Tetrahedron Letters,Vol.30,No.9,pp 1081-1082,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

REDUCTION OF 2,5-DIALKYLPYRROLINES . A KEY STEP IN A SYNTHESIS OF NATURAL INSECTICIDES

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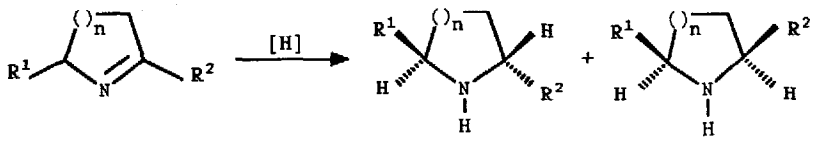
Abstract : The reduction of 2,5-dialkylpyrrolines can be run with a correct selectivity.

We have recently shown that the venom of the ant *Monomorium Minutum* is composed of five alkaloids : two pyrrolines **1a** and **1b** and three trans pyrrolidines **2a**,**b** and **c**[1,2].



1 **2** **3**

	n	R^1	R^2
a	1	$-(CH_2)_7-CH=CH_2$	$-(CH_2)_4-CH=CH_2$
b	1	$-(CH_2)_8-CH_3$	$-(CH_2)_4-CH=CH_2$
c	1	$-(CH_2)_8-CH_3$	$-(CH_2)_5-CH_3$
d	1	$-CH_3$	$-(CH_2)_8-CH_3$
e	1	$-CH_3$	$-(CH_2)_{14}-CH_3$
f	1	$-CH_3$	$-(CH_2)_9-CH=CH_2$
g	2	$-(CH_2)_{10}-CH_3$	$-CH_3$
h	2	$-CH_3$	$-(CH_2)_{10}-CH_3$

2,5-Dialkylpyrrolidines can be obtained by the aminoreduction of 1,4-diketones as 1/1 cis and trans mixture[3], like by the bis alkylation α-to the amino group of formamidines[4]. The stereospecific mercurycyclization[5] of unsaturated amines or other nitrogen derivatives, leads to a stereoselectivity of the reduction by borohydride, which removes the mercury atom.Reduction of pyrroles[6],Δ-3 pyrrolines or cyclic iminiums[7] is more cis selective, but excluded for unsaturated substituents.
Only one stereospecific synthesis of trans 2,5-dialkylpyrrolidines has been described, using a bis nitrone-alkene cycloaddition reaction[8], which is inefficient with ω-dienes.
Recently, H.Yamamoto[9] reported a highly stereoselective reduction of 2,6-dialkylpiperideine **1g** by DIBAH leading either to the cis piperidine **3g** or to the trans piperidine **2g** using [$LiAlH_4$-Me_3Al] and we checked that the same stereoselectivity is observed for the reduction of the piperideine **1g** when a long chain is present instead of a methyl substituent.
Three models of natural pyrrolines were used to run the reduction with hydride reagents : **1d** and **1c** with a long alkyl chain and **1f** with an alkenyl substituent.

Dedicated to Professor A.R. Katritsky, FRS, on the occasion of his 60th birthday.

Table 1 : Stereoselectivity in the reduction of the imine 1 with hydride reagents[a]

Run	Compound	Hydride reagent	Solvent	Ratio[b](2:3)
1	1h	$LiAlH_4$(7 eq)-Me_3Al(7 eq)	THF	95:5
2,3,4	1d,e,f	DIBAH(4 eq)	CH_2Cl_2	0:100
5	1f	DIBAH(4 eq)-$Ti(OiPr_2)_4$(7 eq)	CH_2Cl_2	0:100
6	1d	$LiAlH_4$(25 eq)	Et_2O	20:80
7	1e	$LiAlH_4$(7 eq)-$Ti(OiPr_2)_4$(7 eq)	THF	20:80
8	1e	$LiAlH_4$(7 eq)-$TiCl_4$(7 eq)	THF	30:70
9	1f	$LiAlH_4$(7 eq)-Me_3Al(7 eq)	Et_2O	40:60
10	1f	$LiAlH_4$(7 eq)-Me_3Al(7 eq)	THF	10:90
11	1e	$LiAlH_4$(7 eq)-$Ni(acac)_2$(7 eq)	Et_2O	30:70
12	1f	$NaBH_3CN$(3 eq)-HCl	MeOH	50:50
13	1e	$NaBH_3CN$(3 eq)	AcOH	35:65
14,15	1e,f	$NaBH_4$(3 eq) or (10 eq)	EtOH or Et_2O	50:50
16,17	1e	$NaBH_4$(10 eq)-$TiCl_4$(6 eq)	CH_2Cl_2 or Et_2O	40:60
18	1e	$NaBH_4$(3 eq)-$NiCl_2$(5 eq)	EtOH	40:60
19	1f	$NaBH_4$(3 eq)-$PdCl_2$(1.3 eq)	EtOH	0:100
20	1e	$NaBH_4$(3 eq)	HCOOH	50:50
21	1e	$NaBH_4$(3 eq)	AcOH	70:30
22	1e	$NaBH_4$(3 eq)	iPrCOOH	55:45
23	1e	$NaBH_3(OAc)$ or $NaBH(OAc)_3$(3 eq)	THF	35:65
24	1e	$NaBH_4$(3 eq)-H_3BO_3(3 eq)	CH_2Cl_2	50:50
25	1e	$NaBH_4$(3 eq)-Silicagel	CH_2Cl_2	65:35

a-Unless specified, the experiment afforded 2 and 3 in >93% yield
b-The ratio was determined by ^{13}C n.m.r.

DIBAH always leads stereospecifically to the cis isomer 3 with or without Lewis'acid (entries 2-5) like the piperideine reduction of compound 1g. Besides, $LiAlH_4$ alone or in presence of $TiCl_4$, $Ti(O\text{-}iPr_2)_4$ or Me_3Al exclusively leads to the cis pyrrolidine; these results are in complete opposition to these obtained during the reduction of piperideine 1g (entries 6-11).Meanwhile, $NaBH_4$ gives an equal mixture of 2 and 3, but with $NiCl_2$ or $TiCl_4$ the major component obtained is always the cis isomer (entries 16-18). However, the cis pyrrolidine 3 can only be isolated in the presence of $PdCl_2$, but here, the C=C double bond is unfortunatly also reduced. To stereoselectively prepare the trans isomer 2, $NaBH_4$ reduction was carried out in acidic medium : acetic acid gives the best ratio (70:30). This reduction study will permit a stereoselective or specific access to natural pyrrolidines 2a-c which exhibit a very broad and significant insecticidal activity[1b].

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Aknowledgement:We are grateful to E.I.DuPont de Nemours,Wilmington for financial support.

(Received in France 14 December 1988)