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SPONTANEOUS α-METHYLATION OF AN α-BROMOKETONE FROM DMF: SYNTHESIS AND CRYSTALLINE STRUCTURE OF 1,1'-(3,4-DIPHENYLTHIENO[2,3-*b*]THIOPHENE-2,5-DIYL)BIS(PROPAN-1-ONE)

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Abstract – In this work, we have obtained 1,1'-(3,4-diphenylthieno-[2,3-*b*]thiophene-2,5-diyl-)bis(propan-1-one) (**3**), via recrystallization of 1,1'-(3,4-diphenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(2-bromoethanone) (**2**) from a mixture of DMF and chloroform. Structure of compound **3** was confirmed by single X-ray diffraction. The compound crystallizes in the orthorhombic, Pbcn with a =13.6934 (5) Å, b =19.3166 (6) Å, c =7.4283 (3) Å, V = 1964.86 (12) (Å^3), and Z = 4. Optimized molecular structure calculations with the aid of B3LYP/6-31G (d, p) DFT agreed well with experimental results obtained from X-ray data. Calculations revealed that the two bivalent sulfur atoms have electropositive nature whereas the two O-atoms are electronegative.

INTRODUCTION

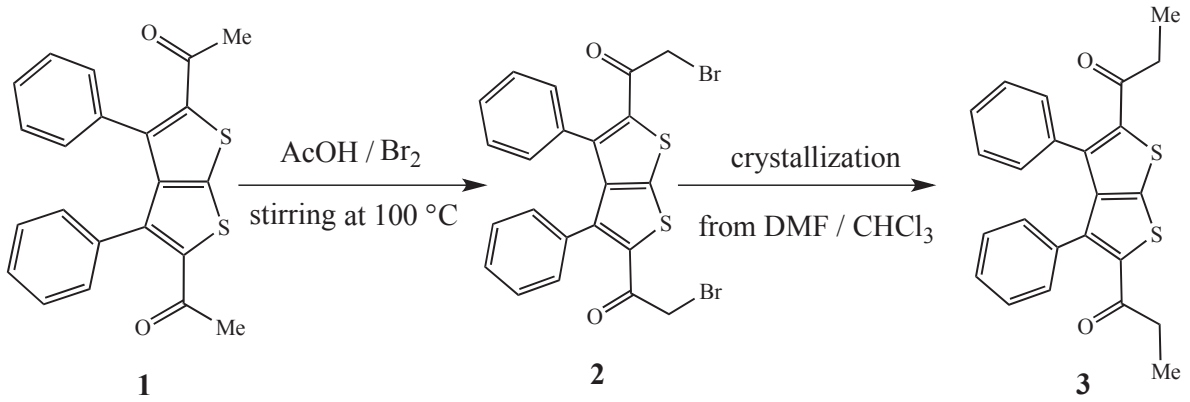
Thienothiophene derivatives have attracted considerable attention from researchers owing to their reactivity, biological activity, and to their structural and therapeutic diversity.[1] These compounds display a variety of interesting biological activities, such as antitumor, antiviral antibacterial, anticancer, antioxidant and α-glucuronidase and α-glucosidase inhibition, antiglaucoma activity, and inhibitors of platelet aggregation and HIV[2-6] properties. Recently, we have described the synthesis and X-ray structure of (2***E***,2'***E***)-1,1'-(3,4-diphenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(3-(dimethylamino)prop-2-en-1-one) along with its antibacterial activity.[9]

On the other hand, scientists employed the thieno[2,3-*b*]thiophene moiety for the design of a novel non-linear optical (NLO) properties system, first described by Mashraqui et al.[10] In view of the broad interest in thiophene-containing compounds, and as a continuation of our recent work,[9] on the synthesis and bioactivity of thiophene derivatives, and due to the substantial biological importance of these species, we describe herein the formation and X-ray structures of a new compound bearing a thienothiophene moiety. Scheme 1 depicts the key reactions that are involved in the formation of compound **3**.

RESULTS AND DISCUSSION

CHEMISTRY

Compound **2** was synthesized as shown in Scheme 1 by bromination of compound **1** which was characterized with the aid of different spectroscopic methods.



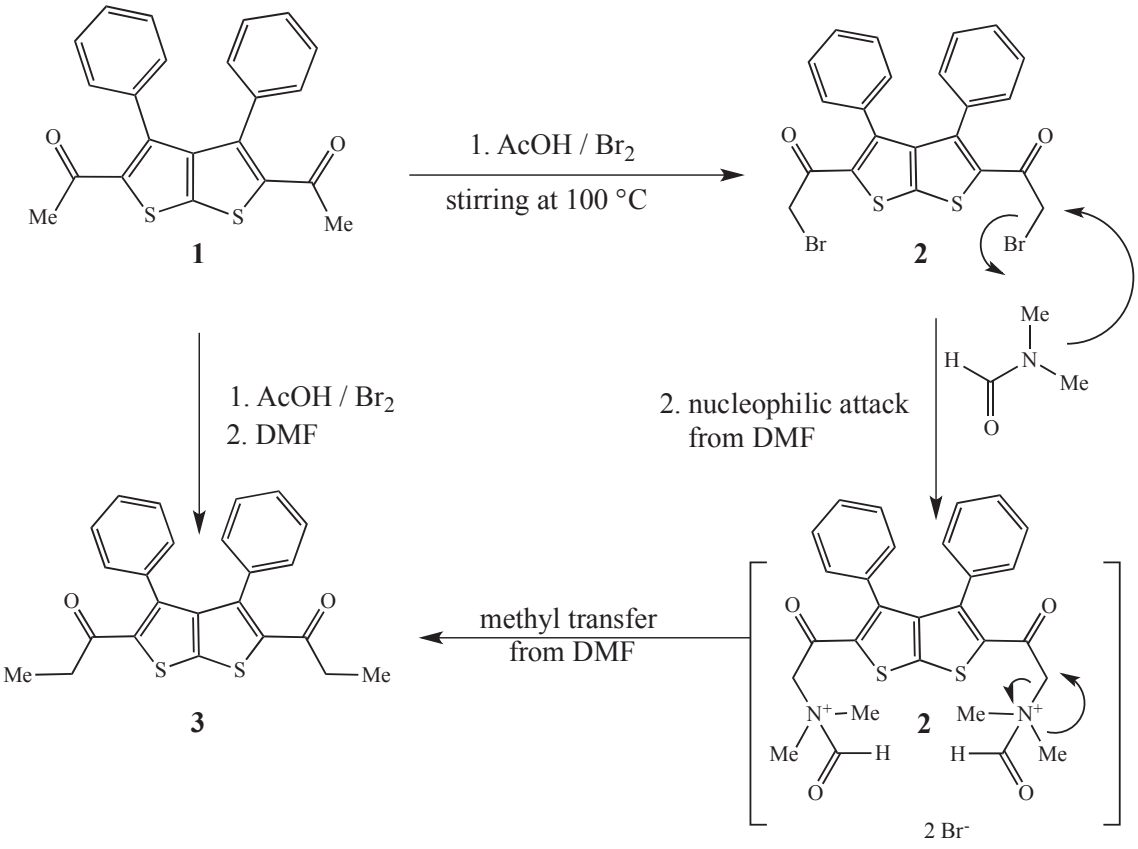
Scheme 1. DMF as carbon source: spontaneous α-methylation of ketones

IR spectrum exhibits absorption bands at 1653 and 1600 cm^{-1} attributed to the C=O and C=C stretching vibrations, respectively. On the other hand, the ^{1}H-NMR spectrum shows a singlet at δ 4.73 ppm due to the methylene hydrogens whereas the phenyl protons appeared as a multiplet at δ 7.52-7.58 ppm. In addition, the signal of the methyl protons of **1** at δ 1.63 ppm has disappeared. Moreover, the ^{13}C-NMR

spectrum is in agreement with the assigned structure; it shows signals for the different carbons in the molecule. Compound **3** was unexpectedly obtained by recrystallization of compound **2** with a mixture of DMF and chloroform. ^{1}H-NMR spectrum of compound **3** indicated the disappearance of the methylene signal at δ 4.73 ppm and appearance of a different one at δ 3.32 ppm, in addition to the appearance of a new methyl group at δ 1.63. On the other hand, ^{13}C-NMR spectrum confirmed the appearance of a new carbon at δ 15.3 and the shift of the carbonyl carbon to (C=O) 176.9 from 185.2 ppm. The mass spectrum of compound **3** showed the molecular ion $[M]^{+}$ at *m/z* = 404 (28%), corresponding to the molecular formula ($C_{24}H_{20}O_2S_2$). Additionally, the structure was confirmed with X-ray crystallography.

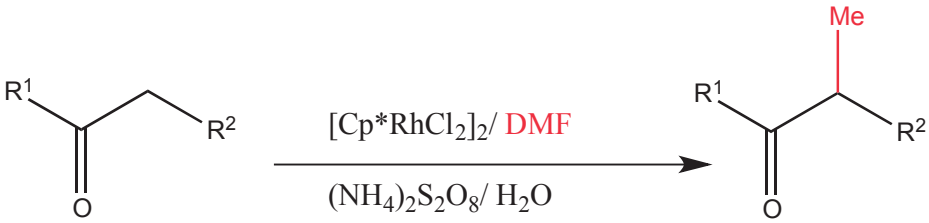
Mechanism of compound 3 formation

An interesting question is why the desired compound **2** undergo in methylation reaction in presence of DMF. Is it DMF indispensible for the methylation reaction Scheme 2. One possible explanation could be that the carbon atom of α-methylene is highly electrophile because of electroattractive effect of both bromine atoms and carbonyl group. This also explains why a good yield of compound **3** was obtained for methylation of **2** (Scheme 2).



Scheme 2. Plausible mechanism of formation of compound **3** via alkylation of **2** by DMF

So this type of reaction constitutes an unprecedented spontaneous non-catalyzed direct methylation of α-bromo-ketone with *N,N*-dimethylformamide (DMF). The reaction should represents a broad substrate scope, tolerating both aryl and alkyl ketones with various functionalised substituents. Mechanistic studies suggest that DMF delivers a methylene fragment. In our knowledge, this is the second example of transfer of methyl from DMF to a ketone compound. The first example was described by Li, et al.[13] in presence of a catalyst (Scheme 3).



Scheme 3. DMF as carbon source: Rh-catalyzed α-methylation of ketones[23]

CRYSTAL STRUCTURE OF COMPOUND 3

Crystallographic data revealed that compound **3** consists of a planar thieno[2,3-*b*]thiophene ring (S1-C2-C2-C3-C4-C3A-C4A-S1A) with two phenyl rings (C5-C10) and (C5A-C10A) with dihedral angles of 64.82° (Figure 1). In the crystal, molecules are linked through intermolecular non-classical hydrogen bonds as depicted in Figure 2. Listed in Tables 1,2 are selected bond lengths and angles, and hydrogen bonds, respectively.

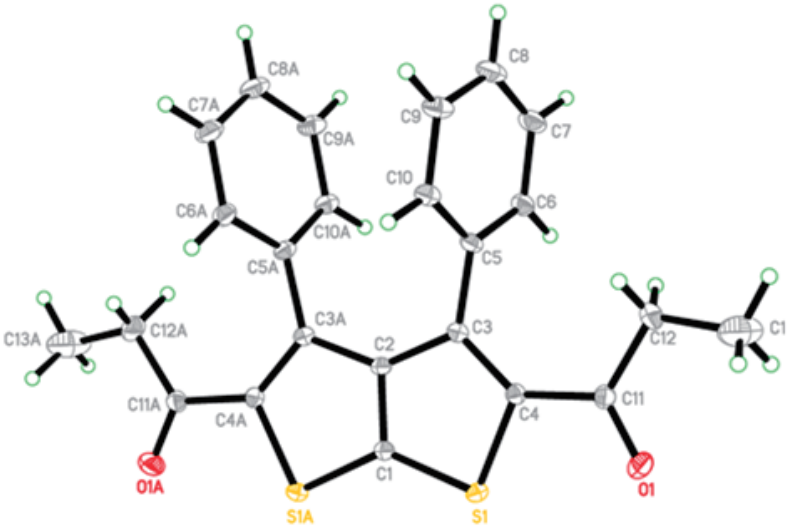


Figure 1. ORTEP diagram of the final X-ray model of compound **3** with displacement ellipsoids drawn at 50% probability level. H-atoms were placed and not included in refinement.

Table 1. Selected geometric parameters (Å, °) of compound **3**

S1—C1	1.706 (2)	O1—C11	1.214 (5)
S1—C4	1.754 (4)		
C1—S1—C4	90.1 (2)	S1—C4—C3	113.4 (3)
S1—C1—C2	113.90 (18)	S1—C4—C11	111.8 (3)
S1—C1—S1^{i}	132.2 (4)	O1—C11—C4	118.9 (4)
S1i—C1—C2	113.90 (18)	O1—C11—C12	120.6 (4)

Symmetry code: (i) −x+1, y, −z+1/2

Table 2. Hydrogen-bond geometry (Å, °) of compound **3**

D—H···A	**D—H**	**H···A**	**D···A**	**D—H···A**
C8—H8A···O1^{ii}	0.9500	2.5500	3.477 (5)	164.00
C13—H13B···O1^{iii}	0.9800	2.4400	3.309 (7)	148.00

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

OPTIMIZED MOLECULAR GEOMETRY OF COMPOUND 3

Listed in Table 3 are data related to the optimized structure and geometric parameters (bond distances and angles) of compound **3** from the B3LYP/6–311G(d,p) calculations; these data are compared with those obtained experimentally from the crystallographic information file (CIF). The optimized structure has C2 point group and is presented in Figure 2. The phenyl group forms an angle of 79.2˚ with the plane passing through the fused thiophene rings. The presence of phenyl groups as bulky substituents attached to the thiophene ring leads to the two O-atoms with syn-configuration to the neighboring S-atom. As a result, the S---O intramolecular distance is predicted to be 2.803 Å (exp. 2.771 Å) which is shorter than the sum of their van der Waals radii; this indicates the presence of significant interaction between the S and O atoms.

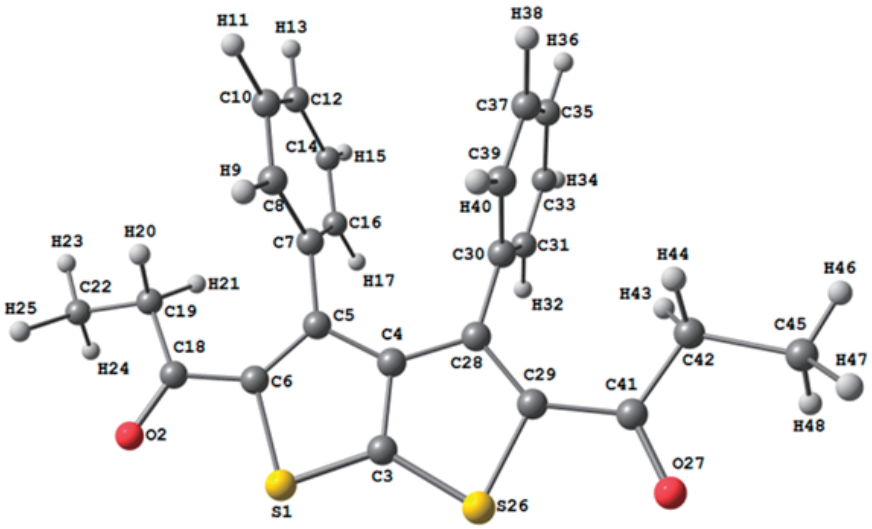


Figure 2. Optimized molecular structure of compound **3**

CONCLUSIONS

1,1'-(3,4-Diphenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(propan-1-one) (**3**) was unexpectedly obtained from recrystallization of 1,1'-(3,4-diphenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(2-bromoethanone) (**2**); its structure was confirmedby X-ray crystallography. Optimized geometric parameters (bond distances and bond angles) calculated using DFT/B3LYP method and 6-311G(d,p) basis set revealed good agreement with those obtained from X-ray structure. In addition, molecular electrostatic potential (MEP) and NBO analysis related to compound **3** revealed the presence of S---O interaction between each S-atom and the adjacent O-atom. Moreover, ICT interactions calculated using NBO method showed the presence of S---O interactions.

In conclusion, a novel method for the α-methylation of α-bromo-ketones with DMF as carbon source could be developed and provide us a general, convenient and spontaneous non catalytic way to access α-methylated ketones. Furthert analytic studies of coproducts and intermefiaries will help us to more understand the dissociation of chloride from compound **2**, while DMF acts as the carbon source.

EXPERIMENTAL

Materials and methods

Chemicals and reagents employed in this work were purchased from commercial sources and were used without further purification. Progress of reaction was followed with TLC using Merck Silica Gel 60 F–254 thin layer plates. Melting points were measured on a Gallenkamp apparatus in open glass capillaries and are uncorrected. We obtained IR Spectra of products, as KBr pellets, with a Nicolet 6700 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with the aid of a Varian Mercury Jeol-400 NMR spectrometer using dimethyl sulfoxide (DMSO-d_6) as solvent and TMS as an internal standard; chemical shifts δ are expressed in ppm units. Mass spectral data were acquired with a Jeol of JMS-600H mass spectrometer. Elemental analysis of compound **2** was carried out on a 2400 CHN Elemental Analyzer. The electronic spectrum of compound **3** was recorded with the aid of a Perkin Elmer, Lambda 35, UV/Vis spectrophotometer, whereas single-crystal X-ray diffraction measurements were accomplished on a Bruker SMART APEX II CCD diffractometer.

Synthesis of 1,1'-(3,4-diphenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(2-bromoethanone) (2) and 1,1'-(3,4-diphenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(propan-1-one) (3)

We prepared compound **2** according to the following general procedure: compound **1** (3.78 g, 10 mmol) was dissolved in 30 mL of glacial acetic acid in a 200-mL Erlenmeyer flask. The mixture was heated, with stirring, to 100 ºC for 10 min, after which bromine (1.1 mL) was added and stirring continued for 1 h. The mixture was then allowed to cool to room temperature and the precipitate was collected by filtration.

The product was recrystallized from glacial acetic acid to afford compound **2** in pure form.

1,1'-(3,4-Diphenylthieno[2,3-*b*]thiophene-2,5-diyl)bis(2-bromoethanone) (2)

Yield 75%; mp 182-184 ºC. IR (cm^{-1}): 1653 (C=O); 1600 (C=C). ^{1}H-NMR (500 MHz, DMSO-d_6) δ (ppm): 4.73 (s, 2H); 7.52-7.58 (m, 5H). ^{13}CNMR (125 MHz, DMSO-d_6) δ (ppm) 35.5 (CH_2), 128.6, 128.8, 129.1, 129.2, 133.3, 138.0, 141.3, 141.4 (Ar-C), 185.2 (C=O). Anal. Calcd for $C_{22}H_{16}Br_2O_2S_2$: C, 49.27; H, 3.01; S, 11.96. Found: C, 49.40; H, 2.96; S, 11.83. Mass spectral data of compound **2** showed the molecular ion $[M]^+$corresponding to the molecular formula $C_{22}H_{16}Br_2O_2S_2$ among others. On the other hand, recrystallization of compound **2** with DMF/$CHCl_3$ (2:1) mysteriously afforded compound **3** in a 90% yield.

X-Ray measurements of 3

Crystals were obtained, as yellow blocks, by slow evaporation from EtOH. A crystal of dimensions 0.46 × 0.37 × 0.36 mm was chosen for data collection. Crystallographic data were acquired with the aid of a Bruker APEXII D8 Venture diffractometer equipped with a CMOS detector and graphite monochromatic Mo Kα radiation (λ= 0.71073 Å) at 100 K, whereas data reduction in addition to cell refinement were accomplished on a Bruker SAINT; structure was solved through the use of SHELXS-97[11,12] (Table 1). All crystallographic data pertaining to compound **3** are available and can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. CCDC number **1430834**.

Table 7. Crystallographic and experimental details related to compound **3**

Parameters	**value**	**Parameters**	**value**
Chemical formula	$C_{24}H_{20}O_2S_2$	Absorption correction	Multi-scanSADABS Bruker 2014
Mr	404.52	T_{min}, T_{max}	0.82, 0.84
Crystal system, space group	Orthorhombic, Pbcn	No. of measured, independent and observed [I> 2σ(I)] reflections	30558, 2262, 2012
Temperature (K)	100	R_{int}	0.057
a, *b*, *c* (Å)	13.6934 (5), 19.3166 (6), 7.4283 (3)	*Refinement*	
V (Å^3)	1964.86 (12)	R[F^2> 2σ(F^2)], wR(F^2), S	0.083, 0.269, 1.09
Z	4	No. of reflections	2262
Radiation type	Mo Kα	No. of parameters	128
μ (mm^{-1})	0.29	No. of restraints	0

Crystal size (mm)	0.46 × 0.37 × 0.36	H-atom treatment	H-atom parameters constrained
Data collection		$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	2.41, −0.63
Diffractometer	CCD area detector diffractometer	CCDC number	**1430834**

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