Regioselective Electrophilic Access to Naphtho[1,2-b:8,7-b′]- and
-[1,2-b:5,6-b′]dithiophenes

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Supporting Information

ABSTRACT: A two-step one purification access to dichloronaphtho[1,2-b:8,7-b′] and [1,2-b:5,6-b′]dithiophenes using bis-alkynaphthyl alkynes and phthalimidesulfenyl chloride as starting materials has been developed. The functionalization of the carbon–chlorine bonds allowed further modification of NDT core, broadening the potential of the methodology.

Compounds containing the benzo[b]thiophene nucleus have found a huge number of applications in medicinal chemistry as well as, more recently, in material science. For example, raloxifene (1) (Figure 1) is a marketed drug used for osteoporosis and estrogen-related cancers;1 several raloxifene analogues show a similar selective estrogen receptor modulator (SERM) activity,2 and many other compounds containing the benzo[b]thiophene skeleton display a broad range of pharmacological effects.3−7 On the other hand, thiophene and benzothiophene derivatives have recently found application in material science for the preparation of OLED and OFET.8 Among these systems, polycrystalline heteroaromatics like naphthodithiophenes (NDTs) 2−4 (Figure 1) are commonly indicated as useful cores for electronic organic devices yet scarcely studied mainly due to the difficulties of preparation.9

Hence, any new approach to the synthesis of the benzothiophene moiety represents an important achievement, and particularly appealing are those methods that allow the easy regioselective fusion of the five-membered ring to a polycrystalline aromatic. Several modern and elegant methods foresee the cyclization of 1-thio-2-unsaturated substituted aryls using stoichiometric or catalytic amounts of a proper promoter.10

Interestingly, in some examples the sulfur atom is directly inserted on the ortho-disubstituted aromatic while promoting the cyclization.9,11 All these methods require the preventive regioselective bis-functionalization of an aromatic skeleton, generally not a trivial task above all when two thiophene units have to be assembled. Several years ago, we reported an easy synthesis of 3-chlorobenzo[b]thiophenes exploiting the reactivity of the phthalimidesulfenyl chloride (PhtNSCl, Pht = phthaloyl, S).12 As described in Scheme 1, the procedure takes advantage of the high stereo- and regioselective electrophilic addition of 5 to alkynyl(or diaryl)alkynes that allowed the preparation of (E)-1-chloro-1-aryl-2-N-thiophthalimides 6.12,13

These very stable crystalline sulfenamides can be cyclized to 3-chlorobenzo[b]thiophenes using a Lewis acid that, probably interacting with the phthalimide nitrogen (vide infra), enhances the electrophilic character of the sulfenic sulfur allowing an intramolecular electrophilic substitution (SEAr). The procedure has been recently optimized, demonstrating its applicability on solid phase and its utility for the preparation of raloxifene analogues using, as an additional final step, the 3-chloro-substituted carbon of benzo[b]thiophene as a supplementary functionalization opportunity in Suzuki−Miyaura (S−

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Figure 1. Raloxifene (1) and model naphthodithiophenes (NDTs) 2−4.
M) or other Pd-catalyzed cross-coupling reactions (Scheme 1).

Obviously, this methodology does not require an ortho-functionalized aromatic system. Thus, it seems particularly feasible for the preparation of polycondensed systems like NDTs 2–4 using bis-alkynylated alkynes as starting materials. These latter, in turn, can be easily prepared via a double-Sonogashira cross-coupling method. Indeed, applying the Sonogashira reaction to 2,7-, 2,6-, and 1,5-bis-naphthoalkynes, we prepared and used bis-naphthoalkynes 7–10, depicted in Figure 2, to verify the applicability of the above-mentioned procedure for the preparation of NDT derivatives.

![Figure 2. Bis-naphthoalkynes 7–10 used in this study.](image)

Compound 7 was reacted with 5 in dry DCM at room temperature for 12 h to give the expected bis-N-vinylthiophthalimide 11 in quite good yield (Scheme 2). The crude was separated in two identical portions; the first was purified by flash chromatography (67% yield of 11) and reacted with AlCl₃ in dry DCM while the second was reacted with AlCl₃ under the same conditions without any previous purification. Satisfied, we verified the formation of 2,9-dibutyl-3,8-dichloronaphtho[1,2-b:8,7-b']dithiophenes (12) as a single regioisomer isolated, in both experiments, in reasonable and comparable yields (52% and 48%, respectively), indicating the possibility to use this procedure to access to NDT systems also avoiding the column chromatography purification of the intermediate N-thiophthalimides (Scheme 2).

Actually, a detailed examination of the ¹H NMR of the crude obtained after the reaction of 5 with 7 showed the formation of tiny amounts of naphthodithiophene 12 directly during the electrophilic addition step. We speculate that, as it occurred in the related i₅zAr of o-diarylamino-N-thiophthalimides leading to [1,4]benzothiazine heterocycles,¹⁵ HCl, reasonably formed during the addition process by reaction of sulfenyl chloride 5 with adventitious traces of water, could also operate as promoter of the i₅zAr process. In order to verify this hypothesis, we kept N-thiophthalimide 11 in dry DCM previously saturated with gaseous HCl, and indeed, we could observe the formation of reasonable amounts of 12 without, however, achieving the complete consumption of the starting material. Enduring to study the ability of protic acids in promoting the i₅zAr, eventually we were able to isolate quite good yield of 12 (65%) reacting crude 11 with 4 equiv of triflic acid in dichloroethane (DCE) at 60 °C (Scheme 2).

Additional information on the actual mechanism of this acid-promoted (Lewis and/or protic) thiophene ring closure from (E)-1-chloro-1-aryl-2-N-thiophthalimides was collected by reacting 11 and AlCl₃ in the presence of stoichiometric amounts of 2,6-ditert-butylpyridine, a hindered base able to trap protons but unable to coordinate AlCl₃. Interestingly, under these conditions, only trace amounts of 12 were observed in the crude reaction mixture, suggesting that the protonation of the sulfenamide nitrogen,¹⁶ more than the interaction with the Lewis acid, is the real trigger event for the cyclization. Thus, in this case,¹⁷ probably, protons are the real promoters of the i₅zAr, and AlCl₃, or the other Lewis acids able to provide the cyclization,¹² serve just to generate protons in the reaction mixture as it occurs in several other peculiar examples recently reported by Spencer.¹⁸

The use of triflic acid as promoter, avoiding the formation of the aluminum salts during the alkaline workup, further simplifies the synthetic procedure, and we operated as depicted in Scheme 2 to cyclize the crude N-thiophthalimides obtained by addition of 5 to alkynes 8 and 9 (see the Experimental Section). Under these conditions, bis-naphthodithiophenes 13 and 14 were isolated, from the corresponding crude N-thiophthalimides as single regioisomers in 78% and 85% yields respectively (Figure 3). On the other hand, the electrophilic addition of 5 to 1,5-bis-alkyne 10 gave the worst results, and the following cyclization, using either TiOH or AlCl₃, afforded moderate yields (42%) of an inseparable 1:1 mixture of NDT 15 and compound 16 containing a thiophene and a six-membered thiapyrene ring (Figure 3).

![Figure 3. NDTs 13–15 and mixed thiophene/thiapyrene derivative 16 prepared in this study.](image)
The results obtained show that the transformation of alkylaryalkynes into 3-chlorobenzothiophene, mediated by sulfonyl chloride 5, can be easily applied for the preparation of NDT derivatives, in particular using 2,6- and 2,7-dialkynyl-substituted naphthalenes as starting material.

Worthy of mention is the possibility to easily isolate the quite uncommon [1,2-b:8,7-b’]dithiophene derivatives like 12 and 13, the former testifying how the proposed procedure is also perfectly tolerated by the primary bromide group. Compounds 12–14 were isolated as single regioisomers as expected due to the high nucleophilicity of the α-position of the naphthalene ring. Indeed, in the case of N-thiophthalamide obtained by addition of sulfonyl chloride 5 to 1,5-bis-substituted alkynyl-naphthalene 10, the high reactivity of α position induces a certain amount of “1 to 8” ring closure (roughly 1/4 of the cyclization processes) leading to the formation of derivative 16 containing a thiophene and a thiapyrene ring system. At the same time, the high reactivity of the naphthalene α-position does not allow the use of the present method to prepare compound 2 (Figure 1) and its syn-isomer, naphtho[2,3-b:7,6-b’]dithiophene.

The above procedure leads to the formation of 3-chloro-2-alkyl-substituted naphthothiophenes. Although α-unsubstituted NDTs are the most useful materials for further application to materials science and “naked” NDTs cannot be prepared with this method, the presence of the chlorine atom, instead of being a drawback, can be exploited as an additional synthetic option. In fact, the carbon–chlorine bond allows the functionalization of the heteroaromatic ring via cross-coupling reactions. For example, DBTs 12 and 14 were reacted with p-methoxyboronic acid using PEPSI-i-Pr as catalyst under S−M cross-coupling conditions to give bis-aryl derivatives 17 and 18 in 66%19 and 89% yield, respectively, as reported in Scheme 3.

Scheme 3

Reagents and conditions: (a) p-methoxyphenylboric acid (3 equiv), K2CO3 (2 equiv), PEPSI-i-Pr (0.1 equiv), toluene, 100 °C, 17–40 h.

This reaction is of particular interest considering that metal-catalyzed cross-coupling processes are often used as the method of choice for the functionalization or the polymerization steps required for transforming thiophene-containing derivatives into materials useful for electronic organic devices. Hence, the procedure described in this paper offers an easy way to obtain NDT derivatives, like 12–14, prearmed for a cross-coupling-based structural modification.

Polycondensed systems 12–18 were fully characterized, and in the case of NDTs 12, 14, 15,17 and 18, suitable crystals for X-ray analysis were obtained, confirming structural attributions.

The solid-state packaging of 12 is quite peculiar: the NDT units are superimposed at 3.51 Å with an alternate little deviation from the molecular axis that prevents a full eclipsing. A columnar structure appears in the crystal with one alky group completely out of the plane of the dithiophene skeleton. Interestingly, the direction of the sulfur atoms (i.e., the convexity of structure 12) is inverted in adjacent rows of such a ‘columnar’ network. On the other hand, compounds 14 and 15 are completely flat, all non-hydrogen atoms, including all sp3 carbons, laying exactly on a plane, giving rise to a tridimensional structure of parallel layers with a different packaging motif at a distance of 3.52 and 3.56 Å, respectively. In particular, in the solid state, NDT 14 shows a network of short contacts (2.77 Å) between a hydrogen of the CH2 linked to the 2-thienyl position and the π-electronic density in the average plane of molecules of the upper and lower layers (see Figure S1_06 in the Supporting Information).

Density functional calculations (Experimental Section) were employed to compute the optimized geometry for each of the compounds 12, 14, 17, and 18 in the gas phase. Expectedly, for all molecules, the HOMO−LUMO orbitals are systematically delocalized on the extended planar aromatic system. HOMO−LUMO energy gaps, reported in Table 1, appear slightly sensitive either to the shape of the NDT skeleton or to the substituent on C3 (i.e., a chlorine or a p-methoxybenzene). Interestingly, in compounds 17 and 18, the additional aromatic substituents on C3 appear to contribute only marginally to the HOMO−LUMO orbitals and, correspondingly, to the narrowing of the energy gap. In these compounds, the p-methoxybenzene moieties are in a tilted, quasi-T-shaped configuration with respect to the NTD skeleton, an effect very likely due to steric hindrance, that is maintained in the crystal phase (HOMO−LUMO orbitals and ORTEP diagrams of 12, 14, 17, and 18 are available as Supporting Information).

The computed band gaps listed in Table 1, confirmed by UV−vis spectra (see the Supporting Information), are in agreement with those reported for similar structures9 and indicate that after suitable structural transformations, such as polymerization or introduction of push−pull termini, the NDTs prepared in this study can reach the HOMO−LUMO gaps required for application in organic electronic devices.

In summary, a simple access to NDT systems, including uncommon naphtho[1,2-b:8,7-b’]dithiophenes, has been achieved using easily available bis-alkylaryalkynes and sulfonyl chloride 5 as starting materials. The procedure foresees two electrophilic processes and required a single purification. The possibility to use the carbon−chlorine bond to further functionalize the NDT core enlarges the scope of this methodology for the preparation of polycjugated heteroacenes with applications in organic electronic devices.

Table 1. HOMO and LUMO Energiesa for NDTs 12, 14, 17, and 18

<table>
<thead>
<tr>
<th>NDT</th>
<th>HOMO (eV)</th>
<th>LUMO (eV)</th>
<th>ΔE (eV)</th>
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<tr>
<td>12</td>
<td>−5.76038</td>
<td>−1.18451</td>
<td>4.57587</td>
</tr>
<tr>
<td>14</td>
<td>−5.61752</td>
<td>−1.32737</td>
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<td>17</td>
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<td>−5.13778</td>
<td>−0.91403</td>
<td>4.22375</td>
</tr>
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</table>

*aCalculated at DFT B3LYP-6-31G* level.

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**EXPERIMENTAL SECTION**

**General Experimental Methods.** Commercially available reagents, catalysts, and ligands were used as obtained, unless otherwise stated, from freshly opened containers without further purifications. Toluene was distilled from sodium, THF was distilled from sodium in the presence of the blue color of benzophenone ketyl, and DCM and dichloroethane (DCE) were distilled from CaCl₂. All of the reactions are monitored by TLC on commercially available precoated plates (silica gel 60 F 254), and the products were visualized with acidic vanillin solution. Silica gel 60, 230–400 mesh, is used for column chromatography. Melting points are uncorrected. ¹H and ¹³C NMR spectra were recorded, unless otherwise noted, in CDCl₃ at 298 K using Bruker DRX 500 and 400 MHz. ¹H NMR spectra were recorded with saturated NH₄Cl (1 x 100 mL) and water (2 x 100 mL). The organic phase was dried over Na₂SO₄, filtered, and evaporated under vacuum to give a brown oil (270 mg). The crude was purified by flash chromatography on silica gel (eluents: DCM/petroleum ether = 1/5) to give bis-alkyne 8 as a colorless oil (140 mg, 37%). ¹H NMR δ: 7.85 (s, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 and 1.6 Hz, 2H); 2.47 (t, J = 7.2 Hz, 4H); 3.03 (t, J = 7.2 Hz, 4H) ppm. ¹³C NMR δ: 132.5; 131.9; 131.0; 129.2; 127.8; 121.0; 87.4; 82.5; 29.5; 24.0 ppm. IR ν: 3066 (C–H stretching); 2972 + 2925 (C–H stretching); 2247 (C=C stretch) cm⁻¹. Anal. Calc. for C₂₂H₂₄Br₂: C, 55.42; H, 3.62. Found: C, 55.5; H, 3.27.

**2,6-Dihex-1-yn-1-yl)naphthalene (8).** Following the general procedure the crude was purified by flash chromatography on silica gel (eluents: DCM/petroleum ether = 4/1) to give bis-alkyne 8 as a colorless oil (140 mg, 37%). ¹H NMR δ: 7.77–7.78 (7H, 7.60–7.62 (4H, 7.45–7.47 (4H, 7.41 (s, 2H), 7.37 (s, 2H), 7.33 (s, 2H); 2.48 (t, J = 7.2 Hz, 4H); 3.01 (t, J = 7.2 Hz, 4H) ppm. ¹³C NMR δ: 132.5; 131.9; 131.0; 129.2; 127.8; 121.0; 87.4; 82.5; 29.5; 24.0 ppm. IR ν: 3066 (C–H stretching); 2972 + 2925 (C–H stretching); 2247 (C=C stretch) cm⁻¹. Anal. Calc. for C₂₂H₂₄Br₂: C, 55.42; H, 3.62. Found: C, 55.5; H, 3.27.

**2,6-Dihex-1-yn-1-yl)naphthalene (9).** Following the general procedure the crude was purified by flash chromatography on silica gel (eluents: DCM/petroleum ether = 1/5) to give 9 as a pale yellow solid (200 mg, 57% yield). Mp: 77–78°C. ¹H NMR δ: 7.86 (as, 2H); 7.66 (d, J = 8.4 Hz, 2H); 7.45 (d, J = 8.4 and 1.6 Hz, 2H); 2.47 (t, J = 7.2 Hz, 4H); 1.68–1.60 (m, 4H). ¹³C NMR δ: 133.4; 130.3; 129.3; 127.4; 121.8; 91.3; 80.8; 30.9; 22.1; 19.3 ppm. IR ν: 3060 (C–H stretching); 2965 + 2931 (C–H stretching); 2241 (C=C stretch) cm⁻¹. Anal. Calc. for C₁₉H₁₆Br: C, 91.61; H, 8.39. Found: C, 91.41; H, 8.44.

**1,5-Di(hex-1-yn-1-yl)naphthalene (10).** Following the general procedure the crude was purified by flash chromatography on silica gel (eluents: DCM/petroleum ether = 1/5) to give 9 as a pale yellow solid (200 mg, 57% yield). Mp: 54–55°C. ¹H NMR δ: 8.31 (d, J = 8.2 and 0.8 Hz, 2H); 7.65 (d, J = 7.0 and 0.8 Hz, 2H); 7.47 (d, J = 8.2 and 7.0 Hz, 2H); 2.58 (t, J = 7.0 Hz, 4H); 1.74–1.67 (m, 4H); 1.62–1.57 (m, 4H); 1.01 (t, J = 7.0 Hz, 6H) ppm. ¹³C NMR δ: 133.4; 130.4; 126.2; 125.7; 122.1; 95.7; 78.5; 30.9; 22.1; 19.3 ppm. IR ν: 3056 (C–H stretching); 2961 + 2926 + 2875 (C–H stretching); 2245 (C=C stretch) cm⁻¹. Anal. Calc. for C₂₁H₁₆: C, 91.61; H, 8.39. Found: C, 91.77; H, 8.19.

The addition of phthalimidesulfenyl chloride 5 to alkynes 7–10 was carried out following previously reported procedures.¹² The preparation of N-thiophthalimide 11 is described as an example of the general protocol. N-Thiophthalimides obtained reacting with alkynes 8–10 were similarly obtained and used after workup without further purifications.

**N-Thiophthalimide (11).** To a solution of alkyne 7 (293 mg, 1.02 mmol) in dry DCM (10 mL) was added dropwise a solution of sulfenyl chloride 5 (485 mg, 2.23 mmol) in dry DCM (22 mL) at −10°C under nitrogen during 1 h. The mixture was stirred at rt for 12 h and then diluted with DCM (30 mL) and washed with water (2 x 30 mL). The organic phase was dried over Na₂SO₄, filtered, and evaporated under vacuum to give a brownish solid (780 mg). Half of this crude (390 mg) was purified by flash chromatography on silica gel (eluents: DCM/petroleum ether = 1/5) to give N-thiophthalimide 11 (as a white solid (140 mg, 67%). Mp: 151–152°C. ¹H NMR δ: 7.90 (as, 2H); 7.83–7.77 (m, 4H); 7.74–7.67 (m, 4H); 7.65 (d, J = 8.4 and 1.6 Hz, 2H); 2.44 (t, J = 8.4 Hz, 4H); 1.80–1.72 (m, 4H); 1.45–1.36 (m, 4H). ¹³C NMR δ: 130.6; 130.0; 129.8; 127.0; 123.8; 32.1; 29.6; 22.5; 13.8 ppm. IR ν: 2965 (C–H stretching); 1784 + 1741 + 1711 (C=O st Pht) cm⁻¹. Anal. Calc. for C₁₉H₁₄Cl₂N₂O₂S: C, 63.77; N, 3.91; H, 4.51. Found: C, 63.63; N, 4.00; H, 4.77.
Cyclization of crude N-thiophalalimides to the corresponding NDTs was carried out using CF3SO3H or (and) AlCl3. Both experimental conditions are reported for the preparation of derivative 12. The procedure with triflic acid is the general protocol used to obtain the other NDTs.

**2,7-Dibutyl-1,6-dichloronaphtho[1,2-b:8,7-b]dithiophene (12).**

(a) With AlCl3. To a solution of 11 (309 mg; 0.43 mmol) in dry DCM (20 mL) kept under nitrogen was added AlCl3 (230 mg; 1.73 mmol) in small portions. A dark violet suspension was formed immediately. The mixture was stirred for 30 min at rt and diluted with DCM (30 mL), and the organic phase was washed with 1 M NaOH (3 × 30 mL) and water (4 × 30 mL). The organic phase was dried over Na2SO4, filtered, and evaporated under vacuum to give a crude (150 mg) purified by flash chromatography on silica gel (eluent: petroleum ether) to give NDT 12 as a white solid (94 mg; 52%).

(b) With CF3SO3H. A vial containing a solution of 11 (150 mg; 0.21 mmol) and CF3SO3H (126 mg; 0.84 mmol) in DCE (23 mL) was stirred at 60 °C for 17 h. The mixture was diluted with DCM (20 mL) and the organic phase washed with saturated Na2CO3 (2 × 30 mL) and water (4 × 30 mL). The organic phase was dried over Na2SO4, filtered, and evaporated under vacuum to give a brown solid (80 mg) that was purified by flash chromatography on silica gel (eluent: petroleum ether) to give NDT 12 as white solid (58 mg; 65%). Mp: 91–92 °C. 1H NMR δ: 7.92 (d, J = 8.6 Hz, 2H); 7.86 (d, J = 8.6 Hz, 2H); 3.09 (t, J = 7.6 Hz, 4H); 1.88–1.81 (m, 4H); 1.56–1.47 (m, 4H); 1.02 (t, J = 7.6 Hz, 6H) ppm. 13C NMR δ: 139.7; 135.0; 130.8; 129.5; 128.5; 127.6; 127.5; 118.3; 118.7; 32.7; 28.3; 22.8; 22.3; 22.2; 13.8 ppm. Anal. Calc. for C22H22Cl2S2 (on the mixture): C, 62.70; H, 5.26. Found: C, 62.62; H, 5.01. X-ray: orthorhombic, space group Pnca (a), with AlCl3.

The crude obtained following the general procedure was purified by flash chromatography on silica gel (eluent: petroleum ether) to give a 1:1 mixture of 15 and 16 as a pale yellow glassy solid (63 mg; 42%).

**2,9-Dibutyl-3,8-dichloronaphtho[1,2-b:8,7-b]dithiophene (17).** In a Schlenk tube under nitrogen to a mixture of p-methoxyphenylboronic acid (51 mg; 0.34 mmol), dry K2CO3 (94 mg; 0.68 mmol), and PEPPSI-Pr (3 mg; 0.04 mmol) was added a solution of NDT 12 (48 mg; 0.11 mmol) in dry toluene (1.5 mL). The mixture was stirred at 100 °C under an inert atmosphere for 17 h. The mixture was then diluted with methyl ether (40 mL) and the organic phase washed with brine (3 × 20 mL). The organic phase was dried over Na2SO4, filtered, and evaporated under vacuum to give a brown oil (130 mg). The crude was purified by flash chromatography on silica gel (eluent: DCM/petroleum ether = 1/4) to give derivative 17 as a white solid (42 mg, 66%) along with the monooaryl derivative mono-17 (white solid, 7 mg, 11%). Mp: 89–90 °C. 1H NMR δ: 7.83 (d, J = 8.4 Hz, 2H); 7.60 (d, J = 8.4 Hz, 2H); 7.38 (dd, J = 6.4 and 2.0 Hz, 4H); 7.07 (dd, J = 6.4 and 2.0 Hz, 4H); 3.92 (s, 6H); 3.02 (t, J = 7.2 Hz, 4H); 1.86–1.81 (m, 4H); 1.48–1.38 (m, 4H); 0.92 (t, J = 7.2 Hz, 4H) ppm. 13C NMR δ: 158.9; 149.1; 143.0; 138.3; 134.4; 132.1; 131.4; 128.7; 127.9; 125.4; 120.5; 113.9; 55.3; 43.3; 28.7; 22.4; 13.8 ppm. MS m/z (int rel) 420 (56% M+); 377 (100); 336 (54). Anal. Calc. for C22H19ClOS2: C, 70.63; H, 5.93. Found: C, 70.38; H, 6.01. X-ray: triclinic, space group P1, a = 9.521 (5) Å, b = 11.540 (5) Å, c = 13.591 (5) Å, α = 84.63 (5)°, β = 87.68 (5)°, γ = 84.95 (5)°, V = 1468.4 (2) Å³, Z = 2, Dcal = 1.277, μ = 1.881 mm−1, F(000) = 600. 16532 reflections were collected with a 4.66 < θ < 72.16 range with a completeness to 96.96%; 5625 were unique, the parameters were 473 and the final R index was 0.0464 for reflections having I > 2σ(I) and 0.0072 for all data. No significant intra or intermolecular interactions were detected.

**2,9-Dibutyl-3-chloro-4-(m-ethyl)phenyl)naphtho[1,2-b:8,7-b]dithiophene (monoo-17).** 1H NMR δ: 7.97 (d, J = 8.7 Hz, 1H); 7.91 (d, J = 8.4 Hz, 1H); 7.86 (d, J = 8.7 Hz, 1H); 7.63 (d, J = 8.4 Hz, 1H); 7.37 (d, J = 9.0 Hz, 2H); 7.07 (d, J = 9.0 Hz, 2H); 3.91 (s, 3H); 3.13 (t, J = 7.2 Hz, 2H); 3.01 (t, J = 7.2 Hz, 2H); 1.93–1.76 (m, 4H); 1.56–1.35 (m, 4H); 0.95 (t, J = 7.2 Hz, 3H) ppm. 13C NMR δ: 159.0; 143.3; 139.5; 138.7; 134.8; 134.4; 131.7; 131.4; 130.9; 129.2; 127.7; 126.3; 125.6; 123.9; 121.1; 118.8; 118.7; 116.0; 55.3; 34.3; 32.7; 28.7; 28.2; 22.4; 22.4; 13.8 ppm. MS m/z (int rel) 492 (87, M+); 449 (100); 203 (29). Anal. Calc. for C29H29ClOS2: C, 70.63; H, 5.93. Found: C, 70.38; H, 6.01. X-ray: triclinic, space group P1, a = 9.521 (5) Å, b = 11.540 (5) Å, c = 13.591 (5) Å, α = 84.63 (5)°, β = 87.68 (5)°, γ = 84.95 (5)°, V = 1468.4 (2) Å³, Z = 2, Dcal = 1.277, μ = 1.881 mm−1, F(000) = 600. 16532 reflections were collected with a 4.66 < θ < 72.16 range with a completeness to 96.96%; 5625 were unique, the parameters were 473 and the final R index was 0.0464 for reflections having I > 2σ(I) and 0.0072 for all data. No significant intra or intermolecular interactions were detected.
as a white solid (80 mg, 89%). Mp: 171–172 °C. H NMR δ: 7.92 (d, J = 8.4 Hz, 2H); 7.56 (d, J = 8.4 Hz, 2H); 7.36 (d, J = 8.7 Hz, 4H); 7.06 (d, J = 8.7 Hz, 4H); 3.91 (s, 6H); 2.91 (t, J = 7.2 Hz, 4H); 1.78–1.67 (m, 4H); 1.42–1.18 (m, 4H); 0.86 (t, J = 7.2 Hz, 6H) ppm. 13C NMR δ: 158.9; 141.1; 137.2; 136.2; 135.4; 131.2; 127.9; 125.7; 121.8; 120.8; 114.0; 55.3; 34.1; 25.6; 22.3; 13.8 ppm. MS (m/z (int rel)) 564 (100 M°); 521 (43); 464 (28). Anal. Calc'd for C26H21O12S: C, 76.5; H, 6.42. Found: C, 75.9; H, 6.63. X-ray: triclinic space group P-1, a = 10.690(1) Å, b = 14.404(1) Å, c = 19.076(1) Å, α = 98.344(3)°, β = 90.870(3)°, γ = 91.061(3)°, V = 2905.0(4) Å³, Z = 2, D = 1.219, µ = 1.901 mm⁻¹, F(000) = 1200. 23272 reflections were collected with a 4.14 < 2θ < 70.66 range with a completeness to θ 95.3%; 10632 were unique, the parameters were 721 and the final R index was 0.0505 for reflections with I > 2σ(I) and 0.0577 for all data. The asymmetric unit contains two independent molecules as they are not equivalent from a crystallographic point of view. It is mainly due to the different torsion angles between sulfur atoms and the alkylic chains. No significant intra- or intermolecular interactions can be detected.


In vivo studies: Despite the widespread use of protons for the detection of intra- or intermolecular interactions, the importance of detecting these interactions cannot be overstated. Angiogenesis inhibitors are used as anti-neoplastic agents, and the ability to detect these interactions is crucial for their evaluation. The characterization of these interactions can provide insights into the structural determinants of the biological activity of these compounds. The detection of such interactions may also have implications for the design of new therapeutic agents.
(19) Compound 17 was isolated along with a small amount (11%) of the corresponding monoarylated derivative (mono-17, see the Experimental Section).
(20) A slow evaporation of a DCM solution of the 1:1 mixture of 15 and 16 allowed the manual selection of colorless plate of pure NDT 15, suitable for X-ray analysis, formed over a dark yellow gummy oil still containing both derivatives.