NMR AND X-RAY CRYSTAL STRUCTURE ANALYSIS OF ARYLATED THIENO[3,2-*b*]THIOPHENE BY C_{sp}^2-H FUNCTIONALIZATION

Đến tòa soạn 20-9-2019

Nguyen Hien, Nguyen Bich Ngan, Duong Quoc Hoan
Department of Chemistry, Hanoi National University of Education

TÓM TẮT

*Ba dẫn xuất aryl của thieno[3,2-b]thiophene (**TT**, **1**) là 2-(anthacene-9-yl)_**TT** (**2**), 2-(anthacene-9-yl)-5-(4-nitrophenyl)_**TT** (**3**), và 2-(anthacene-9-yl)-5,6-di(4-nitrophenyl)_**TT** (**4**) đã được tổng hợp thành công và cấu trúc của chúng được chứng minh trên cơ sở phân tích chi tiết phổ cộng hưởng từ hạt nhân 1D và 2D NMR, phổ khối lượng phân giải cao HR-MS và phân tích phổ X-Ray. Những dẫn xuất này được tổng hợp có sử dụng xúc tác Pd hoạt hóa liên kết C_{sp}^2-H. Dữ liệu phổ cộng hưởng từ hạt nhân NMR và X-Ray đã chứng minh sự chọn lọc cao ở vị trí C-2 và C-5 khi thực hiện phản ứng aryl hóa. Bên cạnh đó phổ X-ray của hợp chất **4** ở 100K cho thấy chất này có cấu trúc phẳng. Đồng thời X-ray cũng chỉ ra tương tác π–π giữa nhân thieno[3,2-b]thiophene và các nhóm thế.*

***Keywords**: thieno[3,2-b]thiophene, direct arylation, regioselective, C-H functionalization, palladium-catalyzed.*

1. INTRODUCTION

Thieno[3,2-*b*]thiophene (**TT**) is a common building block found in a wide range ofp-type organic semiconductors[1], low band-gap conjugated oligomers, dye-sensitizer solar cells [2], and photovoltaiac devices [3].

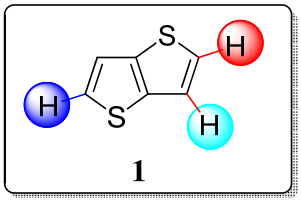


Figure 1. Structure of thieno[3,2-b]thiophene

Compared to thiophenes, **TT**skeleton consists of two fused rigid thiophene rings that limits therotational disorder between the rings, leading to a better π-conjugation.As a result, the incorporation of **TT** units into organic semiconductors has been demonstrated to be beneficial for the improvement of charge transport properties due to the high molecular orbital overlap, promoted by the presence of the sulfur atoms [4].

Very recently, a new donor structure, **di(HTh2BT)DTCTT**, based on a dithienocyclopentathieno[3,2-*b*]thiophene (**DTCTT**) core, was designed and used as the molecular donor in a small molecular organic photovoltaic device (sm-OPV). This compound showed red-shifted absorption (up to 800 nm), a higher HOMO level, and great crystallinity due to its π-extended conjugation. Particularly, the DTCTT-based sm-OPV devices fabricated by spin-coating a blend solution with $PC_{71}BM$ exhibited an remarkable PCE of 2.8% with a J_{sc} of 9.3 mA cm^2, a V_{oc} of 0.73 V, and a FF of 0.42 [5].

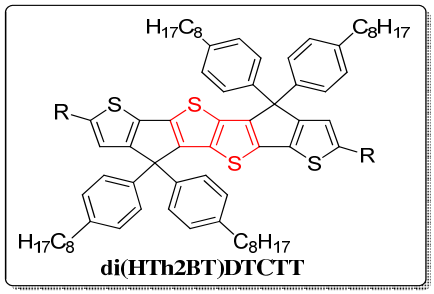


Figure 2. A molecular donor

Containing **TT** moietyin a small molecular organic photovoltaic device

The introduction of aromatic substituents into aconjugated backbone is a well-known method to expand the π-framework. Since its discovery in 1979, the Suzuki-Miyaura reaction, involving the coupling of an organoboron reagent and an organic halide or pseudo-halide in the presence of a palladium or nickel catalyst, has become one of most utilized tools for the construction of a C-C bond [6]. However, this classical cross-coupling reactions requiressometimes tedious but inevitable pre-functionalization of the substrates. In this context, direct C-arylation of aromaticheterocycles by C-H functionalizationis considered to bemoreatom-economic and eco-friendly than the traditional counterpart [7]. Following this trend,a number of methods employing either aryltrifluoroborate salt [8] ,[Ph-I-Ph]BF_4 [9], or aryl halides [10] as coupling partners have been developed. In this work, we report the characterizationof arylated **TT**s synthesized byPd-catalyzed C_{sp}^2-H functionalization of **TT** with aryl halides. Structural study as well as the regioselectivity of the reaction was discussed based on NMR and X-Ray analyses.

2. EXPERIMENTAL

2.1. General notes

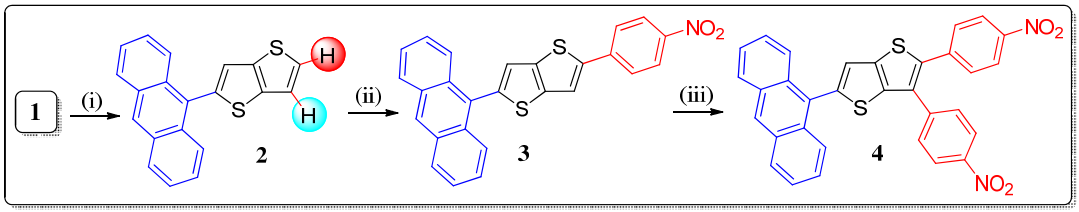
Unless otherwise stated, chemical reagents and solvents for reactions were purchased from Sigma-Aldrich or Merck and were used without further purification. THF were dried by refluxing over sodium wire in the presence of benzophenone as indicator and distilled just before used.Columnchromatography was performed with Merck silica gel 60 (0.040-0.063 µm grade). All reactions were conducted in closed pressure vialsinargon atmosphere.

2.2. Instrumentation

Melting points were measured on a Stuart-Scientific SMP3 apparatus without correction. NMR spectra were recorded on a Bruker Avance 500 NMR spectrometer in $CDCl_3$. Chemical-shift data for each signal were reported in ppm units with tetramethylsilane (TMS) as internal reference, where δ_{TMS} is zero. Splitting patterns are designated as s (*singlet*), d (*doublet*), t (*triplet*),q (*quartet*), m (*multiplet*). HR-ESI-MS measurements were performed on a LQT Orbitrap XL.ESI-MS measurements were acquired on an HPLC-MS Agilent 1100, Agilent Technologies, USA.The intensities for the X-ray determination were collected on a D8 QUEST Bruker (Germany) instrument at 100 K with Mo Kα radiation (λ = 0.71073 Å) using a TRIUMPH monochromator. Standard procedures were applied for data reduction and absorption correction. Structure solution and refinements were performed with SHELX.

2.3. Synthesis

The title compound TT1 was prepared according to the method of Fuller and co-workers from commercially available 3-bromothiophene [11]. The C-H activation reactions of 1with a variousaryl halides resulted in site-selective formation of mono-, di-, and triarylthieno[3,2-*b*]thiophenes2, 3, and 4, respectively (Scheme 1).



*Scheme 1. Synthesis of arylated **TT**s. Conditions: (i) **1** (2.0 eq.), 9-bromoanthracene (1.0 eq.), $Pd(OAc)_2$ (1 mol%), KOAc (2.0 eq.), DMAc, 110 °C, 8 hours; (ii) **2**(1.0 eq.), 1-bromo-4-nitrobenzene(1.1eq.), $Pd(OAc)_2$ (2mol%), KOAc (1.1eq.), DMAc, 130 °C, 14 hours; (iii) **3** (1.0 eq.),1-bromo-4-nitrobenzene(1.1eq.), $Pd(OAc)_2$ (2mol%), KOAc (1.1eq.), 130 °C, 24 hours.*

Procedure for the Pd-catalyzed direct arylation of TT with 9-bromoanthracene. Thieno[3,2-*b*]thiophene **1** (70 mg, 0.5 mmol, 2.0 eq), 9-bromoanthracene (64 mg, 0.25 mmol, 1.0 eq), $Pd(OAc)_2$ (0.56 mg, 1 mol%) , and KOAc (49 mg, 0.5 mmol, 2.0 eq) were dissolved in degased DMAc (5 mL). The resulting reaction mixture was heated at 110 °C under argon atmosphere until TLC (*n*-hexane/ethyl acetate) showed the complete consumption of the starting material (8 hours). The reaction mixture was cooled to room temperature and filtered to remove insoluble impurities. The filtrate was diluted with ethyl acetate, washed with water (3 times), dried over Na_2SO_4, and concentrated under reduced pressure by rotary evaporation. The residue was purified by SiO_2-column chromatography (*n*-hexane/ethyl acetate 99: 1, v/v) to give 2-(anthracene-9-yl)thieno[3,2-*b*]thiophene **2** as a white solid (58 mg, 73%). Mp 243-244 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.54 (1 H, s), 8.03 (2 H, d, J = 8.5 Hz), 7.97 (2 H, d, J = 8.5 Hz), 7.47 (3 H, m), 7.41 (2 H, m), 7.35 (2 H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.0, 140.4, 139.2, 131.8, 131.2, 128.5, 128.4, 128.3, 126.7, 126.5, 126.1, 125.3, 121.6, 119.5. MS-ESI: *m/z* calcd for $C_{20}H_{13}S_2$ $[M+H]^+$ 317.0, found 316.9.

2-(Anthracene-9-yl)-5-(4-nitrophenyl)thieno[3,2-*b*]thiophene3: From **2**(95 mg, 0.3mmol, 1.0 eq),1-bromo-4-nitrobenzene(66 mg, 0.33mmol, 1.1eq), $Pd(OAc)_2$ (1.4 mg, 2mol%), and KOAc (33 mg, 0.33mmol, 1.1eq), **3** was isolated as an orange solid (78.5 mg, 60%) after 14 hours at 130 °C.Mp 307-308 °C;^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.58 (1 H, s), 8.29 (2 H, d, J = 8.5 Hz), 8.06 (2 H, d, J = 8.0 Hz), 7.95 (2 H, d, J = 8.5 Hz), 7.83 (2 H, d, J = 9.0 Hz), 7.77 (1 H, s), 7.49 (2 H, t, J = 7.5 Hz), 7.44 (2 H, t, J = 7.5 Hz), 7.38 (1 H, s); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.6, 142.8, 142.4, 141.3, 140.9, 140.2, 131.6, 131.0, 128.6, 128.3, 127.6, 126.2, 126.1, 125.8, 125.3, 124.4, 121.2, 118.0; HRMS-ESI: *m/z*calcd for $C_{26}H_{15}NO_2S_2Na$ $[M+Na]^+$ 460.0442, found 460.0438.

2-(Anthracene-9-yl)-5,6-di(4-nitrophenyl)thieno[3,2-*b*]thiophene4: From **3** (0.25mmol, 1.0 eq.) and1-bromo-4-nitrobenzene(56 mg, 0.275mmol, 1.1eq), KOAc (27 mg, 0.275mmol, 1.1eq), and $Pd(OAc)_2$ (1.1 mg, 2mol%), **4**was obtained as a pale yellow solid (46 mg, 33%) after 24 hours at 130 °C.Mp 295-296 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.59 (1 H, s), 8.25 (2 H, d, J = 9.0 Hz), 8.22 (2 H, d, J = 8.5 Hz), 8.07 (2 H, d, J = 8.0 Hz), 7.94 (2 H, d, J = 8.5 Hz), 7.68 (2 H, d, J = 9.0 Hz), 7.54 (2 H, d, J = 9.0 Hz), 7.50 (2 H, t, J = 7.0 Hz), 7.45 (1 H, s), 7.43 (2 H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.4, 147.3, 142.5, 142.3, 141.3, 140.5, 138.6, 138.4, 134.3, 131.7, 131.1, 130.2, 130.0, 129.9, 129.5, 128.9, 128.5, 127.3, 126.4, 126.1, 125.4, 124.5, 124.3, 122.1, 114.1; MS-ESI: *m/z*calcd for $C_{32}H_{18}N_2O_4S_2Na$ $[M+Na]^+$ 581.0, found 581.1.

3. RESULTS AND DISCUSSION

A pioneering study for direct arylation of simple heterocyclesusing $Pd(PPh_3)_4$ as catalyst was reported by Ohtaand co-worker [12]. Since then, the direct arylation of heterocycles has been thoroughly studied and become a powerful tool for construction of (hetero)biaryl skeletons. Recently, Doucet's group has developed a facile phosphine-free Pd-catalyzed functionalization of thiophene derivatives [13]. Theoretically, the chemistry of thiophene and the fused-thiophene, **1**, are comparable. Therefore, we applied Doucet's procedure for the direct arylation of **1** with 9-bromoanthracene. In fact, 2-(bromoanthracene-9-yl)_**TT2** was obtained selectively in 73% isolated yield in the presence of $Pd(OAc)_2$as catalyst and KOAcas base in DMAc at 110 °C. Subsequent arylation of **2** (1.0 eq.) with 1-bromo-4-nitrobenzene (1.1eq) under the same condition resulted in site-selective formation of 2-(anthacene-9-yl)-5-(4-nitrophenyl)thieno[3,2-*b*]thiophene **3** in moderate yield (60%). The tri-arylated**TT**,2-(anthacene-9-yl)-5,6-di(4-nitrophenyl)thieno[3,2-*b*]thiophene **4** was thenobtained from **3** and 1-bromo-4-nitrobenzenewith moderate yield (33%).

Structural analysis

NMR data

*2-(Anthacene-9-yl)thieno[3,2-b]thiophene **2**.*

The ^{1}H and ^{13}C NMR spectra of **2**were recored in $CDCl_3$ and analyzed in combination with its HSQC and HMBC spectra (*Fig. 3*). In the ^{1}H NMR spectrum of **2**, the C-10'proton is undoubtedly assigned at 8.54 ppm as the singlet in the most up-field of the aromatic range.

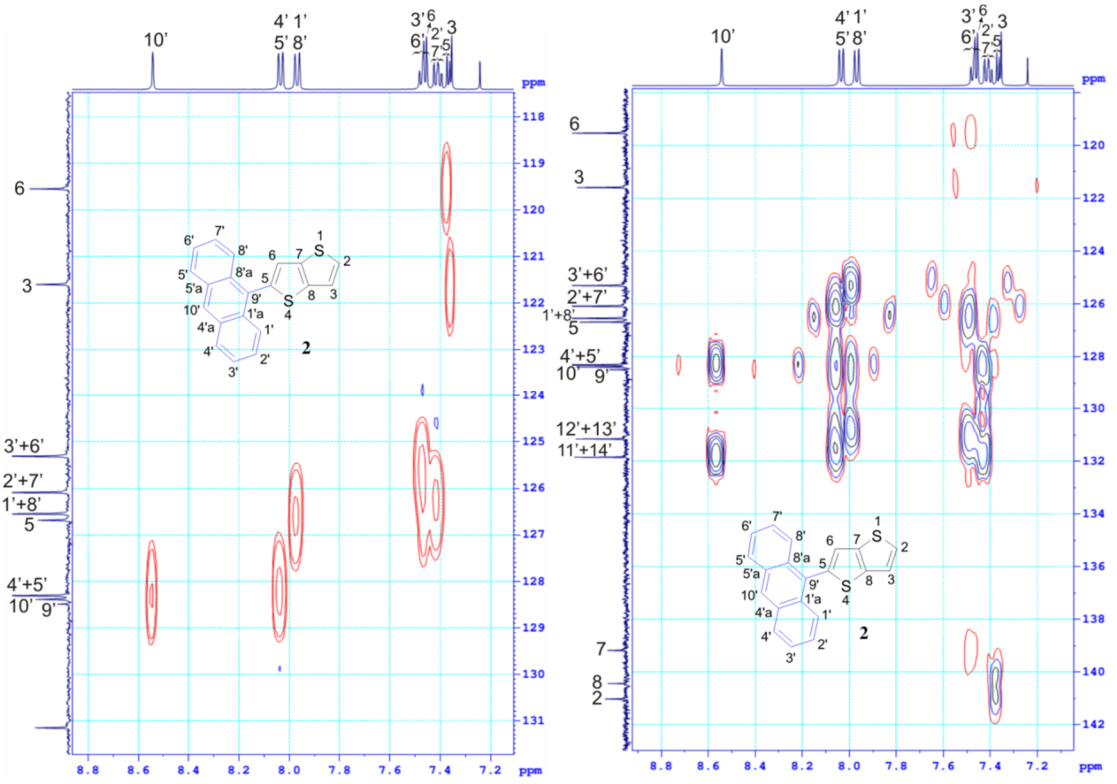


Figure3. HSQC (left) and HMBC (right) spectra of 2

Next, from the cross-peaks of the protons H4'+H5' in the HMBC spectrum, the resonance of the carbons C2'+C7' was determined at 126.1 ppm.Consequently, the resonance of the corresponding protons H2'+H7' which is a triplet centered at 7.41 ppm was identified. Similarly, the cross-peaks of the protons H1'+85' in the HMBC spectrum allowed to locate the resonances of the carbon C3'+C6' and then the protons H3'+H6' in combination with the HSQC spectrum. However, the singlet at 7.35 ppm cann't be exactly assigned to the **TT** proton resonance at the C-2 or the C-3 position. The 2D NMR spectra analysis of **2** is summarized in Table 1. These correlations, however, cann't help to reliably determine the site-selectivity of the direct arylation reaction. For further structural study of the arylated **TT**s, an X-Ray crytal structure of the compound **4** was acquired and analyzed.

Table 1.HMBC analysis of 2

Carbon		**X***	*Carbon*		**X***	*Carbon*		**X***
C	**δ** (ppm)	**H**	**C**	**δ** (ppm)	**H**	**C**	**δ** (ppm)	**H**
C2	141.0	-	C8	140.4	H6	C9'	128.5	H1'/H8'
C3	121.6	-	C1'/C8'	126.5	H3'/H6'	C10'	128.4	H4'/H5'

C5	126.7	H6	C2'/C7'	126.1	H4'/H5'	C1a/C8a	131.4	H2'/ H7'
C6	119.5	H5	C3'/C6'	125.3	H1'/H8'	C4a/C5a	131.2	H3'/H5'
C7	139.2	H5	C4'/C5'	128.3	H10', H2'/H7'	-	-	-

*:*Cross-peaks with protons.*

2-(Anthacene-9-yl)-5-(4-nitrophenyl)thieno[3,2-b]thiophene ***3***.

The structure of **3** was elucidated based on the 1D-NMRas well as HMBC and HSQC spectra (*Fig. 4*).

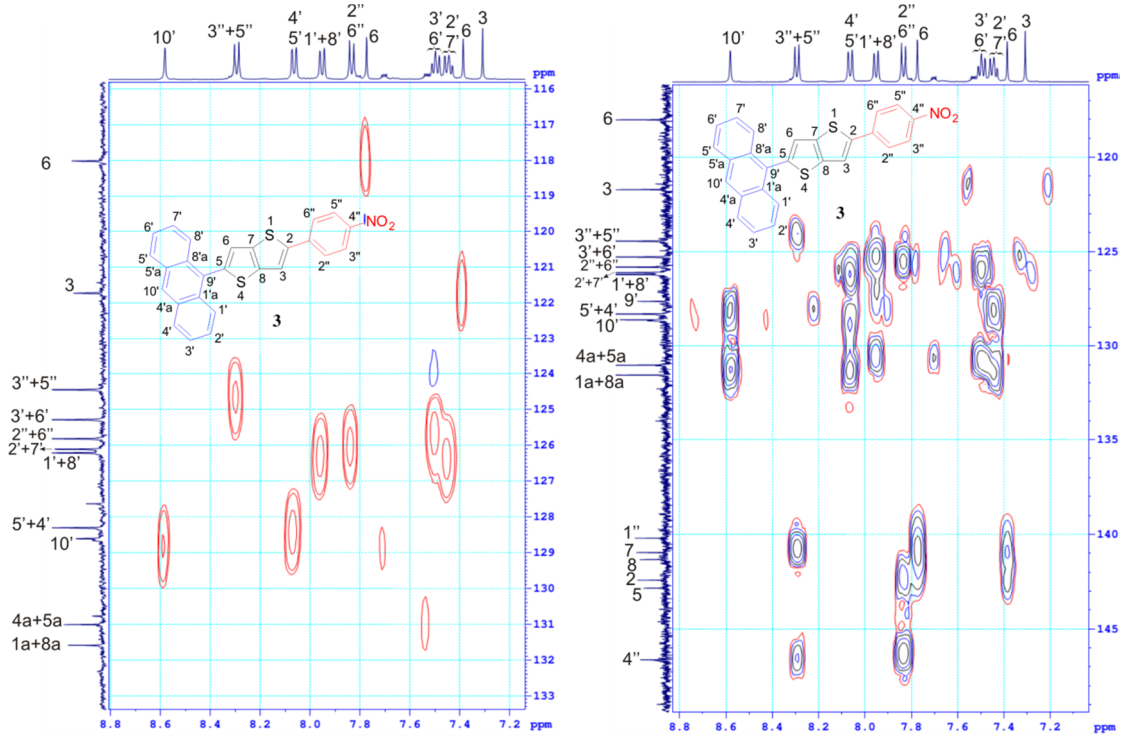


Figure 4. HSQC (left) and HMBC (right) spectra of 3

In general, the position, shape and splitting pattern of the anthracene moiety in **3** remained nearly unchanged in comparison with that of **2**. On the other hand, the two doublets of the **TT** skeleton were not observed. Instead, two new singlets at 7.77 and 7.39 ppm corresponding to the two **TT**'s protons H3 and H6 were observed. These singlets strongly indicated that the second Csp^2-H activation occured on the other side of the **TT** skeleton, namely, at the C-5 position. The successful incorporation of the 4-nitrophenyl substituent was easily recognized by the two doublets centered at 8.29 and 7.83 ppm.

Table 2.HMBC analysis of 3

Carbon		**X***	*Carbon*		**X***	*Carbon*		**X***
C	**δ** (ppm)	**H**	**C**	**δ** (ppm)	**H**	**C**	**δ** (ppm)	**H**
2	142.4	-	1'/8'	126.2	3'/6'	1a/8a	131.6	2', 7'
3	121.7	-	2'/7'	126.1	4'/5'	4a/5a	131.0	3'/6'

5	142.8	2"/6"	3'/6'	125.3	1'/8'	1"	140.2	2"/6", 3"/5"
6	118.0	-	4'/5'	128.3	10', 2'/7'	2"/6"	125.8	6"/2"
7	140.2	3, 6	9’	127.6	1'/8'	3"/5"	124.4	5"/3"
8	141.3	3, 6	10’	128.6	4'/5'	4"	146.6	2"/6", 3"/5"

*:*Cross-peakswith protons.*

The cross-peaks of these two doublets were used to identify the resonances of the two quaternary carbons C1" and C4" of the 4-nitrophenyl moiety at 140.2 and 146.6 ppm, respectively, since the latter is directly connected with the highly electronegative nitrogen of the nitro group. Subsequently, the resonance of quaterary carbons C5 was determined as it correlated with the protons H2"/H6" and H3, while the resonances of C7 and C8 were determined with the cross-peaks with both H3 and H6. The signal of the quaternary carbonof the anthacene moiety was located withthe protons H1"/H8" and H3.The 2D NMR spectra analysis of **2** is summarized in Table 2.

*2-(Anthacene-9-yl)-5,6-di(4-nitrophenyl)thieno[3,2-b]thiophene **4**.*

Similarly, the position, shape and splitting pattern of the anthracene moiety in **4** remained nearly unchanged in comparison with that of **2**and **3**. The successful introduction of one more 4-nitrophenyl group was indicated by the presence of two new doublets corresponding to the two couples of eqalent protons H2'"+H6'" and H3'"+H5'". In addition, thiscross-couplingcould be demonstrated by theresonance of the only **TT** proton left identified as a singlet at 7.46 ppm.

In order to determine the regioselectivity of the third C-H activation reaction, the NOESY spectrum of **4** was recorded (Fig. 5). The cross-peak between the two protons H2" (or H6") and H2'" (or H6'") obviously indicated that the two 4-nitrophenyl groups were on the same side of the **TT** skeleton. Under our catalytic condition, the essential role of the base, KOAc, would support for the concerted metalation deprotonation (CMD) pathway [14]. According to this mechanism, the more acidic proton in an aromatic ring is favourably activated [15]. In the **TT**molecule, the C-2 and C-5 protonsare the most acidic as they are adjacent to the electronegative sulfur atoms.Hence, the first C-H functionalization occured at these favored positions. In 2-(anthracene-9-yl)_**TT2** scaffold, the steric hindrance of the bulkyanthracene moiety may have significant influence on C-3 position. This, in combination with effect of the heteroatom, resulted in the regioselevity of the second arylation at the C-5 position.

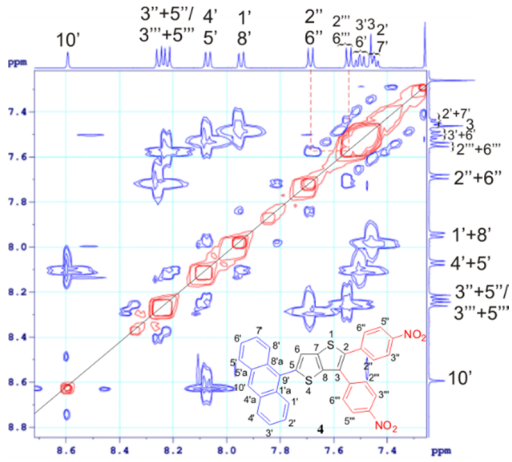


Figure5. NOESY spectra of 4

As indicated by the ^{1}H NMR data, the acidity of the C-6 proton (δ = 7.77 ppm) in **3**is significantly higher than that of the C-3 proton (δ = 7.38 ppm) because the former is close to the electron-withdrawing group, 4-nitrophenyl. Due to the difference in acidity as well as the bulky anthracene, subsequent arylation took place more favourably at the C-6 position (see the next section).

X-Ray crystal structure analysis

To further explore the regioselectivity of the direct arylation reaction, **4** were recrystalized from $CHCl_3$. The structure of **4** was then unambiguosly clarified by single-crystal X-Ray analysis (Fig.5) [16].Using Olex2 [17], the structure was solved with the ShelXT [18] structure solution program using Intrinsic

Phasing and refined with the ShelXL [19] refinement package using Least Squares minimisation.The bond lengths and angles are in good agreement with the average values in the Cambridge Structure Database. The three aromatic rings directly connected with the fused moiety show no coplanar with the thieno[3,2-*b*]thiophene moiety as well as each other. The dihedral angles between mean planes of S11,S12,C11-16with C21-26, C31-36 and C41-54 are 36.65, 45.24, and 73.64º, respectively.These rotationshelp to reduce the repulsion between S11···H22, S12···H36, and S12···H53. In addition, the packing of**4** shows π–π stacking between the fused and the anthracene moieties along the *b*-axis [*Cg*1···*Cg*2^{i} = 3.811 Å; *Cg*1 and *Cg*2^{i} are the centroids of the C49–C53 and S11, C11–14 rings, respectively; symmetry code: (i) -*x*, *y*+1/2, -*z*].

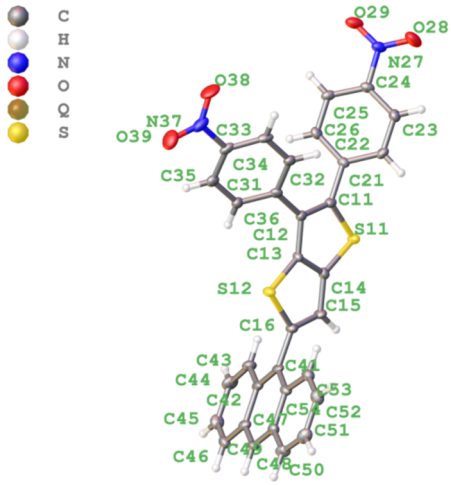


Figure5. X-Ray crystal structure of 4

Main crystal structure parametersof **4** are summarized in table 3.

Table 3. Crystal data and structure refinement for P21

Identification code	P21
Empirical formula	$C_{32}H_{18}N_2O_4S_2$
Formula weight	558.60
Temperature/K	100.0
Crystal system	monoclinic
Space group	$P2_1$
a/Å	8.060(2)
b/Å	9.502(3)
c/Å	16.573(4)
α/°	90
β/°	90.131(8)
γ/°	90
Volume/Å^3	1269.3(6)
Z	2
ρ_{calc}g/cm^3	1.462
μ/mm^{-1}	0.254
F(000)	576.0
Crystal size/mm^3	0.2 × 0.15 × 0.12
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	6.524 to 52.688
Index ranges	-10 ≤ h ≤ 10, -11 ≤ k ≤ 11, -20 ≤ l ≤ 20
Reflections collected	17740
Independent reflections	5139 [R_{int} = 0.0368, R_{sigma} = 0.0426]
Data/restraints/parameters	5139/1/362
Goodness-of-fit on F^2	1.056
Final R indexes [I>=2σ (I)]	R_1 = 0.0305, wR_2 = 0.0557
Final R indexes [all data]	R_1 = 0.0353, wR_2 = 0.0572
Largest diff. peak/hole / e Å^{-3}	0.23/-0.18
Flack parameter	-0.09(3)

4. CONCLUSION

In conclusion, a mono-, a di-, and atriaryl derivatives of thieno[3,2-*b*]thiophene were synthesizedby Pd-catalyzed Csp2-Hfunctionalization reaction.Structures of all compounds wereelucidated by NMR spectroscopy, HR-MS spectroscopy method,and X-Ray crystal structure analysis. The spectrocopic datarevealed a high regio-selectivity of the direct arylation reaction. Besides, the crystal structure of **4** determined at 100K was analyzed to evaluate the planarity, as well as the geometry of the fused ring system. The crystal structures are characterized by π–π stacking between the planar aromatic moieties.

Acknowlegement: We would like to thank Assoc. Prof. Nguyen Hung Huy at the Department of Chemistry, VNU - Hanoi University of Science, 19 Le Thanh Tong Street, Hanoi, Vietnam for his single-crystal X-Ray diffraction measurementand analysis.

REFERENCES

[1]. H. Ito, T. Yamamoto, N. Yoshimoto, N. Tsushima, H.Muraoka, S. Ogawa, *Synthesis and Properties of Thieno[3,2-b]thiophene Derivatives for Application of OFET Active Layer*, Heteroatom Chemistry, **24**, 25-35 (2013).

[2]. M.-W. Lee, J.-Y. Kim, D.-H. Lee, M. J. Ko, *Novel D-π-A Organic Dyes with Thieno[3,2-b]thiophene-3,4-ethylenedioxythiophene Unit as a π-Bridge for Highly Efficient Dye-Sensitized Solar Cells with Long-Term Stability*, ACS Appl. Mater. Interfaces, **6**, 4102−4108 (2014).

[3]. Ji-Hoon Kim, Chang Eun Song, In-Nam Kang, Won Suk Shin and Do-Hoon Hwang , *A highly crystalline low band-gap polymer consisting of perylene and diketopyrrolopyrrole for organic photovoltaic cells***,** Chem. Commun.**, 49**, 3248-3250 (2013).

[4]. M. E. Cinar, T. Ozturk. *Thienothiophenes, Dithienothiophenes, and Thienoacenes: Syntheses, Oligomers, Polymers, and Properties,* Chem. Rev., **115**, 3036–3140 (2015).

[5]. Abe Y., Li H., Yin J., Soci C., Grimsdalea A. C., LamY. M. *A fused thieno[3,2-*b*]thiophene-dithiophene based donor molecule for organic photovoltaics: a structural comparative study with indacenodithiophene,* J. Mater. Chem. C., **4**, 9656-9663 (2016).

[6]. Maluenda, I., Navarro, O., *Recent developments in the Suzuki-Miyaura reaction: 2010–2014*, Molecules, **20**, 7528-7557 (2015).

[7]. Lyons T. W., Sanford, M. S., *Palladium-catalyzed ligand-directed C-H functionalization reactions*, Chem. Rev., **110**, 1147–1169 (2010).

[8]. Zhao, J.; Zhang, Y.; Cheng, K. *Palladium-Catalyzed Direct C-2 Arylation of Indoles with Potassium Aryltrifluoroborate Salts*, J. Org. Chem., **73**, 7428–7431 (2008).

[9]. Phipps, R. J.; Grimster, N. P.; Gaunt, M. J., *Cu(II)-catalyzed direct and site-selective arylation of indoles under mild conditions*, J. Am. Chem. Soc., **130**, 8172–8174 (2008).

[10]. Lebrasseur, N.; Larrosa, I. *Room temperature and phosphine free palladium catalyzed direct C-2 arylation of indoles,* J. Am. Chem. Soc., **130**, 2926–2927 (2008).

[11]. Fuller, L. S., Iddon, B., Smith. K. A., *Thienothiophenes. Part 2.[1] Synthesis, metallation and bromine⟶lithium exchange reactions of thieno[3,2-b]thiophene and its polybromo derivatives*, J. Chem. Soc., Perkin Trans 1, **1**, 3465–3470 (1997).

[12]. Ohta, A. Y. A.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi Y. *Palladium-catalyze Arylation of Furan, Thiophene, Benzo[b]furan and Benzo[b]thiophene*, Heterocycles, **31**, 1951-1958 (1990).

[13]. Bheeter, C. B.; Bera, J. K.; Doucet, H. *Palladium-Catalyzed Direct Arylation of Thiophenes Bearing SO_2R Substituents,* J. Org. Chem. **76**, 6407-6413 (2011).

[14]. Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *Analysis of the concerted metalation-deprotonation mechanism in palladium-catalyzed direct arylation across a broad range of aromatic substrates,* J. Am. Chem. Soc. **130**, 10848 (2008).

[15]. Gorelsky, S. I. *Origins of regioselectivity of the palladium-catalyzed (aromatic)C—H bond metalation–deprotonation,* Coord. Chem. Rev., **257**, 153 (2013).

[16]. The crystal structure of compound **4** was deposed at the Cambridge Crystallographic Data Centre and have been assigned to the deposition number CCDC 1519729. Itcan be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

[17]. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H., *A Complete Structure Solution, Refinement and Analysis Program,* J. Appl. Cryst. **42**, 339-341 (2009).

[18]. Sheldrick, G.M. *Crystal structure refinement with SHELXL*. Acta Cryst. **A71**, 3-8. (2015).

[19]. Sheldrick, G.M. *Crystal structure refinement with SHELXL*. Acta Cryst. **C71**, 3-8 (2015).