads to a mixture of amine 2a (8%) and 1-aza 3-chloro bicyclo (4.1.0) heptane 3b resulting from intramolecular addition of the metal-complexed aminyl radical ⁽⁸⁾ {(55%, m/e 173, δ (CDCl₃) 0.9-1.3 ppm (m, 1) 1.30 ppm (s, 6, 2CH₃), 2.16 ppm (s, 3, NCH₃), 2-2.17 ppm (m, 2), 2.3-2.5 ppm (m, 2), 2.48 ppm (d, 1, 11.5 Hz), 3.2 ppm (d, 1, 11.5 Hz)}.

When treated with tributyl-tin hydride in boiling benzene containing catalytic amounts of azo-bis-isobutyronitrile, the chloride 3b is smoothly reduced into 3a { (m/e 139, δ (CDCl₃) 0.5-0.7 ppm (m, 2), 0.96 ppm (s, 3, CH₃), 1.14 ppm (s, 3, CH₃), 1.5-1.9 ppm (m, 2), 2.05 ppm (s, 3, NCH₃), 2.15-2.4 ppm (m, 3), 2.76 ppm (d, 1, 11.5 Hz)} .

Similarly, photolysis of the N-chloroamine 2b in methanolic solution (UV lamp HANAU TQ 81, 85W, 180 min., -6°) leads, via the neutral aminyl radical ⁽⁹⁾, to a mixture of amine 2a (26%) and bicyclic compounds 3a (5.5%) and 3b (18%).

Normally, neutral ⁽⁹⁾, protonated ⁽¹⁰⁾ or metal-complexed ⁽⁸⁾ aminyl radicals located in the 4-position relative to an olefinic double bond lead to pyrrolidinic systems. In the present case, molecular models show clearly that the five-membered ring transition state is disfavoured by the rigid dimethyl-cyclopropane bridge. Although steric effects are known to alter the regioselectivity ⁽¹¹⁾, such a complete change seems to be quite unusual ⁽³⁾.

These results may be contrasted with the intramolecular addition of cyclopropyl radicals which leads by the expected *exo*-cyclization to bicyclic (3.1.0) systems ⁽¹²⁾. Since ionic addition to methylene cyclopropane might lead to rearrangement reactions, this radical ring closure appears to be useful for the synthesis of various substituted azabicyclic (4.1.0) compounds.

Acknowledgment : We wish to thank Professor Marcel Bertrand for his interest in this work and for valuable discussions.

References

- 1 - J-M. Surzur and L. Stella, *Tetrahedron Lett.*, 2191 (1974) ; L. Stella, B. Raynier and J-M. Surzur, *Tetrahedron Lett.*, 2721 (1977).
- 2 - J.E. Baldwin, *Chem. Comm.*, 734 (1976).
- 3 - For recent reviews see : A.L.J. Beckwith in "Essays on Free Radical Chemistry", Chem. Soc. Special Publ. n°24, p. 239, London, 1970 ; M. Julia, *Acc. Chem. Res.*, 4, 386 (1971) ; M. Julia, *Pure Appl. Chem.*, 40, 553 (1974) , A.L.J. Beckwith and K.U. Ingold, in "Molecular Rearrangements" 2nd ed. ; P. de Mayo ed., Ac. Press., New York, in press ; J-M. Surzur in "Reactive Intermediates", R. Abramovitch ed., Plenum, New York, in press.
- 4 - L.F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, J. Wiley, New York, 1967, p.1180.
- 5 - G. Leandri, H. Monti and M. Bertrand, *Bull. Soc. Chim. Fr.*, 3015 (1974).
- 6 - For all new compounds N.m.r., i.r. and mass spectra were consistent with the proposed structure.
- 7 - J.K. Kerwin, M.E. Wolf, F.F. Owings, B.B. Lewis, B. Blank, A. Magnani, C. Kharash and Y. Georgian, *J. Org. Chem.*, 27, 3628 (1962).
- 8 - J.M. Surzur, L. Stella and P. Tordo, *Bull. Soc. Chim. Fr.*, 115 (1970).
- 9 - J.M. Surzur, L. Stella and P. Tordon *Tetrahedron Lett.*, 3107 (1970).
- 10 - J.M. Surzur, L. Stella and P. Tordo, *Bull. Soc. Chim. Fr.*, 1425 (1975).
- 11 - A.L.J. Beckwith, I.A. Blair and G. Phillipou, *Tetrahedron Lett.* 2251 (1974) ; M. Julia, C. Descoins, M. Baillarge, B. Jacquet, D. Uguen and F.A. Groeger, *Tetrahedron*, 31, 1737 (1975).
- 12 - C. Descoins, M. Julia and H. Van Sang, *Bull. Soc. Chim. Fr.*, 4087 (1971).

(Received in France 2 November 1979)