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Research Article

Synthesis, Characterization, X-Ray Crystal Structure, and Antimicrobial Activity of 1,1′-(3,4-Diphenylthieno[2,3-*b*]thiophene-2,5-diyl)diethanone

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Synthesis of 1,1′-(3,4-diphenylthieno[2,3-*b*]thiophene-2,5-diyl)diethanone (**4**) is reported here. The structure of compound **4** was deduced by ^{1}H-NMR, ^{13}C-NMR, FT-IR, MS, microanalysis, and single-crystal X-ray diffraction. Compound crystallizes in the monoclinic space group *P21/n* with $a = 9.3126(7)$ Å, $b = 9.5867(7)$ Å, $c = 20.2811(15)$ Å, $\alpha = 90^{\circ}$, $\beta = 95.436(2)^{\circ}$, $\gamma = 90^{\circ}$, $V = 1802.5(2)$ Å^3, and $Z = 4$. The molecules are packed in crystal structure by weak intermolecular C10–H10A$\cdots$S1 hydrogen bonding interactions. Compound **4** can be a useful intermediate for the synthesis of diphenylthieno[2,3-*b*]thiophene. Compound **4** was found to be active against Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus pneumoniae*) and Gram-negative bacteria (*Escherichia coli*) and also was found to be active against fungi (*Aspergillus fumigatus* and *Candida albicans*).

1. Introduction

Thienothiophenes skeletons are important in pharmaceutical research because of their versatile biological activities, such as antitumor, antiviral antibacterial, anticancer, antioxidant and β-glucuronidase and α-glucosidase inhibition, antiglaucoma activity, and inhibitors of platelet aggregation properties [1–5]. Because of this thieno[2,3-*b*]thiophenes have been the focus of active research in recent years. We have the synthesis of certain *bis*-heterocycles containing thieno[2,3-b]thiophene derivatives. The molecules that were prepared were found to be potent α-glucosidase inhibitors (IC_{50} = 14.1 ± 0.28 μM) with manyfold more activity than the standard acarbose (IC_{50} = 841 ± 1.73 μM). Indeed, another example incorporating thieno[2,3-*b*]thiophene core was found to be a potent β-glucuronidase inhibition (IC_{50} = 0.003 ± 0.09 μM) several hundred fold more active than standard D-saccharic acid 1,4-lactone (IC_{50} = 45.75 ± 2.16 μM) [6, 7].

The skeleton is identified as valuable scaffold for new heterocyclic compounds [8–11]. The structure of 1,1′-(3,4-diphenylthieno[2,3-*b*]thiophene-2,5-diyl)diethanone (**4**) was unambiguously deduced by single-crystal X-ray diffraction technique. Compound **4** was also screened for *in vitro* antimicrobial activity.

2. Experimental

2.1. General. All the chemicals were purchased from various suppliers, including Sigma-Aldrich and Fluka, and were used without further purification, unless otherwise stated. All melting points were measured on a Gallenkamp melting point apparatus in open glass capillaries and are uncorrected. IR Spectrum was recorded as KBr pellets on a Nicolet 6700 FT-IR spectrophotometer. The NMR spectra were recorded on a Varian Mercury Jeol-400 NMR spectrometer. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) were run in

deuterated dimethyl sulphoxide (DMSO-d_6). Chemical shifts (δ) are referred to in *ppm* while *J*-coupling constants were represented in *Hz*. Mass spectra were recorded on a Jeol of JMS-600 H. Elemental analysis was carried out on Elmer 2400 Elemental Analyzer, CHN mode. The single-crystal X-ray diffraction measurements were performed using Bruker SMART APEXII CCD diffractometer.

2.2. Preparation of 1,1′-(3,4-Diphenylthieno[2,3-b]thiophene-2,5-diyl)diethanone

Method A. A mixture of 1,3-diphenylpropane-1,3-dione (**1**) (22.4 g, 0.1 mol) and anhydrous potassium carbonate (25 g) in DMF (30–40 mL) was stirred vigorously at room temperature for 5 min; then carbon disulfide (7.6 mL, 0.1 mol) was added with continued stirring for 30 min. The resulting reaction mixture was cooled in ice bath, and then chloroacetone (18.5 mL, 0.2 mol) was added with continued stirring for 15 min. Then cooling bath was subsequently removed and the mixture was stirred for further 30 min. The solid product was collected by filtration and washed with water and dried crude product.

Method B. A mixture of 1,3-diphenylpropane-1,3-dione (**1**) (22.4 g, 0.1 mol) and NaOEt (2 mol Na in 30–40 mL absolute EtOH) was stirred vigorously at room temperature for 5 min, and then carbon disulfide (7.6 mL, 0.1 mol) was added with continued stirring for 30 min. The resulting reaction mixture was cooled in ice bath, and then chloroacetone (18.5 mL, 0.2 mol) was added with continued stirring for 15 min; then cooling bath was subsequently removed and the mixture was stirred for further 30 min. The solid product was collected by filtration and washed with water and dried [12, 13].

Yield: 75%; m.p. 265°C; IR (ν_{max}): 1637 (C=O) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.74 (s, 6H, CH_3), 7.00–7.04 (m, 10H, Ph); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 31.37 ($COCH_3$), 191.3 (C=O), 129.23, 129.55, 129.87, 134.79, 138.82, 141.84, 147.68 (Ar–C); MS *m/z* (%): 376 [M+, 60%], 300 (100), 226 (37), 184 (14); anal. calcd. for $C_{22}H_{16}O_2S_2$: C, 70.18; H, 4.28; S, 17.03; found: C, 70.07; H, 4.44; S, 17.11.

2.3. Crystal Structure Determination.

Slow evaporation of glacial acetic acid solution of pure compound **4** yielded colorless crystals. A crystal of dimensions 0.54 × 0.53 × 0.30 mm was selected for X-ray diffraction analysis. Data were collected on a Bruker APEX-II CCD area diffractometer and equipped with graphite monochromatic Mo Kα radiation (λ = 71073 Å) at 293 (2) °K. Cell refinement and data reduction were carried out by Bruker SAINT [14]. SHELXS-97 [15, 16] was used to solve structure (Table 1). The final refinement was carried out by full-matrix least-squares techniques with anisotropic thermal data for nonhydrogen atoms on *F*2. All the hydrogen atoms were placed in calculated positions. The crystal structure **4** (Figure 1) was finally refined with *R* factor of 4.25% for 3362 unique reflections. Molecules were found to be packed in crystal lattice through intermolecular hydrogen bonding (Table 2).

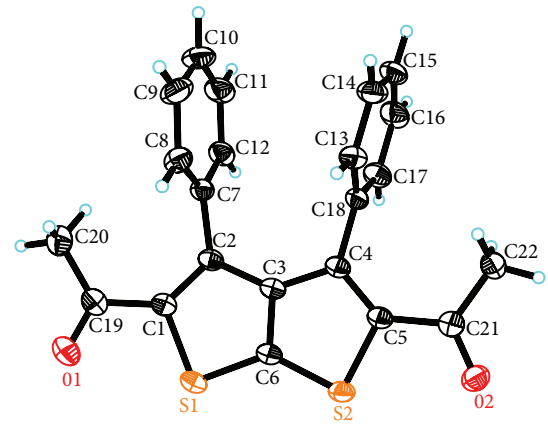


Figure 1: The ORTEP diagram of the final X-ray model of compound **4** with displacement ellipsoids drawn at 30% probability level. H-atoms were placed and not included in refinement.

Table 1: The crystal and experimental data of compound **4**.

Empirical formula	$C_{22}H_{16}O_2S_2$
Formula weight	376.47
Temperature (K)	297(2)
Mo Kα radiations, λ	0.71073 Å
Crystal system	Monoclinic
Space group	*P*21/*n*
a	9.3126(7) Å
b	9.5867(7) Å
c	20.2811(15) Å
β	95.436(2)°
Volume	1802.5(2) Å^3
Z	4
Calculated density	1.387 mg/m^3
Absorption coefficient	0.309 mm^{-1}
F(000)	784
Crystal shape and color	Colorless, block
Crystal size	0.54 × 0.53 × 0.30 mm
θ range	2.02 to 25.50°
h/*k*/*l*	−11,11/−11,11/−24,24
Reflections collected	10407
Reflections unique	3362
(R_{int})	0.0261
R_1 with $I > 2\sigma(I)$	0.0360
R_2 with $I > 2\sigma(I)$	0.0925
R_1 for all data	0.0425
R_2 for all data	0.0980
Goodness of fit	1.042
max/min ρ eÅ^{-3}	0.193/−0.176

2.4. Antifungal Activity.

Tested sample was screened *in vitro* for its antifungal activity against various fungi, namely, *Aspergillus fumigatus* (RCMB 002568) and *Candida albicans* (RCMB 05036). The antifungal activity was performed by agar well diffusion method.

Table 2: Hydrogen bonding data for compound **4**.

D	H	A	D–H	H···A	D···A	D–H···A
C10	H10A	S1[a]	0.9300	2.8500	3.7542(2)	161.00

Symmetry codes: [a] $-1/2 + x, 1/2 - y, -1/2 + z$.

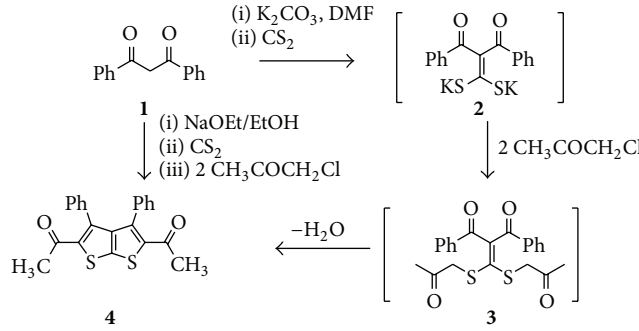
Fungal strains were grown in 5 mL sabouraud dextrose broth (glucose : peptone; 40 : 10) for 3-4 days to obtain 105 CFU/mL cells. The fungal culture (0.1 mL) was spread uniformly on the sabouraud dextrose agar plates by sterilized triangular folded glass rod. Plates were left for 5–10 min so the culture is properly adsorbed on the surface. Now small wells of size 4 mm × 2 mm were cut into the plates with the help of well cutter and bottom of the wells was sealed with 0.8% soft agar to prevent the flow of test sample at the bottom of the well. 100 μL of the tested samples (10 mg/mL) was loaded into the wells of the plates. Compound **4** dissolved in DMSO, while pure DMSO was also used as control. The plates were kept for incubation at 30°C for 3-4 days and then examined for the formation of zones of inhibition. The test was performed three times for each fungus. Amphotericin B was used as standard antifungal drug.

2.5. Antibacterial Activity. Antibacterial activities were investigated by using agar well diffusion method, against the *Staphylococcus pneumonia* (RCMB 010010) and *Bacillus subtilis* (RCMB 010067) {as Gram-positive bacteria} and *Pseudomonas aeruginosa* (RCMB 010043) and *Escherichia coli* (RCMB 0100052) {as Gram-negative bacteria}. The solution of 5 mg/mL of compound in DMSO was prepared for testing against bacteria. Centrifuged pellets of bacteria from 24 h old culture containing approximately 104–106 CFU (colony forming unit) per mL were spread on the surface of nutrient agar (typetone 1%, yeast extract 0.5%, NaCl 0.5%, agar, and 1000 mL of distilled water, pH 7.0) which was autoclaved under 121°C for at least 20 min. Wells were created in medium with the help of sterile metallic bores and then cooled down to 45°C. The activity was determined by measuring the diameter of the inhibition zone (in mm). 100 μL of the tested samples (10 mg/mL) was loaded into the wells of the plates. Solution of compound was prepared in DMSO while DMSO was also loaded as control. The plates were kept for incubation at 37°C for 24 h and then the plates were examined for the formation of zone of inhibition. Each inhibition zone was measured three times by caliper to get an average value. The test was performed three times for each bacterium. Ampicillin and gentamicin were used as antibacterial standard drugs [17].

3. Results and Discussion

*3.1. Title Compound **4** Was Synthesized as Depicted in Scheme 1, in 75% Yield.* The structure was deduced by combined use of IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectral data. Accordingly, the assigned structure was unambiguously established *via* single-crystal X-ray diffraction.

*3.2. Crystal Structure of Compound **4**.* The asymmetric unit contains two molecules. The crystal structure of compound



Scheme 1: Synthetic pathway towards title compound **4**.

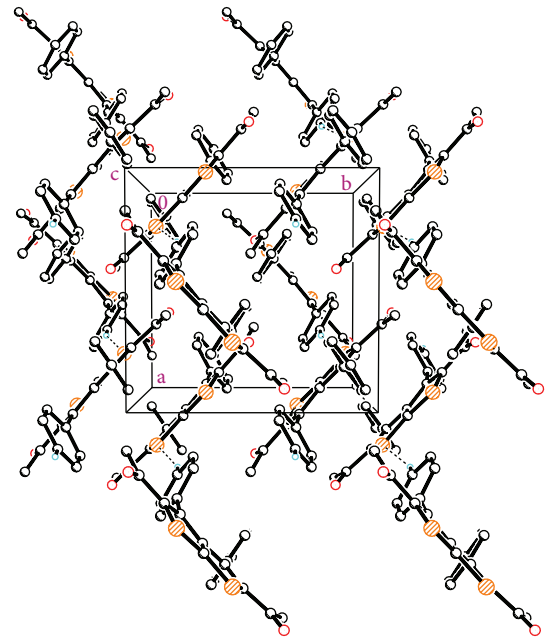


Figure 2: The crystal packing of compound **4**. Dashed line indicates the intermolecular interactions. The hydrogen atoms not involved in intermolecular interactions are omitted for clarity.

4 is composed of two planner thiophene rings (S1/C1-C3/C6 and S2/C3-C5/C6), fused along C3 and C6 plane having two phenyl (C7-C12/C13-C18) rings and ethanone (O1/C19-C20/O2/C21-C22) moieties attached to C1, C2, C4, and C5 atoms (Figure 1). Two thiophene (S1/C1-C3/C6 and S2/C3-C5/C6) and phenyl (C7-C12 and C13-C18) rings are each planner with maximum deviation of 0.011(2) Å for C2 and C6 atoms from the root mean square plane. The crystal molecules are linked *via* C10–H10A···S1 interaction to form chains arranged in a *zigzag* fashion along the *c*-axis (Figure 2).

*3.3. Antimicrobial Activity of Compound **4**.* Compound **4** was evaluated against pathogenic microorganisms representing Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus pneumoniae*), Gram-negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*), and fungi (*Aspergillus fumigatus* and *Candida albicans*), and the activities were compared with standard antibacterial and antifungal standard drug,

Table 3: Antimicrobial activity of compound **4**.

Comp. number	Gram-positive bacteria		Gram-negative bacteria		Fungi	
	Staphylococcus pneumoniae	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Aspergillus fumigatus*	*Candida albicans*
4	12.9 ± 0.63	13.2 ± 0.58	NA	10.8 ± 0.44	18.7 ± 0.36	16.9 ± 0.27
Ampicillin	23.8 ± 0.2	32.4 ± 0.3	—	—	—	—
Gentamicin	—	—	17.3 ± 0.1	19.9 ± 0.3	—	—
Amphotericin B	—	—	—	—	23.7 ± 0.1	25.4 ± 0.1

Inhibition zones (mm).
NA: no activity.

specified in US pharmacopeia at 25 μg/mL. Compound **4** showed a relatively moderate inhibitory effect against Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus pneumoniae*) as compared to standard drug ampicillin. It also showed a relatively moderate inhibitory effect against Gram-negative bacteria (*Escherichia coli*), as comparable to that of the standard drug gentamicin. No activity was observed against *Pseudomonas aeruginosa*. Finally, compound **4** was also found to be active against fungi (*Aspergillus fumigatus* and *Candida albicans*), compared to the standard drug amphotericin B. The results obtained are summarized in Table 3.

4. Conclusion

The synthesis and characterization of a new 1,1′-(3,4-diphenylthieno[2,3-*b*]thiophene-2,5-diyl)diethanone (**4**) were successfully achieved in high yield. The structure of **4** was confirmed finally by single-crystal X-ray diffraction. Compound **4** showed activity effect against Gram-negative bacteria (*Bacillus subtilis* and *Staphylococcus pneumoniae*), Gram-positive bacteria (*Escherichia coli*), and antifungal activity against (*Aspergillus fumigatus* and *Candida albicans*). The pivotal compound **4** can be used as a synthon for new drugs with above cited.

Conflict of Interests

The authors have declared that there is no conflict of interests.

Authors' Contribution

The authors contributed equally to this work.

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