Tetrahedron Letters,Vol.29,No.20,pp 2441-2444,1988   0040-4039/88 $3.00 + .00
Printed in Great Britain   Pergamon Press plc

REACTIONS OF SCHIFF BASE ANIONS WITH ELECTROPHILES :
ROLE OF THE INITIAL STEREOCHEMISTRY

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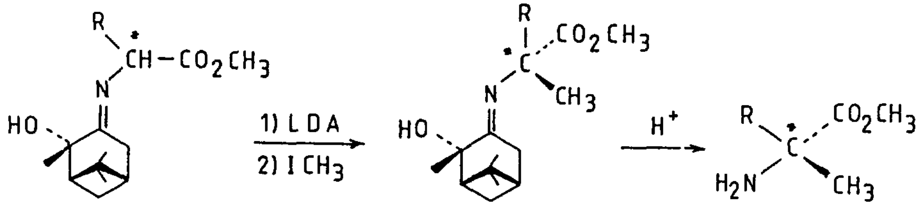
Abstract :*It is shown that the reactivity towards electrophiles of diastereomeric Schiff bases of *R and *S valine, leucine, phenylalanine and norvaline methyl esters with (1S,2S,5S) or (1R,2R,5R) 2-hydroxy 3-pinanone, is highly dependent on the stereochemistry of the starting product.*

In the asymmetric synthesis of α-disubstituted aminoacids and iminoacids[1] via diastereoselective alkylation of Schiff bases prepared from (1R,2R,5R) or (1S,2S,5S) 2-hydroxy 3-pinanone and D,L-aminoesters, we have shown that the chemical and optical yields depend on the substituent R present on the Schiff base before alkylation. In this paper we show that they depend also on the chirality of the substrat.

Firstly, we have investigated the alkylation of the two diastereomers 1a and 1b of the (1S,2S,5S) Schiff base of valine methyl ester (R = iC_3H_7) and we report here our surprising results.



1   2   3

R	*R	*S
$i-C_3H_7$	a	b
$i-C_4H_9$	c	d

R	*R	*S
CH_2Ph	e	f
$n-C_3H_7$	g	h

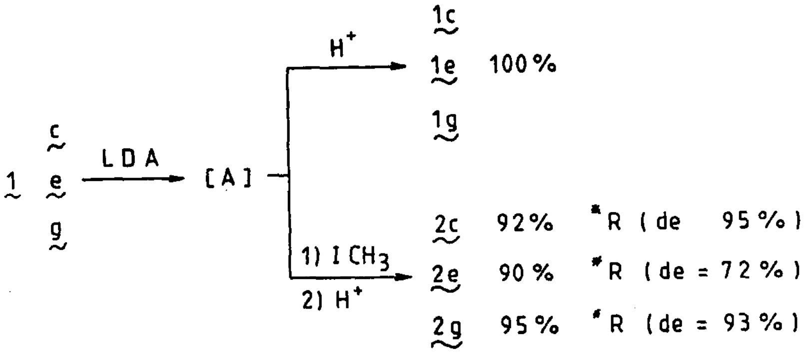
1a and 1b were easily separated by column chromatography (Kieselgel, Merck, ether-hexane 2/1). To lithium diisopropylamide (prepared from BuLi in ether) in THF 1a was added at -80°C ; after 30 min. methyl iodide was introduced, the temperature maintained at - 80°C during 5 h and allowed to reach 0°C in 12 h. 2a was obtained in 60% yield and de>95% (^{1}H-NMR, C_6D_6, only one product was detected). Hydrolysis with 15% citric acid afforded R α-methyl valine 3a (ee>95%).The enantiomeric purity was checked by ^{1}H-NMR spectroscopy in the presence of d-Eu(hfc)$_3$. A similar treatment of 1b resulted only in recovered 1b. In a further experiment, the intermediary lithium compound prepared from 1a was quenched with D_2O and the degree of deuteration (40%) was measured by ^{1}H-NMR and MS. Treatment of 1b in identical conditions gave only unchanged 1b; deuterium was not incorporated.

Seebach et al[2] have observed frequently only partial deuterium incorporation, when lithium enolates generated by lithium diisopropylamide were quenched with a D source. This was explained by a H-bonded complex between the amine and the Li derivative ; some crystalline Li-enolates solvates with secondary amines were isolated by these authors. This type of complex could be responsible for the partial deuteration of 1a ; for 1b it may be questioned whether the proton is removed or not.

The epimerisation of lithium compounds prepared from 1a and 1b was studied :

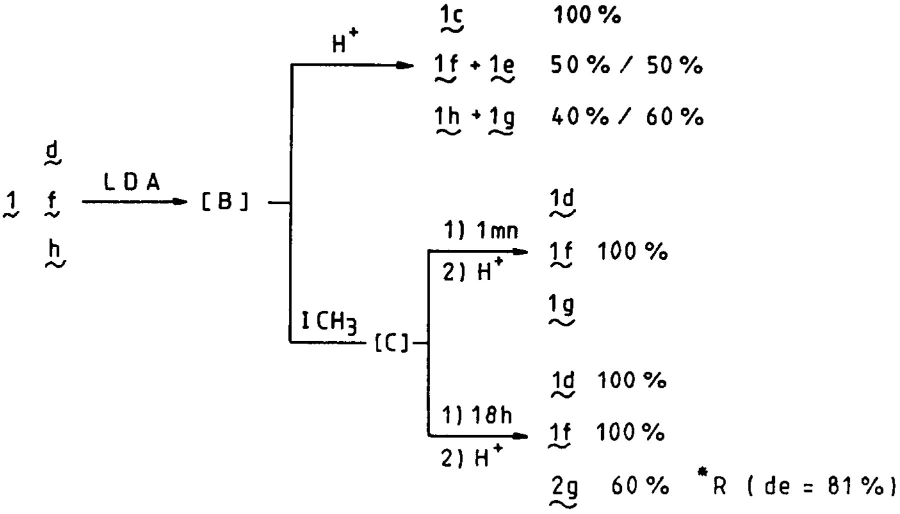
- For 1a no epimerisation at -10°C, only 20% epimerisation at -20°C.
- For 1b no epimerisation was detected even at + 20°C.

In order to ascertain the size effect of the substituent, 3 other Schiff bases with less bulky substituents were examined. The two diastereomers of each Schiff base : leucine methyl ester (R = iC_4H_9 1c, 1d) phenylalanine methyl ester (R = CH_2Ph 1e, 1f) and norvaline methyl ester (R = nC_3H_7 1g, 1h) were separated and treated with LDA and ICH_3 as previously described. The results are summarized in scheme II.



The diastereomers with *R chirality 1c, 1e, 1g in presence of LDA gave an intermediate [A] which after reprotonation led to the starting product; no epimerisation occurred. On treatment with methyl iodide, [A] gave the alkylated Schiff bases 2c, 2e, 2g with excellent chemical yields and optical yields ranging from 72 to > 95%. After hydrolytic cleavage with citric acid at + 20°C, R-aminoesters were obtained ;the alkylation took place with retention of configuration.

The isomers with *S chirality 1d, 1f, 1h in presence of LDA produced lithiated intermediates [B] which after aqueous acidic quenching led to total epimerisation for 1d and racemisation for 1f and 1h. [B] treated with methyl iodide and then immediately (1 mn) with H_2O, gave the starting products. Apparently, methyl iodide plays an important role in the stereochemistry of the new intermediate [C]. (Scheme III).



[B] left in presence of methyl iodide during 18 h led to the alkylated product 2g only from 1h (R = n-C_3H_7) ; after hydrolytic cleavage R-aminoester 3g (ee = 81%) was obtained, indicating that alkylation took place with inversion of configuration. In the other two cases the starting products 1d and 1f were recovered after acidic hydrolysis, to our astonishment no alkylation occurred, (scheme III). In conclusion diastereomers with *R chirality do not epimerise in presence of LDA and are alkylated by methyl iodide with retention of configuration. With the *S diastereoisomers, the behaviour depends on the subtituent R ; with a bulky one (R = i-C_3H_7) no reaction occurred, but it remains to be clarified whether the anion is formed or not. For the three other compounds, the anion is formed but is alkylated with inversion of configuration only when R = n-C_3H_7 .

Similar results were obtained with the Schiff base diastereomers prepared from (1R,2R,5R) 2-hydroxy 3-pinanone :the diastereomers with *S chirality reacted with electrophiles ; the reactivity of the *R diastereomers depended on the substituent R.

It is difficult to propose a model rationalizing these results, nevertheless they could be explained by a chiral anion, the lithium being tightly bonded to the carbon.

Experiments are in progress to confirm this assumption.

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(Received in France 2 January 1988)