Tetrahedron Letters 51 (2010) 4558–4559

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A straightforward synthesis and partial hydrolysis of cysteine-derived 2,5-diketopiperazines

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ARTICLE INFO

Article history:
Received 10 May 2010
Revised 21 June 2010
Accepted 22 June 2010
Available online 25 June 2010

ABSTRACT

A mild and straightforward preparation of cysteine-derived 2,5-diketopiperazines (DKPs) is reported, by cyclization of (*R*)-2,2-dimethyltetrahydrothiazole-4-carboxylic acid hydrochloride or of (*R*)-tetrahydrothiazole-4-carboxylic acid hydrochloride, mediated by HBTU and DIEA. One DKP has been characterized by X-ray analysis, while the other has been hydrolyzed to *cyclo*-Cys-Cys. The preparation of this latter compound has been previously reported to be troublesome and low yielding.

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2,5-Diketopiperazines (DKPs) are a class of compounds useful in medicinal chemistry, combinatorial chemistry, and targeted organic synthesis.[1] A variety of DKPs have been found to possess interesting biological properties such as antitumor,[2] antimicrobial,[3] and antiviral activities.[4]

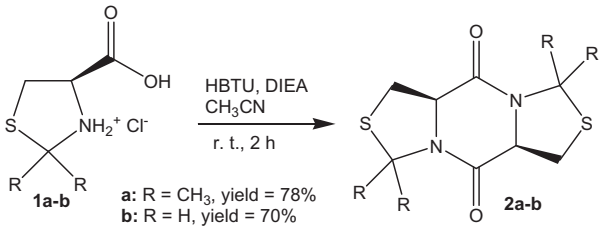
DKPs are usually prepared by cyclization of deprotected dipeptides.[5] This reaction takes place easily with aliphatic or aromatic amino acids, such as alanine, valine, or phenylalanine, while several problems occur when derivatized amino acids are used. More recently, some methods for the preparation of DKPs in one step from unprotected α-amino acids have been reported, but they are not mild and cannot be applied for the preparation of DKPs derived from cysteine.[6]

On the contrary, a couple of synthesis of some DKPs derived from protected L-cysteine has been reported by a three-step procedure, starting from thiazoline-4-carboxylic acid derivatives.[7] Herein we report a one-step synthesis of (*R*)-2,2-dimethyltetrahydrothiazole-4-carboxylic acid hydrochloride **1a**[8] or (*R*)-thiazole-4-carboxylic acid hydrochloride **1b**[9] (Scheme 1).

The 2,5-diketopiperazines **2a** and **2b** were obtained by the simultaneous formation of the two amide bonds, by reaction with HBTU in the presence of diisopropylethyl amine (DIEA) in acetonitrile. In both cases the reaction takes place for 2 h and with high yields. A similar result has been obtained if DIEA is replaced with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). An inert atmosphere is not necessary.[10]

While compound **2b** has previously been fully characterized,[7] **2a** has never been characterized and has been reported only as a *by*-product.[11,12] Therefore, we grew crystals from methanol and carried out a single crystal X-ray diffraction study.[13] The molecular structure of **2a** consists of a central DKP ring in a boat conformation fused with two outer thiazolidine rings in a half-chair conformation (Fig. 1).

The crystal packing of **2a,** shown in Figure 2, is characterized by the presence of intermolecular hydrophobic interactions and C–H···O hydrogen bonds. All carbonylic oxygens of the DKP ring participate in the weak intermolecular non classic H-bonds with



Scheme 1. Synthesis of **DKPs 2a** and **2b**.

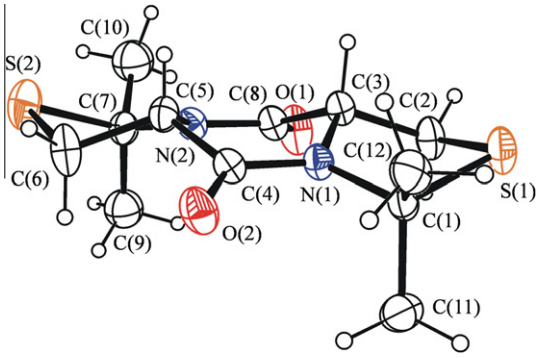


Figure 1. ORTEP drawing of **2a**.

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doi:10.1016/j.tetlet.2010.06.108

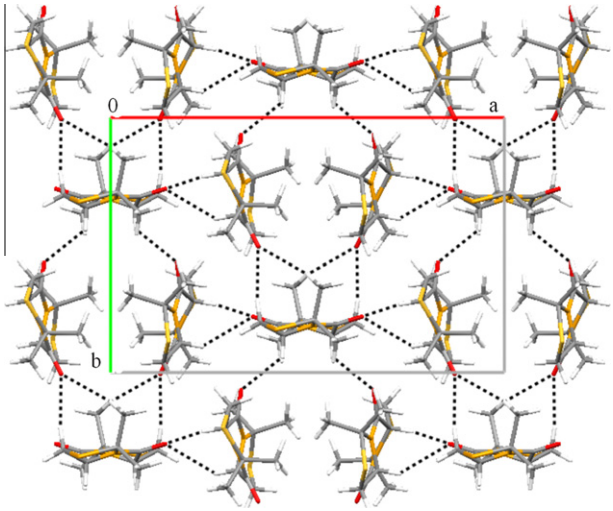
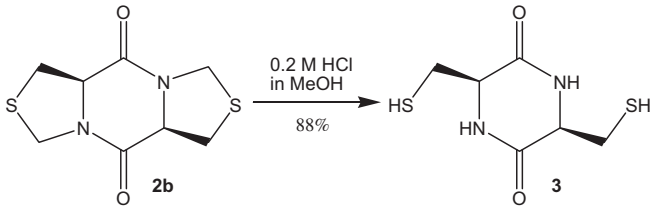


Figure 2. View down the *c* axis of the crystal packing of **2a**. Dotted lines indicate the weak intermolecular H-bonds.



Scheme 2. Synthesis of *cyclo*-Cys-Cys **3**.

the methyne and methyl hydrogens of neighboring molecules thus generating layers perpendicular to the *c* axis. Hydrophobic contacts between methyl and methylene groups of different layers further stabilize the packing of **2a** giving a 3D network.

Finally DKP **2b** was hydrolyzed to obtain *cyclo*-L-cysteine-L-cysteine **3**. The preparation of **3** has been reported in the past, following a different pathway, that is troublesome and requires several steps.[14] Furthermore **3** has never been fully characterized.[15]

In our approach, compound **2b** was stirred with 0.2 M HCl in methanol at room temperature for 24 h. Compound **3** was obtained as a white solid simply by filtration of the reaction mixture in 88% yield (Scheme 2).

In contrast, DKP **2a** does not react at all under several reaction conditions. After prolonged reaction times at high temperature, the molecule decomposes with the formation of a complex mixture. The remarkable stability of **2a** is probably due to the high steric hindrance of the four methyl groups present on the tetrahydrothiazole rings.

In conclusion, we have reported a very mild and straightforward synthesis of cysteine-derived 2,5-diketopiperazines that affords the desired compounds in short times and high yields. Furthermore, *cyclo*-L-Cys-L-Cys was easily prepared; in the past this compound had been obtained only by a troublesome and low yielding method.

Acknowledgments

We are grateful to Ministero dell'Università e della Ricerca Scientifica (PRIN 2008) and Università di Bologna (Funds for selected topics) for financial support. C.T. is grateful to Fondazione del Monte di Bologna e di Ravenna for financial support.

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10. *Experimental procedure for the formation of 2,5-diketopiperazines* **2a** *and* **2b**: A solution of (*R*)-2,2-dimethyltetrahydrothiazole-4-carboxylic acid hydrochloride **1a** (0.2 g, 1 mmol) or of (*R*)-2,2-dimethyltetrahydrothiazole-4-carboxylic acid hydrochloride **1b** (0.17 g, 1 mmol) and HBTU (0.4 g, 1.00 mmol) in dry acetonitrile (15 mL) was stirred under inert atmosphere for 10 min at room temperature. Then DIEA (3.2 mmol, 0.56 mL) in dry acetonitrile (10 mL) was added dropwise at room temperature. The solution was stirred for 3 h under inert atmosphere, then acetonitrile was removed under reduced pressure and replaced with ethyl acetate. The mixture was washed with brine, 1 N aqueous HCl (3 × 30 mL), and with 5% aqueous $NaHCO_3$ (1 × 30 mL), dried over sodium sulfate, and concentrated in vacuo. The product **2a** was obtained pure after recrystallization from methanol, while the product **2b** was obtained pure after silica gel chromatography (DCM 100%→DCM/ethyl acetate 80:20 as the eluant).
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12. *Characterization data for* **2a**: mp = 218 °C; $[\alpha]_D^{20} = -96.8$ (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2, 3 mM): *ν* 1685, 1675, 1671 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): *δ* 1.84 (s, 3H, Me), 1.8 (s, 3H, Me), 3.28 (ABX, 2H, *J* = 6.2, 10.4, 12.4 Hz, CH_2S), 4.60 (dd, *J* = 6.2, 10.2 Hz, CHN); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 27.7, 29.6, 30.0, 66.2, 73.0, 163.7.
13. Crystal data for **2a**: $C_{12}H_{18}N_2O_2S_2$, *M* = 286.40, monoclinic. space group *C*2 (No. 5), *a* = 17.576(4), *b* = 11.309(3), *c* = 10.749(2) Å, *β* = 93.442(3)°, *V* = 2132.7(8) Å^3, *F*(0 0 0) = 912, *μ*(Mo Kα) = 0.371 cm^{-1}, D_c = 1.338 g cm^{-3}, *T* = 296 K. Intensity data were collected on a SMART Apex II diffractometer with graphite-monochromated radiation (*λ* = 0.71073 Å). A total of 4169 independent reflections were collected of which 3901 were considered observed [$I > 2\sigma(I)$]. The structure was solved by direct methods (SIR97) [see: Altomare, A.; Burla, M.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–118] and subsequent Fourier syntheses and refined by full-matrix least-squares on F^2 (SHELXTL) [see: Sheldrick, G.M. SHELXTLplus Version 5.1 (Windows NT version)-Structure Determination Package; Bruker Analytical X-ray Instruments Inc.: Madison, WI, 1998], using anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were added in geometrically idealized positions and treated as riding atoms. The structure was eventually refined to *R* = 0.0673 (wR_2 = 0.1924). Crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre as Supplementary publication number CCDC 776236. Copies of the data can be obtained, free of charge, via www.ccdc.cam.ac.uk (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; fax. +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk).
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15. *Characterization data for* **3**: mp = 172 °C; $[\alpha]_D^{20} = -44.3$ (*c* 0.7, H_2O); IR (nujol): *ν* 3379, 1650 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): *δ* 3.26 (d, 2H, *J* = 6.8 Hz, CH_2S), 4.57 (t, *J* = 6.8 Hz, CHN); ^{13}C NMR (DMSO-d_6, 100 MHz): *δ* 33.6, 64.1, 169.6.