



Molecular Crystals and Liquid Crystals

Publication details, including instructions for authors and subscription information:

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Version of record first published: 01 Mar 2010

To cite this article: B. Dinesh, H. R. Manjunath, S. Naveen, K. Abiraj, A. Ramesh Baba, D. Channe Gowda, M. A. Sridhar & J. Shashidhara Prasad (2010): Synthesis and Crystal Structure of S-ethyl-2(tert-butoxycarbonylamino)-4-methyl-pentanethioate, *Molecular Crystals and Liquid Crystals*, 517:1, 161-166

To link to this article: <http://dx.doi.org/10.1080/15421400903483940>

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Synthesis and Crystal Structure of S-ethyl-2(tert-butoxycarbonylamino)- 4-methyl-pentanethioate

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S-ethyl-2(tert-butoxycarbonylamino)-4-methyl-pentanethioate (Boc-Leu-SEt) was synthesized by the mixed anhydride method IBCF/HOBt. The product obtained was characterized by ¹H NMR, MS, and IR techniques, and finally confirmed by X-ray diffraction method. The compound crystallizes in the orthorhombic space group P2₁2₁2₁ with cell parameters a = 9.674(8) Å, b = 10.659(7) Å, c = 16.219(13) Å with Z = 4. The structure exhibits both inter and intramolecular hydrogen bonds of the type N–H···O and C–H···O. The molecule possesses a chiral center at C9.

Keywords Anhydride method; hydrogen bonds; thiol ester; X-ray diffraction

Introduction

Thiol esters are key intermediates in a variety of synthetic transformations [1]. They have been used for the synthesis of ketones, *via* organocuprates [2], Grignard reagents [3], or silylacetylenes [4]. Thiol esters can also be reduced to the corresponding aldehydes using a variety of reducing agents such as di-isobutylaluminium hydride (DIBAL) [5], lithium [6], or triethylsilane [7]. Also, they can be transformed to the hydroxymethyl moiety with sodium borohydride [8] or other strong reducing agents [9]. Macrolactonization through thiol esters was accomplished in the preparation of a variety of natural products as detailed in the literature [10]. They have also been utilized for the synthesis of β -lactams [11]. Further, thiol esters play an important role in the development of thiol drugs. They protect the unstable thiol moiety, increase the activity of the drug, and mask the undesired odor and taste of the native thiol [12].

Peptide thiol esters have been useful in cyclic peptide synthesis [13] and native chemical ligation [14]. α -Amino thiol esters have also attracted significant interest

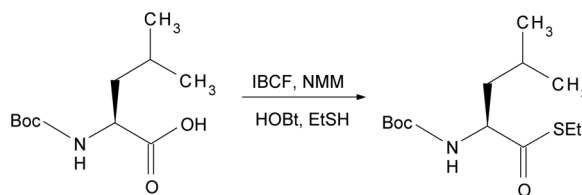
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as they can be used for the synthesis of polypeptides, α -amino aldehydes, and α -amino ketones [15–17]. In this context and as a part of our ongoing research on thiol esters and their crystal structures, we have synthesized the title compound, and herein we report its synthesis and crystal structure.

Thiol esters can be prepared easily from the corresponding carboxylic acids via the acid chlorides or mixed anhydrides, or by utilizing various dehydrating agents such as dicyclo-hexylcarbodiimide (DCC) or 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide (EDCI) [18]. For the synthesis of N-protected amino thiol esters, the mixed anhydride method using isobutyl chloroformate (IBCF) is found to be more adequate and efficient.

Experimental

General: Butoxycarbonylamino-4-methyl-pentanethioate-hydroxide (Boc-Leu-OH) and 1-hydroxybenzotriazole (HOBt) were purchased from Advanced Chem. Tech. (Louisville, KY, USA). IBCF and N-methylmorpholine (NMM) were purchased from Sigma Chemical Co. (St. Louis, MO). Ethanethiol (EtSH) was purchased from Sigma Aldrich Chem. Pvt. Ltd. (Bangalore, India). All solvents and reagents used for the synthesis and analysis were of analytical grade. TLC was carried out on silica gel plates obtained from Whatman Inc. ^1H NMR spectra were obtained on an AMX-400 MHz instrument. The method employed for synthesis is shown in Fig. 1.



Synthesis of Boc-Leu-SEt

To Boc-Leu-OH (2.311 g, 10 mmol), dissolved in acetonitrile (30 ml) and cooled to 0°C , NMM (1.1 ml, 10 mmol) was added. To this solution, IBCF (1.3 ml, 10 mmol) was added dropwise, stirring while maintaining the temperature at 0°C . After stirring the reaction mixture for 10 minutes at this temperature, HOBt (1.55 g, 10 mmol) was added. The reaction mixture was stirred for an additional 10 min, and EtSH (0.75 ml, 10 mmol) was added slowly. After 20 min, the pH of the solution was adjusted to 8 by the addition of NMM. The reaction mixture was stirred overnight at room temperature. Acetonitrile was removed under reduced pressure. The residue was taken into CHCl_3 , washed consecutively with 0.01 N cold HCl, aqueous NaHCO_3 and water and dried over Na_2SO_4 . The crude product was recrystallized from ethanol; yield 2.36 g (86%), Melting Point: 210°C .

^1H NMR (400 MHz, CDCl_3): δ 1.12 (d, 6 H, $^{\delta}\text{CH}$ & $^{\epsilon}\text{CH}$), 1.21 (t, 3 H, CH_3), 1.26 (s, 9 H, $(\text{CH}_3)_3$), 1.76 (t, 2 H, $^{\beta}\text{CH}$), 1.71 (m, 1 H, $^{\gamma}\text{CH}$) 3.13 (m, 2 H, CH_2), 3.98 (m, 1 H, $^{\alpha}\text{CH}$), 8.56 (s, 1 H, NH).

[Calculated % C 66.66, H 4.97, N 8.64, O 19.73, Found % C 66.65, H 4.98, N 8.65 O 19.74].

Crystal Structure Determination

A single crystal of the title compound with dimensions of $0.3 \times 0.27 \times 0.25$ mm was chosen for an X-ray diffraction study. The data were collected on a DIPLabo Image Plate system with graphite monochromated MoK_α radiation. Thirty-six frames of data were collected at room temperature by the oscillation method. Successive frames were scanned in steps of 5° per minute with an oscillation range of 5° . Image processing and data reduction were done using Denzo [19]. The reflections were merged with Scalepack [20]. All of the frames could be indexed using a primitive orthorhombic lattice. The structure was solved by direct methods using SHELXS-97 [21]. All of the non-hydrogen atoms were revealed in the first Fourier map itself. Full-matrix least squares refinement using SHELXL-97 [21] with isotropic temperature factors for all the atoms converged the residuals to $R_1 = 0.1816$.

Table 1. Experimental crystallographic data

Empirical formula	$\text{C}_{13} \text{H}_{25} \text{N} \text{O}_3 \text{S}$
Formula weight	275.40
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Cell dimensions	$a = 9.674(8)$ Å $b = 10.659(7)$ Å $c = 16.219(13)$ Å
Volume	$1672(2)$ Å ³
Z	4
Density(calculated)	1.094 Mg/m^3
Absorption coefficient	0.195 mm^{-1}
F_{000}	600
Crystal size	$0.3 \times 0.27 \times 0.25$ mm
Theta range for data collection	2.29° to 25.01°
Index ranges	$-11 \leq h \leq 11$ $-12 \leq k \leq 12$ $19 \leq l \leq 19$
Reflections collected	2838
Independent reflections	2838 [$R(\text{int}) = 0.0000$]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2838/0/169
Goodness-of-fit on F^2	1.121
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0459$, $wR2 = 0.1248$
R indices (all data)	$R1 = 0.0588$, $wR2 = 0.1473$
Absolute structure parameter	0.87(14)
Largest diff. peak and hole	0.226 and -0.367 e.Å^{-3}
Deposition number	CCDC 619574

Table 2. Bond lengths (Å) and bond angles (°)

Atoms	Length	Atoms	Length
N1-C2	1.350(3)	C9-C10	1.526(4)
N1-C9	1.454(3)	C10-C11	1.519(4)
C2-O3	1.213(3)	C11-C12	1.524(6)
C2-O4	1.331(3)	C11-C13	1.546(6)
O4-C5	1.491(3)	C14-O15	1.211(3)
C5-C8	1.506(5)	C14-S16	1.762(3)
C5-C6	1.507(5)	S16-C17	1.802(4)
C5-C7	1.514(4)	C17-C18	1.498(7)
C9-C14	1.517(4)		
Atoms	Angle	Atoms	Angle
C2-N1-C9	121.7(2)	N1-C9-C10	110.4(2)
O3-C2-O4	126.4(2)	C14-C9-C10	110.4(2)
O3-C2-N1	123.8(2)	C11-C10-C9	114.8(3)
O4-C2-N1	109.8(2)	C10-C11-C12	111.6(3)
C2-O4-C5	120.3(2)	C10-C11-C13	108.5(4)
O4-C5-C8	102.1(2)	C12-C11-C13	111.5(4)
O4-C5-C6	110.5(2)	O15-C14-C9	121.3(3)
C8-C5-C6	112.8(3)	O15-C14-S16	123.3(2)
O4-C5-C7	109.4(2)	C9-C14-S16	115.4(2)
C8-C5-C7	110.1(3)	C14-S16-C17	100.4(2)
C6-C5-C7	111.7(3)	C18-C17-S16	112.9(3)
N1-C9-C14	112.7(2)		

Results and Discussion

Refinement of non-hydrogen atoms with anisotropic parameters was started at this stage. The hydrogen atoms were placed at chemically acceptable positions and were allowed to ride on the parent atoms 169 parameters were refined with 2838 unique reflections which saturated the residuals to $R_1 = 0.0459$. The highest peak and the deepest hole in the final difference map are 0.209 and -0.266 e.Å^{-3} , respectively. The details of crystal data and refinement are given in Table 1.[†] Table 2 gives the list of bond distances and bond angles of non-hydrogen atoms, respectively. Figure 1 represents the ORTEP [22] diagram of the molecule with thermal ellipsoids drawn at 50% probability.

The bond lengths and bond angles are in good agreement with the standard values. The S16-C17 bond length of 1.802(4) Å agrees satisfactorily with those found in other thiol esters [23]. The torsion angle values of $55.1(4)^\circ$ and $-6.1(5)^\circ$ for C10-C9-C14-O15 and C9-N1-C2-O3, respectively, indicate that the carbonyl groups at C14 and C2 are oriented in *synclinal* and *-synperiplanar* conformations

[†]CCDC 619574 contains the supplementary crystallographic data for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(0)1223-336033).

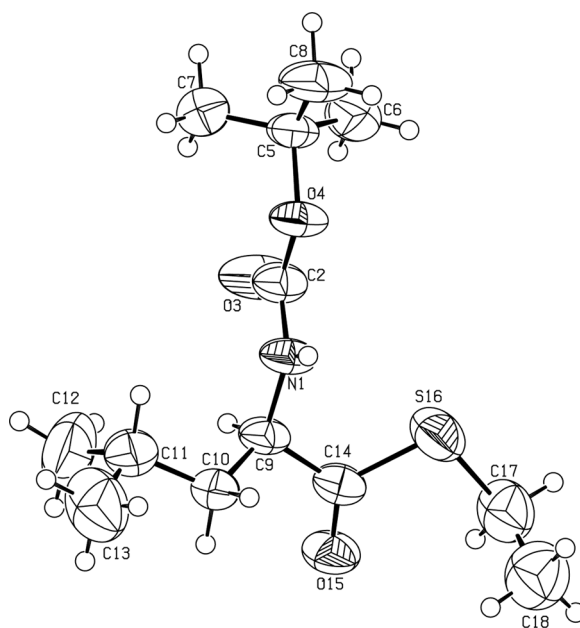


Figure 1. ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability.

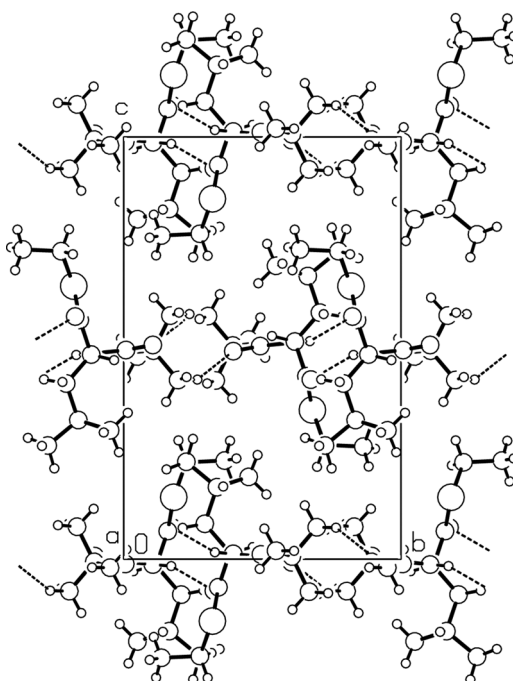


Figure 2. Packing of the molecules when viewed down the *a* axis. The dashed lines represent the intermolecular hydrogen bonds.

respectively. Conjugation between O4 and the carbonyl double bond C2=O3 is observed as shown by the bond distances of 1.331(3) Å and 1.491(3) Å for O4=C2 and O4=C5, respectively. These values are in agreement with those found in other thiol esters [23]. The molecule possesses a chiral center at C9. The dihedral angle between the least squares planes of Boc and Leu moieties is 73.2(8)°. The conformation of the Boc group defined by the rotation angle about C6–O8, $\omega_o = -178.8(4)^\circ$ is *trans*. Here, the N1–C9–C14–S16 and C2–N1–C9–C14 torsion angles are $-1.1(4)^\circ$ and $100.7(4)^\circ$, respectively. The structure exhibits both inter and intramolecular hydrogen bonds of the type N–H \cdots O and C–H \cdots O. The intermolecular hydrogen bonds are N1–H1 \cdots O5 which has a length of 3.018(3) Å and an angle of 158° while C7–H7C \cdots O3 has a length of 3.360(5) Å and an angle of 152° with symmetry codes $1/2+x, 1/2-y, -z$ and $1/2+x, -1/2-y, -z$, respectively. The stability of the crystal structure can be accounted for by these hydrogen bonds. The packing of the molecules when viewed down the *a* axis indicate that the molecules are interlinked by the hydrogen bonds to form a chain like structure.

Acknowledgments

The authors would like to express their thanks to DST, Government of India for financial assistance under the project SP/I2/FOO/93.

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