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Cyclization of δ,ε-Acetylenic Amines and Aminoacids into Cyclic Enamines. A Very Efficient and Simple Access to Polysubstituted Pyrrolidines.

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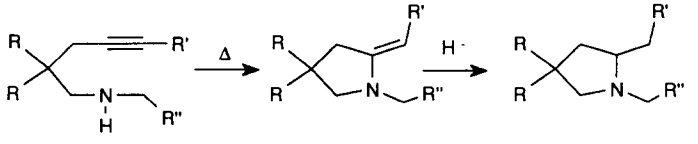
Abstract *: The thermolysis of δ,ε-acetylenic amines and aminoacids led to cyclic enamines which after reduction with $NaBH(OAc)_3$ were transformed into polysubstituted pyrrolidines.*

The development of new methods for the preparation of nitrogen containing five-membered rings, such as pyrrolidines derivatives continues to be an active front of research since these systems are found in a large variety of natural and bioactive products.[1] Among the carbon-nitrogen bond forming processes, the hydroamination of olefins and of alkynes by addition of amines onto carbon-carbon multiple bonds is a simple and attractive approach.[2] Such reactions are known to proceed, for olefins, with alkali metals in liquid ammonia at rather high temperatures and under high pressure but the yields remain modest, and rather poor selectivities are observed.[3] Transition metal-mediated additions is an alternative approach to achieve the hydroamination of multiple bonds. Catalysts involving Pd°, $CpTiCl_3$, CuCl, $AgBF_4$, HgY_2 as well as organolanthanides complexes have been proposed.[4] Anionic cyclization of δ-alkynylamines have also been reported.[5]

Here we would like to report a very simple synthesis of polysubstituted pyrrolidines through the thermal isomerization of δ-acetylenic amines (**I**→**II**) followed by reduction of the intermediate enamines (**II**→**III**).



I **II** **III**

For instance, 1-(benzylamino)pent-4-yne **1** was isomerized into enamine **2** (50 % after purification on alumina) upon heating to 210 °C for 2h. The relative configuration of **2** was established by NOE experiments in its ^1H NMR spectrum. As the enamine **2** was a sensitive compound, it was better not isolating it, but reducing it directly with $NaBH(OAc)_3$ (1.4 eq) in the presence of AcOH (1 eq) in CH_2Cl_2 (20 °C). Under these conditions, the corresponding amine **3** was formed and isolated in a yield of 55 %. The yield could be raised to

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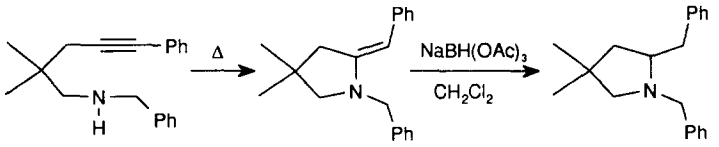
91 % when **1** was heated at 150 °C for 50 min in the presence of acetic acid (1 eq) followed by reduction with $NaBH(OAc)_3$ in CH_2Cl_2.

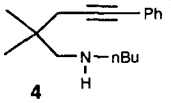
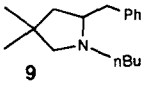
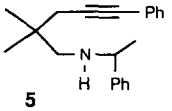
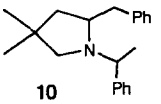
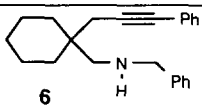
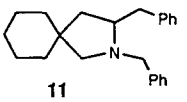
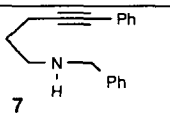
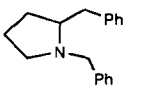
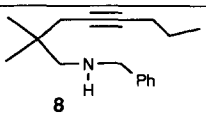


1 **2** **3**

Conditions	compound 2 isolated yield	compound 3 isolated yield
210 °C, 2 h	50 %	--
1) 210 °C, 2 h 2) $NaBH(OAc)_3$, AcOH	--	55 %
1) 150°C, 50 min, AcOH (1eq) 2) $NaBH(OAc)_3$	--	91 %

In order to test the generality of the method, we repeated these reaction with δ,ε-acetylenic amines **4** - **8**. Our results are summarized in Table I.

Table I : Thermolysis of N-alkyl-δ,ε-acetylenic amines.

Starting material	Conditions	Product	Isolated yield
 **4**	**A)** 180 °C, 2 h **B)** 150 °C, 50 min, AcOH (1 eq)	 **9**	58 % 95 %
 **5**	**A)** 210 °C, 27 h **B)** 150 °C, 17 h, AcOH (1 eq)	 **10**	35 % 66 %
 **6**	**A)** 200 °C, 2.5 h **B)** 150 °C, 1.5 h, AcOH (1 eq)	 **11**	60 % 97 %
 **7**	**A)** 200 °C, 2 h **B)** 150 °C, 1 h, AcOH (1 eq)	 **12**	-- 5 %
 **8**	**A)** 200 °C, 2 h **B)** 150 °C, 1 h, AcOH (1 eq)	-- --	-- --

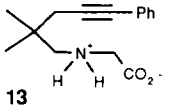
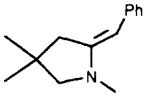
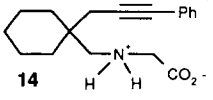
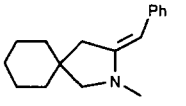
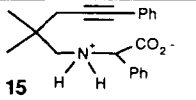
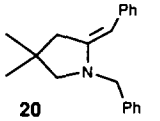
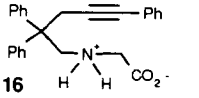
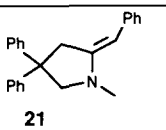
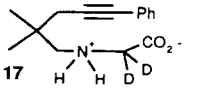
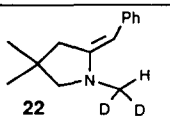
Method A : δ,ε-acetylenic amines (1 mmol) were heated neat at 180°C - 210°C for 2.0 - 2.5 h. After dilution at room temperature with CH_2Cl_2 (3 mL), $NaBH(OAc)_3$ (1.4 eq) and AcOH (1.0 eq) were added at room temperature.[6] After 15 h at 20 °C and after usual workup the amine was purified by flash chromatography on silica gel.

Method B : δ,ε-acetylenic amines (1 mmol) were heated at 150 °C for 1.0 h - 3.0 h in the presence of AcOH (1 eq). The reaction mixture was dissolved in CH_2Cl_2 (3 mL) at room temperature and $NaBH(OAc)_3$ (1.4 eq) was added.[6] After 15 h at 20 °C and after usual workup the amine was purified by flash chromatography on silica gel.

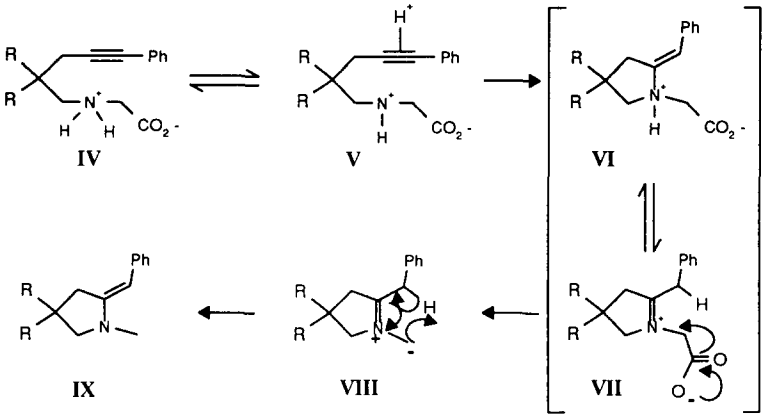
As for **1**, the acid-catalyzed hydroamination reported in Table I (method B) led to better yields than the thermal isomerization (method A). A phenylalkyne is required for success as the alkylacetylenic amine **8** failed to give the expected pyrrolidine. Furthermore, the intramolecular hydroamination fails in the absence of substituents at C-3, thus showing the importance of Thorpe-Ingold effect for the success of the isomerisation of the δ-acetylenic amines.

We have also found that the thermolysis of δ,ε-acetylenic aminoacids,[7] at a temperature near their melting point, produced *N*-alkyl cyclic enamines (see Table II). For derivatives **13**, **14**, **16**, **17** the cyclization occurs at 150 °C and the yields are nearly quantitative. For compound **15**, the temperature required for the melting and then for the cyclization is higher (195 °C) and therefore some degradation occurs.

Table II : Thermolysis of δ,ε-phenylacetylenic aminoacids

Starting material	t °C, h	Product	Isolated yield
 **13** m.p. = 154 - 156 °C	150 °C, 2 h	 **18**	97 %
 **14** m.p. = 160 - 162 °C	150 °C, 2 h	 **19**	97 %
 **15** m.p. = 204 - 206 °C	195 °C, 0.5 h	 **20**	67 %
 **16** m.p. = 123 - 125 °C	150 °C, 1 h	 **21**	92 %
 **17** m. p. = 154 -156 °C	150 °C, 2 h	 **22**	95 %

The relative configuration of **18** was established by NOE experiments in its ^1H NMR spectrum. Intramolecular protonation of the alkyne (**IV→V**) activates the addition of the amino group to the alkyne with formation of a *Z*-benzylidene pyrrolidinium intermediate (**V→VI**). This latter compound undergoes a prototropic shift (**VI→VII**), generating an iminium intermediate that is decarboxylated if derived from α-aminoacid.[8] This generates the ylid **VIII** which finally isomerize into **IX**.



This work demonstrates that the thermal and acid-promoted cyclization of δ,ε-acetylenic amines and aminoacids is a very efficient approach to the preparation of polysubstituted pyrrolidines.

Acknowlegments : We thanks Mr F. Lafon, President of the Laboratoires F. Lafon, for financial support.

References :

1. a) Bull, L. B.; Culvenor, C. C. J.; Dick, A. T. *The Pyrrolizidine Alkaloids*; North-Holland Publishing Co: Amsterdam, The Netherlands, **1968**. b) *Natural Occuring Pyrrolizidine Alkaloids*; Rizk, A.-F. M., Ed; CRC: Boston, **1991**. c) Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Am. Chem. Soc.* **1996**, *118*, 8266-8277 and references therein.
2. General references : a) Chekulaeva, I. A.; Kondrat'eva, L. V. *Russ. Chem. Rev.* **1965**, *34*, 669-680. b) Gibson, M. S. *The Chemistry of the Amino Group*; S. Patai, Ed.; Interscience: New York, **1968**, 61-65. c) Challis, B. C.; Butler, A. R. *ibid.* **1968**, 292. d) Suminov, S. I.; Kost, A. N. *Russ. Chem. Rev.* **1969**, *38*, 884-899. e) Jäger, V.; Viehe, H. G. *Houben-Weyl, Methoden der Organishen Chemie*; Thieme Verlag: Stuttgart, **1977**, Vol. 5/2a, 713-724. f) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, **1992**, 768-770 and references therein.
3. a) Howk, B. W.; Little, E. L.; Scott, S. L.; Whitman, G. M. *J. Am. Chem. Soc.* **1954**, *76*, 1899-1902. b) Pez, G. P.; Galle, J. E. *Pure Appl. Chem.* **1985**, *57*, 1917-1926.
4. Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295-9306, and references therein.
5. Tokuda, M.; Fujita, H.; Suginome, H. *Tetrahedron Lett.* **1990**, *31*, 5353-5356.
6. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849-3862.
7. Compounds **18-22** were obtained pure by heating compounds **13-17** without any solvent under an argon atmosphere.
8. Dose, K. *Chem. Ber.* **1957**, 1251.

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