Tetrahedron Letters, Vol. 33, No. 25, pp 3633-3636, 1992
Printed in Great Britain

0040-4039/92 $5.00 + (
Pergamon Press Ltd

1-BROMOALKYNES AS π-NUCLEOPHILES IN ACYLIMINIUM ION CYCLIZATIONS. A FORMAL SYNTHESIS OF LUPININE AND EPILUPININE.

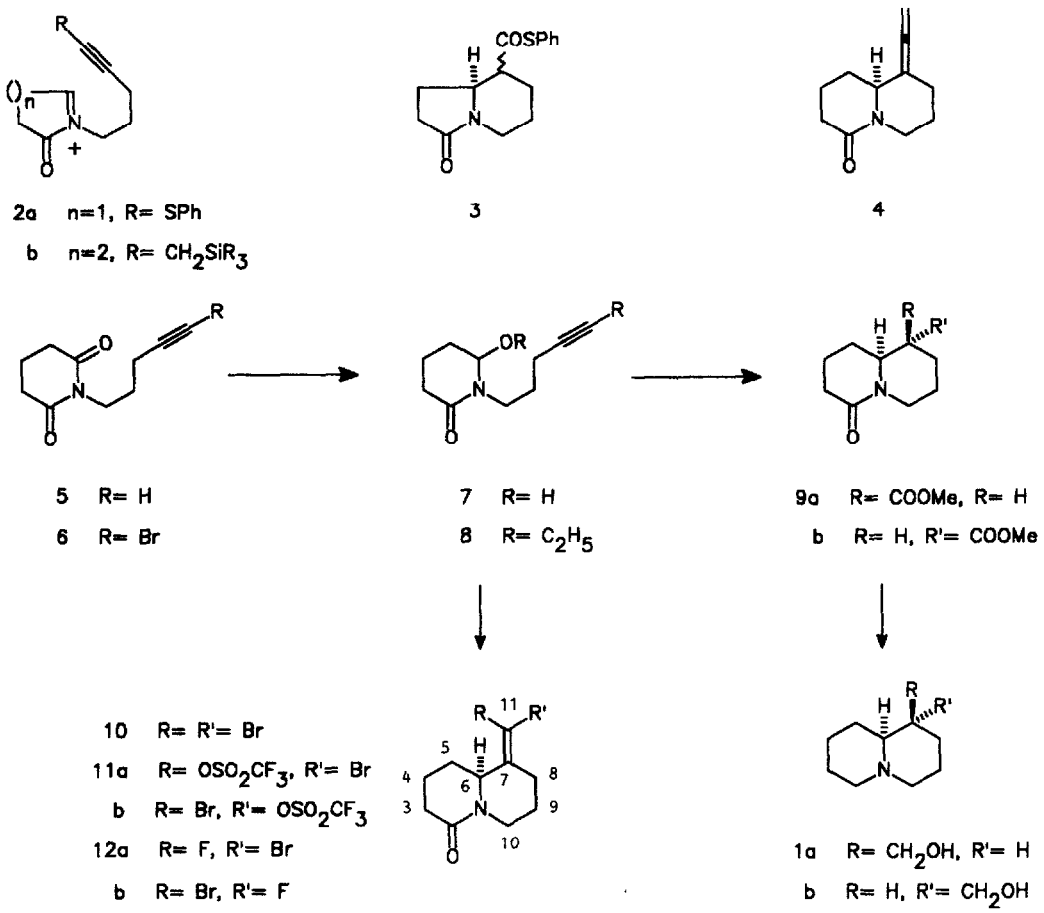
J.P. Gesson,* J.C. Jacquesy and D. Rambaud
Laboratoire de Chimie XII, associé au CNRS
40, avenue du Recteur Pineau, 86022-Poitiers (France)

Abstract: *The use of a 1-bromoalkyne as π-nucleophile in the α-N-acyliminium ion cyclization of a glutarimide derivative results in the formation of a single bromoenol triflate **11** in triflic acid-trifluoroacetic acid and of a mixture (E/Z: 4/1) of bromofluoro derivatives **12a,b** in HF. **11** is quantitatively converted to esters **9a,b** which are also obtained after trifluoroacetic acid treatment and methanolysis. **9a,b** are known precursors of lupinine and epilupinine.*

Introduction: The cyclization of α-N-acyliminium ions with various π-nucleophiles is one of the reaction most important for the construction of numerous alkaloid structures. Speckamp and Hiemstra have reviewed the aspects of this reaction which has been mainly applied to iminium ions generated from cyclic imides such as glutarimide (or succinimide) derivatives.[1] The heterocycles thus obtained are obvious precursors of quinolizidine (or indolizidine) alkaloids such as, for example, lupinine **1a** and epilupinine **1b**, two aminoalcohols which are popular targets used to illustrate methodologies developed for the construction of the 1-aza-bicyclo-[4.4.0]-decane skeleton.[2]

The use of alkynes as terminators in such cyclizations has been already studied by Speckamp who has shown that if terminal alkynes afford ketones arising from endo-type ring closure, other substituted alkynes lead to a mixture of ketones (from endo or exo-type) depending on ring strain and stability of the intermediate vinyl cations.[3] Only in the case of electronically biased alkynes **2** with R= SPh[4] or CH_2-SiR_3[5] are 5-endo or 6-exo dig cyclizations cleanly observed to give in the first case a phenylthio ester **3** (HCOOH, 20°C, 18h) and in the second one an exocyclic allene **4** (CF_3COOH-CH_2Cl_2, -20°C, 2h).

The easy preparation of 1-bromoalkynes together with their expected higher stability in more acidic conditions leads us to investigate their behavior in such cyclizations. Initial results obtained in the glutarimide series are described here. The required alkyne **5** has been already prepared from glutarimide and 1-chloro-4-pentyne in high yield using solid PTC.[6] Bromination to **6**[7] is best carried out by the method of Hofmeister[8] ($AgNO_3$ cat., NBS, anhydrous acetone) in 91% yield. Subsequent reduction by $NaBH_4$ affords the hydroxylactam **7**[7] (88-96%) by the method of Chamberlin[9] or the ethoxylactam **8**[7] (93%) by the method of Speckamp.[10] These two lactams are then submitted to various acidic conditions.



Trifluoroacetic acid induced cyclization:

Treatment of **7** (or **8**) with CF_3COOH (50 eq., 20°C, 2h) followed by addition of excess MeOH and heating (reflux, 3h) affords a mixture of esters **9a,b** in a 45/55 ratio (60%) which can be equilibrated to 68/32 by cat. MeONa in MeOH. When the same reaction is conducted in CF_3COOH (4 eq.)-CH_2Cl_2 followed by methanolysis, the above mixture of esters **9a,b** is obtained in only 13% yield together with the dibromoalkene **10**[7] (26%). The unexpected formation of the latter may be explained by *in situ* decomposition of the intermediate bromoenol trifluoroacetate to liberate a bromide ion.

Trifluoroacetic acid/Triflic acid induced cyclization:

Since lowering the acidity of the CF_3COOH medium by addition of acetic acid resulted only in enamide formation, enhancing the acidity by addition of triflic acid was then considered (H_0= -7).[11] Thus treatment of **7** with CF_3SO_3H (2 eq.)-CF_3COOH (8 eq.) in CH_2Cl_2 (20°C, overnight) affords, after evaporation in vacuo and extraction with CH_2Cl_2, **11**[7] as an oil in 70% isolated yield. The formation of this stable bromoenol triflate in a stereospecific manner is particularly noteworthy. Although the gross structure of **11**

is consistent with ^{1}H and ^{13}C NMR, IR and MS, the unambiguous determination of the double bond stereochemistry (*i.e.* **11a** or **11b**) is more difficult since, to our knowledge, no bromoenol triflate has been reported in the literature. Comparison of the NMR spectra of the dibromo derivative **10** with that of **11** show similar sp_3 carbon signals apart from one (δ 25.6 or 27.1 ppm for **10** and 22.4 ppm for **11**) which may be assigned to C-5 and a shielding of the pseudo-axial H-6 in **11** (δ 4.20, dd, J= 11.2 and 4.3 Hz) compared to **10** (δ 4.42, dd, J= 11.1 and 4.2 Hz). Taking into account these observations and the NMR signals of the bromofluoro derivatives obtained in HF (*vide infra*), it may be assumed that an E configuration is the most probable for **11** (*i.e.* **11a**). Treatment of **11** with MeONa in MeOH quantitatively gives esters **6a,b** in a 32/68 ratio.

HF induced cyclization:

Anhydrous HF (H_0= -10) is also able to promote the cyclization of **7** (or **8**) to give after 3h at 0°C an unseparable mixture of the bromofluoro derivatives **12a,b**[7] (53%) in a 4 to 1 ratio as judged by NMR. The major isomer, **12a**, is characterized by a signal for H-6 at 4.13 ppm (dd, J= 11.2 and 4.4 Hz), while **12b** shows the same signal at 4.58 ppm (partly hindered by H-10). The signals observed for C-6 and C-8 are noteworthy: 59.6 ppm (d, J= 2.5 Hz) for C-6 and 26.4 ppm (d, J= 4 Hz) for C-8 for **12a** and 57.3 (d, J= 4 Hz) and 27.6 (d, J= 3 Hz) for **12b**. The expected higher value for ^{3}J trans[12] probably refers to the major isomer **12a** as E, an assumption which is difficult to confirm by the observed chemical shifts of C-6 and C-8. It is also interesting to note that C-5 appears as a doublet (J= 3 Hz) at 21.6 ppm for **12a**, while a singlet is observed for **12b** at 23.4 ppm.

Discussion: The preliminary results described here show that a readily available 1-bromoalkyne may be a good terminator in α-N-acyliminium ion cyclizations. The deactivation of the alkyne moiety allows the use of more acidic conditions leading to different cyclized products depending on the nucleophile. Usually cyclization with alkynes is supposed to be a concerted process (trans addition),[13] but the stereochemistry of addition of anhydrous acids to alkynes is variable. For example addition of HCl to 3-hexyne is trans[14] while addition of CF_3COOH is not stereospecific.[15] In the case of a stabilized vinylic carbenium ion[16] the stereochemistry may be different: addition of HCl to 1-phenylpropyne occurs mainly cis.[17] The possible reversible trapping of the intermediate vinylic carbenium ion under these conditions (which may explain the formation of the more stable isomers) needs to be further studied as well as the chemistry of the unusual bromoenol triflate isolated from a triflic acid/trifluoroacetic acid medium.[18] Finally the formation of esters **6a,b,** which have been already reduced to lupinine and epilupinine,[9,19] represents a formal synthesis of these alkaloids in only 6 steps from glutarimide and 1-chloro-4-pentyne (37 % overall yield)

Acknowledgments: We thank CNRS and Pierre Fabre Médicaments, Castres for financial support and Dr. D. Bigg and Dr. J.F. Patoiseau (PF Med.) for helpful discussions.

REFERENCES AND NOTES

1. Speckamp, W.N.; Hiemstra, H. *Tetrahedron*, **1985**, *41*, 4367.
2. (a) Célérier, J.P.; Haddad, M.; Saliou, S.; Lhommet, G.; Dhimane, H.; Pommelet, J.C.; Chuche, J. *Tetrahedron*, **1989**, *45*, 6161. (b) Morley, C.; Knight, D.; Share, A.C. *Tetrahedron:Asymmetry*, **1990**, *1*, 147 and references cited therein.
3. Schoemaker, H.E.; Boer-Terpstra, Tj.;Dijkink, J.; Speckamp, W.N. *Tetrahedron*, **1980**, *36*, 143. Hamersma, J.A.M.; Nossin, P.M.M.; Speckamp, W.N. *Tetrahedron*, **1985**, *41*, 1999.

4. Nossin, P.M.M.; Speckamp, W.N. *Tetrahedron Lett.* **1979**, *20*, 4411.
5. Hiemstra, H.; Speckamp, W.N. *Tetrahedron Lett.* **1983**, *24*, 1407.
6. Gesson, J.P.; Jacquesy, J.C.;Rambaud, D. *Bull.Soc.Chim.Fr.* in press.
7. All new compounds have been characterized by ^1H (200 MHz) and ^{13}C NMR (50.3 MHz), IR, MS and HRMS or elemental analysis. Selected NMR data ($CDCl_3$, TMS as internal standard, J in Hz) of new compounds are given below.
6: ^1H NMR: δ 1.76 (p, 2H, J= 7, H-2'), 1.95 (m, 2H, J= 6.4, H-4), 2.24 (t, 2H, J= 7, H-3), 2.66 (t, 4H, J= 6.4, H-3) and 3.84 (t, 2H, J= 7, H-1') ppm.
7: ^1H NMR: δ 3.36 (m, 1H, J= 6.8, H-1'), 3.69 (m, 1H, J= 6.8, H-1') and 4.99 (s, 1H, H-6) ppm.
8: ^1H NMR: δ 1.24 (t, 3H, J= 7.5, CH_3), 3.26 (m, 1H, J= 14 and 7, H-1'), 3.52 (m, 2H, J= 8, H-7), 3.63 (dt, 1H, J= 14 and 7, H-1') and 4.60 (m, 1H, H-6) ppm.
10: ^1H NMR: δ 2.83 (dd, 1H, J= 7.8 and 12, H-10ax), 4.42 (dd, 1H, J= 4.2 and 11.1, H-6), 4.59 (dd, 1H, J= 8.2 and 12, H-10eq) ppm. ^{13}C NMR: δ 168.9 (C-2), 143.8 (C-7), 83.6 (C-11), 62.8 (C-6), 37.8 (C-10), 31.5 (C-3), 27.1 (C-5 or C-8), 25.6 (C-8 or C-5), 21.6 (C-9), 19.8 (C-4) ppm.
11: ^1H NMR: δ 2.73 (dd, 1H, J= 12 and 8.1, H-10ax), 4.20 (dd, 1H, J= 11.2 and 4.3, H-6ax) and 4.55 (dd, 1H, J= 12 and 8, H-10eq) ppm. ^{13}C NMR: δ 168.2 (C-2), 138.8 (C-7), 118.3 (q, J= 319, CF_3), 114.6 (C-11), 61.1 (C-6), 38.1 (C-10), 31.7 (C-3), 25.9 (C-5 or C-8), 22.4 (C-5 or C-8), 21.9 (C-9) and 20.1 (C-4) ppm.
12a,b: ^1H NMR: δ 2.78 (dd, 1H, J= 12 and 7.7, H-10ax), 4.13 (dd, 0.8H, J= 11.2 and 4.4, H-6ax**a**) and 4.58 (dd, 1.2H, J= 12 and 8, H-10eq and H-6ax**b**) ppm. ^{13}C NMR: δ 169.3 (C-2), 131.6 (C-7), 122.5 (d, J= 286) and 122.4 (d, J= 297) (C-11), 59.6 (d, J= 2.5, C-6**a**), 57.3 (d, J= 4, C-6**b**), 38.6 and 38.0 (C-10), 31.9 and 31.7 (C-3), 27.6 (d, J= 3, C-8**b**), 26.4 (d, J= 4, C-8**a**), 23.4 (C-5**b**), 21.7 (d, J= 3 , C-5**a**), 20.0 and 19.9 (C-9) and 19.2 and 19.1 (C-4) ppm.
8. Hofmeister, H.; Annen, C.; Laurent, H.; Wiechert, R. *Angew.Chem.Int.Ed.Engl.* **1984**, *23*, 727.
9. Chamberlin, A.R.; Nguyen, H.D.;Chung, J.Y.L. *J.Org.Chem.* **1984**, *49*, 1682.
10. Hubert, J.C.; Wijnberg, J.B.P.A.; Speckamp, W.N. *Tetrahedron,* **1975**, *31*, 1437.
11. Ohwada, T.;Yamagata, N.;Shudo, K. *J.Am.Chem.Soc.* **1991**, *113*, 1364.
12 Breitmaeir, E.; Voelter, W. *Carbon-13 NMR Spectroscopy;* VCH: Weinheim; New-York. 1987.
13. Stang, P.J. *Progress in Physical Organic Chemistry,* **1973**, *10*, 205.
14. Fahey, R.C.; Lee, D.J. *J.Am.Chem.Soc.* **1967**, *89*, 2780.
15. Peterson, P.E.; Duddey, J.E. *J.Am.Chem.Soc.* **1966**, *88*, 4990.
16. Fahey, R.C.; Lee, D.J. *J.Am.Chem.Soc.* **1966**, *88*, 5555.
17. Hanack, M. *Acc.Chem.Res.* **1976**, *9*, 364.
18. The structure of the intermediate vinylic carbenium ion may be either linear or bent.[13,17] Addition of the nucleophile on the less hindered face of a linear carbenium ion or addition on the more stable bent carbenium ion will produce the same isomer: **11a** or **12a**.
19. Okita, M.; Wakamatsu, T.; Ban, Y. *Heterocycles,* **1983**, *20*, 401.

(Received in France 19 February 1992)