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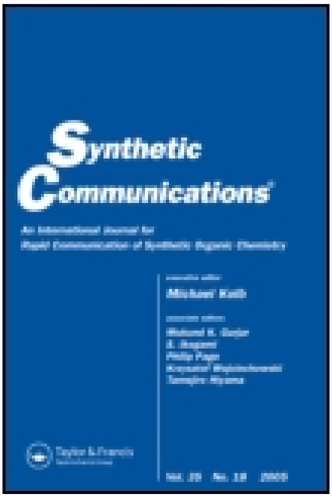

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Synthesis and Crystal Structure of (Z)-Ethyl 5-(phenylamino)-3-(phenylimino)-3H-1,2-dithiole-4-carboxylate

Mehtab Parveen [a], Sayed H. Mehdi [a], Mohammad N. Siddiqui [b] & Mohammed B. Fettouhi [b]

[a] Department of Chemistry, Aligarh Muslim University, Aligarh, UP, India

[b] Department of Chemistry, King Fahd University of Petroleum and Minerals, Dahran, Saudi Arabai

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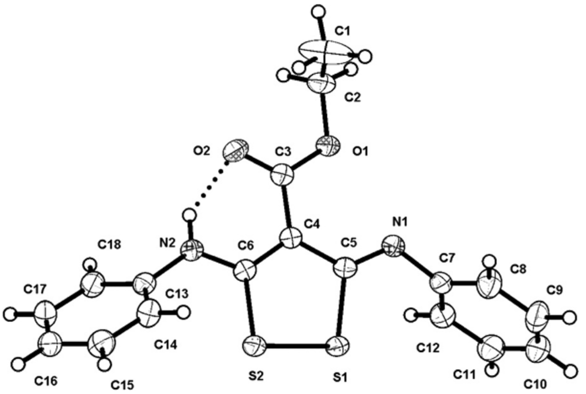
SYNTHESIS AND CRYSTAL STRUCTURE OF (*Z*)-ETHYL 5-(PHENYLAMINO)-3-(PHENYLIMINO)-3H-1,2-DITHIOLE-4-CARBOXYLATE

Mehtab Parveen,[1] Sayed H. Mehdi,[1] Mohammad N. Siddiqui,[2] and Mohammed B. Fettouhi[2]
[1]*Department of Chemistry, Aligarh Muslim University, Aligarh, UP, India*
[2]*Department of Chemistry, King Fahd University of Petroleum and Minerals, Dahran, Saudi Arabai*

GRAPHICAL ABSTRACT



Abstract *The compound (Z)-ethyl 5-(phenylamino)-3-(phenylimino)-3H-1,2-dithiole-4-carboxylate **3** has been synthesized by the reaction of ethylacetoacetate **1** and phenylisothiocyanate **2**. Its structure has been established by ^{1}H NMR, ^{13}C NMR, infrared, mass spectra, and x-ray crystallography.*

Keywords Crystal structure; synthesis; (*Z*)-ethyl 5-(phenylamino)-3-(phenylimino)-3H-1,2-dithiole-4-carboxylate

INTRODUCTION

Dithioles are used as additives to motor oils to inhibit metal corrosion.[1,2] Some dithioles exhibit pronounced physiological activity[3] and are important reagents in the synthesis of various organo-sulfur compounds.[4] Methods for the preparation of substituted dithioles have been developed.[4] In the 1990s, it was

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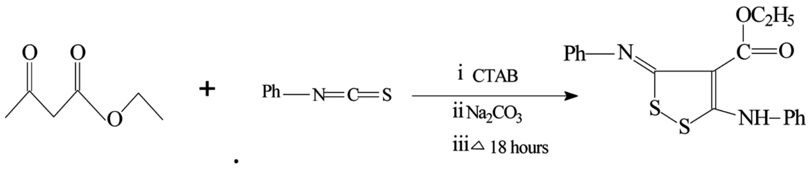
Address correspondence to Mehtab Parveen, Department of Chemistry, Aligarh Muslim University, Aligarh 202002, UP, India. E-mail: mehtab.organic2009@gmail.com

discovered that dithiole derivatives may be used as anticancer drugs.[5,6] They also inhibit the replication of HIV viruses.[7] 1,2-Dithiole derivatives have a gene-repairing function and are capable of repairing damaged DNA.[8,9] They prevent the formation of tumors because of their unique electronic structure and thus induce cancer resistance in the human body.[10] There has been great interest in the anticancer activity of dithiole derivatives and related compounds.[11]

Keeping in mind the medicinal importance of dithiole derivatives, we planned to synthesize the dithiole moiety by reaction with ethylacetoacetate **1** and phenylisothiocyanate **2** in the presence of phase-transfer catalyst cetyltrimethyl ammonium bromide (CTAB) and Na_2CO_3. The reaction was carried out in different molar ratios of ethylacetoacetate and phenyl isothiocyanate. In the molar ratio 1:1, the reaction gave a known compound, carbamothioate,[12] along with some unresolved products. Its structure was established by infrared (IR), ^{1}H NMR, ^{13}C NMR, and mass spectrographic (MS) spectra and confirmed by x-ray crystallography. When the reaction was repeated under similar conditions in molar ratios 1:2 and 1:3, some unresolved products were obtained. Finally, the reaction was carried out in the molar ratio 1:4 and furnished a novel crystalline compound named (*Z*)-ethyl 5-(phenylamino)-3-(phenylimino)-3H-1,2-dithiole-4-carboxylate **3**, which was characterized on the basis of modern spectroscopic techniques: IR, ^{1}H NMR, and MS. Its molecular structure was further confirmed by single-crystal x-ray analysis.

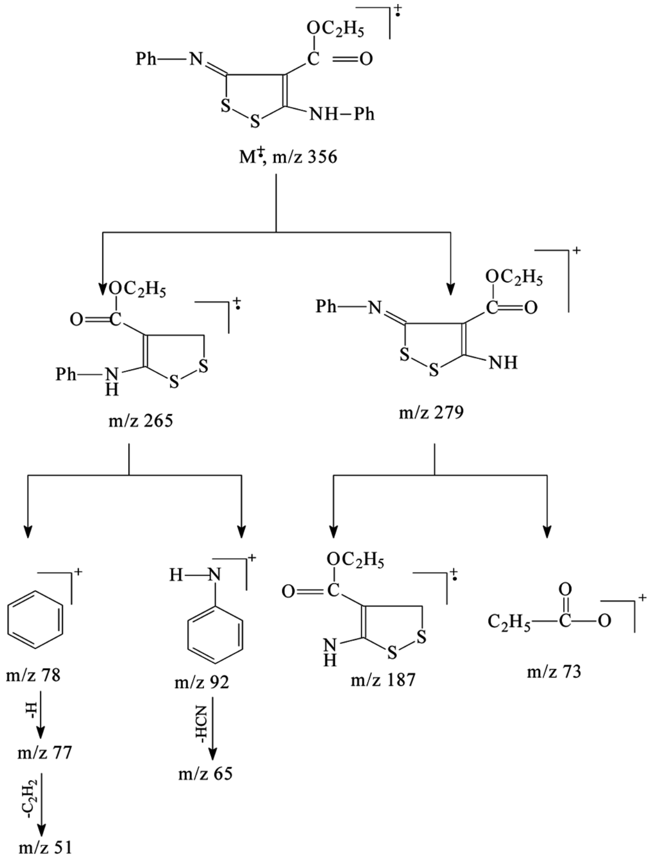
RESULTS AND DISCUSSION

A mixture of ethylacetoacetate **1** and phenylisothiocyanate **2** in molar ratio 1:4 was taken in benzene. A catalytic quantity of phase-transfer catalyst CTAB and sodium carbonate as a base were also added along with 1–2 drops of water. The reaction mixture was then heated on water bath for 18 h. After the usual workup followed by crystallization with chloroform–alcohol, it afforded compound **3**, mp 155 °C.



1 **2** **3**

The elemental analysis of the compound **3** corresponded to the molecular formula $C_{18}H_{16}N_2O_2S_2$. Its IR spectrum exhibits strong absorption bands at 3476, indicating the presence of a N-H group. Other bands observed were 1682 (C=O), 1388 cm^{-1} (C-N), etc. The ^{1}H NMR spectrum of the compound displayed a singlet at δ 9.6, which was assigned to N-H protons. A triplet and quartet at δ 1.48 and 4.44 were attributed to methyl and methylene groups respectively. Two multiplets centered at δ 7.6 and 7.8 were ascribed to two benzene rings in the compound. The structure was further suggested by its ^{13}C NMR spectrum,[13a–c] which showed a peak at δ 168 assigned to carbonyl carbon of ester. C-3, C-4, and C-5 carbons of the dithiole ring were observed at δ 153.1, 99, and 144.1, respectively. Imine and amine phenyl



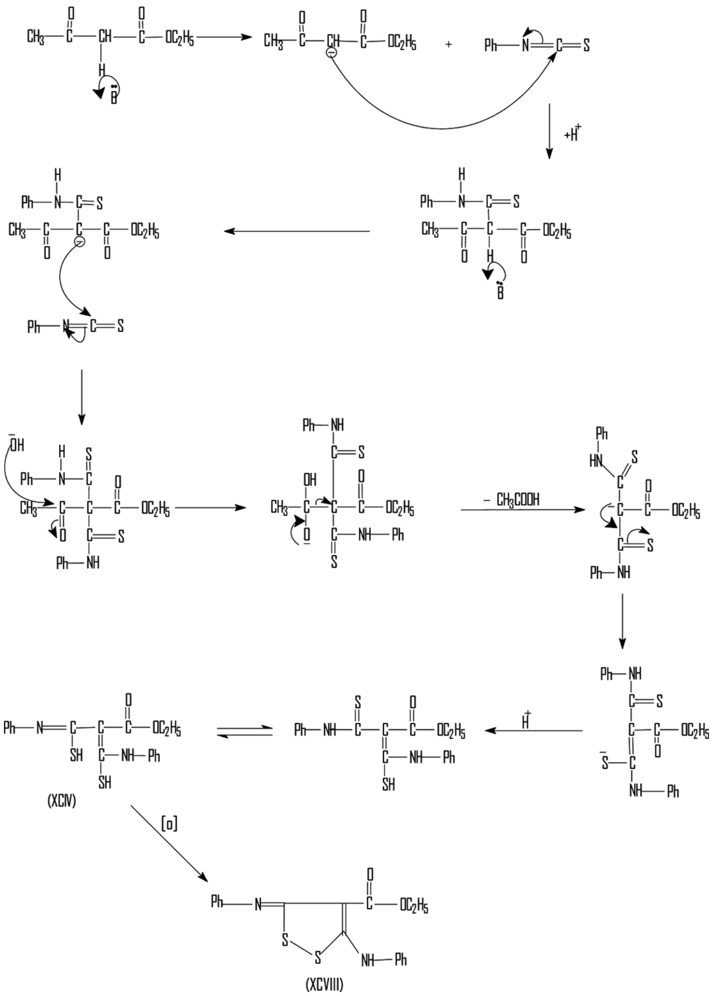
Scheme 1. Scheme of mass fragmentation of compound **3**.

carbons appeared at δ 117.0–149. Peaks at δ 62.1 and 14.2 were assigned to methylene and methyl carbons respectively. The structure was further supported by its mass spectrum, which gave molecular ion peak $[M^+]$ at m/z 356; other notable peaks were observed at m/z 279, 265, 187, 92, 91, 77, 65, 51, etc. The mass fragmentation pattern of compound **3** is given in Scheme 1.

The formation of compound **3** under the condition is proposed in Scheme 2.

Crystal Structure Determination of Compound 3

The structure of compound **3** was also conformed by x-ray analysis. The disulfide five-membered ring is essentially planar. The S–S bond distance is 2.0642 (11) Å, and the two C–S bond distances are 1.755 (3) Å and 1.816 (3) Å. These values are in the range known for cyclic disulfides.[14,15] The compound adopts the *Z* configurations around the imine (C=N) bond, and the conformation of the amino group is stabilized by an intramolecular hydrogen bonding interaction characterized by a N_2–H_1—O_2 distance of 1.912 Å. The torsion angles between the heterocycle and



Scheme 2. Probable mechanism for formation of the title compound.

the two phenyl rings are 61.5(5)° and −113.0(4)° for the amine and imine phenyls respectively. Selected bond lengths (Å) and bond angles (°) for compound **3** are given in Tables 1 and 2 and Figure 1.

On the basis of these results, the compound **3** was characterized as (*Z*)-ethyl-5-(phenylamino)-3-(phenylimino)-3H-1,2-dithiole-4-carboxylate **3**, which is reported here for the first time.

CONCLUSION

The present report describes the first successful attempt to synthesize novel (*Z*)-ethyl 5-(phenylamino)-3-(phenylimino)-3H-1,2-dithiole-carboxylate (II) using a simple synthetic methodology.

Table 1. Crystallographic data of compound **3**

Compound	**3**
Empirical formula	$C_{18}H_{16}N_2O_2S_2$
Formula weight	356.45
Crystal color and shape	Yellow, parallele piped
Crystal size (mm)	Triclinic
Space group	P-1
Temperature (K)	297
Radiation	Mo Kα ($\lambda = 0.71073$ Å)
ρ_{calc} (g cm^{-3})	1.348
a (Å)	5.7396 (8)
b (Å)	12.2162 (16)
c (Å)	14.1234 (1)
α (°)	112.120 (2)
β (°)	97.848 (2)
γ (°)	100.699 (2)
V (Å^3)	878.0 (2)
Z	2
μ (mm^{-1})	0.316
Transmission coefficient	0.879–0.975
Measured reflections	7749
Independent reflections (R_{int})	4034 (0.0229)
Observed reflections [$I > 2\sigma(I)$]	2765
R_1, w R_2 $2\sigma(I)$	0.0560, 0.1352
R_1, w R_2 (all data)	0.0849, 0.1463
Number of variables	222
$\delta\rho_{min}$, $\delta\rho_{max}$ (e Å^{-3})	−0.210, 0.395
Goodness of fit on F^3	1.108

EXPERIMENTAL

Instruments and Materials

All melting points were observed on a Kofler hot block and are uncorrected. IR specta were obtained neat on a Perkin-Elmer 1800 Fourier transform (FT)–IR spectrophotometer. IR values are given in centimeters^{-1}. NMR spectra were recorded in $CDCl_3$ on a Bruker AV 500 (500 MHz) with $(CH_3)_4Si$ as internal standard, and its values are given in parts per million (ppm, δ). Mass spectra were measured on Jeol D-300 (E_I mode) and Jeol S × 102/DA-6000 (FAB mode) mass spectrophotometers. All reagents and solvents were commercially obtained and of analytical grade. In x-ray crystallography, a crystal was mounted on a glass fiber. Diffraction data were recorded on a Bruker-Axs Smart Apex system equipped with a graphite monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å). The data were collected using SMART. The data integration was performed using SAINT. An empirical absorption correction was carried out using SADABS. The structure was solved with the direct methods and refined by full matrix least square methods based on F^2, using the structure determination and graphics package SHELXTL based on SHELX 97. The amine hydrogen atom was located on a difference Fourier map and refined isotropically. All other hydrogen atoms were included at calculated positions using a riding model. Crystallographic data are given in Table 1. Selected bond lengths and angles are

Table 2. Bond lengths and bond angles of compound **3**

Bond	Value
S1–C5	1.816 (3)
S1–S2	2.0642 (11)
S2–C6	1.755 (3)
O1–C3	1.324 (3)
O1–C2	1.463 (4)
O2–C3	1.220 (4)
N1–C5	1.258 (3)
N1–C7	1.421 (4)
N2–C6	1.341 (4)
N2–C13	1.432 (4)
N2–H1	0.84 (3)
C3–C4	1.468 (4)
C4–C6	1.379 (4)
C4–C5	1.457 (4)
C5–S1–S2	96.64 (10)
C6–S2–S1	94.90 (10)
C3–O1–C2	117.1 (2)
C5–N1–C7	119.8 (2)
C6–N2–C13	126.3 (3)
C6–N2–H1	109 (2)
C13–N2–H1	124 (2)
O2–C3–O1	121.2 (3)
O2–C3–C4	123.2 (3)
O1–C3–C4	115.5 (3)
C6–C4–C5	118.0 (3)
C6–C4–C3	118.4 (3)
C5–C4–C3	123.6 (3)
N1–C5–C4	128.2 (3)
N1–C5–S1	120.0 (2)
C4–C5–S1	111.8 (2)
N2–C6–C4	126.0 (3)
N2–C6–S2	115.8 (2)
C4–C6–S2	118.1 (2)

given in Table 2. Complete bond lengths and bond angles, anisotropic thermal parameters, and calculated hydrogen coordinates are deposited as supplementary materials.

Preparation of (Z)-Ethyl 5-(Phenylamino)-3-(phenylimino)-3H-1,2-dithiole-4-carboxylate 3

A solution of ethylacetoacetate (1.26 ml, 10 mmol) in dry benzene (50 ml) was refluxed with phenylisothiocyanate (4.76 ml, 10 mmol). A catalytic quantity of phase-transfer catalyst CTAB (0.073 g, 0.0002 mol) and Na_2CO_3 (2.12 g, 0.02 mol) as a base, along with a catalytic amount of water, were also added. The reaction mixture was heated on water bath for 18 h. After the usual workup in ether and evaporation of the solvent, it gave a semisolid, which was purified by column chromatography (silica gel mesh size 230–400) using benzene–ethylacetate (9:1) as

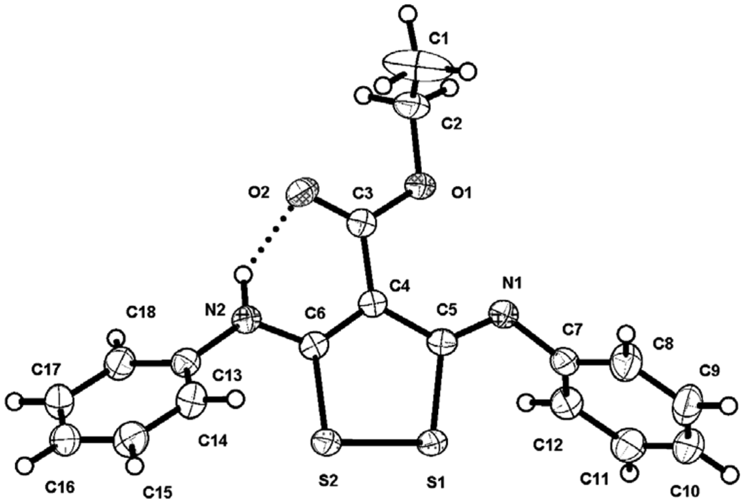


Figure 1. ORTEP diagram showing the conformation for (*Z*)-ethyl-5-(phenylamino)-3-(phenylimino)-3H-1,2-dithiole-carboxylate.

eluting solvent. The fraction obtained was crystallized with $CHCl_3$–EtOH to yield a yellow crystalline compound **3**. Yield: 150 mg; mp: 155 °C. $C_{18}H_{16}N_2O_2S_2$ (C, 60.65; H, 4.52; N, 7.86; O, 8.98; S, 17.99%), MS *m*/*z* (rel. int.), 356 $[M^{+\cdot}]$ (2.2), 279 (3.1), 265 (2.6), 187 (5.6), 92 (7.6), 91 (24.8), 77 (70.5), 65 (30.5), 51 (67.9); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.48 (3H, t, CH_3), 4.44 (2H, q, CH_2), 7.60–7.80 (10H, m, aromatic protons), 9.60 (1H, s, NH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 168.0 (C=O of ester), 153.1 (C-3 of dithiole ring), 149.0–117 (carbons of amine and imine phenyl), 62.1 (OCH_2), 14.2 (CH_3).

Supplementary Data

The supplementary x-ray data are available from the CCDC, 12 Union Road, Cambridge CB21EZ, UK, on request, quoting the deposition no. 622413.

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