Tetrahedron Vol. 48, No. 41, pp. 8947-8952, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Flash Vacuum Thermolysis of Oxazolidines : a New Way to Reactive Azomethine Ylids. Intramolecular Cycloaddition Reactions towards Pyrrolizidines Synthesis.

Ronan Bureau[a], Jacques Mortier[b] and Marc Joucla*[c]

a. Groupe de physicochimie structurale associé au CNRS, Université de Rennes I, Campus de Beaulieu, 35042 Rennes, France.

b. Present address : Rhône-Poulenc Agrochimie 14-20 rue Pierre Baizet BP 9163, 69263 Lyon, France.

c. Present address : Unité mixte CNRS / Rhône-Poulenc, Rhône-Poulenc Industrialisation, 24 rue Jean Jaurès BP 166, 69151 Décines Charpieu, France.

(*Received in Belgium* 15 *July* 1992)

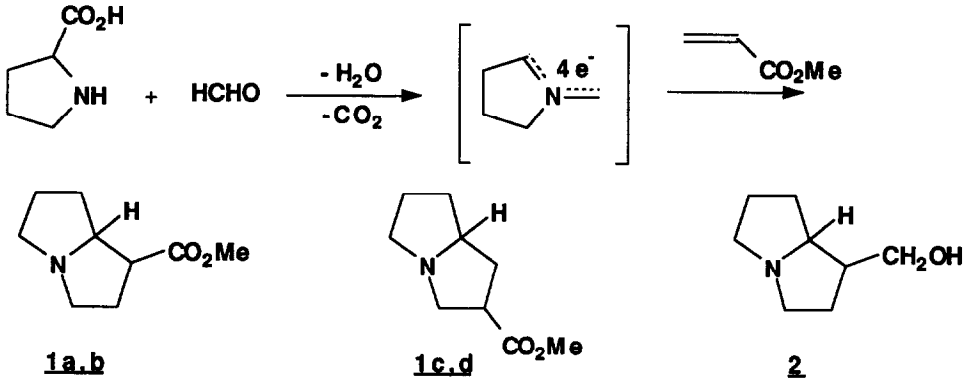
Key words : 1,3-dipolar cycloaddition ; 1,3-dipolar cycloreversion ; oxazolidines ; azomethine ylids ; flash vacuum thermolysis.

Abstract : The flash vacuum thermolysis of oxazolidines followed by an intramolecular cycloaddition reaction allowed an orientation towards the synthesis of dihydroxy pyrrolizidines compounds.

In the past decade azomethine ylids have received more attention as reactive synthons to build-up five membered heterocycles. Several new methods have appeared to prepare these intermediates and they have been fully reviewed [1, 2, 3]. In contrast few examples have been described involving an azomethine ylid cycloaddition reaction as the key step in the synthetic sequence.

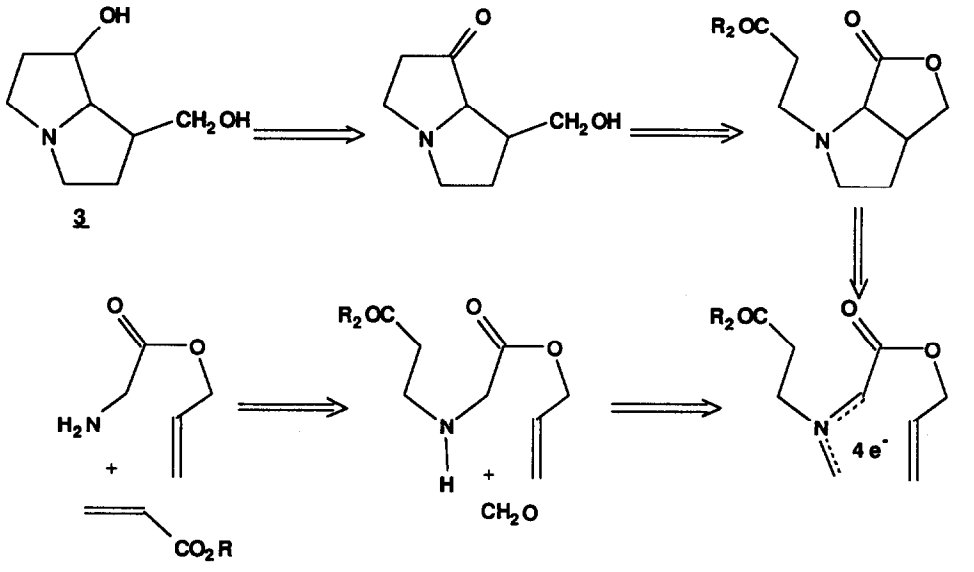
To our knowledge four examples of the intramolecular reaction are known for allokaïnic acid [4], α-lycorane [5], eserethole [6] and (-) kaïnic acid [7] synthesis.

Since aminoacids react with carbonyl derivatives to give azomethine ylids by loss of water and carbon dioxide [8, 9], we carried out the reaction of proline, formaldehyde and methylacrylate. The reaction worked well in benzene at reflux and we recovered in a quantitative yield pyrrolizidine **1** as a mixture of four stereo and regio isomers (25 / 25 / 25 / 25) .**1a,b** compounds could be valuable intermediates to isoretronecanol and trachelanthamidine alkaloïds **2** synthesis[10].

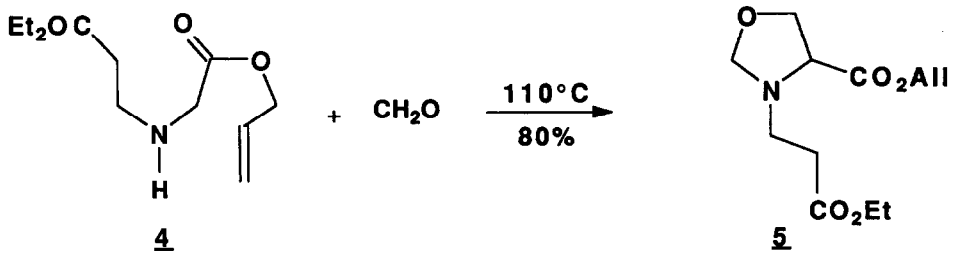


To overcome this lost of selectivity we looked at the intramolecular cycloaddition reactions to build up in a selective way the pyrrolizidine ring. As a model we chose the dihydroxy pyrrolizidine family **3** to which hastanecine, turneforcidine, platynecine and dihydroheliotridane belong.

The retrosynthetic scheme is as follows :



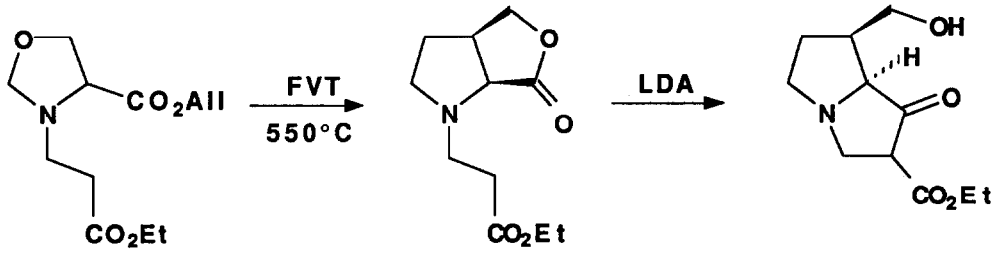
Michaël-type addition of allylic ester of glycine on ethyl acrylate led to 95% of recovered aminoester **4**. The reaction of **4** with an excess of formaldehyde gave rise to oxazolidine **5** rather than the cycloadduct **6** at reflux of toluene (80%).



4 5

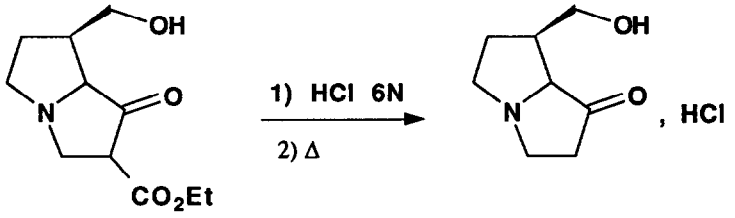
Flash vacuum thermolysis of oxazolidine 5 [11, 12, 13, 14] led to pyrrolidine 6 (82%) . As we expected, we observed a good stereo and regioselectivity of the cycloaddition and only one diastereoisomer was obtained. The temperature of thermolysis is of great importance to obtain 6 in a good yield.

The Dieckmann condensation [15] used to transform pyrrolidine 6 into pyrrolizidine 7 was better achieved in dry THF using excess LDA as the base. Other bases like sodium ethanolate or potassium terbutylate gave bad yields whatever the conditions.



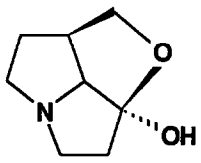
5 6 7

Hydrolysis of ester 7 was performed with HCl and decarboxylation occured on heating led to 8 as a pyrrolizidinium hydrochloride. Neutralization by gaseous ammonia gave rise to pyrrolizidine 9 (49%).



7 8

^{13}C and ^{1}H NMR spectra showed that this compound exists as a single hemiacetal stereoisomer. This pyrrolizidine can be a valuable intermediate to alkaloïd synthesis.



9

We have shown in this work that azomethine ylid reactions allow to build precursors of pyrrolizidine alcaloïds. Futhermore, flash vacuum thermolysis appears as a clean technique to synthetize organic compounds of interest.

Experimental

Methods. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 300 WB (300 MHz) (Centre Régional de Mesures Physiques de l'Ouest : CRMPO) and for routine spectra (80 MHz) with a Bruker CW 80 (^{1}H) and Bruker WP 80 DS (^{13}C) (CRMPO). Chemical shifts are reported in δ units down field of internal reference (tetramethylsilane). Deuterochloroform was used as the solvent. The coupling constants are quoted in Hertz and the notations used are : s, singulet ; d, doublet ; t, triplet ; q, quartet ; m, multiplet. High resolution mass spectrometry (HRMS) data, for exact measurements, were recorded on a varian MAT 311 instrument (CRMPO). All melting points and boiling points are uncorrected. Bulb to bulb distillation were run on a Büchi GKR 50. Elemental analysis were performed by the Service Central de Microanalyse du CNRS. For the flash vacuum thermolysis procedure, see the publications of J.M.Denis and J.C.Guillemin [16].

Materials. Proline, paraformaldehyde, methylacrylate are commercially available and were used without further purification.

Formation of the pyrrolizidine **1** :

2g of proline (0,017 mole), 2g of paraformaldehyde (0,067 mole), 0,86 g of methylacrylate (0,01 mole) and 250 ml of benzene were introduced in a 500ml round-bottled flask equipped with a Dean-Stark trap and a reflux condenser, and stirred at reflux for 3 hours. The mixture was cooled, filtered and the solvent removed under vacuum. The pyrrolizidine was purified by bulb to bulb distillation. Yield, based on starting alkene, is given for purified compounds. We obtained 1,2g of pyrrolizidine **1** (70%), Bp_{18mbar} : 100-110°C.

HRMS, $C_9H_{15}NO_2$, calculated : 169.1103, found : 169.1105.

Analyse ($C_9H_{15}NO_2$), calculated : C : 63.88, H : 8.93, N : 8.28, found : C : 63.55, H : 8.95, N : 8.17.

Formation of the aminoester **4** :

3,76g of chlorydrate of allylglycinate (prepared by a method described in the litterature[17]) (0,03 mole), 3,03g of triethylamine (0,03 mole), 5g of ethylacrylate (0,05 mole) and 100ml of alcohol at 95° were introduced in a flask. After stirring the mixture for 12 hours at room temperature, the solvent was removed and 100ml of carbontetrachloride added. After filtration and removal of carbontetrachloride, we obtained **4** with a yield of 95%. **4** was used without purification.

^{1}H NMR (80 MHz) δ 1.27 (3H, t, J = 7.2Hz), 2.12 (1H,s), 2.52 (2H, m), 2.92 (2H, m), 3.45 (2H,s), 4.15 (2H, q, J = 7.2Hz), 4.62 (2H, m), 5.30 (2H, m), 5.90 (1H, m).

Formation of the oxazolidine **5** :

In a well stirred 250 ml round-bottled flask fitted with a Dean-Stark trap and a reflux condenser, we introduced 4,3g of aminoester **4** (0,02 mole), 4g of paraformaldehyde (0,13 mole) and 100ml of toluene. The reaction was stirred at reflux during 2 hours. The mixture was cooled, filtered and the solvent removed under vacuum. We obtained 4,1g of oxazolidine **5** (80%), $Bp_{0,03mbar}$: 90°C.

^{1}H NMR (80 MHz) δ 1.30 (3H, t, J = 7.2Hz), 2.55 (2H, m), 3.06 (2H, m), 3.70 (1H, dd, J = 5.2 ; 7.8Hz), 3.85 (1H, dd, J = 5.2 ; 7.8Hz), 4.12 (1H, dd, J = 7.8 ; 7.8Hz), 4.14 (2H, q, J = 7.2Hz), 4.38 (2H, s), 4.65 (2H, m), 5.32 (2H, m), 5.92 (1H, m).

^{13}C NMR (20 MHz) δ 14.22 (q, J = 127Hz), 34.76 (t, J = 130Hz), 50.83 (t, J = 139Hz), 60.58 (t, J= 147Hz), 65.15 (d, J = 142Hz), 65.73 (t, J = 141Hz), 67.5 (t, J = 156Hz), 87.4 (t, J = 158Hz), 118.8 (t, J = 156Hz), 132.0 (d, J = 156Hz), 171.6 (s), 172.0 (s).

HRMS, [M-·$CH_2CH{=}CH_2$]$^+$, calculated : 216.0817, found : 216.0857

Analyse ($C_{12}H_{19}NO_5$), calculated : C : 56.02, H : 7.44, N : 5.44, found : C : 55.49, H : 7.37, N : 5.74.

Formation of pyrrolidine **6** :

After flash vacuum thermolysis of 4g of oxazolidine **5** (0,015 mole) at 550°C under a pressure of 2 10^{-2} mbar, we obtained 2,8g of pyrrolidine **6** (0,012 mole) (82%), $Bp_{0,03mbar}$: 110°C.

^1H NMR (300 MHz) δ 1.22 (3H, t, J = 7.2Hz), 1.77 (1H, m), 2.18 (1H, m), 2.61 (2H, m), 2.94-3.06 (2H, m), 3.11 (1H, m), 3.20 (1H, m), 3.46 (1H, d, J = 8.7Hz), 4.09 (1H, dd, J = 3.9 ; 9.3Hz), 4.12 (2H, q, J = 7.2Hz), 4.43 (1H, dd, J = 7.8 ; 9.3Hz).

^{13}C NMR (20 MHz) δ 14.77 (q, J = 127Hz), 31.1 (t, J = 132Hz), 34.3 (t, J = 132Hz), 38.9 (d, J = 137Hz), 49.0 (t, J = 136Hz), 53.9 (t, J = 138Hz), 60.3 (t, J = 147Hz), 64.7 (d, J = 145Hz), 72.8 (t, J = 151Hz), 172.3 (s), 176.4 (s).

HRMS, $C_{11}H_{17}NO_4$, calculated : 227.1157, found : 227.1156.

Formation of pyrrolizidine **7** :

Under nitrogen, 18,33ml of nBuLi (1,6M in hexane (0,029 mole)) were added at -78°C to 2,22g of diisopropylamine in 30ml of anhydrous tetrahydrofuran. Under stirring, we let the temperature of the mixture rise to RT then the reaction was cooled to -78°C and 2g of pyrrolidine **6** (0,009 mole) in 10ml of anhydrous tetrahydrofuran were slowly added. After one hour at -30°C, the reaction was quenched by 0,890ml of methanol (0,022 mole). The solvent was removed and a flash chromatography on silica column with methanol as solvent (Rf : 0,2) led to 1,38g of pyrrolizidine **7** (0,006 mole) (67%).

HRMS, $C_{11}H_{17}NO_4$, calculated : 227.1157, found : 227.1156.

Formation of pyrrolizidine **9** :

50ml of HCl 6N were added to 1,38g of pyrrolizidine **7** (0,006 mole). The reaction was heated 3 hours at reflux then the mixture was cooled and HCl 6N removed. After removal of the remaining water with ethanol, the mixture was diluted in 30ml of methanol and stirred at 0°C. Gaseous ammonia was slowly added to this solution and the end of the neutralization was controlled by a pH paper.The solution was filtrated and the solvent removed. After a chromatography on SiO_2 column with methanol as solvent (Rf : 0,16) and recrystalisation with acetone, we obtained 0,46g of pyrrolizidine **9** (mp : 120°C) (49%).

^1H NMR (300MHz) δ 1.68 (1H, m), 2.05 (3H, m), 2.55-2.95 (4H, m), 3.15 (1H, m), 3.75 (1H d, J= 7.7Hz), 3.82 (1H, d, J = 8.8 ; 0Hz), 4.19 (1H, dd, J = 8.8 ; 5.5Hz).

^{13}C NMR (75MHz) δ 31.2 (t, J = 129.8Hz), 37.8 (t, J = 130.2Hz), 44.88 (d, J = 137Hz), 52.6 (t, J= 139.1Hz), 54.4 (t, J = 137.7Hz), 74.2 (t, J = 146.5Hz), 78.1 (d, J = 142.4Hz), 114.1 (s).

HRMS, $C_8H_{13}NO_2$, calculated : 155.0946, found : 155.0949.

Analyse ($C_8H_{13}NO_2$), calculated : C : 61.91, H : 8.44, N : 9.03, found : C : 61.51, H : 8.41, N: 9.33.

References

1. Lown, J.W.; " 1,3-dipolar cycloaddition chemistry "; A.Padwa Ed.; Wiley and Sons; New York, **1984**, references indicated.
2. Vedejs, E.and West, F.G. *Chem.Rev*, **1986**, *86*, 941-955.
3. Tsuge, O. and Kanemasa, S. *Adv.Heterocyclic Chem.*, **1989**, *45*, 231-236.
4. Deshong, P. and.Kell, O.A.*Tetrahedron Lett.*, **1986**, *27*, 3979-3982.
5. Wang, C-L.J.; Ripka, W.C.and Confalone, P.T.*Tetrahedron Lett.*, **1984**, *25*, 4613-4616.
6. Smith, R. and Livinghouse, T*J.Org.Chem.*, **1983**, *48*, 1554-1557.
7. Takano, S.; Iwabuchi, Y and Ogasawara, K. *J.Chem.Soc.Chem.Commun.*, **1988**, 1204-1205.
8. Joucla, M. and Mortier, J*J.Chem.Soc.Chem.Commun.*, **1985**, 1566-1567.
9. Joucla, M. and J.Mortier, J. *Bull.Soc.Chim.Fr.*, **1988**, 579-583.
10. Terao, Y.; N.Imaï, N.; Achiwa, K. and Sekiya, M. *Chem.Pharm.Bull.*, **1982**, *30*, 3167-3170.
11. Joucla, M. and Mortier, J.*Tetrahedron Lett.*, **1987**, *28*, 2973-2975.
12. Joucla, M.; Mortier,J. and Bureau, R.*Tetrahedron Lett.*, **1987**, *28*, 2975-2976.

13. Bureau, R. and Joucla, M.*Tetrahedron Lett.*, **1990**, *32*, 6017-6020.
14. Bureau, R.; Mortier, J. and Joucla, M.*Bull.Soc.Chim.Fr.* (submitted for publication).
15. March, J. "*Advanced organic chemistry* " 3rd edition, J.Wiley and Sons, **1985**.
16. Guillemin, J.C. and Denis, J.M.*Angew.Chem., Int.Ed.Engl.*, **1982**, *21*, 690 ; *Angew.Chem.Suppl.*, **1982**, 1515.
17. Guttman, S., *Helv.Chim. Acta*, **1961**, *44*, 721.

Acknowledgement

We thank Doctors J.M.Denis and J.C.Guillemin for helpful discussions in monitoring flash vacuum thermolysis technology.