Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 9, pp. 2145-2148, 1995

0957-4166/95 $9.50+0.00

0957-4166(95)00286-3

Determination of the Absolute Configuration of α-Amino-2-alkylthiazoles by Circular Dichroism.

Francisco L. Merchán, Pedro Merino, Isabel Rojo, and Tomás Tejero*

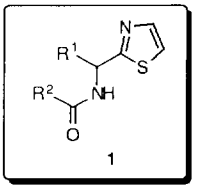
Departamento de Química Orgánica, Facultad de Ciencias-ICMA, Universidad de Zaragoza-CSIC, Zaragoza, Spain.

Alessandro Dondoni

Dipartimento di Chimica, Laboratorio di Chimica Organica , Università, Ferrara, Italy.

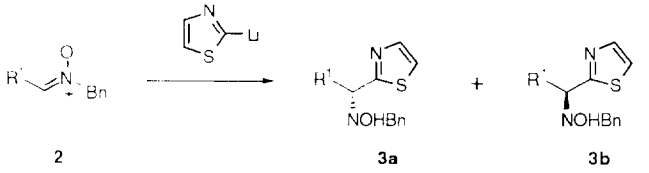
Abstract: Correlation between absolute configuration at the α-centre of the thiazole ring in the title compounds and the sign of their Cotton effect (CE) in the range 217-230 nm is reported.

α-Amino-2-alkylthiazoles **1** are an interesting class of compounds which are present in natural products with antineoplastic activity. Among these products are dolastatin 10,[1] or marine sponges metabolites such as dysidenin,[2] isodysidenin[3] and dysideathiazoles.[4] Likewise, α-amino-2-alkylthiazoles **1** can be seen as direct precursors of α-aminoaldehydes via thiazole-to-formyl conversion (Dondoni's reaction).[5] Since it is well-known that α-aminoaldehydes are important building blocks in Organic Synthesis,[6] compounds **1** can be considered key intermediates in several synthetic approaches to Natural Products.



1

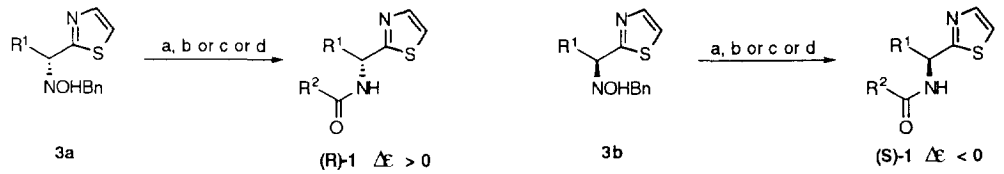
We have recently reported a new methodology for the stereoselective synthesis of α-amino-2-alkylthiazoles **1** by the addition of 2-lithiothiazole to chiral nitrones **2** derived from either α-alkoxyaldehydes or αaminoaldehydes (Scheme 1).[7] The stereochemistry in the addition step was controlled by precomplexation of **2** with Lewis acids in the case of α-alkoxynitrones[8] or by changing in the N-protecting groups in the case of α-aminonitrones.[9]



2 **3a** **3b**

Scheme 1

α-Substituted-(hydroxyaminomethyl)thiazoles **3** were reduced and debenzylated by the action of aqueous titanium (III) chloride, and the resulting primary amines were transformed into the N-protected derivatives **1** (Scheme 2). Absolute configuration at the new stereogenic centre in the α-position to the thiazole ring was determined by one of the following methods: a) synthesis from "chiral pool" and comparison with obtained products,[1b] b) X-ray diffraction analysis, when crystals of good quality were accesible,[4,8,9] c)



Scheme 2: a) $TiCl_3$, CH_3OH, H_2O; b) Boc_2O, dioxane; (c) Cbz-Cl, dioxane; (d) Ac_2O, DMPA, Py

chemical correlation to known structures[8c] or d) degradation to α-aminoacids by oxidation of the thiazole ring.[10] Several difficulties were found in these determinations, mainly those associated with the easily epimerization at the α-position of 2-substituted thiazoles,[10a] resulting that, in some cases, first assignation of absolute configuration was proved to be erroneous.[11]

In this paper we wish to report a direct and facile method for determining the absolute configuration of the α-position in α-amino-2-alkylthiazoles **1** using the dichroic circular method.

The CD spectra of a representative set of α-amino-2-alkylthiazoles were examined (Figure 1). In all cases, a Cotton effect (CE) in the range 217-230 nm, which correlated with the absolute stereochemistry at the α-centre, was observed. The magnitude of CEs measured, although weak ($\Delta\varepsilon$=1-4) was definite enough for our purposes. Recently, the assignment of absolute configuration of 2-furfurylcarbinols[12] and 2-furfurylcarbilamines[13] has been reported, however due to the weakness of the CEs, preparation of benzoylated derivatives was necessary in order to use the exciton coupling method.[14]

The results of our investigation are presented in Table 1. Compounds **1** with R configuration showed a positive CE, while those with S configuration exhibited a negative CE. Hence, pairs of α-amino-2-alkylthiazoles epimeric at the α-position, presented CD spectra with inverted sign of their CE (compare entries 1-2, 3-4, 11-12, 13-14 or 16-17). It is noteworthy that changes of the N-protecting group on configurationally identical α-amino-2-alkylthiazoles did not affect that general behaviour (entries 4,5,6). The nature of group R^1 on the 2-aminomethylthiazole moiety had a little effect on the magnitude, and none on the sign of CEs measured, being independent of the other chiral centres. In this study, we include different R^1 substituents such as hydroxyalkyl or aminoalkyl, both open chain and cyclic ones. In some cases, several weaker CEs were detected in the range 240-260 nm, but no correlation with absolute configurations was observed. As a final test we also include the CD spectra of (S)-boc-Dolaphenin **1o** (entry 15),[15] which showed the expected correlation. Finally, we have used the correlation described above in the assignment of the absolute configuration of epimeric compounds **1p** and **1q**, synthesized from the corresponding C-glycosyl aldehyde,[16] for which no proof of their stereochemistry at the α-thiazole centre was accesible.

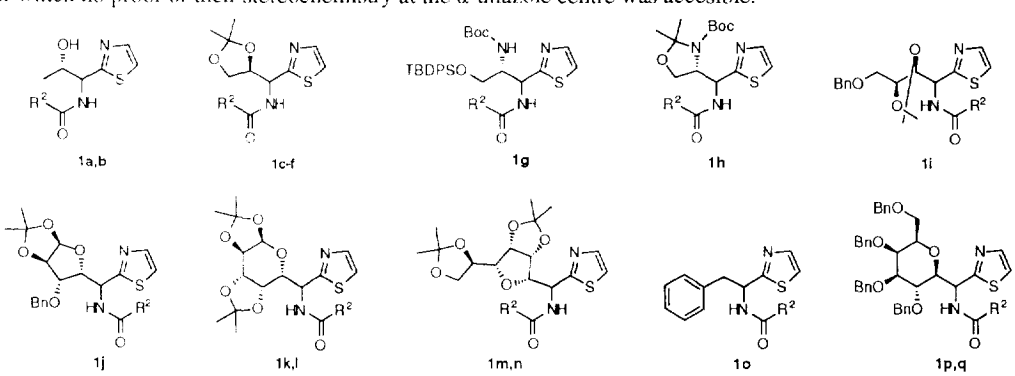


Figure 1: α-amino-2-alkylthiazoles studied by circular dichroism

Table 1. Chiroptical data for α-amino-2-alkylthiazoles **1**

Entry	Compound	R^2-CO	Configuration	$\Delta\varepsilon^{max}$ (λ nm)[a]	$[\alpha]_D^{20}$ (c $CHCl_3$)
1	**1a**	Boc	**R**	+ 2.68 (226)	+63.9 (1.58)
2	**1b**	Boc	**S**	- 3.23 (228)	-25.3 (1.87)
3	**1c**	Cbz	**R**	+ 1.43 (224)	-10.8 (2.22)
4	**1d**	Cbz	**S**	- 2.05 (224)	- 2.0 (0.30)
5	**1e**	Boc	**S**	- 1.59 (223)	+ 3.5 (0.75)
6	**1f**	Ac	**S**	- 2.08 (217)	-50.2 (0.53)
7	**1g**	Boc	**R**	+ 1.99 (225)	+ 3.5 (0.35)
8	**1h**	Boc	**R**	+ 2.03 (224)	- 4.8 (0.46)
9	**1i**	Boc	**R**	+ 1.36 (221)	-21.0 (1.61)
10	**1j**	Boc	**S**	- 1.64 (224)	- 7.5 (0.83)
11	**1k**	Ac	**R**	+ 1.76 (222)	-42.2 (0.45)
12	**1l**	Ac	**S**	- 1.53 (223)	-69.8 (0.45)
13	**1m**	Boc	**R**	+ 2.27 (223)	+ 6.4 (0.50)
14	**1n**	Boc	**S**	- 2.00 (223)	- 2.3 (1.02)
15	**1o**	Boc	**S**	- 1.75 (227)	+25.5 (0.60)
16	**1p**	Boc	**R**	+ 2.34 (230)	+14.6 (0.90)
17	**1q**	Boc	**S**	- 2.03 (223)	+ 4.9 (0.48)

(a) Recorded in spectrograde methanol on a JASCO J-710 dichrograph at 20° C

This compounds showed in their CD spectra the same pattern that compounds **1a-o**; whereas **1p** exhibited a positive CE (entry 16) and in consequence was tentatively assigned as R, compound **1q** showed a negative CE (entry 17), and so the S configuration was attributed.

Although defining the major conformers of α-amino-2-alkylthiazoles in solution is of difficulty,[17] calculations using MNDO routine[18] for the model α-acetylamino-2-ethylthiazole **4** show that in the preferred conformations the α-H atom nearly eclipses the thiazole ring plane (Figure 2). In this conformations, the alkyl and amino substituents are located on both sides of the thiazole ring plane and the CEs measured may come from the different rotatory contribution of this groups.

Figure 2 Low energy conformers of (R)α-acetylamino-2-ethylthiazole **4**

In spite of the amide and carbamate groups present absortions in a near range, the CEs measured can not arise from this cromophores. In fact, (S)-N-boc-phenylalaninol only showed a CE at 216 nm with $\Delta\varepsilon$ = -0.18. On the other hand, removal of acetyl group in **11** gave a primary amine **5** which showed a CD spectrum similar to the parent compound (229 nm, $\Delta\varepsilon$ = -1.23, figure 3).

Since it has been described that the rotatory contribution of an alkyl group is larger than that of an amino group in the α-amino substituted benzene cromophore,[19] a thiazole sector rule can be tentatively proposed for these cases, assuming that the effects are similar in both cromophores (Figure 4). A support to this hypothesis

emerges from the fact that the CD spectra described for α-amino-2-alkylthiazole-4-carboxylic acid derivatives are in agreement with the proposed rule.[20]

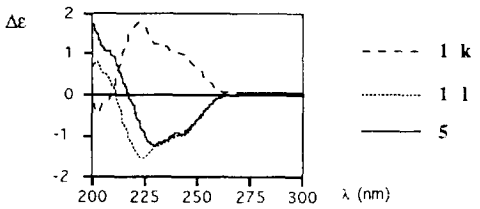


Figure 3: CD espectra of compounds **1k**,**1l** and **5**.

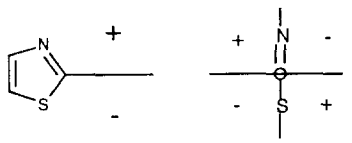


Figure 4: Thiazole sector rule proposed

In summary, the usefulness of the dichroic circular method to establish the absolute configuration at the α-position in α-amino-2-alkylthiazoles has been demonstrated. Further studies involving the generality and the scope of the proposed rule, as well as the application in the absolute configuration assignment in other α-substituted thiazoles are currently in progress in our laboratory.

Acknowledgements: *Financial support from DGICYT (PM92-0253) is gratefully acknowledged and one of us (I.R.) is also grateful to CAPV for a fellowship.*

REFERENCES AND NOTES

1. (a) Pettit, G. R.; Kamano, Y.; Herald, C. L.; Tuinman, A. A.; Boettner, F. E.; Kizu, H.; Schmidt, J. M.; Baczynskyj, L.; Tomer, K. B.; Bontems, R. J. *J. Am. Chem. Soc.*, **1987**, *109*, 6883-6885. (b) Pettit, G. R.; Singh, S. B.; Hogan, F.; Lloyd-Williams, P.; Herald, D. L.; Burkett, D. D.; Clewlow, P. J. *J. Am. Chem. Soc.*, **1989**, *111*, 5463-6465.
2. Kazlauskas, R.; Lidgard, R. O.; Wells, R. J. *Tetrahedron Lett.*, **1977**, *18*, 3183-3186.
3. Charles, C.; Braekman, J. C.; Daloze, D.; Tursch, B.; Karlsson, R. *Tetrahedron Lett.*, **1978**, *19*, 1519-1520.
4. Unson, M. D.; Rose, C. B.; Faulkner, D. J.; Brinen, L. S.; Steiner, J. R.; Clardy, J. *J. Org. Chem.*, **1993**, *58*, 6336-6334.
5. (a) Dondoni, A. Carbohydrate Synthesis via Thiazoles. In *Modern Synthetic Methods*; Scheffold, R. Ed.; Verlag Helvetica Chimica Acta: Basel, 1992. (b) Dondoni, A.; Marra, A.; Perrone, D. *J. Org. Chem.*, **1993**, *58*, 275-277.
6. (a) Reetz, M. T. *Angew. Chem. Int. Ed. Engl.*, **1991**, *30*, 1531-1546. (b) Jurczack, J.; Golebiowski, A. *Chem. Rev.*, **1989**, *89*, 149-164.
7. Franco, S.; Junquera, F.; Merchan, F.; Merino, P.; Tejero, T. *Synth. Commun.*, **1994**, *24*, 2537-2550.
8. (a) Dondoni, A.; Franco, F.; Merchan, F.; Merino, P.; Tejero, T. *Tetrahedron Lett.*, **1993**, *34*, 5475-5478. (b) Dondoni, A.; Franco, F.; Merchan, F.; Merino, P.; Tejero, T. *Synlett*, **1993**, 78-80. (c) Dondoni, A.; Franco, F.; Junquera, F.; Merchan, F.; Merino, P.; Tejero, T.; Bertolasi, V. *Chemistry, A European Journal* , **1995**, *1*, (in press).
9. Dondoni, A.; Merchan, F.; Merino, P.; Tejero, T.; Bertolasi, V. *J. Chem. Soc., Chem. Commun.*, **1994**, 1731-1733
10. (a) Biskupiak, J. E.; Ireland, C. M. *J. Org. Chem.*, **1983**, *48*, 2302-2304. (b) Wasylyk, J. M.; Biskupiak, J. E.; Costello, C. E.; Ireland, C. M. *J. Org. Chem.*, **1983**, *48*, 4445-4449.
11. (a) See Charles, C.; Braekman, J. C.; Daloze, D.; Tursch, B. *Tetrahedron*, **1980**, *36*, 2133-2135 and ref. 3; for a correction see Biskupiak, J. E.; Ireland, C. M. *Tetrahedron Lett.*, **1984**, *25*, 2935- 2936. (b) See Dondoni. A.; Junquera, F.; Merchan, F.; Merino, P.; Tejero, T. *Tetrahedron Lett.*, **1992**, *33*, 4221-4221; for a correction see ref. 8a.
12. Gawronski, J.; Radocki, D.; Jurczack, J. Pakulski, Z.; Raczko, J.; Ramza, J.; Zamojski, A. *J. Org. Chem.*, **1990**, *55*, 1118-1120.
13. Zhou, W.-S.; Zhu, X. Y.; Cheng, J.-F. *Tetrahedrom: Asymm.*, **1993**, *4*, 1501-1504.
14. Nakanishi, K.; Berova, N. The Exciton Chirality Method. In *Circular Dichroism: Principles and Applications*, Nakanishi, K.; Berova, N.; Woody, R. W. Eds.; VCH Publishers, Inc.; New York. 1994; pp. 361-398.
15. Irako, N.; Hamada, Y.; Shioiri, T. *Tetrahedron*, **1992**, *48*, 7251-7264.
16. Dondoni, A.; Scherrmann, M.-C. *J. Org. Chem.*, **1994**, *59*, 6404-6412.
17. Data available from X-ray diffraction analysis reveal the presence in the solid state of very different conformations betwen thiazole ring and α-amino group depending on the case and so, lack of utility.
18. Dewar, M. J. S.; Theil, W. *J. Am. Chem. Soc.*, **1977**, *99*, 4907-4917.
19. Smith, H. E.; Fontana, L. P. *J. Org. Chem.* **1991**, *56*, 432-435.
20. Bredenkamp, M. W.; Holzapfel, C. W.; Van Zyl, W. J. *Synth. Commun.*, **1990**, *20*, 2235-2249.

(*Received in UK 28 July* 1995)