HIGHLY DIASTEREOMER SELECTIVE ACYLATION OF 2,5-DIALKYLPYRROLIDINES. A VERSATILE ROUTE TO *Trans*-2,5-DISUBSTITUTED CYCLIC AMINO ALCOHOLS

Anne Fleurant, Cyrille Grandjean, Olivier Provot, Sylvie Rosset, Jean Pierre Célérier, and Gérard Lhommet*

Université P. et M. Curie, Laboratoire de Chimie des Hétérocycles, associé au CNRS, 4, Place Jussieu, 75252 Paris cedex 05 France

Abstract - Diastereoisomeric mixtures of *cis*- and *trans*- disubstituted pyrrolidines are separated by kinetically controlled acylation with benzyl chloroformate.

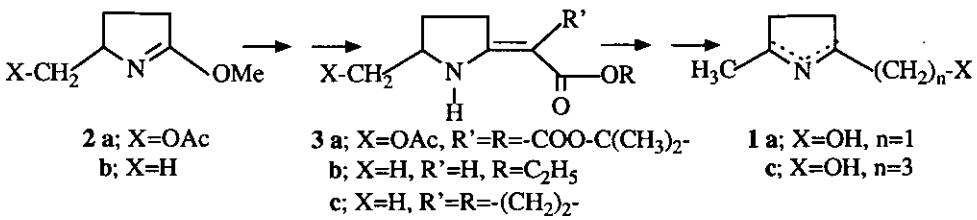
Important biological activities[1] displayed by *trans*-2,5-disubstituted pyrrolidine alkaloids have stimulated the development of synthetic strategies for the construction of this class of compounds.[2] However, a separative step is often necessary even in cases where the diastereoselectivity of products is high.
Our interest in the alkaloid syntheses such as *trans*-2,5-dialkylpyrrolidines from *Monomorium minutum*, a pyrrolizidine from *Solenopsis xenovenenum*, and gephyrotoxin type indolizidines from dentrobatid frogs stems from their biological activities and has led us to investigate an easy approach to the formation of functionalized *trans*-2,5-disubstituted pyrrolidines.

We have recently reported[3] the reduction of pyrroline (**1**) (X=CH_3, n=14) with sodium borohydride in ethanol, leading to the corresponding diastereoisomeric mixtures of *trans*- and *cis*-2,5-dialkylpyrrolidines (**4**) and (**5**). Though *trans*- pyrrolidines (**4**) (X=CH_3, n=14) were formed predominantly in acetic acid, the separation of diastereoisomers was always difficult.

Here we describe an easy method for the separation of *trans*- and *cis*-2,5-dialkylpyrrolidines utilizing selective acylation of hydroxyalkylpyrrolidines (**5**) (n=1~3).

Reduction of pyrrolines (**1a,c**) and β-enamino ester (**3b**) with sodium borohydride gave diastereoisomeric mixtures of *trans*- and *cis*- disubstituted pyrrolidines (**4**) and (**5**).
β-Enamino esters (**3**) were prepared from lactams by condensation of lactim ethers (**2**) with active

methylene derivatives (Scheme 1).



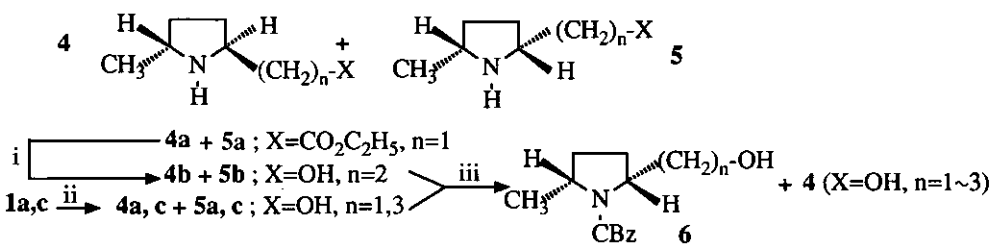
Scheme 1

Lactim ether (**2a**) and Meldrum's acid reacted[4] in chloroform with a catalytic amount of $Ni(acac)_2$ to give corresponding β-enamino ester (**3a**). Similary, cyclic β-enamino ester (**3b**) was prepared from lactim ether (**2b**) followed by monodecarboxylating-transesterification reaction[4] with sodium ethoxide. Finally, condensation of lactim ether (**2b**) with 2-acetylbutyrolactone[5] led to β-enamino lactone (**3c**).

Decarboxylation of compounds (**3a**) and (**3c**) in acidic medium (25% HCl) afforded imines (**1a**) and (**1c**), respectively (Scheme 1).

Hydroxyalkylpyrrolidines (**4b**) and (**5b**) (X=OH, n=2) were obtained by reduction of a mixture of β-amino esters (**4b**) and (**5b**) ($X=CO_2C_2H_5$, n=1) using lithium aluminium hydride (Scheme 2).

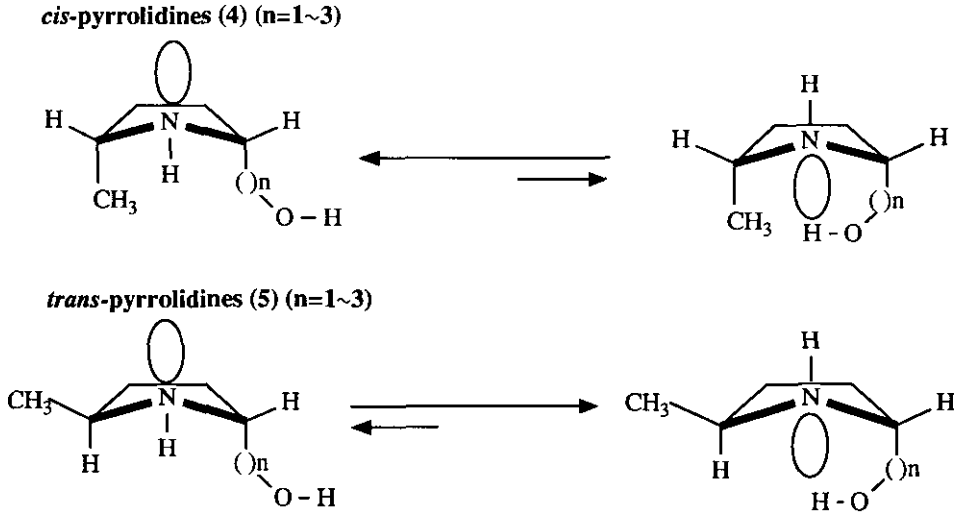
The separation of amino alcohols (**4**) and (**5**) (X=OH, n=1~3) is effected by reaction of the mixture with benzyl chloroformate in water at low temperature.[6] *Cis*-carbamate (**6**) (n=1~3) was extracted from the aqueous reaction mixture with $CHCl_3$. The remained aqueous layer was saturated with K_2CO_3 and extracted with $CHCl_3$, affording pure *trans*-pyrrolidines (**4**) (X=OH, n=1~3)[7] with good yields (90%).



Reaction conditions: i) $LiAlH_4$; ii) $NaBH_4$, C_2H_5OH; iii) $ClCOOCH_2Ph$, (1 eq.), $NaHCO_3$, H_2O, 0°C.

Scheme 2

The hydroxyalkyl substituents in the pyrrolidine ring have significant effect on the diastereoselectivity of this reaction. The intramolecular hydrogen bonding between the lone pair of the nitrogen and the hydroxyl function may decreases the nucleophilicity of nitrogen atom. In *cis*-compounds (**4**) (n=1~3), steric hindrance impedes such a chelation because of the more favorable trans position of the lone pair with regard to the two substituents (Scheme 3). On the other hand, for *trans*-pyrrolidines (**5**) (n=1~3), one of the two conformational situations permits a chelation which lessens the reactivity (Scheme 3). The presence of an hydroxy group is necessary for the diastereoselectivity of the acylation because no selectivity is observed for mixtures of 2,5-dialkyl-pyrrolidines (**4**) and (**5**)(X=H).



Scheme 3

Meanwhile, functionalized *trans*-pyrrolidines (**5**) (n=1~3) are acylated in same conditions, but at higher temperatures (80°C).

In conclusion, we report an easy and general method for separation of *cis*- and *trans*-2,5-disubstituted pyrrolidine alcohols by chemical means which we interpret as a consequence of internal hydrogen bondings that modify the course of acylation with benzyl chloroformate. This kinetically controlled separation is a good method obtaining key intermediates for preparation of *trans* natural products.

ACKNOWLEDGEMENT

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6. n=1, 5 h at 0°C; n=2, 3, 0.5 h at 0°C, then 1.5 h at room temperature.
7. (2*S*,5*R*)-2-Hydroxymethyl-5-methylpyrrolidine (**5**) (n=1; X=OH): bp_{15} 113°C;[8] ^{1}H-nmr δ ($CDCl_3$) 1.21 (d, 3H, J=7 Hz), 1.20-1.55 (m, 2H), 1.82-1.96 (m, 2H), 3.10-3.25 (m, 1H), 3.28-3.48 (m, 3H), 3.90-4.10 (br s, 1H), 4.80-5.10 (m, 1H); ^{13}C-nmr δ ($CDCl_3$) 20.4, 27.8, 34.2, 53.6, 59.6, 64.5; $[\alpha]_D^{21}$ +1.50° (c=1.91, EtOH).
   (±)-2-(1-Hydroxyethyl)-5-methylpyrrolidine (**5**) (n=2; X=OH): bp_{15} 105°C; ^{1}H-nmr δ ($CDCl_3$) 1.04 (d, 3H, J=7 Hz), 1.30-1.75 (m, 4H), 1.80-2.30 (m, 2H), 3.05-3.25 (m, 1H), 3.40-3.65 (m, 1H), 3.70-3.95 (m, 4H); ^{13}C-nmr δ ($CDCl_3$) 20.8, 31.0, 32.3, 37.7, 52.7, 56.6, 60.5.
   (2*S*,5*R*)-2-(1-Hydroxypropyl)-5-methylpyrrolidine (**5**) (n=3; X=OH):[5] bp_{25} 138°C; ^{1}H-nmr δ ($CDCl_3$) 0.97 (d, 3H, J= 7Hz), 1.04-1.15 (m, 1H), 1.16-1.27 (m, 1H), 1.28-1.37 (m, 1H), 1.38-1.55 (m, 3H), 1.77-1.86 (m, 1H), 3.01-3.10 (m, 1H), 3.35-3.41 (m, 1H), 3.42-3.49 (m, 1H), 3.76-4.18 (m, 2H); ^{13}C-nmr δ ($CDCl_3$) 20.8, 30.1, 32.4, 34.2, 34.3, 52.8, 57.7, 62.0; $[\alpha]_D^{22}$ -25.1° (c=1, CH_2Cl_2).
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