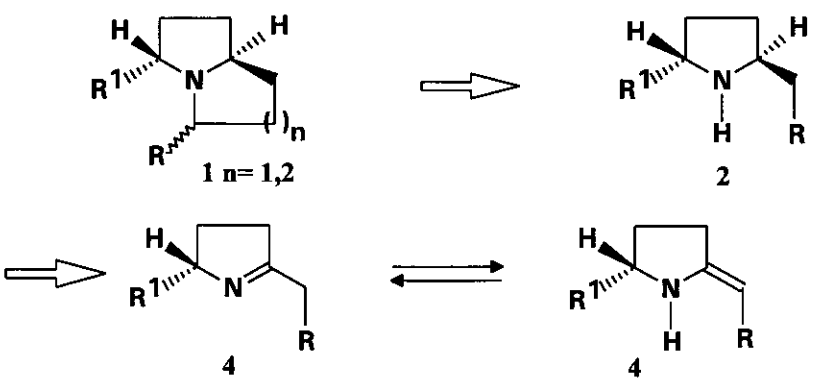
DIASTEREOSELECTIVE REDUCTION OF CYCLIC IMINES AND β-ENAMINO ESTERS

Giang Vo Thanh, Jean-Pierre Célérier, Anne Fleurant, Cyrille Grandjean, Sylvie Rosset, and Gérard Lhommet*

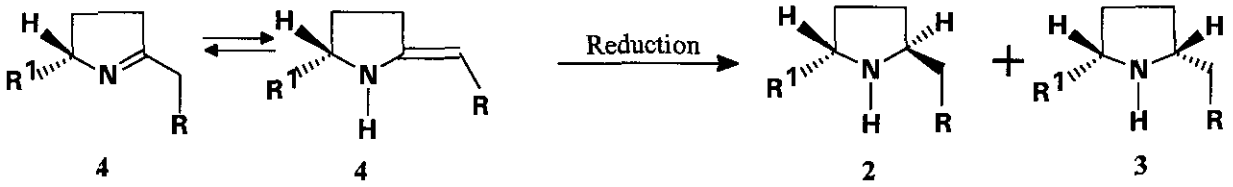
Université Pierre et Marie Curie, Laboratoire de Chimie des Hétérocycles, URA 408. 4 Place Jussieu, 75252 Paris cedex 05, France

Abstract - The chemical and diastereoselective reduction of cyclic imines and β-enamino esters has been investigated and exploited as an efficient method of synthesis of *trans* disubstituted pyrrolidines.

Important biological activities[1] displayed by *trans*-2,5-disubstituted pyrrolidines (**2**),[1] pyrrolizidines (**1**) (n=1) and indolizidines (**1**) (n=2) have stimulated the development of synthetic strategies for the construction of this class of compounds.[2] Cyclic imines such as Δ-1-pyrrolines (**4**) (R=alkyl) which are components of ants'venoms and β-enamino esters (**4**) ($R=CO_2R'$) are also precursors of *trans*-2,5-disubstituted pyrrolidines (**2**) which have always their stereochemistry fixed during the reduction step of cyclic imines or β-enamino esters.



In connection with our work on the use of cyclic β-enamino esters in the heterocyclic chemistry, especially for the formation of cyclic imines by direct hydrolysis and decarboxylation of β-enamino esters,[3,4] we report herein a general investigation on the diastereoselective reduction of cyclic imines and enamines.



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Δ-1-Pyrrolines (**4**) and β-enamino esters (**4**) are diastereoselectively transformed into *cis*-disubstituted pyrrolidines (**3**) by a catalytic hydrogenation[5,6] (as shown in Table 1).

Table 1. Catalytic hydrogenation of cyclic imines (**4**) and β-enamino esters (**4**)

Imines or Enamines	R^1	R	Reducing Agent	Yield %	Pyrrolidines *cis* **3** / *trans* **2**
4b	Me	$C_{14}H_{29}$	H_2 / Raney Ni / 100 bar	60	94 / 6
4g	Me	CO_2Et	H_2 / Raney Ni / 100 bar	98	98 / 2
4a	Me	C_8H_{17}	H_2 / PtO_2 / 1 bar	75	96 / 4
4f	Me	CO_2Me	H_2 / PtO_2 / 1 bar	98	92 / 8
4c	CH_2OH	H	H_2 / Raney Ni / 100 bar	96	94 / 6
4h	CH_2OH	CO_2Me	H_2 / Raney Ni / 100 bar	98	94 / 6
4c	CH_2OH	H	H_2 / PtO_2 / 1 bar	75	80 / 20
4e	CH_2OH	C_8H_{17}	H_2 / PtO_2 / 1 bar	80	87 / 13
4d	CH_2OH	C_6H_{13}	H_2 / PtO_2 / 1 bar	80	94 / 6
4h	CH_2OH	CO_2Me	H_2 / PtO_2 / 1 bar	98	92 / 8

Chemical reductions of imines (**4**) and β-enamino esters (**4**) (R^1=CH_3) have permitted to prepare *trans*-pyrrolidines (**2**) leading to a slight excess of *trans*-isomer only when using sodium triacetoxyborohydride or B_2H_6, (as shown in Table 2). It can be noted that a mixture of $LiAlH_4$/Me_3Al, which afforded *trans*-dialkylpiperidines,[7] was not efficient with five membered ring imines or enamines.

Table 2. Chemical reduction of cyclic imines (**4**) and β-enamino esters (**4**)

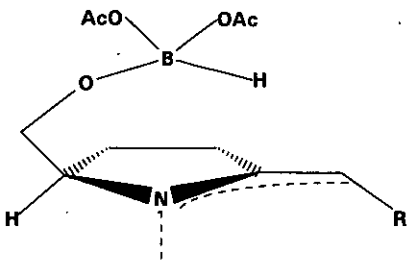
Imines or Enamines	R^1	R	Reducing Agent	Yield %	Pyrrolidines *Cis* **3** / *Trans* **2**
4b	Me	$C_{14}H_{29}$	$LiAlH_4$ / Me_3Al [b]	75	70 / 30
4g	Me	CO_2Et	B_2H_6 / THF [b]	65	40 / 60
4b	Me	$C_{14}H_{29}$	$NaBH_4$ / MeOH [b]	90	50 / 50
4f	Me	CO_2Me	$NaBH_4$ / MeOH [b]	95	50 / 50
4a	Me	C_8H_{17}	$NaBH_4$ / AcOH [b]	70	40 / 60
4g	Me	CO_2Et	$NaBH_4$ / AcOH [b]	92	50 / 50
4c	CH_2OH	H	$LiAlH_4$ / Me_3Al [b]	75	70 / 30
4h	CH_2OH	CO_2Me	B_2H_6 / THF [b]	65	40 / 60
4c	CH_2OH	H	DIBAH / -78°C	50	45 / 55
4c	CH_2OH	H	$NaBH_4$ / MeOH [b]	90	50 / 50
4h	CH_2OH	CO_2Me	$NaBH_4$ / MeOH [b]	95	50 / 50
4h	CH_2OH	CO_2Me	$NaBH_4$ / H_2SO_4 [b]	50	50 / 50
4h	CH_2OH	CO_2Me	$(CH_3)_4NBH_4$ / H_2O [b]	84	50 / 50
4c	CH_2OH	H	$NaBH(OAc)_3$ [a] / PhMe [b]	75	75 / 25
4c	CH_2OH	H	$NaBH_4$ / AcOH / PhMe [b]	70	30 / 70
4h	CH_2OH	CO_2Me	$NaBH_4$ / AcOH / PhMe [b]	92	50 / 50
4c	CH_2OH	H	$NaBH_4$ / AcOH / Ph Me / -10°C	80	15 / 85
4d	CH_2OH	C_6H_{13}	$NaBH_4$ / AcOH / Ph Me / -10°C	60	30 / 70
4h	CH_2OH	CO_2Me	$NaBH_4$ / AcOH / MeCN [b]	80	30 / 70
4h	CH_2OH	CO_2Me	$NaBH_4$ / AcOH / MeCN / 0°C	92	10 / 90

[a] Commercially available [b] Room temperature

In the course of the directed reductions of hydroxy ketones by polyacetoxyborohydrides,[8] we have investigated the reduction of hydroxymethylpyrrolidine (**4**) and hydroxymethyl-β-enamino esters (**4**) using hydrides. In fact, the hydroxy group was in a good position to interact with reducing agent and then could permit an *anti* attack of the hydride.

When chemical reduction conditions were studied, best results were performed using sodium borohydride and acetic acid according to the results of Palmieri *et al.*[9] but no significant d.e. was observed with DIBAH at low temperatures.[10] However, the choice of the solvent is important : toluene for imines (**4**) and acetonitrile for β-enamino esters (**4**). Sodium triacetoxyborohydride has to be prepared *in situ* from

sodium borohydride (3 eq.) and acetic acid (30 eq.) due to the non selectivity observed with commercial reducing agent.



Sodium polyacetoxyborohydride is a versatile reducing agent for the diastereoselective reduction of cyclic imines and cyclic β-enamino esters. Good diastereomeric excesses are obtained for the preparation of *trans*-disubstituted pyrrolidines when one of the substituents is bearing a hydroxy function permitting an intramolecular *anti* attack of the hydride. A performing separation of the two diastereoisomers can after be done by a diastereocontroled carbamatation leading to pure *cis* or *trans* compounds.[11]

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