Pergamon

Tetrahedron Letters 40 (1999) 2891–2894

TETRAHEDRON LETTERS

The Stereochemistry of the Addition of Titanium Enolates of *N*-Propionyl-Oxazolidin-2-ones to 5- and 6-Membered *N*-Acyliminium Ions

Ronaldo A. Pilli,*[a] Conceição de Fátima Alves,[a] Maria Alice Böckelmann,[a] Yvonne P. Mascarenhas,[b] J. Geraldo Nery[b] and Ivo Vencato[c]

[a]*Instituto de Química, Unicamp, Cx. Postal 6154, 13083-970 Campinas, SP, Brazil*
[b]*Instituto de Física e Química, USP, São Carlos, Brazil*
[c]*Departamento de Química, UFSC, Florianópolis, SC, Brazil*

Received 24 December 1998; revised 15 February 1999; accepted 16 February 1999

Abstract

The stereochemistry of the addition of the *N*-propionyl titanium enolates **2a** and **2b** to 5- and 6-membered 2-ethoxycarbamates **1a-f** was investigated. The addition proceeded stereoselectively to afford the corresponding (**2S,1'S**)-2-substituted pyrrolidines as the major diastereoisomer. Despite the lack of reactivity between 2-ethoxypiperidine **1b** and *N*-propionyl titanium enolates **2a** and **2b**, less bulky carbamate groups on 2-ethoxypiperidines **1d** and **1f** restored reactivity and the corresponding 2-substituted piperidines were obtained in moderate to good yields although with poor diastereoselection.

Keywords: Titanium enolates, *N*-acyliminium ion, 2-substituted pyrrolidines and piperidines, β-amino acid derivatives.

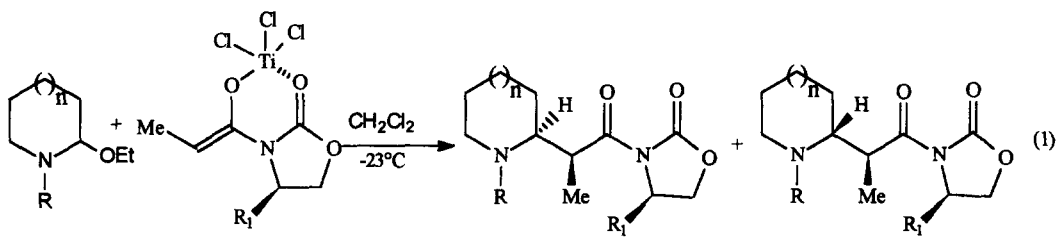
Despite their limited distribution in Nature, β-amino acids and their derivatives display relevant biological activity and are important building blocks for the construction of natural products, pharmaceutically active compounds and modified peptides with enhanced *in vivo* stability. Not surprisingly a number of methods for their enantioselective preparation are reported in the literature.[1,2] Among the synthetic approaches, the addition of chiral nucleophiles to imines stands as an attractive solution which has been particularly useful in the synthesis of chiral, non-racemic β-lactams.[3,4] Far less explored are methods for the preparation of cyclic α,β-disubstituted β-amino acids and their derivatives.

Nagao and coworkers first revealed that the addition of tin enolates derived from chiral 3-acyl-1,3-thiazolidine-2-thiones to 4-acetoxy-2-azetidinone, 5-acetoxy-2-pyrrolidinone and 6-acetoxy-2-piperidinone occured with high diastereoselection through a chelated six-membered transition state.[5] The method also performed well when applied to *N*-methyl 5-acetoxy-2-pyrrolidinone but the stereochemical outcome was different and an open transition state was proposed to account for the observed results.[6]

During our studies on the stereochemistry of the addition of prochiral and chiral carbon nucleophiles to cyclic *N*-acyliminium ions[7] we have investigated the addition of boron and titanium enolates to *N*-Boc-2-ethoxypyrrolidine (**1a**) and *N*-Boc-2-ethoxypiperidine (**1b**). Upon

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00398-6

addition of a CH_2Cl_2 solution of either 2-ethoxycarbamate **1a** or **1b** to a previously formed solution of achiral titanium(IV) enolate **2a** in CH_2Cl_2 at -23°C, a gradual fading of the deep burgundy color of the enolate solution was observed.[8] Racemic 2-substituted pyrrolidine **3aa** was isolated in 72% yield (**3aa**:**4aa**=14:1, Table 1), after column chromatography on silica gel (eq. 1). Surprisingly, the reaction did not proceed with 2-ethoxypiperidine **1b** even when the reaction mixture was allowed to stir at room temperature for several hours.



1a n=0, R=Boc
1b n=1, R=Boc
1c n=0, R=Cbz
1d n=1, R=Cbz
1e n=0, R=COOMe
1f n=1, R=COOMe

2a R_1=H
2b R_1=Bn

3aa-3fb

4aa-4fb

The diastereoselection observed in the formation of **3aa** led us to examine the impact of chiral nucleophile **2b** in the process. In the event, titanium enolate **2b** afforded 2-substituted pyrrolidines **3ab/4ab** in 80% yield as 9:1 mixture. The reaction of the boron enolates corresponding to **2a** and *ent*-**2b** with **1a** afforded (±)-**3aa** and *ent*-**3ab**, respectively, as a single diastereoisomer. The absolute configuration of *ent*-**3ab** was established by X-ray diffraction analysis as (2R,1'R) (Fig.1).[9] However, the proclivity to loose the Boc group depending on the batch of n-Bu_2BOTf employed and the non-reproducible yields led us to routinely employ the corresponding titanium (IV) enolates.

Basic hydrolysis of (-)-**3ab** and (+)-**4ab** (LiOH, H_2O_2, THF/H_2O, 0°C) afforded the corresponding optically pure β-amino acids ($[\alpha]_D$ -30,9 (c 4.1, CH_2Cl_2) and +71.1 (c 3.2, CH_2Cl_2), respectively) in 92% and 90% yield, respectively, which were shown to be diastereoisomeric by ^1H- and ^{13}C-NMR spectroscopy. However, the absolute configuration of the minor isomer **4ab** remains to be unambiguously established.

Less bulky carbamate groups as in 2-ethoxypiperidines **1d** and **1f** promoted reaction with titanium enolates **2a** and **2b** and the corresponding 2-substituted piperidines were obtained in moderate to good yields but with poor diastereoselectivity (Table 1). In one case, the (2S,1'S) stereochemistry of the major stereoisomer (**3db**) was firmly established by X-ray diffraction analysis (Fig. 2).[10]

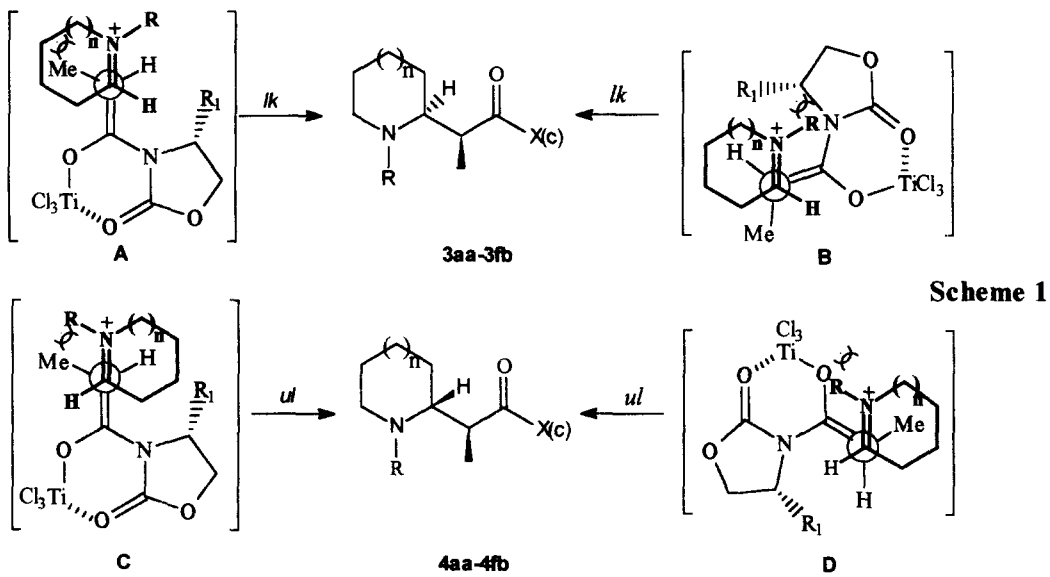
The reactions of the corresponding 2-ethoxypyrrolidines **1c** and **1e** with titanium enolates **2a** and **2b** were accompanied by some erosion of the diastereoisomeric ratio although with the same facial selection previously observed for **1a** (Table 1). As an example, removal of the *N*-Boc group (CF_3CO_2H, CH_2Cl_2, 0°C) and *N*-protection with $ClCO_2Bn$ or $ClCO_2Me$ (K_2CO_3, acetone, rt) of a 9:1 mixture of **3ab/4ab** afforded a 9:1 mixture of **3cb/4cb** or **3eb/4eb**, respectively.

Table 1

Entry	n	R	R_1	Product	Yield(3:4ratio)[a,b]
1	0	Boc	H	**3aa:4aa**	72% (14:1)
2	1	Boc	H	**3ba:4ba**	---
3	0	Boc	Bn	**3ab:4ab**	80% (9:1)[c]
4	1	Boc	Bn	**3bb:4bb**	---
5	0	Cbz	H	**3ca:4ca**	67% (6:1)
6	1	Cbz	H	**3da:4da**	50% (2:1)
7	0	Cbz	Bn	**3cb:4cb**	57% (4:1)
8	1	Cbz	Bn	**3db:4db**	50% (2:1)[c]
9	0	COOMe	H	**3ea:4ea**	36% (10:1)
10	1	COOMe	H	**3fa:4fa**	70% (1:1)[c]
11	0	COOMe	Bn	**3eb:4eb**	50% (5:1)
12	1	COOMe	Bn	**3fb:4fb**	61% (2:1)

[a] Diastereoisomeric ratio was determined in the crude mixture by ^{1}H-NMR spectroscopy (300 MHz) in $CDCl_3$ at 50°C; [b] Yields are reported after purification of the crude mixture by column chromatography; [c]Diastereoisomers separated by flash chromatography.

The preference for the *lk* topology[11] observed in the reactions involving **1a** and the lack of reactivity displayed by **1b** were ascribed to the steric hindrance between methylene groups in the half-chair conformation of the *N*-acyliminium ion corresponding to **1b** and the methyl group in **2b** during an antiperiplanar approach (see **A**, Scheme 1) which is partially relieved in the reactions involving the more flattened *N*-acyliminum ion derived from **1a**.



Scheme 1

A synclinal approach as depicted in **B** would be prevented in the reactions involving **1a** and **1b** due to the steric interactions between the Boc group and the oxazolidinone ring but would account for the formation of the major stereoisomer in the reactions of 2-ethoxypiperidines **1d** and **1f**. The decrease of the spacial requirements of the carbamate group in **1c** and **1e** would also allow the participation of a *ul* topology such as that depicted in **C** thus accounting for the lower diastereoselection observed in their reactions with **2a** and **2b**.

In summary, we have shown that the reactivity and the levels of diastereoselection in the reaction of *N*-carbamoyl-2-ethoxypyrrolidines and *N*-carbamoyl-2-ethoxypiperidines are modulated by the nature of the carbamate group. Chiral non-racemic 2-substituted pyrrolidine **3ab** was prepared in good yield and diastereoselection through the addition of chiral titanium enolate **2b** to *N*-Boc-2-ethoxypyrrolidine **1a**, providing a ready access to the corresponding β–amino acids. The application of this methodology[12] to the asymmetric synthesis of alkaloids and pharmacologically active piperidines is under investigation.

Acknowlegements. FINEP, FAPESP, FAEP-Unicamp, and CNPq for financial support and fellowships.

References and Notes

1. Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3.
2. Cole, D. C. *Tetrahedron* **1994**, *50*, 9517.
3. a) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383; b) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377.
4. Pilli, R. A.; Russowsky, D. *Trends in Organic Chemistry* **1997**, *6*, 101.
5. a) Nagao, Y.; Dai, W-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Am. Chem. Soc.* **1988**, *110*, 289; b) Nagao, Y.; Dai, W-M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Org. Chem.* **1990**, *55*, 1148; c) Nagao, Y.; Kumagai, T.; Nagase, Y.; Tamai, S.; Inoue, Y.; Shiro, M. *J. Org. Chem.* **1992**, *57*, 4232.
6. Nagao, Y.; Dai, W-M.; Ochiai, M. *Tetrahedron Lett.* **1988**, *29*, 6133.
7. a) Pilli, R. A.; Alves, C. F.; Böckelmann, M. A *11th International Conference on Organic Synthesis*, Amsterdam, **1996**, Book of Abstracts pp 71; b) Pilli, R. A.; Russowsky, D. *J. Org. Chem.* **1996**, *61*, 3187.
8. Evans, D. A.; Urpi, F.; Somers, T.C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215.
9. The addition of the di-n-butylboron enolate corresponding to *ent*-**2b** to **1a** afforded *ent*-**3ab** in 50% yield: $[\alpha]_D$ +39.6 (c 2.6, CH_2Cl_2); Mp: 178.0-178.8°C; ^{1}H-NMR (300MHz, 50°C, $CDCl_3$): δ 1.13 (d, 3H, J=6.5), 1.45 (s, 9H), 1.77- 1.88 (m, 1H), 1.88- 1.98 (m, 3H), 2.63 (dd, 1H, J=10.2 and 13.4), 3.26-3.32 (m, 1H), 3.40-3,60 (m, 2H), 4.11 (dd, 1H, J=3.5 and 9.0), 4.12 (dd, 1H, J=9.0 and 15.1), 4.26 (qt, J=5.6, 1H), 4.23-4.37 (m, 1H); 4.65 (m,1H); 7.19-7.35 (m, 5H). ^{13}C-RMN (75MHz, 50°C, $CDCl_3$): 12.4, 23.9, 28.4, 28.6, 28.6, 38.3, 40.7, 47.3, 57.8, 66.2, 79.5, 127.3, 129.0, 129.4, 135.8, 152.9, 154.8, 175.3; IR: 1782, 1691 cm^{-1}. Anal. Calc for $C_{22}H_{30}N_2O_5$: C, 65.65; H, 7.51; N 6.90. Found: C, 65.81; H, 7.45; N, 7.06. X-Ray analysis carried out by Y. P. Mascarenhas and J. G. Nery (Fig 1.). Lists of refined coordinates and esds have been deposited at the Cambridge Crystallographic Data Centre.
10. Compound (-)-**3db**: $[\alpha]_D$ -163.5 (c 1.3, CH_2Cl_2); Mp 123.2-123.9°C; ^{1}H-NMR (300MHz, 50°C, $CDCl_3$): δ 1.19 (d, 3H, J=6.2), 1.34-1.52 (m, 1H) , 1.54-1.70 (d, 4H, J=5.5), 1.74-1.90 (d, 1H, J=6.2), 2.50 (dd, 1H, J=8.2 and 11.2), 3.08-3.20 (m, 1H), 3.14 (dd, 1H, J=2.8 and 13.4), 4.02-4.22 (m, 3H), 4.59-4.78 (m, 3H), 5.05 (d, 1H, J=12.8), 5.11 (d, 1H, J=12.5), 7.00-7.50 (m, 10H); ^{13}C-NMR (75MHz, 50°C, $CDCl_3$): δ 15.2, 19.0, 25.4, 25.5, 36.0, 37.8, 40.2, 54.7, 55.3, 65.9, 67.1, 127.3, 127.9, 128.0, 128.5, 129.0, 129.6, 135.7, 137.3, 153.8, 155.6, 175.9; IR: 1776, 1770 cm^{-1}; HRMS: calcd for $C_{26}H_{30}N_2O_5$: 450.2155; found: 450.2152. X-Ray analysis carried out by I. Vencato (Fig 2.). Lists of refined coordinates and esds have been deposited at the Cambridge Crystallographic Data Centre.
11. For an unambiguous specification of the steric course of asymmetric syntheses, see: Seebach, D.; Prelog, V. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 654.
12. A representative experimental procedure follows: To a soln. of $TiCl_4$ (1.1 equiv.) in CH_2Cl_2 (2.5 mL) at 0°C was added a soln. of (R)-4-benzyl-N-propionyl-2-oxazolidinone **2b** (1.0 equiv.) in CH_2Cl_2 (2.0 mL) followed by the addition of diisopropylethylamine (1.1 equiv.) after 5 min. The reaction mixture was stirred at 0°C for 1 h and then cooled to -23°C when a soln. of α-ethoxycarbamate **1a** (1.1 equiv.) in CH_2Cl_2 (4.5 mL) was added dropwise. The reaction mixture was stirred at -23°C for 45 min., and then quenched with satd. aq. NH_4Cl (4.0 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (9:1 hexane-ethyl acetate as eluent) to afford **3ad** (72% yield) and **4ad** (8% yield).

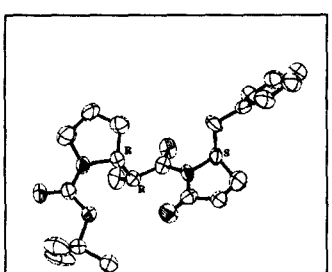


Fig 1. ORTEP drawing of *ent*-**3ab**.

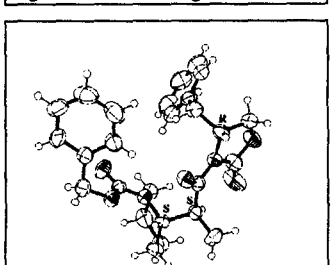


Fig 2.ORTEP drawing of (-)-**3db**.