

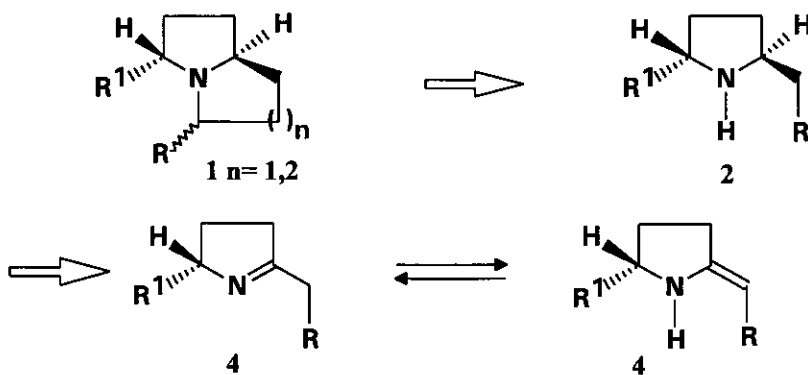
DIASTEREOSELECTIVE REDUCTION OF CYCLIC IMINES AND β -ENAMINO ESTERS

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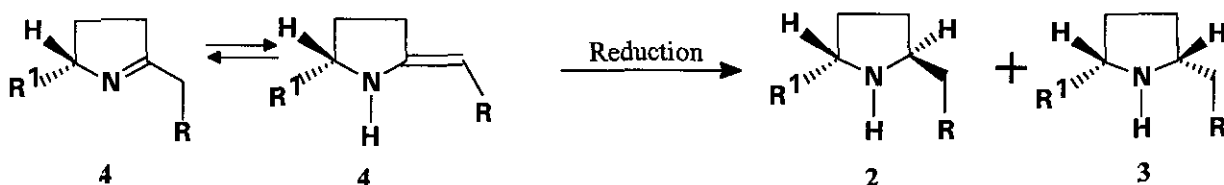
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Abstract - The chemical and diastereoselective reduction of cyclic imines and β -enamino esters has been investigated and exploited as an efficient method of synthesis of *trans* disubstituted pyrrolidines.

Important biological activities¹ 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 =CO₂R') 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.



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 <i>cis</i> 3 / <i>trans</i> 2
4b	Me	C ₁₄ H ₂₉	H ₂ / Raney Ni / 100 bar	60	94 / 6
4g	Me	CO ₂ Et	H ₂ / Raney Ni / 100 bar	98	98 / 2
4a	Me	C ₈ H ₁₇	H ₂ / PtO ₂ / 1 bar	75	96 / 4
4f	Me	CO ₂ Me	H ₂ / PtO ₂ / 1 bar	98	92 / 8
4c	CH ₂ OH	H	H ₂ / Raney Ni / 100 bar	96	94 / 6
4h	CH ₂ OH	CO ₂ Me	H ₂ / Raney Ni / 100 bar	98	94 / 6
4c	CH ₂ OH	H	H ₂ / PtO ₂ / 1 bar	75	80 / 20
4e	CH ₂ OH	C ₈ H ₁₇	H ₂ / PtO ₂ / 1 bar	80	87 / 13
4d	CH ₂ OH	C ₆ H ₁₃	H ₂ / PtO ₂ / 1 bar	80	94 / 6
4h	CH ₂ OH	CO ₂ Me	H ₂ / PtO ₂ / 1 bar	98	92 / 8

Chemical reductions of imines (4) and β -enamino esters (4) (R¹=CH₃) have permitted to prepare *trans*-pyrrolidines (2) leading to a slight excess of *trans*-isomer only when using sodium triacetoxyborohydride or B₂H₆, (as shown in Table 2). It can be noted that a mixture of LiAlH₄/Me₃Al, 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)

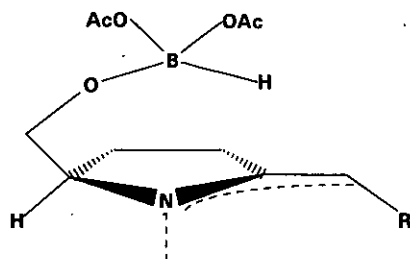
Imines or Enamines	R ¹	R	Reducing Agent	Yield %	Pyrrrolidines <i>Cis 3 / Trans 2</i>
4b	Me	C ₁₄ H ₂₉	LiAlH ₄ / Me ₃ Al ^b	75	70 / 30
4g	Me	CO ₂ Et	B ₂ H ₆ / THF ^b	65	40 / 60
4b	Me	C ₁₄ H ₂₉	NaBH ₄ / MeOH ^b	90	50 / 50
4f	Me	CO ₂ Me	NaBH ₄ / MeOH ^b	95	50 / 50
4a	Me	C ₈ H ₁₇	NaBH ₄ / AcOH ^b	70	40 / 60
4g	Me	CO ₂ Et	NaBH ₄ / AcOH ^b	92	50 / 50
4c	CH ₂ OH	H	LiAlH ₄ / Me ₃ Al ^b	75	70 / 30
4h	CH ₂ OH	CO ₂ Me	B ₂ H ₆ / THF ^b	65	40 / 60
4c	CH ₂ OH	H	DIBAH / -78°C	50	45 / 55
4c	CH ₂ OH	H	NaBH ₄ / MeOH ^b	90	50 / 50
4h	CH ₂ OH	CO ₂ Me	NaBH ₄ / MeOH ^b	95	50 / 50
4h	CH ₂ OH	CO ₂ Me	NaBH ₄ / H ₂ SO ₄ ^b	50	50 / 50
4h	CH ₂ OH	CO ₂ Me	(CH ₃) ₄ NBH ₄ / H ₂ O ^b	84	50 / 50
4c	CH ₂ OH	H	NaBH(OAc) ₃ ^a / PhMe ^b	75	75 / 25
4c	CH ₂ OH	H	NaBH ₄ / AcOH / PhMe ^b	70	30 / 70
4h	CH ₂ OH	CO ₂ Me	NaBH ₄ / AcOH / PhMe ^b	92	50 / 50
4c	CH ₂ OH	H	NaBH ₄ / AcOH / Ph Me / -10°C	80	15 / 85
4d	CH ₂ OH	C ₆ H ₁₃	NaBH ₄ / AcOH / Ph Me / -10°C	60	30 / 70
4h	CH ₂ OH	CO ₂ Me	NaBH ₄ / AcOH / MeCN ^b	80	30 / 70
4h	CH ₂ OH	CO ₂ Me	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 diastereocontrolled carbamatation leading to pure *cis* or *trans* compounds.¹¹

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