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ALKYLATION AND PROTONATION OF CHIRAL SCHIFF BASES : DIASTEREOSELECTIVITY AS A FUNCTION OF THE NATURE OF REACTANTS

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Abstract : The factors controlling the diastereoselective alkylation and protonation reactions of chiral Schiff bases prepared from 2-hydroxypinan-3-one and α-aminoesters are reported : nature of the ester, of the alkylating agent and of the base.

For several years we have been engaged in the study of reactions of lithiated Schiff bases, prepared from 2-hydroxypinan-3-one[1] and α-amino esters, with electrophiles. So we have been able to prepare several optically pure mono and disubstituted α-amino acids[2], imino acids[3], functionalized amino acids[4]. The method has also been extended to the asymmetric synthesis of aminophosphonic acids[5], ß-lactams[6] and of constituents of natural products : H.C. Toxine[7], leucinostatine[8].

Several surprising results have been obtained from our previous studies :

a) alkylation in the reverse sequence preferentially gave the same Schiff base diastereomer[2].

b) the chirality of the starting aminoester plays a prominent role on the course of the reaction[9].

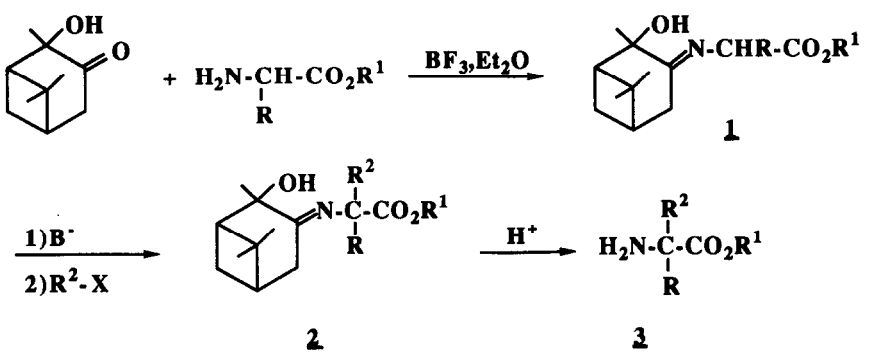
In order to clarify the mechanism of these reactions we were interested in investigating the factors influencing the steric course of the reaction and in particular :

a) the steric encumbrance of the ester substituant R^1,.

b) the substituant R present on the Schiff base before alkylation,

c) the nature of the alkylating agent R^2X,

d) the nature of the base,



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Recently SOLLADIE CAVALLO and coll[10], after the synthesis of DABA by this method, published a model which does not explain our results.

RESULTS

1) The steric encumbrance of the ester substituent R^1

The first results[1] in the laboratory were obtained with methyl esters because the methoxy group was very useful to determine the diastereoisomeric excesses by NMR. During the study on the synthesis of optically pure R amino acids at an industrial scale[11] by alkylation of Schiff bases(prepared from glycine esters and S,S,S 2-hydroxypinan-3-one) in presence of LDA (the dianion being generated by treatment of the Schiff base in THF at -80°C by two equivalents of LDA), we noticed that the chemical yield was not dependent on R^1 but the diastereomeric excess was related to the size of the ester group (Table I). So with R = t-Bu we could go from the first step : preparation of 2-hydroxy pinan-3 one to the last step : obtention of the amino acid without purification at any stage, only one cristallisation of the amino acid was necessary to obtain an analytical and optically pure sample.

Table I

R	R^1	R^2	Yield %	d.e. %
H	CH_3	ß-naphtyl CH_2	80	50
H	t-Bu	ß-naphtyl CH_2	80	>98
CH_3	CH_3	$CH_2 = CH - CH_2$	61	69
CH_3	i-Bu	$CH_2 = CH - CH_2$	57	>98
CH_3	t-Bu	$CH_2 = CH - CH_2$	7	>98

Starting from alanine ($R=CH_3$), both the chemical yield and the diastereomeric excess were dependent on R^1 ; so starting with α-substituted amino esters the t-Bu group cannot be used, the chemical yield is very poor, however the i-Bu group gave good results.

2) The substituent R present on the Schiff base before alkylation and the nature of the alkylating agent.

All the results described in Table II were obtained starting from Schiff bases prepared from R,R,R, 2-hydroxypinan-3 one and racemic α-amino acid methyl ester using as alkylating agent bromides (activated) iodides (non-activated) and LDA (two equivalents) as base in THF.

For the same alkylating agent the chemical yield and the diastereomeric excess depend on the substituent R (Table II compare entries 1 and 2, 3 and 4, 14 and 15).The d.e. are better with non activated alkylating agents than with activated ones (compare entries 2 and 3, 9 and 11..) In contrast Mc INTOSH[17] obtained higher d.e. with activated halides than with non-activated halides when camphor was used as chiral auxiliary. Recently YAOZHONG[18] described an excellent asymmetric synthesis of R and S α-substituted benzylamines by alkylation of a chiral ketimine prepared from 2-hydroxy pinan-3-one and benzylamine ; in this case diastereoselectivity was not dependent on the nature of the

alkyl halide. In our case, it seems that when the two substituents R and R^2 are of about the same size, the d.e. is bad (entries 2 and 15).

Table II

Entry	Product	R	R^2	Yield %	d.e. %	Amino ester Configuration	
1	2a	CH_3	CH_2-CH=CH_2	71	69	3a	S[12]
2	2b	n-C_3H_7	CH_2-CH=CH_2	72	16	3b	
3	2c	n-C_3H_7	CH_3	82	90	3c	S[13]
4	2d	i-C_3H_7	CH_3	30	>98	3d	S[14]
5	2e	i-C_4H_9	CH_3	46	>98	3e	
6	2f	Ph-CH_2	CH_3	47	77	3f	S[12]
7	2f	CH_3	$PhCH_2$	73	46	3f	S[12]
8	2g	i-C_4H_9	$PhCH_2$	68	42	3g	
9	2h	CH_3	CH_2-C=CH	78	52	3h	
10	2c	CH_3	n-C_3H_7	85	80	3c	S[13]
11	2d	CH_3	i-C_3H_7	69	>98	3d	S[14]
12	2i	H	-$(CH_2)_4$I	65	>98	3i	S[15]
13	2j	CH_3	-$(CH_2)_4$I	71	>98	3j	S[16]
14	2k	$PhCH_2$	-$(CH_2)_4$I	55	70	3k	
15	2l	n-C_3H_7	-$(CH_2)_4$I	56	5	3l	

Amino esters of the same configuration were obtained starting from the Schiff base of phenylalanine methyl ester and introducing a methyl substituent (entry 6) and starting from the Schiff base of alanine methyl ester and introducing a benzyl substituent (entry 7); the same is true for entries 4 and 11.. Recently FUKUMOTO[19] obtained a similar result during the alkylation of chiral half esters of monosubstituted malonic acids in presence of LDA ; in this case, there is an acid functional group and in our case an hydroxyl group which are additional chelating sites.

3) The nature of the base

In all cases reported to date, the dianion was generated using two equivalents of LDA in THF solution and thus two equivalents of diisopropylamine were present during the alkylation reaction.

We have examined the role of the base starting from the imine of alanine methyl ester with S,S,S 2-hydroxy pinan-3 one. Four bases have been studied (LDA, LTMP, t-BuOK, t-BuOLi). The results are summarized in Table III. With t-BuOLi the starting product was always recovered, the alkylation reaction does not occur, whatever the experimental conditions used. For the other three bases, the results show that the chemical yields are not affected by the base ;however the base plays a prominent role on the steric course of the reaction.The diastereomeric excesses are better with lithiated bases than with t-BuOK.

Table III

R^2	Base	Yield %	d.e. %	Configuration
$CH_3(CH_2)_2$	LDA	73	90	R
	LTMP	69	97	R
	t-BuOK	76	39	S
$Ph-CH_2$	LDA	70	44	R
	LTMP	68	54	R
	t-BuOK	76	24	S
$CH_2=CH-CH_2$	LDA	61	69	R
	LTMP	60	71	R
	t-BuOK	68	15	S

These results can be explained by different structures of the intermediates. In alkylation reactions, starting from the Schiff base of alanine methylester and S,S,S 2-hydroxy pinan-3 one, with LDA and LTMP, aminoesters of R configuration were obtained, wheras t-BuOK led to aminoesters of predominant S configuration. With this last base we have examined the steric course of the alkylation reaction by methyl iodide starting from the imine of phenylalanine methyl ester. At -90°C, the reaction is very rapid and gives two products : a monoalkylated one (on α-carbon) (51% yield, d.e. = 76%, R configuration) and a dialkylated one(on α-carbon and on the hydroxyl group of the pinanone) (9%) yield). If the reaction temperature is raised (-40°C) the percent of the monoalkylated product falls (37,5%) ; the dialkylated one is obtained in 62,5% yield. Finally, when t-BuOK is used in the reverse sequence, products of opposite configuration are obtained, the alkylating agent entering from the hydroxyl side.

In protonation reactions (CH_3CO_2H, pH=4) (Table IV) whatever the base, starting from the Schiff base prepared from S,S,S 2-hydroxy pinan-3 one and alanine ester, R amino esters were obtained. Like in the alkylation reactions the steric encumbrance of the ester plays a role, with the t-butyl ester no or partial epimerisation was detected.

Table IV

R^1	Initial Conf of the aminoester	Base	Yield	d.e	Conf.
CH_3	R + S	LDA	87	51	R
		LTMP	85	50	R
		t-BuOK	88	26	R
CH_3	R^{20}	LDA	88	68	R
		LDA ($+n-C_3H_7I$)	82	85	R
t-Bu	R	LDA	90	>98	R
t-Bu	S	LDA	90	95	S

CONCLUSION

All these results cannot be explained by the model of SOLLADIE CAVALLO, in particular the role of the ester group and the obtention of the same diastereomer after alkylation by the reverse sequence in presence of LDA.

Whatever the structures of the lithiated intermediates, it is probable that the alkylating agent enters the aggregates[21] before reaction, to produce an intermediate different in structure and/or solvation. This fact seems to be substantiated by the different results obtained in protonation reactions in absence or in presence of the alkylating agent(see Table IV and reference 9) .

So, to have more information we are beginning an NMR study of the different enolates.

EXPERIMENTAL

Reagents and solvents were purified in the usual way. LDA was prepared from BuLi in ether. Spectra were recorded with the following instruments : ^{1}H NMR : Varian EM 360 and Brucker 250. Mass Spectra : Jeol JMS DX 100 and DX 300. Optical rotations were determined with a Perkin Elmer model 141 polarimeter. Enantiomeric purity was checked by ^{1}H NMR spectroscopy on the aminoester (0.15-0.2 M $CDCl_3$/TMS in the presence of 0.2-0.6 mole equivalent of d-Eu(hfc)$_3$)

General procedure for reactions of Schiff bases with electrophiles

The Schiff base (1 mmol) dissolved in dry THF (5 ml) was added under nitrogen at -80°C to a stirred suspension of the base (2,3 mmol) in dry THF (16 ml), the mixture was stirred for 15 min. more. For the alkylation reactions, after the addition of the alkylating agent dissolved in THF (5 ml), the mixture was stirred at -80°C for 4H and allowed to reach slowly -30°C (14h). The reaction was followed by T.L.C. (Kieselgel Merck 60 F_{254})

For protonation reactions, at -80°C after 15 min (formation of the dianion) an aqueous solution of acetic acid was added (pH =4). In the two cases, the mixture was poured into a solution of NH_4Cl, the aqueous phase extracted with ether (3x70ml) ; the organic layer was dried ($MgSO_4$), evaporated (t<50°C) and the residue chromatographed over silica gel (eluent :ether-hexane).

2a (R = CH_3 R^2 = CH_2-CH=CH_2) Rf = 0.6 (2:3) MS EI M^+ : 293

^{1}H-NMR ($CDCl_3$) δ : 0.9 (s,3H); 1.35 (s,3H); 1.5 (s,3H); 1.53 (s,3H); 1.7-2.9 (m-9H); 3.8 (s,3H); 5.2-6.3 (m,2H); 5.7-6.3 (m,1H).

^{1}H-NMR (C_6D_6) δ : 0.73 (s,3H); 1.18 (s,3H); 1.5(s,3H); 1.6 (s,3H); 1.65-2.9 (m,9H); 3.46 (s,3H); 5.16 (m,2H); 5.76-6.3 (m,1H).

2b (R = n-C_3H_7) (R_2 = CH_2-CH=CH_2) Rf = 0.8 (3:2) MS EI M^+ : 321

^{1}H-NMR ($CDCl_3$) δ : 0.9 (s,3H); 0.92 (t,3H, J=6Hz); 1.32 (s,3H); 1.5 (s,3H); 1.55-2.9(m,13H); 3.78 (s,3H); 5.25 (m,2H); 5.6-6.1 (m,1H).

^{1}H-NMR (C_6D_6) δ : 0.76 (s,3H); 0.92 (t, 3H, J=6Hz); 1,16 (s,3H); 1.2-2.9 (m,1H); 3.4 (s,3H); 5,15 (m,2H); 5.9 (m,1H).

2c (R = n-C_3H_7 R^2 = CH_3) Rf = 0.35 (1:2) MS EI M^+ : 295. Anal. Calcd. for $C_{17}H_{27}NO_3$: C,69.62; H,9.21; N,4.77. Found C, 69.71 ; H,9.10; N,4.85.

^{1}H-NMR (CCl_4) δ : 0.85 (s,3H); 0.96 (t,3H,J = 6Hz); 1.3 (s,3H); 1.35 (s,3H); 1.38 (s,3H); 1.4-2.2 (m,8H); 2.3 (s,2H); 2.46 (s,1H); 3.68 (s,3H).

^{1}H-NMR (C_6D_6) δ : 0.7 (s,3H); 0.9 (t,3H, J=6Hz); 1.13 (s,3H); 1,43 (s,3H); 1.56 (s,3H); 1.2-2.3 (m,8H); 2.36 (s,2H); 2.7 (s,1H); 3.4 (s,3H).

2d (R = i-C_3H_7 R^2 CH_3) Rf = 0.46 (3:2) MS EI M^+ : 295

^{1}H-NMR ($CDCl_3$) δ : 0.9 (s,3H); 0.93 (d, 3H, J = 7Hz); 1.05 (d,3H, J=7Hz); 1.3 (s,3H); 1.35 (s,3H); 1.5 (s,3H); 1.8-2.5 (m,7H); 2.76 (s,1H); 3.8 (s,3H).

^{1}H-NMR (C_6D_6) δ : 0.76 (s,3H); 0.86 (d,3H, J=7Hz); 1.02 (d,3H, J=7Hz); 1.23 (s,3H); 1.36 (s,3H); 1.63 (s,3H); 1.7-2.5 (m,7H); 2.73 (s,1H); 3.5 (s,3H).

2e (R = i-C_4H_9 R^2 = CH_3) Rf : 0.66 (1:1) MS EI M^+ : 309.

^{1}H-NMR ($CDCl_3$) δ : 0.93 (s,3H); 0.96 (d,3H, J=2Hz); 1.06 (d,3H, J = 2Hz); 1.4 (s,3H); 1.55 (s,6H); 1.6-3 (m,10H); 4 (s,3H).

^{1}H-NMR (C_6D_6) δ : 0.7 (s,3H); ; 0.9 (d,3H, J=2Hz) ; 0.96 (d,3H, J= 2Hz); 1.12 (s,3H); 1.42 (s,3H); 1.52 (s,3H); 1.6-2.7 (m,10H); 3.34 (s,3H).

2f (R = Ph CH_2 R^2 = CH_3) Rf = 0.62 (2:1) MS EI M^+ : 343

^{1}H-NMR (CCl_4) δ : 0.76 (s,3H); 1.26 (s,6H); 1.35 (s,3H); 1.5-2.6 (m,7H) 3.1 (s,2H); 3.6 (s,3H); 7.2 (s,5H).

^{1}H-NMR (C_6D_6) δ :0.7 (s,3H); 1.16 (s,3H); 1.43 (s,3H); 1.6 (s,3H); 1.7-2.5 (m,8H); 2.86 (s,1H); 3.43 (s,3H); 7.33 (m,5H).

2g (R = i-C_4H_9 R^2 = Ph-CH_2) Rf = 0.60 (1:1) MS EI M^+ : 385

^{1}H-NMR (CCl_4) δ : 0.83 (s,3H); 0.9 (d,3H,J=6Hz); 1.0 (d,3H,J=6Hz); 1.3 (s,3H); 1.43 (s,3H); 1.5-2.4 (m,10H); 3.3 (m,2H); 3.55 (s,3H); 7.3 (s,5H).

^{1}H-NMR (C_6D_6) δ : 0.73 (s,3H); 0.86 (d,3H, J=6 Hz); 0.93 (d,3H,J=6Hz); 1.13 (s,3H); 1.6 (s,3H); 1.3-2.5 (m,10H); 3.33 (s,3H); 3.46 (m,2H); 7.15-7.7 (m,5H).

2i (R = H R^2 = -$(CH_2)_4$-I) Rf = 0.45 (6:1) MS EI M^+ : 421

^{1}H-NMR (CCl_4) δ : 0.85 (s,3H); 1.33 (s,3H); 1.45 (s,3H); 1.5-2.6 (m,13H); 3.15 (t,2H,J=6Hz); 3.7 (s,3H); 4.1 (t,1H, J=6Hz).

2j (R = CH_3 R^2 =-$(CH_2)_4$-I) Rf = 0.76 (4:1) MS EI M^+ : 435

^{1}H-NMR (CCl_4) δ : 0.9 (s,3H); 1.4 (s,3H); 1.46 (s,6H); 1.62-2.7 (m,13H); 3,43 (t,2H, J=6Hz); 3.98 (s,3H).

2k (R= Ph-CH_2 R^2= -$(CH_2)_4$ I) Rf = 0.54 (1:1) MS EI M^+ : 511

^{1}H-NMR (CCl_4) δ : 0.85 (s,3H); 1.3 (s,3H); 1.43 (s,3H); 1.4-2.5 (m,15H); 3.45 (t,2H, J= 6Hz); 3.63 (s,3H).

Transesterification reaction[20]

To Schiff base of alanine isobutyl ester (prepared from S,S,S 2-hydroxy pinan-3 one) (50 mmol) in dry MeOH (250 ml) is added freshly distilled $Ti(OiPr)_4$ (5 mmol). The mixture is refluxed 90 min. under N_2. The solvent is evaporated, the residue dissolved in ether (100 ml) is treated by water (5ml). The organic phase is decanted and dried ($MgSO_4$). After evaporation of the solvent the yellowish residue is chromatographed (silica gel-hexane/ether 3-2).

Hydrolysis of Schiff bases

The Schiff base (1.5 mmol) dissolved in a mixture of THF (7 ml) and 15% citric acid (6 ml) (pH = 2.5-3) was stirred at 25°C (for disubstituted imines) and at 0°C (for monosubstituted imines) during 24 to 72 h (followed by T.L.C.). After evaporation of THF under reduced pressure , the mixture was extracted with toluene (3x20 ml). The aqueous phase was neutralized by sodium carbonate (pH = 7 to 7.5) and extracted with ether (5x20 ml). The organic phase was dried ($MgSO_4$) evaporated under reduced pressure. If necessary the amino ester was purified on column chromatography (eluant : ether-methanol)

3a:(85%) $[\alpha]_D$ = -6° (c=2.3, $CHCl_3$) MS EI M^+ : 143

^{1}H-NMR (CCl_4) δ : 1.3 (s,3H); 1.5 (s,2H); 2.35 (m,2H); 3.78 (s,3H); 5.2 (m,2H); 5.55-6.1 (m,1H).

3c:(87%) $[\alpha]_D$ = + 17°.1 (c=0.84, $CHCl_3$) MS EI M^+ : 145

^{1}H-NMR (CCl_4) δ : 0.85-0.95 (m,3H); 1.1-1.65 (m,4H); 1.23 (s,3H); 1.3 (s,2H); 3.64 (s,3H).

3d :(77%) $[\alpha]_D$ = + 13°5 (c=2.4, $CHCl_3$) MS EI M^+ : 145.

^{1}H-NMR (CCl_4) δ : 0.85 (d,3H,J=4Hz); 0.95(d,3H,J=4Hz); 1.23(s,3H); 1.28(s,2H); 1.65-2.1 (m,1H); 3.8 (s,3H).

3f : (79%) $[\alpha]_D$ = + 3°.2 (c=3.16, $CHCl_3$) MS EI M^+ : 193.

^{1}H-NMR (CCl_4) δ : 1.35 (s,3H); 1.38 (s,2H); 2.68-3.18 (AB system 2H, J=15 Hz); 3.7 (s,3H); 7.26 (m,5H).

3j: (78%) $[\alpha]_D$ = +8°1 (c=5, $CHCl_3$) MS EI M^+ : 157.

^{1}H-NMR (CCl_4) δ : 1.25 (s,3H); 1.0-2.3 (m,6H); 2.5-3.3 (m,2H); 3.03 (s,1H); 3.7 (s,3H).

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