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Tertiary amines : a decisive factor in the stereoselective addition of (*R*)-pantolactone to N-phthalyl valine ketene

Monique Calmes*, Jacques Daunis, Nathalie Mai

Laboratoire des Aminoacides, Peptides et Protéines, UPRESA 5075, Universités Montpellier I et II

Place E. Bataillon, 34095 Montpellier cedex 5, France

Abstract *: The stereoselective base-catalyzed addition of (R)-pantolactone to the ketene derived from racemic N-phthalyl valine is reported. The R or S configuration of the newly generated asymmetric centre of the pantolactonyl ester is highly dependent on the tertiary amine catalyst employed.*

INTRODUCTION

As part of our work concerning amino acid deracemization,[1-3] we have explored the base catalysed stereoselective addition of an alcohol to various amino ketenes[4] derived from racemic amino acids.

Up to now this reaction has not been well documented. Pracejus[5] showed that in the presence of a chiral tertiary amine, addition of methanol to a phthalylamino ketene afforded the corresponding phthalylamino acid methyl ester in very modest to 33% enantiomeric excess. Hegedus[6] obtained amino acid esters in high diastereoisomeric excess by the stereoselective addition of achiral alcohols to chirally derivatized chromium amino ketene complexes generated by photolysis of the corresponding chromium amino carbene complexes.

In previous work[2,3] we considered a simpler way *viz.* the triethylamine catalyzed diastereoselective addition of a chiral alcohol to various phthalylamino ketenes. As chiral alcohol we used (*R*)-pantolactone which is both very efficient[2,3,7] and commercially available. Rather unexpected results were obtained depending on the amino acid used. In the case of arylglycine ketenes, a very high stereoselectivity (d.e.>97%) was obtained at -78°C and the newly generated stereogenic centre of the phthalylamino acid pantolactonyl ester had the *R*-configuration. On the contrary, with alkylglycine ketenes, this new centre had the *S*-configuration and the stereoselectivity depended greatly on the bulkiness of the amino acid side chain. Depending on the experimental conditions, this diastereoselectivity was better when the reaction was carried out at 0°C, ranging from 63 to94% for unbranched amino acids but being very modest (*d.e.*<42%) for branched amino acids (leucine and valine).

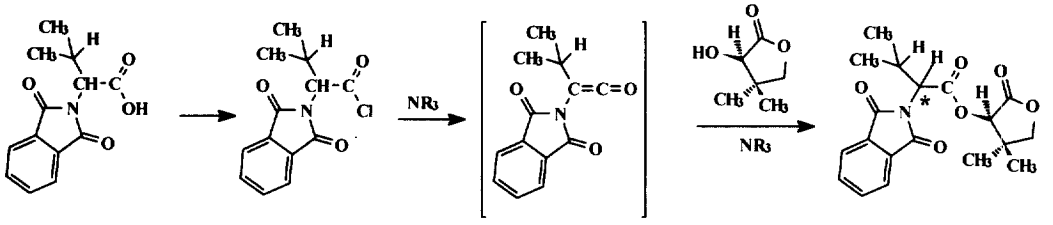
Our aim was to uncover factors promoting stereoselectivity in the addition of (R)-pantolactone to

* Corresponding author. E. mail : monique@ampir1.univ-montp2.fr ; Fax : 04 67 14 48 66

alkylglycine ketenes at 0°C, in order for this methodology to be considered as a possible alternative to the present popular stereoselective protonation of amino ester enolates,[8] a reaction which is very efficient but generally only at low temperatures (-78°C). We considered two factors capable of improving the diastereoselectivity of the addition of (*R*) pantolactone to amino ketenes : the solvent and the tertiary amine used as catalyst. Indeed, it has been previously reported that diastereoisomeric excesses of aryl propionic acid esters resulting from the stereoselective addition of alcohol to the corresponding ketenes were solvent and base dependent.[9-12] Moreover, it was noted in two papers that, depending on the catalyzing base, the *d.e.* could be strongly modified and, surprisingly, stereoselectivities could even be inverted. Thus, in the base catalyzed addition of methanol to the phenyl methyl ketene,[11] replacing the N-benzyl-(*S*)-prolinol propionate catalyst with a polymer counterpart (N-benzyl-(*S*)-prolinol polyacrylate) methyl esters with opposite optical rotations were obtained. Moreover, in the case of addition of (*R*)-pantolactone to ketene derived from ketoprofen,[12] the predominance of one or the other diastereoisomeric pantolactonyl ester also depended on the tertiary amine catalyst (triethylamine or DBU).

RESULTS

In order to assess the influence of these two factors, we selected the very hindered racemic N-phthalyl-valine as a test amino acid, since, under the previously considered conditions,[3] it afforded the corresponding (*R*,*R*)-pantolactonyl ester in both low selectivity and yield (Scheme 1). All the reactions were carried out at 0°C, since, at lower temperatures, the reactivity was very poor and at higher temperatures the stereoselectivity decreased.



Scheme 1

Firstly we considered solvents of different polarities (Table 1). Under standard conditions, *i.e.* addition of a mixture of triethylamine and (*R*)-pantolactone to N-phthalyl valine acid chloride, yields are very similar, ranging from 73 to 83%, except for chlorobenzene. It seems very difficult to correlate polarity with *d.e.* Since the best *d.e.* (42%) resulted from the use of THF, it was used as solvent in all subsequent experiments.

Table 1 : Solvent dependence of the diastereoselectivity of N-phthalyl valine pantolactonyl ester

solvent	polarity	yield	*d.e.*% of ester	C_α config
CS_2	0.15	79	31	*S*
toluene	0.29	83	34	*S*
chlorobenzene	0.30	42	23	*S*
dichloromethane	0.42	73	32	*S*
THF	0.45	80	42	*S*
acetonitrile	0.65	81	9	*S*

Base : $N(C_2H_5)_3$; temperature : 0°C

We then replaced triethylamine by bases of various bulkiness or basicity, the results being recorded in Table 2. We first used trimethylamine since Pracejus[5] showed that starting from a bulky phthalylamino acid chloride, such as ter-leucine, the corresponding ketene was more easily generated with trimethylamine than with the sterically more bulky triethylamine. In the case of N-phthalyl valine acid chloride, the use of trimethylamine led to an improvement in both chemical yield and *d.e.* of the corresponding pantolactonyl ester (entry 1). But surprisingly, the generated stereogenic centre has the *R*-configuration in place of the *S*-configuration found when triethylamine is used. With slightly bulkier bases (entries 2 and 3), the percentage of the *R,R* diastereoisomer decreases and that of the *S,R* diastereoisomer increases.

Further increase in base bulkiness (entries 5 and 6) gave rise to a drastic drop in *d.e* and no selectivity could even be observed.

For all the previous amines, the nitrogen may be inverted thus sterically hindering the approach of a nucleophile. Accordingly, we next used tricyclic tertiary amines[13] (entries 7 and 8) for which inversion at nitrogen is impossible. In this case, the *(R,R)*-configuration of the ester was favored and both chemical yield and *d.e.* were close to those resulting from the use of trimethylamine. Likewise, with pyridine or collidine (entries 9 and 10) the generated stereogenic centre had the *R*-configuration but yields were very low, particularly in the case of a bulkier pyridine (entry 11) for which the esterification did not occur. With very basic bulky bases, DBU or phosphazene base P_1-Bu^t (entries 12 and 13), chemical yields were high but no selectivity was obtained in both cases.

We then tried to improve the *d.e.* of the ester by using a chiral base (double induction, entries 14-16). Only (-) nicotine (entry 16) gave good results, comparable to those resulting from the action of $N(CH_3)_3$. In order to know if the 71% *d.e.* was the result of a matching or a mismatching effect with *(R)*-pantolactone, we repeated the reaction using *(S)*-pantolactone (entry 17). In this case the *d.e.* strongly decreased and the C_α configuration was inverted.

This one-pot reaction takes place in two steps from acid chloride : first dehydrochlorination with a stoichiometric amount of base to provide the ketene, followed by base-catalyzed stereoselective addition of alcohol. Each step certainly requires different basic properties.

Table 2 : Base dependence of the diastereoselectivity of N-phthalyl valine pantolactonyl ester

entry	base	yield	*d.e.*% of esters	C_α config
1	$N(CH_3)_3$	85	75	*R*
2	$N(CH_3)_2C_2H_5$	84	36	*R*
3	$N(C_2H_5)_2CH_3$	83	11	*R*
4	$N(C_2H_5)_3$	80	42	*S*
5	N-methyl morpholine	77	5	*S*
6	DIEA	71	0	*rac*
7	quinuclidine	90	72	*R*
8	DABCO	79	66	*R*
9	pyridine	16	15	*R*
10	collidine	7	66	*R*
11	2,6-diBu^t-4-methyl pyridine	0	-	-
12	DBU	88	0	*rac*
13	phosphazene base P_1-Bu^t	99	0	*rac*
14	(-) brucine*	0	-	-
15	(-) sparteine	15	7	*S*
16	(-) nicotine	81	71	*R*
17	(-) nicotine**	78	47	*S*
18	(-) N,N'-dimethyl phenylethylamine	79	0	*rac*
19	$N(C_2H_5)_3$/DIEA	78	25	*S*
20	$N(CH_3)_2C_2H_5$/DIEA	82	41	*R*
21	$N(C_2H_5)_3$/DABCO	98	64	*R*
22	$N(C_2H_5)_3$/quinuclidine	68	66	*R*
23	$N(C_2H_5)_3$/pyridine	57	15	*R*
24	$N(C_2H_5)_3$/collidine	91	70	*R*
25	$N(CH_3)_2C_2H_5$/collidine	77	59	*R*
26	$N(C_2H_5)_3$/2,6-diBu^t-4-methyl pyridine	52	39	*S*
27	$N(CH_3)_2C_2H_5$/2,6-diBu^t-4-methyl pyridine	87	40	*R*
28	$N(C_2H_5)_3$/(-) nicotine	81	53	*R*
29	$N(CH_3)_2C_2H_5$/(-) nicotine	87	48	*R*
30	$N(CH_3)_2C_2H_5$/PBu^t_3	79	33	*R*
31	$N(CH_3)_2C_2H_5$/$P(C_6H_5)_3$	78	34	*R*
32	$N(C_2H_5)_3$/PBu^t_3	81	41	*S*
33	$N(C_2H_5)_3$/$P(C_6H_5)_3$	79	42	*S*
34	$N(C_2H_5)_3$/LiCl	97	40	*R*
35	$N(CH_3)_2C_2H_5$/LiCl	94	43	*R*
36	$N(CH_3)_3$/LiCl	96	80	*R*
37	quinuclidine/LiCl	97	67	*R*
	quinuclidine/LiCl -30°C	96	85	*R*

Solvent : THF; temperature : 0°C, *brucine is insoluble in THF, **with (*S*) pantolactone

Indeed with some bases, such as collidine, 2,6-diterbutyl-4-methyl pyridine or sparteine, the ketene could not be easily formed since esters were obtained in very poor chemical yields. However, these might be good catalysts.

Accordingly, we used successively two different bases : a stoichiometric amount of dimethylethylamine or triethylamine to provide the ketene and, after a short time, simultaneous addition of 0.5 equivalents of the catalyzing base and of the chiral alcohol.

In most cases, addition of the second base altered the *d.e.* with respect to the use of 1.5 equivalents of the first base alone. Addition of DIEA did not modify the *S* or *R*-configuration resulting from the sole use of $N(C_2H_5)_3$ or $N(C_2H_5)_2CH_3$ (entries 19 and 20). However, in the first case the *d.e.* decreased (42 to 25%) whilst it did not change in the second case. On the contrary, in the case where $N(C_2H_5)_3$ was first added, the subsequent addition of DABCO, quinuclidine or pyridine derivatives with (*R*)-pantolactone (entries 21-24) promoted the opposite *R* configuration. The results were close to those obtained when the second base was used alone (entries 7 and 22, 8 and 21, 9 and 23, 10 and 24). Both the cases involving collidine (entries 24 and 25) are exemplary; the *d.e.'s* were close to those resulting from the use of collidine alone (entry 10), but chemical yields were high (91 and 77% instead of 7%). Probably the first base afforded the ketene whilst collidine was the catalyzing base. The addition of the very bulky 2,6-diterbutyl-4-methyl pyridine following the action of $N(C_2H_5)_2CH_3$ or $N(C_2H_5)_3$ in neither cases gave a notable modification of the *d.e.* (entries 26 and 27).

When the second base was (-) nicotine (entries 28 and 29), the *R* configuration was promoted as observed when nicotine was the sole base; in both cases the *d.e.*'s were slightly decreased.

We then replaced the tertiary amine catalyst by a phosphine (entries 30-33), but there were no obvious changes or improvements compared to the use of $N(CH_3)_2C_2H_5$ or $N(C_2H_5)_3$ as sole base.

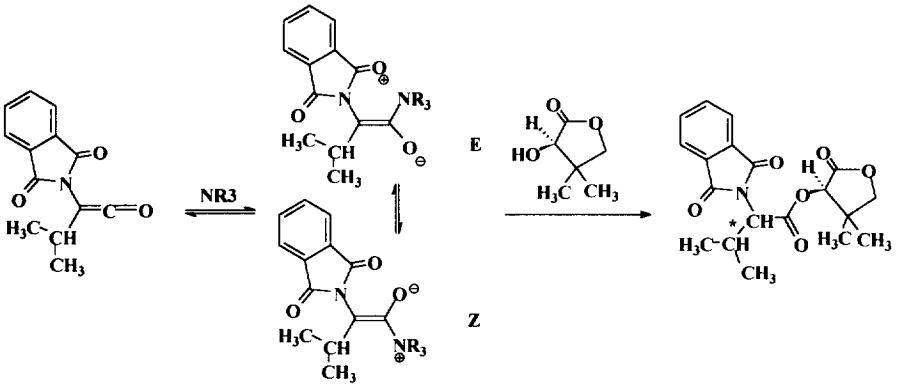
In summary, no general improvement resulted from the use of two successive bases; only collidine associated with $N(C_2H_5)_3$ gave improvements in both yield and *d.e.*

Finally we introduced additives into the reaction mixture (LiCl, LiOTf, KCl, $ZnCl_2$, $MgBr_2$ or $Ti(OiPr)_4$) before addition of the $N(C_2H_5)_3$ /pantolactone mixture. An unexpected influence of such additives has been noted in the case of the asymmetric alkylation of enolates.[14] In our case only LiCl modified the course of the reaction, the others being ineffective. With LiCl, the reaction was very clean and the esterification very fast (the reaction went to completion in 15 minutes instead of 1 h). The chemical yield was almost quantitative and the configuration of the newly generated stereogenic centre (*d.e.*= 40%) was opposite to that resulting from the same reaction carried out in the absence of an additive (entry 34). A 0.2 equivalent of LiCl was sufficient to catalyze the reaction, but a 0.7 equivalent gave the best results. The best reaction temperature was always 0°C, since at -20°C or at +20°C the *d.e.'s* were lowered (respectively to 22% and 24%). Replacement of $N(C_2H_5)_3$ by $N(CH_3)_2C_2H_5$ modified neither the diastereoselectivity nor the yield (entry 35). The best *d.e.'s* were obtained by associating LiCl with less sterically hindered tertiary amines, trimethylamine at 20°C (entry 36) or quinuclidine at -30°C (entry 38). The *R,R* diastereoisomer was then obtained in 85% *d.e.*

In conclusion, we have emphasized the vital role of the catalyzing tertiary amine in the stereoselective addition of (*R*)-pantolactone to the N-phthalyl valine ketene and the base dependency of the obtained *R,R* or *S,R* diastereoisomer. Moreover, we showed that LiCl is a very expedient additive, as already reported for enolates.[14]

It may greatly improve both chemical yields and *d.e.* and in all cases it promoted the *R,R* diastereoisomer whatever the base.

Several possible mechanims of base-catalyzed addition of alcohols to ketenes have been proposed and discussed in the literature.[4,5] From our results, it seems that the determining step (Scheme 2) was the formation of two E and Z enolate-like species in equilibrium, the E/Z ratio being dependent on the tertiary base. Each species next reacted stereoselectively with (R)-pantolactone to afford the corresponding *R,R* or *S,R* ester. The remarkable effect on the stereoselectivity of LiCl is difficult to rationalize. It was probably the result of a E/Z ratio change of the enolate-like species resulting from possible mixed aggregate as already observed for enolates[14].



Scheme 2

In the case of very basic amines, such as DBU or phosphazene base P_1-Bu^t (entries 12 and 13) a racemic product was obtained. Probably, under our experimental conditions (addition of a mixture of amine and alcohol to an acid chloride), a strong base was able to first afford the alcoholate before ketene formation which then rapidly substituted the acid chloride without modification of the configuration of the Cα of the starting acid chloride. Conversely, when such a strong base was added before addition of pantolactone, the yields dropped drastically and the *d.e.*'s were low, as previously observed.[3]

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EXPERIMENTAL

Tetrahydrofuran (THF) was freshly distilled under argon from sodium and benzophenone; triethylamine (NEt_3) was distilled from KOH and ninhydrin. Thin layer chromatography (tlc) was carried out on silica gel (60 F_{254}, Merck 5715) and spots revealed with UV light or iodine vapours (eluent : ether/hexane 8/2).

Diastereoisomeric excesses (*d.e.*) were determined on crude products from ^1H NMR spectra (DMSO-d_6) by integration of the 3'-C*H* signal of the (*R*)-pantolactonyl moiety of the couple of diastereoisomers and / or by HPLC (column Chirasphere Merck, 25cm x 4mm, flow : 1ml/min, hexane/*iso*propanol 90/10).

(*R,R*) or (*S,R*) N-phthalyl valine pantolactonyl esters

To a mixture of *(R)* or *(S)* N-phthalyl valine (1 mmole), (*R*)-pantolactone (130mg, 1.1 mmoles) and 4-dimethylaminopyridine (0.05 equiv.) in 6 ml of CH_2Cl_2 was added 1 equivalent of dicyclohexylcarbodiimide (206 mg) at 0°C. The mixture was stirred at room temperature for 12 h, dicyclohexylurea was filtered off and the solution was evaporated under vacuum. The residue was poured into ethyl acetate (5 ml) and allowed to stand for 1 hour at -15°C. The remaining dicyclohexylurea was filtered off and the solution was washed successively with a saturated aqueous solution of citric acid (3 x 6ml) and saturated $NaHCO_3$ (3 x 6 ml). It was then dried over Na_2SO_4 and evaporated under vacuum. The white solid was purified by column chromatography (eluent : hexane/ethyl acetate 3/2)

(R,R) N-phthalyl-valine pantolactonyl ester

Mp = 88-89°C. $[\alpha]_D$ -14.9° (c=1, CH_2Cl_2). FAB/MS M+H$^+$ 360. ^1H NMR (DMSO-d_6) δ = 0.66 (s, 3H, 4'-*H*$_3$), 0.90 (d, J = 6.8 Hz, 3H, CHC*H*$_3$), 1.05 (s, 3H, 4'-C*H*$_3$), 1.12 (d, J = 6.8 Hz, 3H, CHC*H*$_3$), 2.66 (m, 1H, C*H*(CH$_3$)$_2$), 3.97 (d, J = 8.6 Hz, 1H, 5'-HC*H*), 4.11 (d, J = 8.6 Hz, 1H, 5'-HC*H*), 4.76 (d, J = 7.6 Hz, 1H, C*H*-COO), 5.70 (s, 1H, 3'-C*H*), 7.97 (m, 4H, *H*-phthalyl).$C_{19}H_{21}NO_6$ (359.38) : calcd.: C 63.50 % H 5.89% N 3.90%. Found : C 63.62% H 5.97% N 3.79%.

(S,R) N-Phthalyl-valine pantolactonyl ester

Mp = 106-107°C.$[\alpha]_D$: -22.8° (c=1, CH_2Cl_2). FAB/MS : M+H$^+$ 360. ^1H NMR (DMSO-d_6) δ = 0.98 (s, 3H, 4'-C*H*$_3$), 1.16 (s, 3H, 4'-C*H*$_3$), 0.90 (d, J = 6.8 Hz, 3H, CHC*H*$_3$), 1.12 (d, J = 6.8 Hz, 3H, CHC*H*$_3$), 2.66 (m, 1H, C*H*(CH$_3$)$_2$), 4.02 (d, J = 8.6 Hz, 1H, 5'-HC*H*), 4.12 (d, J = 8.6 Hz, 1H, 5'-HC*H*), 4.76 (d, J = 7.6 Hz, 1H, C*H*-COO), 5.65 (s, 1H, 3'-C*H*), 7.97 (m, 4H, *H*-phthalyl). $C_{19}H_{21}NO_6$ (359.38) : calcd.: C 63.50 % H 5.89% N 3.90%. Found : C 63.41% H 5.73% N 3.97%.

General procedure for the diastereoselective addition of (R)-pantolactone to N-phthalyl valine ketene

Method I

To a stirred solution cooled to 0°C of N-phthalyl-*(RS)*-valine chloride (1 mmole) in 3 ml of anhydrous THF, under argon, was added at 0°C a precooled solution of tertiary amine (1.5 equiv) and (*R*)-pantolactone (0.14 g, 1.1 mmoles) in 2 ml of THF. After 1 h at this temperature (the reaction was monitored by tlc, eluent : ether/hexane 8/2), a 1N citric acid solution (10 ml) was added and the reaction mixture was allowed to warm to room temperature. The solution was extracted with AcOEt (20 ml) and the organic layer was washed

successively with water, a saturated sodium bicarbonate solution, brine and dried over sodium sulfate. Evaporation under vacuum gave the pantolactonyl ester. Yields and d.e. are recorded in Table 2

Method 2

To a stirred solution cooled to 0°C of N-phthalyl-*(RS)*-valine chloride (1 mmole) in 3 ml of anhydrous THF, under argon, was added at 0°C a precooled solution in THF of 1 equiv of the first tertiary amine. After 1 minute a solution of 0.5 equiv of the second tertiary amine and (*R*)-pantolactone (0.14 g, 1.1 mmoles) in 3 ml of THF was added and the resulting solution was treated as previously. Yields and d.e. are recorded in Table 2

Method 3

Following method 1, the solution in THF of tertiary amine and (*R*)-pantolactone was added to a stirred solution of N-phthalyl-*(RS)*-valine chloride and LiCl (0.7 equiv). Yields and d.e. are recorded in Table 2

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