First International Electronic Conference on Synthetic Organic Chemistry (ECSOC-1), www.mdpi.org/ecsoc/, September 1-30, 1997

[A0007]

(S)-6-Isopropyl-5-Phenyl-1,2,3,6-Tetrahydro-2-Pyrazinone: A New Chiral Glycine Equivalent for the Synthesis of (Z)-a,b-Didehydro-a-Amino Acid Derivatives

Tomas Abellan, Carmen Najera* and Jose M. Sansano

Departamento de Quimica Organica, Universidad de Alicante. E-03080 Alicante, Spain. Tel. +34 6 5903728, Fax +34 6 5903549, E-mail: cngroup@ua.es

Received: 14 July 1997 / Uploaded: 21 July 1997/Updated: 17 September 1997

With biographical summary

Abstract: The preparation of *N*-Boc-protected (*S*)-6-isopropyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone from (*S*)-valine and glycine in seven steps and its reactivity with carbonyl compounds affording stereoselectively (*Z*)-didehydroamino acids derivatives is reported in this communication.

Keywords: Amino acids-didehydro, phase-transfer catalysis, carbonyl compounds, tetrahydro-2-pyrazinone.

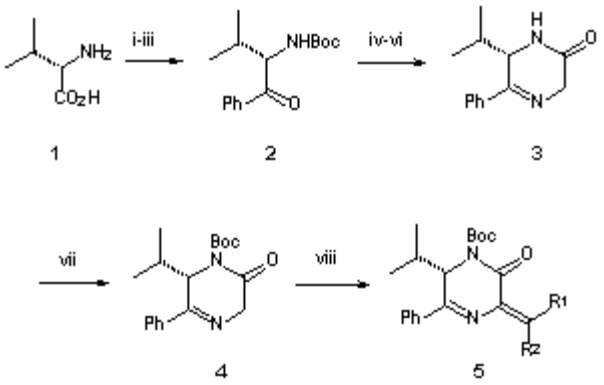
Introduction

a,b-Didehydro-a-amino acids (DDAAs) derivatives are important components of peptides and direct precursors of a-amino acids owing to the recent achievements in the asymmetric hydrogenation as well as in Michael type additions, cyclopropanation and Diels-Alder reactions [1-4]. Naturally occurring molecules such as azinomicins and phytotoxic proteins contain this atomic array in their structures, and it is well known that *N*-acyl DDAAs derivatives increase the activity of b-lactamic antibiotics. In this communication we report the preparation of a new chiral glycine equivalent with pyrazinone structure and its use for the stereoselective synthesis of chiral DDAAs derivatives [5].

Discussion

The glycine iminolactam **4** was prepared from (*S*)-valine **1** in a seven-step route in 58% overall yield. Amino acid **1** was transformed into the b-amino ketone **2** (78% yield) which, after deprotection, was acylated with glycine and cyclized to the pyrazinone **3** (85% yield). Finally, the amido group of compound **3** was protected with di-*tert*-butyldicarbonate and a catalytic amount of 4-dimethylaminopyridine (DMAP) obtaining the pyrazinone **4** (87% yield).

The reaction of pyrazinone **4** with aldehydes and acetone under solid-liquid phase-transfer catalysis, using tetra-*n*-butylammonium bromide (TBAB) and potassium carbonate in dry acetonitrile at room temperature, afforded DDAAs derivatives **5** in good yields. The proposed (*Z*)-configuration of **5** was assigned according to the reported C-H coupling constants between the carbonyl group and the methyne group[2b. By other hand, the methylene derivative was generated upon reaction of **4** with Eschenmosher's salt at room temperature (Table, entry 1).



Reagents: i) Boc_2O, dioxane/water. ii) TBTU, $Me_2NH.HCl$, Et_3N, MeCN. iii) PhMgBr, THF. iv) $ButCOOCOCH_2NHBoc$, THF. v) HCl, AcOEt. vi) K_2CO_3. vii) Boc_2O, DMAP, THF. viii) R^1R^2CO, TBAB, K_2CO_3, MeCN.

Table. Synthesis of DDAAS Derivatives 5.

Entry	R^1R^2CO	R^1	R^2	Yield(%)[a]	$[\alpha]_D^{25b}$
1	—— [c]	H	H	88	-118.9
2	MeCHO	H	Me	88	-101.3
3	EtCHO	H	Et	86	-179.3
4	*i*-PrCHO	H	*i*-Pr	83	-129.3
5	*t*-BuCHO	H	*t*Bu	47	-90.8
6	PhCHO[d]	H	Ph	85	-156.8
7	Me_2CO	Me	Me	51	+59.5

aIsolated yield based on compound 4. bIn CH_2Cl_2. cEschenmosher salt was used. dA 1:1 mixture of Na_2CO_3 and K_2CO_3 was used.

The application of these chiral pyrazinones to the asymmetric synthesis of several types of amino acids are being pursued in our laboratory.

Conclusion

We have prepared a new chiral glycine equivalent (S)-6-isopropyl-5-phenyl-1,2,3,6-tetrahydro-2-pyrazinone which reacts with aldehydes under phase-transfer catalysis conditions at room temperature affording (Z)-alpha,beta-didehydro-alpha-amino acids derivatives stereoselectively.

Experimental Part

The full experimental section of precursors will be described elsewhere. General Procedure for the Synthesis of Compounds 5 (e.g. when R1=H, R2=Et): A suspension of pyrazinone 4 (1mmol), K2CO3 (3mmol), Bu4NBr (0.1mmol) and propionaldehyde (3mmol) in dry acetonitrile (5ml) was stirred for 20 h at room temperature. The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel) affording product 5 (R1=H, R2=Et) in 86% yield.

TLC (Hexane/EtOAc 3:2): Rf 0.83.

IR (neat): 3061, 1772-1716, 1625 and 823.

1H-NMR (300 MHz, acetone-d6): 0.83, 0.87 (2d, 6H), 1.11 (t, 3H), 1.54 (s, 9H), 2.13 (m, 1H), 2.60, 2.73

(2m, 2H), 5.61 (d, 1H), 6.73 (t, 1H) and 7.50-8.08 (m, 5H).

13C-NMR (75 MHz, acetone-d6): 13.35, 19.08, 19.87, 21.03, 27.96, 35.43, 59.65, 83.38, 128.12, 129.53, 131.87, 137.82, 137.84, 140.20, 161.55 and 163.92.

MS (ESI): 357 (M^++1, 17%).

References and Notes

1. a) Schmidt, U.; Lieberknecht, A.; Wild, J. Didehydroamino acids (DDAA) and didehydro peptides (DDP). Synthesis 1988, 159-172. b) Duthaler, R. A. Recent developments in the stereoselective synthesis of alpha-amino acids. Tetrahedron 1994, 50, 1539-1650.

2. a) Alami, A.; Calmes, M.; Daunis, J.; Escale, F.; Jacquier, R.; Roumestant, M.-L.; Viallefont, P. Asymmetric syntheses of cis and trans 2-methyl and 2-ethyl-1-amino cyclopropanecarboxylic acids. Tetrahedron:Asymmetry 1991, 2, 175-178. b) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. Efficient asymmetric synthesis of amino acids through hydrogenation of the didehydroamino acid residue in cyclic imino-ester derivatives. Ibid. 1992, 3, 567-572.

3. a) Schickli, C. P.; Seebach, D. Stereoselective conversions of t-butyl rac-(R), or (S)-5-alkylidene-2-t-butyl-3-methyl-4-oxo-1-imidazolidinecarboxilates (Chiral 2,3-dehydroamino acid derivatives) and preparation of some nonproteinogenic amino acids. Liebigs Ann. Chem. 1991, 669-684. b) Williams, R. M.; Fegley, G. J. Asymmetric synthesis of 1-aminocyclopropane-1-carboxilic acid derivatives. J. Am. Chem. Soc. 1991, 113, 8796-8806.

4. Alcaraz, C.; Fernandez, M. D.; de Frutos, M. P.; Marco, J. L.; Bernabe, M.; Foces-Foces, C.; Cano, F. H. Asymmetric synthesis of 1-amino-2-phenyl(alkyl)cyclopropanecarboxylic acids by diastereoselective cyclopropanation of highly functionalized monochiral olefines. Tetrahedron 1994, 50, 12443-12456.

5. For related oxazinones see: Chinchilla, R.; Falvello, L. R.; Galindo, N.; Najera, C. Asymmetric synthesis of alpha-methyl alpha-amino acids by diastereoselective alkylation of optically active 6-isopropyl-3-methyl-2,3-dihydro-6H-1,4-oxazin-2-ones. Angew. Chem. Int. Ed. Engl. 1997, 36, 995-997.

C. Najera

C. Najera was graduated from University of Zaragoza in1973 and obtained her doctorate in chemistry from the University of Oviedo in 1979. She spent postdoctoral stays with Prof. D. Seebach at the ETH (Zurich), Prof. J. E. Baldwin at the Dyson Perrins Laboratory (Oxford), Prof. E. J. Corey at Harvard University and Prof. J.-E. Backwall at Uppsala University. She became assistant professor in 1985 at the University of Oviedo and full professor in 1993 at the University of Alicante. Her current research interest is focussed in organometallic chemistry, sulfones, amino acids and asymmetric synthesis.

J. M. Sansano

J. M. Sansano was graduated in 1988 and obtained his Ph.D. in 1994 in chemistry from the University of Alicante. He spent a two years postdoctoral stay with Prof. R. Grigg at the University of Leeds and he is working in Prof. Najera's group as associated researcher since october of 1996.

T. Abellan

T. Abellan was graduated in chemistry from University of Alicante in 1996 and then he started his Ph.D. studies in Prof. Najera's group.

Comments

During 1-30 September 1997, all comments on this poster should be sent by e-mail to ecsoc@listserv.arizona.edu with A0007 as the message subject of your e-mail. After the conference, please send all the comments and reprints requests to the author(s).
