Pergamon

Tetrahedron Letters, Vol. 35, No. 30, pp. 5397-5400, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01093-5

SYNTHESIS OF PEPTIDE THIAZOLINES FROM β-HYDROXYTHIOAMIDES. AN INVESTIGATION OF RACEMIZATION IN CYCLODEHYDRATION PROTOCOLS

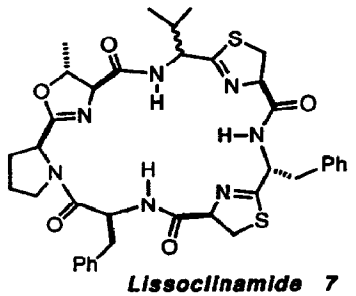
Peter Wipf*,[1] and Paul C. Fritch

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, U.S.A.

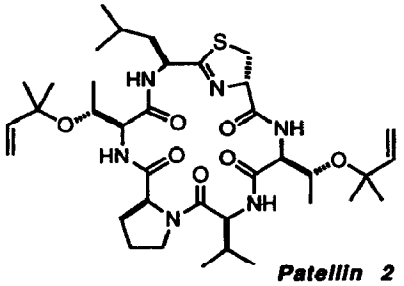
Abstract: The formation of thiazolines from β-hydroxythioamides under TsCl/Et$_3$N, $SOCl_2$, and Mitsunobu conditions leads to extensive epimerization at the C(2) *exo* methine position. In contrast, thiazolines of >94% diastereomeric purity are isolated when the Burgess cyclodehydration protocol is applied.

Thiazolines are important building blocks in pharmaceutical agents and biologically active natural products.[2] Especially, thiazoline rings are characteristic structural segments of marine cyclopeptide alkaloids such as lissoclinamides,[3] patellins,[4] bistratamides,[5] and others[6] (Figure 1).[7] The conformation of these macrocycles is critically influenced by the thiazoline geometry.[6] To a much greater extent even than oxazolines, however, thiazolines have a tendency to epimerize chiral centers attached to the C(2) position (Figure 2).[8] In the context of our planned synthesis of lissoclinamide 7, we were therefore interested in determining the extent of epimerization in the preparation of thiazolines from β-hydroxythioamide **1**. To date, only one alternative protocol, the condensation of amino acid imidates with cysteine derivatives, has been reported to proceed without noticeable loss of stereochemical integrity.[9]

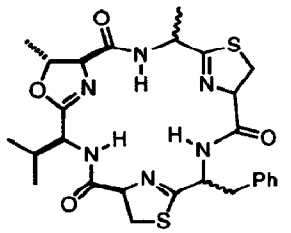
Figure 1.



Lissoclinamide 7

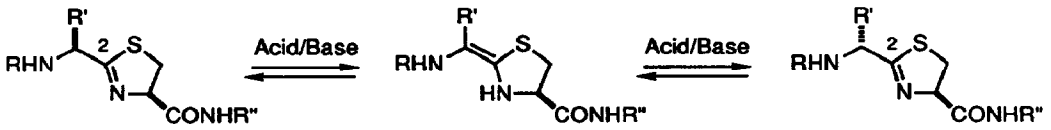


Patellin 2



Bistratamide A

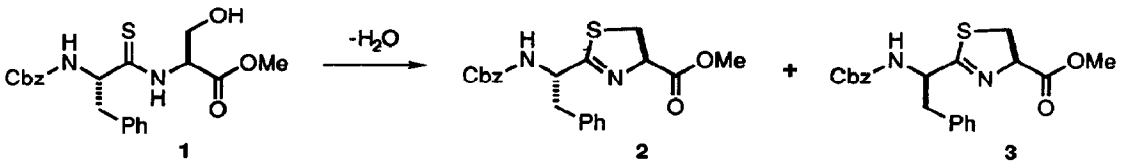
Figure 2.



The results of our study are summarized in Table 1. Cyclodehydration of *N*-protected thiopeptide methyl ester **1** with tosylchloride in the presence of 3.6 equiv of triethylamine[10] resulted in the formation of a 1 : 1 mixture of the epimeric thiazolines **2** and **3** in 40% yield (entry 1). This complete loss of stereochemical integrity at the exocyclic chiral center can be explained by the relatively harsh reaction conditions, e.g. heating in the presence of excess amine. The thionyl chloride induced ring closure[11] provided only a marginal increase in yield, but no improvement of the extensive degree of epimerization (entry 2).

The Mitsunobu reaction[12] has been successfully applied to the formation of peptide oxazolines and aziridines from β-hydroxy-α-amino acids.[13,14] There are also reports on the formation of thiazolines under Mitsunobu conditions,[13a,b,14] but side-chain epimerization has not been investigated. Due to the high electrophilicity of the triphenylphosphine/diisopropylazodicarboxylate (DIAD) reagent, cyclodehydration of **1** occurred rapidly at low temperatures. A 78 : 22 ratio of **2** and **3** was formed in 80% yield (entry 3). Even though this 56% de represented a significant improvement over the previous protocols, it was too low for applications in total synthesis. These limitations were overcome by the use of $MeO_2CNSO_2NEt_3$, the Burgess reagent, for the cyclization of thioamide **1** (entry 4).[15] Use of this reagent was recently shown to be superior to other protocols for the formation of enantiomerically pure oxazolines.[16] Indeed, treatment of **1** with 1.1 equiv of Burgess reagent at 65 °C for 10 min led to the formation of **2** in 96% yield and >94% de.[17]

Table 1. Epimerization in the cyclodehydration of Cbz-L-ψ[CSNH]Phe-L-Ser-OMe (**1**).



1 **2** **3**

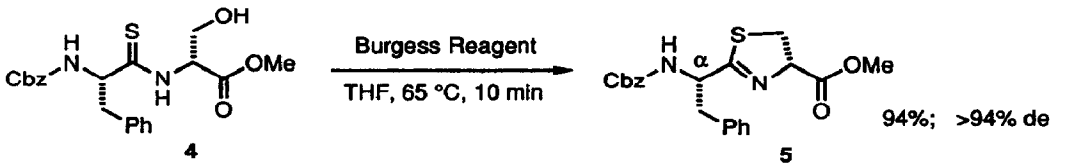
Entry	Method	Yield [%]	Ratio **2** : **3**
1	TsCl, Et_3N, CH_2Cl_2, 42 °C, 1 h	40	1 : 1
2	1. $SOCl_2$, 0 °C, 2 h; 2. Pyridine, THF, 0 °C, 15 min	49	1 : 1
3	Ph_3P, DIAD, CH_2Cl_2, -78→22 °C, 30 min	80	78 : 22
4	Burgess-Reagent, THF, 65 °C, 10 min	96	> 97 : 3

The ratio of **2** : **3** in these studies was determined by integration of the methyl ester signals in 500 MHz ^1H NMR.[18] As a reference sample for the minor isomer **3**, the enantiomeric **5** was prepared by cyclodehydration of D-serine derived thioamide **4** with Burgess reagent (Scheme 1).

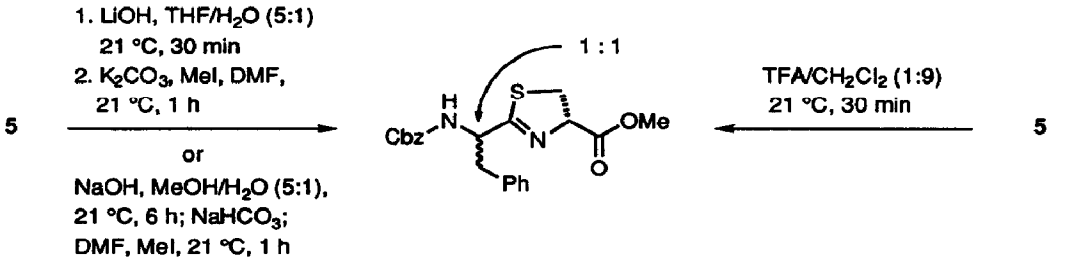
Diastereomers **2** and **5** were also used to determine the half-life of epimerization at the exocyclic stereocenter of thiazolines. A 0.05 M solution of **2** in $CDCl_3$ epimerized to a 1 : 1 mixture of **2** and **3** in the presence of 0.2 equiv of triethylamine with a half-life of 10 days at room temperature. An increase in temperature or the addition of protic solvents significantly accelerated this process. Treatment of **5** with 1.1 equiv of lithium hydroxide in THF/H_2O (5 : 1) at 21 °C for 30

min, for example, led to complete epimerization at C(α), probably due to a deprotonation-reprotonation mechanism (Scheme 2). After methylation of the acid in DMF with MeI in the presence of K_2CO_3, or direct treatment of the sodium carboxylate with MeI, a 1 : 1 ratio of C(α)-epimers of **5** was detected in ^1H NMR. Acid treatment of **5** was similarly problematic. A 30 min exposure to TFA/CH_2Cl_2 (1 : 9) at 21 °C led again to complete epimerization at the *exo* methine of the thiazoline ring. Since both acid and base treatments represent standard manipulations in peptide chemistry, these results reflect the substantial stereochemical hazards that have to be considered in the synthesis of thiazoline-containing products.

Scheme 1



Scheme 2



In conclusion, we have found that cyclodehydration of β-hydroxythioamides with the Burgess protocol[15] provides peptide thiazolines in high yield with less than 3% epimerization at the C(2) *exo* methine position. Since synthetic manipulations on compounds containing these heterocycles are greatly hampered by the extremely facile epimerization at the C(2) exocyclic position,[3,8] Burgess cyclization of readily accessible thioamide precursors is an attractive strategy for the total synthesis of stereodefined *Lissoclinum* peptides.

Acknowledgment. This work was supported by the National Institutes of Health (R01 AI34914).

References and Notes

1. Eli Lilly Grantee, 1993-1994; Alfred P. Sloan Research Fellow, 1994-1995; recipient of an American Cyanamid Faculty Award, 1994.
2. For recent lead references, see: (a) Hoveyda, H. R.; Karunaratne, V.; Orvig, C. *Tetrahedron* **1992**, *48*, 5219. (b) Ragab, F. A.; Hussein, M. M.; Hanna, M. M.; Hassan, G. S.; Kenawy, S. A. *Pharmazie* **1993**,

48, 808. (c) Aszodi, J.; Bonnet, A.; Chantot, J. F.; Costerousse, G.; Didierlaurent, S.; Teutsch, G. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2231. (d) Hamamichi, N.; Hecht, S. M. *J. Am. Chem. Soc.* **1993**, *115*, 12605. (e) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 5566. (f) Pattenden, G.; Thom, S. M. *J. Chem. Soc. Perkin Trans. I* **1993**, *21*, 1629. (g) Shindo, K.; Yamagishi, Y.; Kawai, H. *J. Antibiot.* **1993**, *46*, 1638. (h) Kunze, B.; Jansen, R.; Pridzun, L.; Jurkiewicz, E.; Hunsmann, G.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1993**, *46*, 1752. (i) Mulqueen, G. C.; Pattenden, G.; Whiting, D. A. *Tetrahedron* **1993**, *49*, 5359.

3. (a) Degnan, B. M.; Hawkins, C. J.; Lavin, M. F.; McCaffrey, E. J.; Parry, D. L.; van den Brenk, A. L.; Watters, D. J. *J. Med. Chem.* **1989**, *32*, 1349. (b) Schmitz, F.; Ksebati, M. B.; Chang, J. S.; Wang, J. L.; Hossain, M. B.; van der Helm, D. *J. Org. Chem.* **1989**, *54*, 3463. (c) Hawkins, C. J.; Lavin, M. F.; Marshall, K. A.; van den Brenk, A. L. v. d.; Watters, D. J. *J. Med. Chem.* **1990**, *33*, 1634.
4. Zabriskie, T. M.; Foster, M. P.; Stout, T. J.; Clardy, J.; Ireland, C. M. *J. Am. Chem. Soc.* **1990**, *112*, 8080.
5. Degnan, B. M.; Hawkins, C. J.; Lavin, M. F.; McCaffrey, E. J.; Parry, D. L.; Watters, D. J. *J. Med. Chem.* **1989**, *32*, 1354.
6. McDonald, L. A.; Foster, M. P.; Phillips, D. R.; Ireland, C. M.; Lee, A. Y.; Clardy, J. *J. Org. Chem.* **1992**, *57*, 4616.
7. For a recent excellent review, see: Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771.
8. The rate of isomerization at the C(2) *exo* methine position of thiazolines is significantly greater than C(4) epimerization: (a) Konigsberg, W.; Hill, R. H.; Craig, L. C. *J. Org. Chem.* **1961**, *26*, 3867. (b) Hirotsu, Y.; Shiba, T.; Kaneko, T. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1870. (c) Yonetani, K.; Hirotsu, Y.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3302.
9. North, M.; Pattenden, G. *Tetrahedron* **1990**, *46*, 8267. However, for a report on complete amino acid racemization with this procedure, see ref. 8b.
10. (a) Attenburrow, J.; Elliott, D. F.; Penny, G. F. *J. Chem. Soc.* **1948**, 310. (b) Nakajima, K.; Kawai, H.; Takai, M.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 917.
11. Elliott, D. F. *J. Chem. Soc.* **1949**, 589; *ibid.* **1950**, 62.
12. (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.
13. (a) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 7026. (b) Nakajima, K.; Sasaki, H.; Neya, M.; Morishita, M.; Sakai, S.; Okawa, K. *Peptide Chemistry* **1982**, *20*, 19. (c) Galeotti, N.; Montagne, C.; Poncet, J.; Jouin, P. *Tetrahedron Lett.* **1992**, *33*, 2807. (d) Vorbrüggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, *49*, 9353.
14. Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267.
15. (a) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907. (b) Wipf, P.; Miller, C. P. *J. Am. Chem. Soc.* **1992**, *114*, 10975.
16. (a) Salvatore, B. A.; Smith, A. B., III *Tetrahedron Lett.* **1994**, *35*, 1329. (b) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *58*, 1575.
17. **2**: A solution of 112.2 mg (0.269 mmol) of thioamide **1** in 5.3 mL of THF was treated with 70.6 mg (0.296 mmol) of Burgess reagent and heated for 10 min at 65 °C. The reaction mixture was cooled to 21 °C, concentrated *in vacuo*, and the residue was chromatographed on SiO_2 (40% EtOAc/hexanes) to afford 102.7 mg (96%) of **2** as a white solid: Mp 115-116.5 °C; $[\alpha]_D$ +47.4° (*c* 1.5, $CDCl_3$, 21 °C); IR (neat) 3320, 3030, 2965, 1734, 1716, 1699, 1684, 1558, 1539, 1533, 1522, 1506, 1496, 1456, 1437, 1238, 698 cm^{-1}; ^1H NMR δ 7.38-7.21 (m, 8 H), 7.18-7.15 (m, 2 H), 5.43 (d, 1 H, *J* = 8.2 Hz), 5.13- 5.04 (m, 3 H), 4.93-4.89 (m, 1 H), 3.78 (s, 3 H), 3.64 (t, 1 H, *J* = 11.1 Hz), 3.53 (t, 1 H, *J* = 9.6 Hz), 3.24 (dd, 1 H, *J* = 5.7, 13.9 Hz), 3.09 (dd, 1 H, *J* = 6.6, 13.9 Hz); ^{13}C NMR δ 175.0, 170.5, 155.3, 136.1, 135.7, 129.4, 128.3, 128.2, 127.9, 127.8, 126.7, 77.6, 66.6, 54.3, 52.5, 39.4, 35.2; MS (EI) *m/e* (rel intensity) 398 (M^+, 7), 307 (7), 290 (18), 263 (6), 248 (4), 231 (5), 213 (3), 188 (10), 108 (12), 91 (100), 79 (15), 65 (12), 59 (10); HRMS calcd for $C_{21}H_{22}N_2O_4S$: 398.1300, found: 398.1297.
18. **2**: δ 3.78 (s, 3 H, OMe); **3** & **5**: δ 3.80 (s, 3 H, OMe).

(*Received in USA* 11 *May* 1994; *accepted* 3 *June* 1994)