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INTRAMOLECULAR CYCLIZATION OF ω-PRIMARY AMINO ELECTROPHILIC OLEFINS TO FUNCTIONALIZED PYRROLIDINES AND PIPERIDINES.

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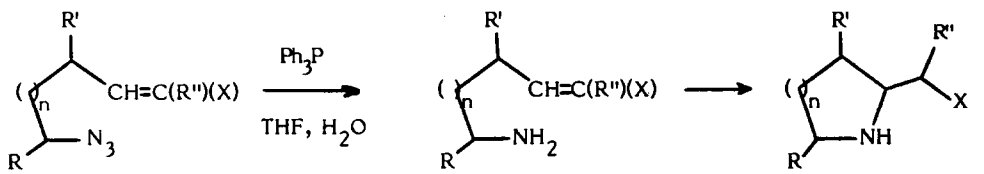
Abstract - The intramolecular 1,4-Michael type addition of in situ chemoselectively generated primary amines bearing an electrophilic double bond in the ω position leads to functionalized pyrrolidines and piperidines under very mild conditions.

The synthesis of pyrrolidines and piperidines bearing a functionality α to the nitrogen atom may be achieved in essentially two different ways. The first one starts from the alicyclic amines and requires an activation of the position α to nitrogen by conversion to imines [1], α-aminonitriles [2], N-nitrosated amines [3], formamidine derivatives [4] or α-methoxylated amines [5]. In the second one, the heterocycles result from the creation of a carbon-nitrogen bond by an intramolecular cyclization of an ω-aminoolefin mediated by mercury [6], silver [7], palladium [8], the Nicolaou's reagent N-phenylselenophthalimide (N-PSP)[9] or by an intramolecular ring opening of ω-aminoepoxides [10]. Pyrrolidines and piperidines are also accessible via the 1.3 dipolar cycloaddition of nitrones to olefins [11], the substitution of α-acyliminium intermediates [12] and the intramolecular addition of α-acylamino radicals [13]. The intramolecular 1,4-Michael type addition of an ω-amino electron deficient olefin has scarcely been used to build nitrogen heterocycles [14]. This may result from the difficulty of generating chemoselectively a primary amine in the presence of this sensitive functionality. In this note, we describe an easy access to functionalized pyrrolidines and piperidines using a 1,4 Michael type addition according to the reaction sequence outlined below.



1 : n = 1 3 5
2 : n = 2 4 6

R, R', R" = H, CH_3; X = CO_2CH_3, CN.

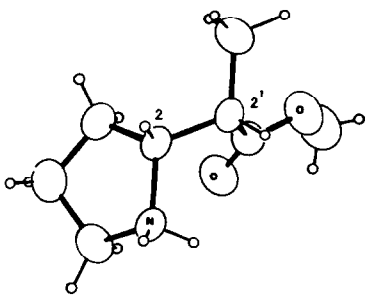
The starting azides **1** and **2** were obtained in good yields using Wittig reagents [15] as a mixture of geometrical isomers (E/Z ⩾ 95/5 for X = CO_2CH_3 and 6/4 to 8/2 for X = CN). The azides **1** and **2** were then reduced to the primary amines **3** and **4** respectively using Ph_3P and water in THF [16] at room temperature for 12 hours. The azides **1** and **2** are prone to intramolecular 1,3 dipolar cycloaddition leading to bicyclic triazolines, the thermal evolution of which has been studied in detail [15]. Therefore, the reduction step being exothermic, it is necessary, in certain cases (**1b, 1c, 2a** and **2b**) to add a THF solution of Ph_3P to a solution of the azides maintained at -50°C. The cyclization step, a 1,4 Michael type addition, occurred smoothly leading to pyrrolidines **5** or piperidines **6** which were isolated in good yields (see table) by bulb to bulb distillation after removal of most of the triphenylphosphine oxide by filtration. Performing the reduction step at 4°C allowed the isolation of the transient primary amines **3** and **4** in two cases (**3c** : $Eb_{0.5}$ = 35-40°C, 85 % ; **4c** : $Eb_{0.5}$ = 50-55°C, 78 %). **5** and **6** were obtained as a mixture of diastereoisomers **5'**, **5"** and **6'**, **6"**, a good diastereoselection being observed (8/2 and 9/1) in all cases except for **6c**. These reactions are under kinetic control. The geometry of the starting olefin does not seem to have much influence on the stereochemical outcome of the cyclization step. For example, starting from 95/5 and 67/33 E/Z mixtures of the azides **2d** led to the same 9/1 mixture of piperidines **6'd** and **6"d**.

Table [17] - Synthesis of pyrrolidines **5** and piperidines **6**.

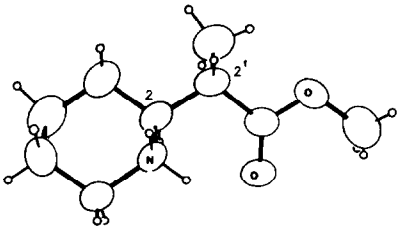
N°	R	R'	R"	X	**5'/5"** or **6'/6"**	Yield %[a]	m.p.°C[b]
5b	H	H	H	CN	-	74	132-3 *
5c	H	H	CH_3	CO_2CH_3	90/10	78	118-120 **
6a	H	H	H	CO_2CH_3	-	60	168-170 *
6b	H	H	H	CN	-	83	170-2 *
6c	H	H	CH_3	CO_2CH_3	55/45	86	171-3 **
6d	H	CH_3	H	CO_2CH_3	90/10	83	126-8 **
6e	CH_3	H	H	CO_2CH_3	80/20	82	128-9 **
6f	H	CH_3	H	CN	86/14	71	158-160 **
6g	CH_3	H	H	CN	90/10	77	164-166 **

(a) Yields are of isolated pure products. (b) * : m.p. of the hydrochloride ; ** : m.p. of the picrate.

The stereochemistry of **5c** and **6c** was established unambiguously by an X-ray analysis of the picrates of the major isomers **5'c** (**5'c**, $(NO_2)_3C_6H_2OH$, m.p. 128°C (acetone)) and **6'c** (**6'c**, $(NO_2)_3C_6H_2OH$, m.p. 180°C (acetone)).

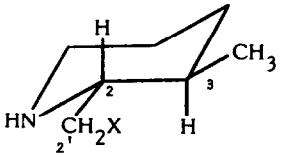


ORTEP drawing of **5'c**, $(NO_2)_3C_6H_2OH$ [18]

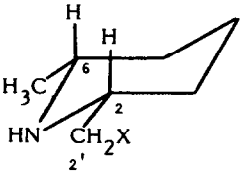


ORTEP drawing of **6'c**, $(NO_2)_3C_6H_2OH$ [18]

From the above ORTEP drawings, it can be seen that **5'c** is the R(S), R(S) diastereoisomer while **6'c** is the S(R), R(S) one. The analysis of the 300 MHz ^1H NMR spectra of the corresponding free amines gave $^3J_{H_2H_{2'}}$ = 7.6 Hz for **5'c** and $^3H_{H_2H_{2'}}$ = 8.8 Hz for **6'c**.



6'd : X = CO_2CH_3
6'f : X = CN



6'e : X = CO_2CH_3
6'g : X = CN

The 2,3 disubstituted piperidines **6'd** and **6'f** were shown to have their substituents in a trans diequatorial relationship by examination of the 300 MHz ^1H NMR spectra. For example, in **6'd**, $^3J_{H_3\,ax\;H_4\,eq}$ = 2.4 Hz and $^3J_{H_2H_3\,ax}$ = $^3J_{H_3\,ax\;H_4\,ax}$ = 10.8 Hz. The stereochemistry of the 2,6-disubstituted piperidines **6e** and **6g** was established by comparison with the ^1H and ^{13}C data available for the four diastereoisomers of the methyl esters of dihydropalustramine [19] and shown to be cis diequatorial for the major isomers **6'e** and **6'g** [20].

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17 - All the compounds reported in this note gave satisfactory analytical and spectroscopic data.

18 - The picrate anions have been removed for clarity.
Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K..

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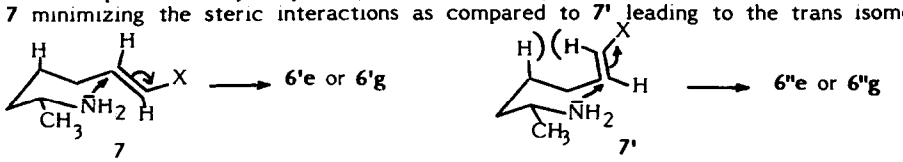
20 - Piperidines **6e** and **6g** were formed under kinetic control. That the more stable cis isomers were obtained preferentially may be the result of a cyclization via a chain-like transition state **7** minimizing the steric interactions as compared to **7'** leading to the trans isomers.



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