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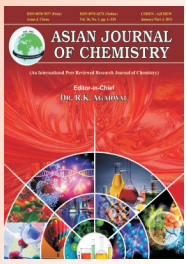

Synthesis, Characterization and X-Ray Crystal Structure of 3-Methyl-4-oxo-7-phenyl-4,7-dihydrothieno[2,3-*b*]pyridine-2-carboxyxlic Acid Ethyl Ester

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Synthesis of 3-methyl-4-oxo-7-phenyl-4,7-dihydrothieno[2,3-*b*]pyridine-2-carboxylic acid ethyl ester (**3**) is described. The structure of the title compound **3** is confirmed by NMR, FT-IR, MS, CHN microanalysis, and X-ray crystallography. Compound **3** is a useful, functionalized pyrido thiophene derivative that can be transformed to novel heteroaromatics of potential pharmacological activities.

Keywords: Thieno[2,3-*b*]pyridine, Enaminones, X-Ray.

INTRODUCTION

Enaminones are readily accessible and versatile synthetic synthon for heterocycles synthesis and reactions. These intermediates have been manipulated by condensation with different electrophilic and nucleophilic reagents to build novel heterocyclic systems of potential biological activities including: pyridino[2,3-*d*] pyrimidin-4-one, pyrido[2,3-*d*] [1,2,4]triazolino-[4,3-*a*]pyrimidin-4-one and pyrido[2,3-*d*] [1,2,4]triazolino-[4,5-*a*]pyrimidin-5-one[1], pyrazolo[3,4-*d*]pyrimidin-4-one and pyrazolo[1,5-*a*] pyrimidine derivatives[2], thiophene derivatives incorporating pyrazoles, pyrimidines, [1,2,4]triazolo[1,5-a]pyrimidine and benzo[4,5]imidazo[1,2-*a*]pyrimidine rings[3], isoquinoline[4] and natural products and their analogues[5,6].

Moreover, thieno[2,3-*b*]pyridine system and its derivatives are privileged structures exhibiting remarkable pharmacological activities such as antimicrobial[7,8], anticancer[9,10], antiviral[11,12], antiinflammatory[13], antihypertensive[14] and estrogenic activities[15]. Moreover, several derivatives of thieno[2,3-*b*]-pyridine system were prepared and tested as potential bioisosters of the antibacterial quinolones including norfloxacin, ciprofloxacin and ofloxacin[16,17].

In view of the above mentioned facts and in continuation of our interest in the chemistry of thiophene and its derivatives[18-21] to develop new candidates of potential biological activities we have chosen compound **1** as starting material for synthesis of new condensed heterocyclic compounds containing thieno[2,3-*b*]pyridine moiety. The structure of 3-methyl-4-oxo-7-phenyl-4,7-dihydrothieno[2,3-*b*]pyridine-2-carboxyxlic acid ethyl ester (**3**) was deduced by single-crystal X-ray diffraction technique.

EXPERIMENTAL

All the chemicals were purchased from Sigma-Aldrich, Fluka *etc.*, 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 Spectra were measured 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 chloroform ($CDCl_3$). Chemical shifts (δ) are referred in terms of ppm and *J* -coupling constants are given 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 X-ray diffraction measurements of compound **3** were collected by using Bruker SMART APEXII D8 Venture diffractometer.

Preparation of 3-methyl-4-oxo-7-phenyl-4,7-dihydrothieno[2,3-*b*]pyridine-2-carboxyxlic acid ethyl ester (3): To a solution of acetyl thiophene (**1**) (1 mmol) in dry dioxane (20 mL) and *N*,*N*-dimethylformamide-dimethylacetal (DMF-DMA) (1.32 mL, 1 mmol) was added. The reaction mixture was refluxed for 2 h. After cooling, the precipitated product was filtered off, washed with methanol and recrystallized from

EtOH (96 %) to afford the title compound **3**, as a pale yellow crystals (74 %) , mp. 244 °C; IR (KBr, ν_{max}, cm^{-1}): 3054 (CH-ar.), 2981 (CH aliph.), 1692 (CO), 1621 (COO), 1587 (C=C), 1532, 1483, 1455, 1367, 1250, 1116, 1069, 1013, 824, 764, 699; ^{1}H NMR (400 MHz; $CDCl_3$) 1.33 (3 H, t, *J* 7.2, CH_3), 3.04 (3 H, s, CH_3), 4.31 (2 H, q, *J* 7.2, CH_2), 6.37 (1 H, d, *J* 7.6, CO-CH=CH), 7.44 (1 H, d, *J* 7.6, CO-CH=CH), 7.48-7.52 (2 H, m, ph), 7.57-7.64 (3 H, m, ph); ^{13}C NMR (100 MHz; $CDCl_3$) 176.93 (C=O), 162.71 (OCO), 154.39 (S-C_q-N), 146.54 (C_q-CO), 141.86 (C_q-ph), 139.52 (=CH-N), 130.61 (2*m*-CH-ph), 130.26 (*p*-CH-ph), 128.45 (C_q-CH_3), 125.50 (2*o*-CH-ph), 118.03 (-S-C_q-COO),115.93 (=CH-CO), 61.18 (CH_2), 15.51 (CH_3-CH_2-), 14.34 (CH_3); MS *m/z* (%): 313.37 [M^+, 95 %]; Anal. Calcd. for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82; N, 4.47; found: C, 65.18; H, 4.81; N, 4.50.

Crystal structure determination: Slow evaporation of ethanol solution of pure compound **3** yielded colorless crystals. A crystal of dimensions, 0.46 × 0.33 × 0.12 mm was selected for X-ray diffraction analysis. Data were collected on a Bruker APEX-II D8 Venture area diffractometer, equipped with graphite monochromatic MoK$_\alpha$ radiation at 293 (2) °K. Cell refinement and data reduction were carried out by Bruker SAINT[14]. SHELXS-97[22] was used to solve structure. The final refinement was carried out by full-matrix least-squares techniques with anisotropic thermal data for nonhydrogen atoms on F2. All the hydrogen atoms were placed in calculated positions (Tables 1-3). The crystal structure of **3** is given in Fig. 1.

The structure of **4c** was confirmed by X-ray crystal structure analysis (Bruker AXS GmbH). CCDC-994940 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

TABLE-1
CRYSTAL AND EXPERIMENTAL DATA OF COMPOUND **3**

$C_{17}H_{15}NO_3S$	V = 1487.45 (10) Å^3
M_r = 313.37	Z = 4
Monoclinic, $P2_1/n$	Mo K$_\alpha$ radiation
a = 10.8270 (4) Å	μ = 0.23 mm^{-1}
b = 8.1912 (3) Å	T = 293 K
c = 17.2855 (7) Å	0.46 × 0.33 × 0.12 mm
β = 104.0000 (12)°	-

TABLE-2
SELECTED GEOMETRIC PARAMETERS (Å, °)

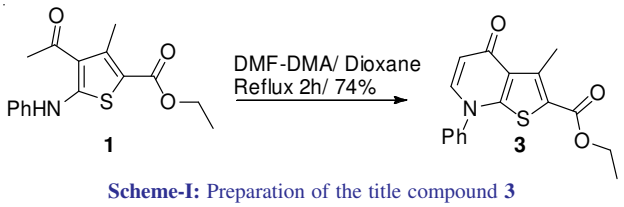
S1-C12	1.7476 (14)	O3-C14	1.2115 (19)
S1-C13	1.7179 (16)	N1-C6	1.4469 (19)
O1-C14	1.340 (2)	N1-C7	1.368 (2)
O1-C15	1.453 (2)	N1-C13	1.3682 (18)
O2-C9	1.242 (2)	-	-
C12-S1-C13	89.77 (7)	S1-C12-C11	113.66 (11)
C14-O1-C15	117.05 (13)	S1-C12-C14	118.13 (12)
C6-N1-C7	120.25 (12)	S1-C13-N1	122.95 (11)
C6-N1-C13	121.91 (12)	S1-C13-C10	113.67 (11)
C7-N1-C13	117.83 (12)	N1-C13-C10	123.37 (14)
N1-C6-C1	119.20 (13)	O1-C14-O3	123.76 (15)
N1-C6-C5	118.91 (14)	O1-C14-C12	111.26 (13)
N1-C7-C8	122.34 (14)	O3-C14-C12	124.97 (15)
O2-C9-C8	122.28 (15)	O1-C15-C16	106.93 (15)
O2-C9-C10	123.99 (14)	-	-

RESULTS AND DISCUSSION

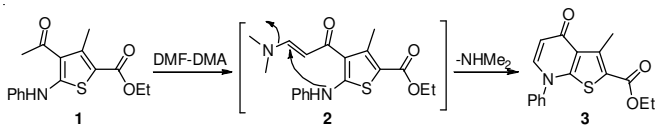
Heating of acetyl thiophene derivatives **1** with dimethylformamide-dimethylacetal (DMF-DMA) afforded compound **3**.

The structure of compound **3** was established by analysis of its spectroscopic data including IR, ^{1}H, ^{13}C NMR and X-ray structure of single crystal. The IR spectrum of **3** indicated the absence of band due to NH group. The ^{1}H NMR spectrum revealed the following information; the absence of the signals due to CH_3 of the acetyl group and the NH of the starting material indicating formation of a new product. The presence of two doublets at δ 6.37 ppm and 7.44 ppm corresponding to the α and β protons of the 4-oxo-pyridine ring, respectively with coupling constant value of 7.6 Hz that is consistent with *cis* configuration as a result of ring formation. The ^{13}C NMR spectrum of the purified compound revealed the disappearance of the signal corresponding to the CH_3 group of the starting material, presence of two signals at δ 115.93 and 139.52 ppm corresponding to α and β CH groups, respectively, also there were two carbonyl carbons at δ 176.93 ppm for (C=O) and at δ 162.71 ppm for (OCO), respectively.

From the mechanistic point of view compound **3** is presumably formed as a result of intramolecular conjugate addition of the nucleophilic nitrogen onto the further end of the double bond (β-carbon) of the intermediate enaminone **2** with elimination of a dimethylamine molecule resulting in formation of Michael product **3** as depicted in **Scheme-II**.



Scheme-I: Preparation of the title compound **3**



Scheme-II: Proposed mechanistic pathway for formation of 3-methyl-4-oxo-7-phenyl-4,7-dihydrothieno[2,3-*b*]pyridine-2-carboxyxlic acid ethyl ester **3**

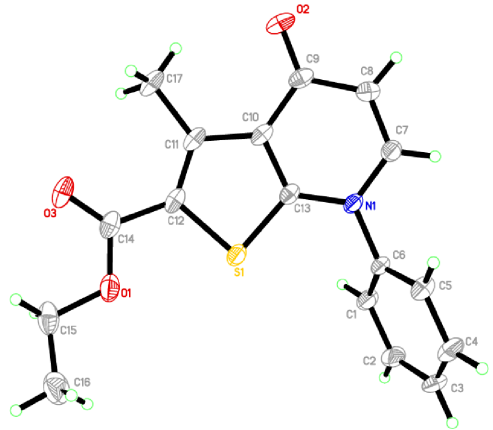


Fig. 1. ORTEP diagram of the final X-ray model of compound **3** with displacement ellipsoids drawn at 30 % probability level. H-atoms were placed using geometrical constraints and included in the refinement

TABLE-3
HYDROGEN-BOND GEOMETRY (Å, °)

D-H···A	D-H	H···A	D···A	D-H···A
C1-H1A···O2i	0.9300	2.3800	3.218 (2)	150.00
C3-H3A···O2ii	0.9300	2.4000	3.267 (2)	155.00
C7-H7A···O3iii	0.9300	2.2500	3.1734 (19)	174.00
C17-H17A···O3	0.9600	2.5800	2.992 (2)	106.00
C17-H17B···O2	0.9600	2.3200	3.014 (2)	128.00

Symmetry codes: (i) -x, -y + 1, -z + 1; (ii) x + 1/2, -y + 3/2, z-1/2; (iii) x-1/2, -y + 3/2, z-1/2

Crystal structure of compound 3: The asymmetric unit contains one molecule. The crystal structure of compound **3** is composed of two fused thiophene and dihydropyridine rings (S1/C10-C13) and N1/C7-C10/C13), fused together at C10 and C13 and having one phenyl ring (C1-C6) attached to N1 atom and carboxy ethyl side chain (C14/O3/O2/C15-C16) attached to C12 atom (Fig. 1). The fused thiophene (S1/C10-C13) and dihydropyridine ring N1/C7-C10/C13) are planar with maximum deviation of -178.41(14) for atom C10. The dihedral angle between the dihydrothieno[2,3-*b*]pyridine ring system and the phenyl ring is 63.1(2) Å. In the crystal; molecules are linked *via* C-H…O interactions to form chains along the a-axis (Fig. 2).

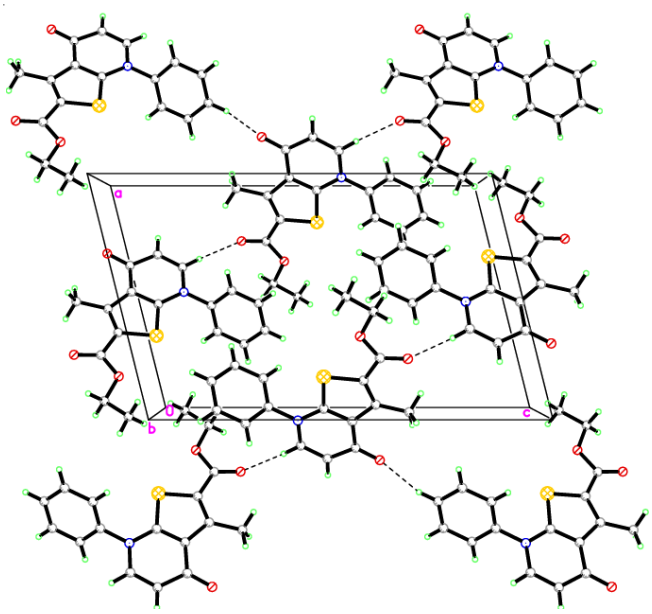


Fig. 2. Crystal packing of compound **3**. Dashed line indicates the intermolecular interactions

Conclusion

The synthesis and characterization of 3-methyl-4-oxo-7-phenyl-4,7-dihydrothieno[2,3-*b*]pyridine-2-carboxyxlic acid ethyl ester (**3**), have been successfully described. The structure of the title compound **3** was confirmed *via* its spectroscopic data and X-ray structure of a single crystal. Compound **3** can be used as a new lead for synthesis of fused heterocycles incorporating biologically important dihydrothieno [2,3-*b*]pyridine moiety.

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