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ORIGINAL PAPER

Synthesis and Crystal Structure of Tert-butyl 2-((phenylthio)-carbonyl)pyrrolidine-1-carboxylate

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Abstract Tert-butyl 2-((phenylthio)carbonyl)pyrrolidine-1-carboxylate, was synthesized by using iso-butoxycarbonyl chloride (i-BuOCOCl) via mixed anhydride method. The obtained product was characterized spectroscopically and finally confirmed by X-ray diffraction studies. The title compound $C_{16}\,H_{21}\,N\,O_3\,S$ crystallizes in the triclinic space group $P1$ with the cell parameters $a = 6.0250(7)$ Å, $b = 8.2820(13)$ Å, $c = 8.7700(14)$ Å, $\alpha = 102.352(4)°$, $\beta = 102.993(11)°$, $\gamma = 90.279(8)°$, $V = 415.89(10)$ Å^3 and $Z = 1$. The proline ring in the structure is in a envelope conformation. The structure exhibits intermolecular hydrogen bonds of the type C–H...O.

Keywords Thiol ester · Anhydride method · Envelope conformation

Introduction

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 [1]. Organic compounds with the thiol ester group are key intermediates in many synthetic transformations [2]. They have been used for the synthesis of ketones, via organocuprates [3], Grignard reagents [4] or silylacetylenes [5]. Thiol esters can also be reduced to the corresponding aldehydes using a variety of reducing agents such as di-isobutylaluminium hydride (DIBAL) [6], lithium [7] or triethylsilane [8]. Also, they can be reduced to the corresponding hydroxymethyl moiety with sodium borohydride [9] or other strong reducing agents [10]. Macrolactonization through thiol esters was accomplished in the preparation of a variety of natural products as detailed in the literature [11]. They have also been utilized for the synthesis of β-lactams [12]. Peptide thiol esters are key building blocks in contemporary ligation chemistry for polypeptide synthesis such as the thioester method [13] and native chemical ligation [14]. α-Amino thiol esters have also attracted significant interest as they can be used for the synthesis of polypeptides, α-amino aldehydes and α-amino ketones [15–17]. In this context, it is interesting to study the crystal structure of α-amino thiol esters. Thiol esters can be easily prepared from the corresponding carboxylic acids via the acid chlorides or mixed anhydrides, or by utilizing various dehydrating agents such as dicyclohexylcarbodiimide (DCC) or 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (EDCI) [18]. For the synthesis of N-protected amino thiol esters, the mixed anhydride method using iso-butoxycarbonyl chloride (i-BuOCOCl) is found to be more adequate and efficient.

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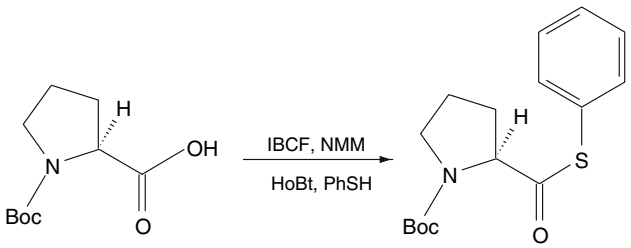

Scheme 1 Reaction scheme

Table 1 Experimental crystallographic data

Empirical formula	C_{16} H_{21} N O_3 S
Formula weight	307.40
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	*P*1
Cell dimensions	a = 6.0250(7) Å
	b = 8.2820(13) Å
	c = 8.7700(14) Å
	α = 102.352(4)°
	β = 102.993(11)°
	γ = 90.279(8)°
Volume	415.89(10) $Å^3$
Z	1
Density(calculated)	1.227 Mg/m^3
Absorption coefficient	0.203 mm^{-1}
F_{000}	164
Crystal size	0.3 × 0.27 × 0.25 mm
Theta range for data collection	2.44–32.61°
Index ranges	$-7 \leq h \leq 7$
	$-12 \leq k \leq 12$
	$-12 \leq l \leq 12$
Reflections collected	3,284
Independent reflections	3,284 [R(int) = 0.0000]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3,284/3/194
Goodness-of-fit on F^2	1.067
Final R indices [$I > 2\ \sigma(I)$]	$R1$ = 0.0465, $wR2$ = 0.1343
R indices (all data)	$R1$ = 0.0591, $wR2$ = 0.1586
Extinction coefficient	0.29(4)
Largest diff. peak and hole	0.209 and –0.266 e.$Å^{-3}$
Deposition number	CCDC 613082

Table 2 Bond Lengths (Å) and Bond Angles (°)

Atoms	Length	Atoms	Length
N1–C6	1.350(4)	C9–C11	1.494(5)
N1–C2	1.452(4)	C9–C10	1.516(5)
N1–C5	1.465(4)	C13–O14	1.181(4)
C2–C13	1.533(4)	C13–S15	1.792(3)
C2–C3	1.538(5)	S15–C16	1.780(3)
C3–C4	1.503(7)	C16–C21	1.380(5)
C4–C5	1.512(8)	C16–C17	1.387(5)
C6–O7	1.223(4)	C17–C18	1.389(5)
C6–O8	1.340(4)	C18–C19	1.374(7)
O8–C9	1.472(4)	C19–C20	1.364(6)
C9–C12	1.494(6)	C20–C21	1.394(5)
Atoms	**Angle**	**Atoms**	**Angle**
C6–N1–C2	123.9(2)	O8–C9–C10	109.9(3)
C6–N1–C5	122.7(3)	C12–C9–C10	109.1(4)
C2–N1–C5	112.5(3)	C11–C9–C10	114.7(5)
N1–C2–C13	113.1(3)	O14–C13–C2	123.5(3)
N1–C2–C3	102.9(3)	O14–C13–S15	124.2(2)
C13–C2–C3	111.5(3)	C2–C13–S15	112.3(2)
C4–C3–C2	104.2(4)	C16–S15–C13	102.4(2)
C3–C4–C5	103.4(3)	C21–C16–C17	120.5(3)
N1–C5–C4	102.8(4)	C21–C16–S15	122.8(3)
O7–C6–O8	125.5(3)	C17–C16–S15	116.5(3)
O7–C6–N1	124.6(3)	C16–C17–C18	118.9(4)
O8–C6–N1	109.9(3)	C19–C18–C17	120.8(4)
C6–O8–C9	123.1(3)	C20–C19–C18	119.9(3)
O8–C9–C12	102.4(3)	C19–C20–C21	120.6(4)
O8–C9–C11	109.7(3)	C16–C21–C20	119.3(4)
C12–C9–C11	110.4(4)		

Experimental

General

1-(Tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (Boc-Pro-OH) and 1-hydr-oxybenzotriazole (HOBt) were purchased from Advanced Chem. Tech. (Louisville, Kentucky, USA). Isobutylchloroformate (IBCF) and *N*-methylmor-pholine (NMM) were purchased from Sigma Chemical Co. (St. Louis, MO). Phenyl thiol (PhSH) 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. ^{1}H NMR spectra were obtained on an amx-400 MHz instrument.

Synthesis of Tert-butyl 2-((phenylthio)carbonyl) pyrrolidine-1-carboxylate

To 1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid (Boc-Pro-OH) (2.152 g, 10 mmol), dissolved in acetonitrile (30 mL) and cooled to 0°C was added NMM (1.1 mL, 10 mmol). To this solution, isobutylchloroformate (IBCF) (1.3 mL, 10 mmol) was added dropwise under stirring while maintaining the temperature at 0°C. After stirring the reaction mixture for 10 min at this temperature, 1-hydroxybenzotriazole (HOBt) (1.55 g, 10 mmol) was added. The reaction mixture was stirred for an additional 10 min and phenylthiol (PhSH) (1.05 mL, 10 mmol) was added slowly. After 20 min, the pH of the solution was adjusted to 8 by the addition of *N*-methylmorpholine (NMM) and the reaction mixture was stirred over night at room temperature. Acetonitrile was removed under reduced pressure. The residue was taken into chloroform,

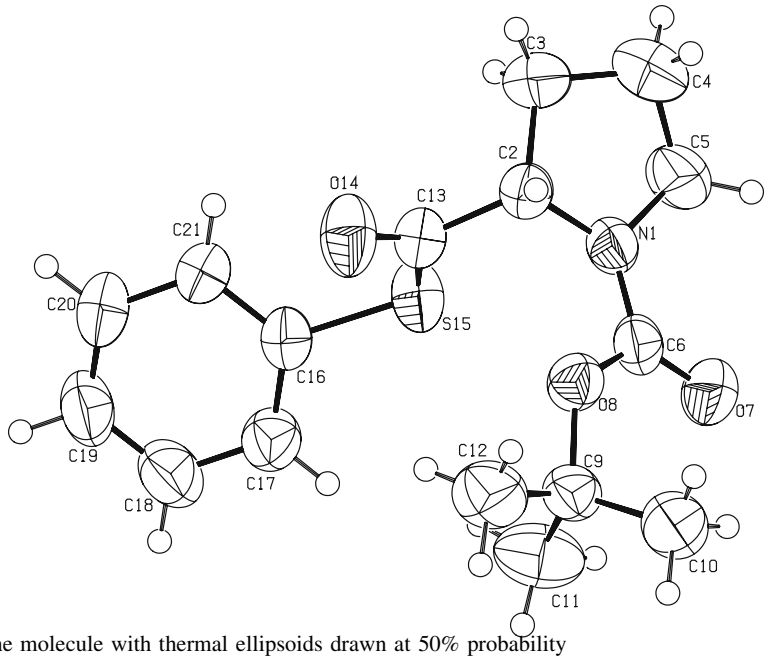

Fig. 1 ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability

washed consecutively with 0.01 N cold HCl, aqueous sodiumbicarbonate and water and dried over sodium sulphate. The crude product was recrystallized from ethanol; yield 2.52 g (82%).

^{1}H NMR (400 MHz, $CDCl_3$)

δ (s, 9H, $(CH_3)_3$, 2.10–2.15 (m, 2H, $^{\gamma}$CH), 2.29–2.36 (m, 2H, $^{\beta}$CH), 3.32 (t, 2H, $^{\delta}$CH), 4.21 (m, 1H, $^{\alpha}$CH), 7.21 (m, 5H, Ar–H).

Crystal Structure Determination

A single crystal of the title compound with dimensions $0.3 \times 0.27 \times 0.25$ mm was chosen for X-ray diffraction study. The data were collected on a DIPLabo Image Plate system equipped with a normal focus, 3 kW sealed X-ray source [graphite monochromated MoK_{α}]. The crystal to detector distance is fixed at 120 mm with a detector area of 441×240 mm^2. Thirty six frames of data were collected at room temperature by the oscillation method. Each exposure of the image plate was set to a period of 400 s. Successive

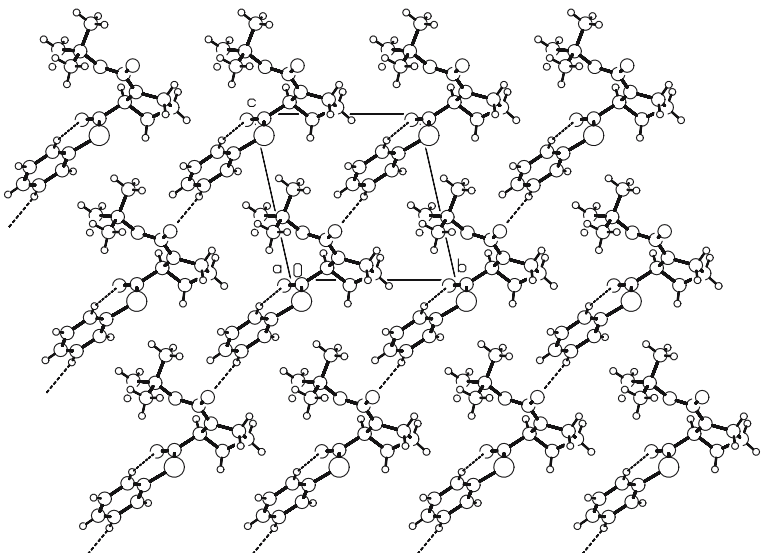

Fig. 2 Packing of the molecules when viewed down the *a* axis. The dashed lines represent the intermolecular C–H...O hydrogen bonds

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 the frames could be indexed using a primitive triclinic lattice. The structure was solved by direct methods using SHELXS-97 [21]. All the non-hydrogen atoms were revealed in the first Fourier map itself. Full-matrix least squares refinement using SHELXL-97 [22] with isotropic temperature factors for all the atoms converged the residuals to R_1=0.1290.

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. 194 parameters were refined with 3,284 unique reflections which saturated the residuals to R_1 = 0.0465. 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.[1] Table 2 gives the list of bond distances and bond angles of non-hydrogen atoms respectively. The bond lengths and bond angles are in good agreement with the standard values. Figure 1 represents the ORTEP [23] of the molecule with thermal ellipsoids at 50% probability. The proline ring can adopt different conformations as a result of its relative flexibility [24]. A study of the torsion angles, asymmetric parameters and least-squares plane calculations reveals that the proline ring in the structure is in an envelope conformation on C4 with the atom N1 deviating 0.036(3) Å from the least-squares plane defined by the atoms C2/C3/C4/C5. This has been confirmed by the puckering parameters q_2 = 0.3660(65) Å and ϕ = 279.4(7)°. A ring puckering analysis [25] shows that the proline ring has a weighted average ring bond distance of 1.4817(23,169) Å and a weighted average absolute torsion angle of 21.31(22,614)°. The dihedral angle between the proline ring and the thiophenyl ester moiety is 55.35(14)° while it is 15.6(2)° between the proline ring and the Boc group. The C=O bond lengths of ester (C13–O14=1.182(5) Å) and thiol-ester are (C6–O7=1.223(5) Å) respectively. This can be attributed to the strong resonance of the thiol-ester group. The carbonyl group at C13 is oriented in *-antiperiplanar* conformation while the carbonyl group at C6 is oriented in *-synperiplanar* conformation as indicated by the torsion angle values of –95.3(4)° and –12.4(5)° for C3–C2–C13–O14 and C5–N1–C6–O7 respectively. The conformation of the Boc group defined by the rotation angle about C6–O8, ω_o = 169.0(2)° is *trans*. The bond N1–C6 makes an angle of 76.72(26)° and is in the equatorial plane with respect to the proline ring while the bond C2–C13 makes an angle of 49.04(25)° bisecting the plane of the proline ring. The structure exhibits intermolecular hydrogen bonds of the type C–H...O. The stability of the crystal structure can be accounted by these hydrogen bonds. The intermolecular hydrogen bond C17–H17...O14 which is between the thiophenyl moiety and the carbonyl group has a length of 3.393(5) Å and an angle of 161° with a symmetry code 1 + *x*, *y*, *z* while the other hydrogen bond, C20–H20...O7 between the thiophenyl moiety and the ester carbonyl group has a length of 3.329(5) Å and an angle of 151° with symmetry code –1 + *x*, –1*y*, –1 + *z*. Figure 2 shows the packing of the molecules when viewed down the *a* axis which indicate that the molecules are stacked in pairs and are interlinked by hydrogen bonds to form a polymeric chain.

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[1] CCDC 613082 contains the supplementary crystallographic data for this paper. 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.

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