Tetrahedron Letters 50 (2009) 4670–4673

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A facile synthesis of α-substituted thiophenes from a functionalized 2-aminothiophene by homo- and cross-coupling reactions

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ARTICLE INFO

Article history:
Received 16 February 2009
Revised 25 May 2009
Accepted 1 June 2009
Available online 6 June 2009

ABSTRACT

A series of new α-substituted thiophenes with elongated π-conjugation are prepared by homo- and cross-coupling reactions. An efficient one-step synthesis of a key intermediate, a substituted 2-iodothiophene, via aprotic diazotization of a Gewald-like 2-aminothiophene is reported.

The design and synthesis of well-defined organic molecules for polymeric, electronic semiconducting, and non-linear optical materials (NLO) have been very important in recent years. Donor–acceptor-substituted heteroaromatic compounds occupy a prominent position in modern research because of their advanced features (e.g., spectral characteristics, fast non-linear optical response, and low dielectric constant).[1] Thiophene-based π-conjugated oligomers are among the most extensively studied systems. They behave as very efficient electron relays and exhibit increased π-overlap between the connected thiophene units. Moreover, their chemical, environmental, and thermal stabilities, and wide possibility of functionalization make oligothiophenes attractive for real-life application as electronic and optical materials [light emitting diode (LED) devices, integrated optics)].[2] Synthetic efforts have been focused on improving the properties of oligothiophene-based compounds (current materials being limited in terms of multifunctionality and price), with particular interest on their molecular architecture.[3]

We report herein a rapid and simple synthesis of thiophene building blocks **2–7**, from inexpensive and easily obtainable substituted 2-aminothiophene **1** (Fig. 1).

The designed derivatives exhibit the potential to be integrated into polymers with tunable electronic and optical properties.[4]

As for the synthesis of symmetrical biaryls and biheteroaryls, the typical method for the preparation of symmetrical bithiophenes is the classic Ullmann reaction. The process of reductive homo-coupling is usually carried out with the corresponding iodides and requires an excess of copper(0) or copper(I) salts.[5]

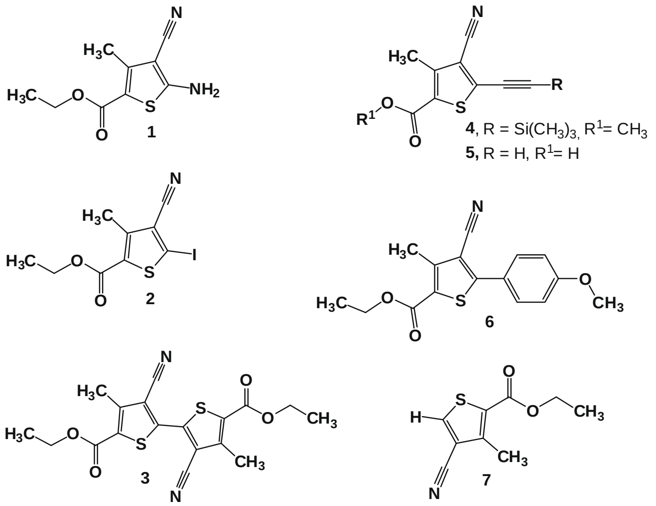

Figure 1. Functionalized thiophenes **1–7**.

Our first goal was to synthesize the key intermediate, 2-iodo-substituted thiophene **2**, from 2-aminothiophene **1**, the latter being prepared by the Gewald reaction.[6]

Heterocycles bearing an amino group are transformed into the corresponding iodo derivatives with sodium nitrite at low temperatures in two steps: diazotization of the amine in acidic media (HCl, H_2SO_4) and subsequent reaction with iodine or KI.[7] In an alternative process, aromatic amines are converted into the appropriate aryl iodides using a triazene masking group. Treatment of aryl-dialkylsubstituted triazenes with methyl iodide or iodine at high temperatures generally gives aryl iodides and traces of starting material.[8] Both

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doi:10.1016/j.tetlet.2009.06.006

methods rely on in situ preparation of the ammonium salts which act as substrates in subsequent deaminations.

Due to the fact that substituted 2-aminothiophenes can exhibit the properties of their tautomers, the imines, they are generally unsuitable for diazotization reactions. Substitution with an electron-withdrawing group at the other α-position stabilizes the aromatic character of 2-aminothiophene and allows the successful diazotization. Nevertheless, the formed thiophene 2-diazonium salts undergo loss of nitrogen and self-coupling resulting in polymers of indeterminate structures.[9] A recent method for the iodination of aromatic amines has proven to be an efficient procedure for the diazotization–iodination of substituted 2-aminothiophenes.[10] This sequence occurs in one-pot using sodium nitrite in acetonitrile in the presence of *p*-toluenesulfonic acid (Scheme 1).[11]

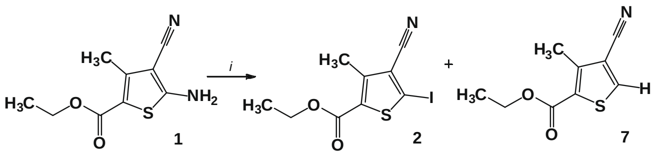
The results of our trials to obtain ethyl 4-cyano-5-iodo-3-methylthiophene-2-carboxylate (**2**) utilizing two traditional methods (A and B) and an improved procedure (C) are summarized in Table 1. The reaction was accomplished only under moderate reaction conditions (method C), a fact that supports actual observations of difficulties associated with diazotization of substituted 2-aminothiophenes due to their amphoteric nature. Product **2** was obtained as a mixture with the product **7** of the deamination reaction, both isolated in the ratio 3:1 after chromatographic separation (Scheme 1, Table 1).

As discussed in our earlier work, ethyl 4-cyano-5-iodo-3-methylthiophene-2-carboxylate (**2**) forms a dimer by the association of two monomers through intermolecular CN···I Lewis acid–base interactions (Fig. 2a). A weak intramolecular CH···O interaction is also characteristic of thiophene monomer **2** (Fig. 2b).[12]

After replacement of the amino group with iodine, we turned our attention to explore the possibility of preparing symmetrical bithiophene **3** via Ullmann reaction. The copper-mediated homocoupling of 2-iodothiophene **2** in DMF generated diethyl 3,3′-dicyano-4,4′-dimethyl-2,2′-bithiophene-5,5′-dicarboxylate (**3**) in 41% yield (Scheme 2).[13] The corresponding dehalogenated thiophene **7** was formed in 39% yield as a by-product (Scheme 2).[14]

The ethoxycarbonyl and cyano groups present in 2,2-bithiophene **3** are well-characterized as structure-directing synthons in molecular engineering. Related compounds such as polyaromatics and polypyrroles, exhibit the properties of supramolecular aggregates with excellent photophysical and electrochemical properties.[15]

In the course of our investigations of thiophene-containing building blocks with tailored properties, we were interested in the use of substituted 2-iodothiophene **2** in cross-coupling reactions, which when compared to Ullmann homo-coupling offers additional advantages in terms of tolerating a broader range of functionalized substituents.[16] Using Sonogashira coupling,[17] we replaced iodine with an alkynyl chain. Reaction of **2** with trimethylsilylacetylene using bis(triphenylphosphine)palladium(II) chloride in THF in the presence of di-*iso*-propylamine enabled the introduction of an ethynyl chain with a trimethylsilyl functionality.[18] As 'Cu-free' reaction conditions were used, the corresponding 2,2′-bithiophene **3** and deiodinated thiophene **7** were formed (Scheme 3), and separated from the cross-coupled product **4** using column chromatography. Subsequent deprotection of the trimethylsilyl group with 30% NaOH gave the target 5-ethynylthiophene **5** (Scheme 3).[19]



Scheme 1. Diazotization–iodination of ethyl 5-amino-4-cyano-3-methylthiophene-2-carboxylate **1** under various conditions. (i) Method A, B or C (for the reaction conditions see Table 1).

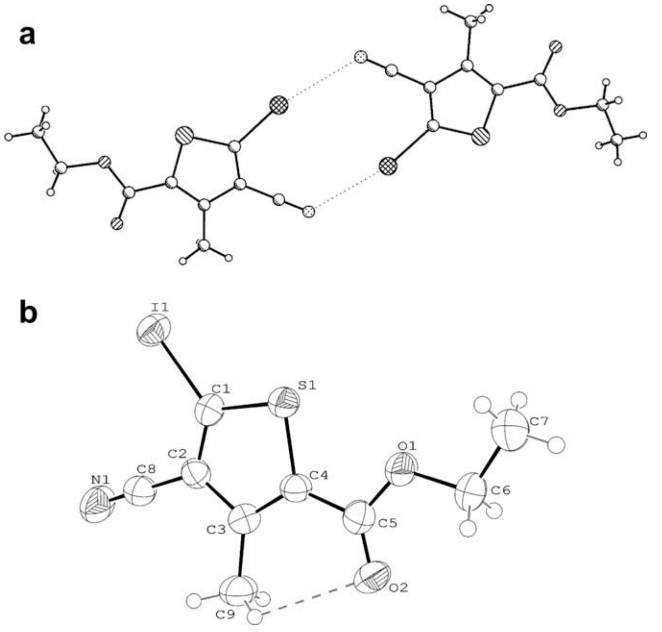
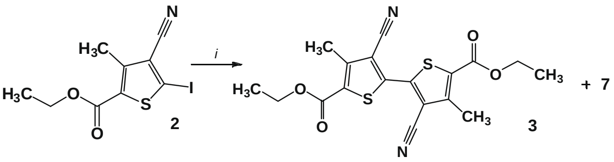


Figure 2. Crystal structure of ethyl 4-cyano-5-iodo-3-methylthiophene-2-carboxylate (**2**); (a) dimer formed through CN···I intermolecular interactions between two monomers, (b) single molecule in the unit cell.[12]

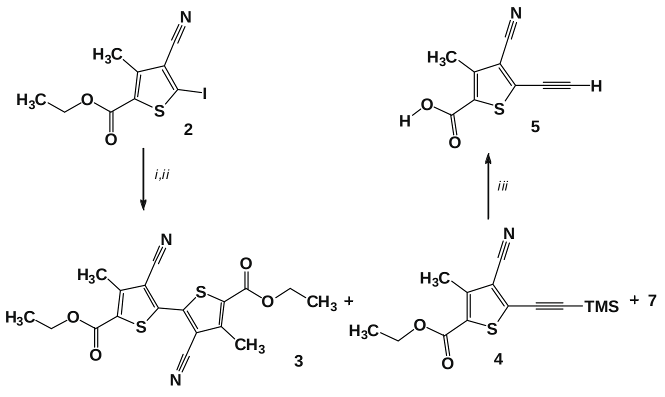


Scheme 2. Synthesis of diethyl 3,3′-dicyano-4,4′-dimethyl-2,2′-bithiophene-5,5′-dicarboxylate (**3**) via Ullmann homo-coupling. Reagents and conditions: (i) Cu(0) powder (10 equiv), DMF (155 °C), 18 h, 41% of **3** and 39% of **7**.

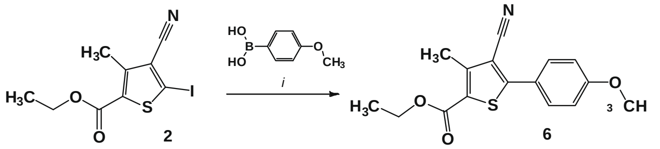
Functionalized heteroaromatic compounds, such as ethyl 4-cyano-5-ethynyl-3-methylthiophene-2-carboxylate (**5**), are under current investigation in the development of organic-based structural and functional thin films. It has been shown, that Parylene film ('poly-*para*-xylylene-like thin film') deposited on a liquid substrate offers very useful properties for microelectrochemical system (MEMS) applications.[20] Systematic approaches to such polymers resulted in a variety of new micro/nano systems having potential for real-life applications as particles in molecular electronics, surface acoustic waves, or deformable mirrors and lenses.[21]

Table 1
Reaction conditions for the diazotization–iodination reaction of **1** to afford ethyl 4-cyano-5-iodo-3-methylthiophene-2-carboxylate (**2**)

	Reaction conditions (reagents, temperature, time)	Yield of **2** (%)	Ratio of **2**:**7**
Method A	$NaNO_2$, H_2SO_4 (0 °C), 30 min, I_2 (0 °C), 4 h	0	–
Method B	$NaNO_2$, HCl (−5 °C), 30 min, Et_2NH, MeI (80 °C), 4 h	0	–
Method C	$NaNO_2$, KI, *p*-TsOH (15 °C), 3 h	73	3:1



Scheme 3. Synthesis of α-ethynyl-substituted thiophene **5**. Reagents and conditions: (i) Pd(PPh3)4Cl2 (0.05 equiv), trimethylsilylacetylene (1.1 equiv), CuBr (0.05 equiv), (*i*-Pr)2NH , THF, reflux, 12 h; (ii) chromatographic separation yields: 20% of **3**, 30% of **4**, 20% of **7**, (iii) 30% NaOH aq, THF–CH$_3$OH (20:1), 50 °C, 5 h, 65%.



Scheme 4. Suzuki reaction of 4-cyano-5-iodo-3-methylthiophene-2-carboxylate (**2**) with *p*-methoxyphenylboronic acid. Reagents and conditions: (i) Pd(dppf)Cl$_2$ (0.2 equiv), Et$_3$N, toluene 80 °C, 16 h, 71%.

In cross-coupling reactions 2-iodothiophenes analogous to derivative **2**, are attractive synthetic alternatives to the corresponding halides (chlorides, bromides) or triflates. In addition, iodine-containing molecules are more reactive and often prevent the formation of by-products. We have demonstrated these features in the preparation of α-arylsubstituted thiophene **6** via Suzuki reaction.[22] Reaction of 2-iodinated thiophene **2** with 2 equiv of commercially available *p*-methoxyphenylboronic acid using Pd(dppf)Cl$_2$ in the presence of triethylamine gave the α-(*p*-methoxy)phenyl-substituted product **6** in 71% yield without formation of any by-products (Scheme 4).[23]

In all our studies, except the Suzuki reaction (Scheme 4), ethyl 4-cyano-3-methylthiophene-2-carboxylate (**7**)[14] was formed as a major by-product resulting from a side de-diazotization reaction (Scheme 2) and from cationic or radical pathways due to the presence of Cu(I) salts formed during radical coupling (Scheme 2) or when used as a co-catalyst (Scheme 3). The presence of a Cu(I) salt was the main reason why during the Sonogashira coupling, the product of a radical reaction (symmetrical 2,2′-bithiophene **3**) was formed (Scheme 3). Deamination of 2-aminothiophene **1** via the iodide **2** was very efficient if the adjusted procedure was applied (Table 1, method C), displaying none of the complications observed with typical methods (Table 1, methods A and B).

These results have not been optimized for a broader range of substituted 2-aminothiophenes but constitute the first report on effective diazotization–iodination of these heterocyclic amino compounds. The scope and utility of iodinated products are demonstrated via metal-catalyzed homo- and cross-coupling reactions. Furthermore, the prepared α-functionalized thiophenes represent important organic molecules suitable for further investigation in materials and medicinal chemistries.

Acknowledgments

This work was supported by the Ministry of Education of the Slovak Republic—VEGA Grant Nos. 1/4453/07 and 1/4300/07 and UK Grant No. UK/102/2009.

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11. *Ethyl 4-cyano-5-iodo-3-methylthiophene-2-carboxylate* (**2**): To a solution of *p*-TsOH (36.0 mmol, 6.4 g) in MeCN (50 mL) was added ethyl 5-amino-4-cyano-3-methylthiophene-2-carboxylate (**1**, 12.0 mmol, 2.5 g). The resulting suspension of the amine salt was cooled to 10–15 °C, and to this was added, gradually, a solution of NaNO$_2$ (24.0 mmol, 1.6 g) and KI (30.0 mmol, 5.2 g) in H$_2$O (10.0 mL). The reaction mixture was stirred for 10 min then allowed to warm to rt and stirred for a further 3 h. The reaction mixture was poured into water (120 mL) and then a saturated solution of K$_2$CO$_3$ was added carefully until pH 9–10 (ca. *15–20 mL, foams intensely*). The mixture was washed with a 2 M aq solution of Na$_2$CO$_3$ (30 mL) and extracted into ethyl acetate (3 × 30 mL). The combined organic layer was dried with Na$_2$SO$_4$ and evaporated to dryness to give a mixture of the compounds **2** and **7** (in the ratio 3:1). The crude mixture was chromatographed over silica gel using a mixture of *n*-hexane/ethyl acetate (70:30) to give iodinated thiophene **2** in 73% yield (2.8 g) and deaminated thiophene **7**[14] in 24% yield (0.56 g). Product **2** was recrystallized from hexane by slow solvent evaporation to afford colorless needle-shaped crystals; mp = 122–125 °C; λ_{max}(CHCl$_3$) = 283.21 nm; ν_{max}(KBr) = 3398 (br), 2229, 1719, 1537, 1416, 1364, 1148, 760 cm^{-1}; δ_H (300 MHz, CDCl$_3$) 4.34 (q, ^3J = 6.2 Hz, 2H, CO$_2$*CH$_2$*CH$_3$), 2.68 (s, 3H, CH$_3$), 1.37 (t, ^3J = 6.2 Hz, 9.3 Hz, 3H, CO$_2$CH$_2$*CH$_3$*); δ_C (75 MHz, CDCl$_3$) 160.27 (*CO$_2$*CH$_2$CH$_3$), 147.56 (C-2), 134.25 (C-3), 124.30 (C-4), 114.69 (CN), 92.37 (C-5), 61.0 (CO$_2$*CH$_2$*CH$_3$), 15.39 (CH$_3$), 14.21 (CO$_2$CH$_2$*CH$_3$*). Anal. Calcd for C$_9$H$_8$INO$_2$S (321.13): C, 33.66; H, 2.51; N, 4.36. Found: C, 33.69; H, 2.49; N, 4.33. Mass (ESI) *m*/*z* (%) 343.24 (M+Na).
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13. *Diethyl 3,3′-dicyano-4,4′-dimethyl-2,2′-bithiophene-5,5′-dicarboxylate* (**3**): A mixture of **2** (4.8 mmol, 1.54 g) and copper powder (40 mmol, 2.4 g) in dry DMF was stirred at 155 °C under a N$_2$ atmosphere for 18 h. The mixture was then filtered through Celite and washed with cold dichloromethane (5–10 mL). The filtrate was washed with a 1 M solution of HCl (5 mL) and H$_2$O (5 mL) and the separated organic layer was dried over Na$_2$SO$_4$. Evaporation of the solvent afforded a mixture of products **3** and **7** (ratio 1:1) which was readily separated

by column chromatography over silica gel using *n*-hexane/ethyl acetate (70:30) to give bithiophene **3** in 41% yield (764 mg) and dehalogenated thiophene **7**[14] in 39% yield (365 mg). Product **3** was recrystallized from *n*-hexane to afford yellow crystals, mp = 208–210 °C; $\lambda_{\max}(\mathrm{CHCl_3})$ = 345.66 nm; $\nu_{\max}$(KBr) = 2924, 1719, 1263, 1146, 760 cm^{-1}; δ_{H} (300 MHz, CDCl$_3$) 4.40 (q, ^3J = 6.0 Hz, 4H, 2 × CO$_2$*CH*$_2$CH$_3$), 2.72 (s, 6H, CH$_3$), 1.40 (t, ^3J = 6.0 Hz, 8.9 Hz, 6H, 2 × CO$_2$CH$_2$*CH*$_3$); δ_{C} (75 MHz, CDCl$_3$) 160.60 (2 × *CO*$_2$CH$_2$CH$_3$), 147.86 (C-5, C-5′), 142.34 (C-2, C-2′), 130.23 (C-3, C-3′), 113.97 (C-4, C-4′), 113.51 (CN), 62.09 (2 × CO$_2$*CH*$_2$CH$_3$), 15.34 (CH$_3$), 14.26 (2 × CO$_2$CH$_2$*CH*$_3$). Anal. Calcd for $C_{18}H_{16}N_2O_4S_2$ (388.46): C, 55.65; H, 4.15; N, 7.21. Found: C, 55.67; H, 4.17; N, 7.19. Mass (ESI) *m/z* (%) 388.26.

14. *Ethyl 4-cyano-3-methylthiophene-2-carboxylate* (**7**): formed as a by-product of the deamination[11] and dehalogenation reactions[13,18] as a light yellow powder, mp = 90–93 °C; $\nu_{\max}$(KBr) = 3314 (br), 1712, 1627, 1510, 1294, 903, 820 cm^{-1}; δ_{H} (300 MHz, CDCl$_3$) 7.89 (s, 1H, H-5), 4.29 (q, ^3J = 6.1 Hz, 2H, CO$_2$*CH*$_2$CH$_3$), 2.21 (s, 3H, CH$_3$), 1.30 (t, ^3J = 6.1 Hz, 8.6 Hz, 3H, CO$_2$CH$_2$*CH*$_3$); δ_{C} (75 MHz, CDCl$_3$) 161.8 (*CO*$_2$CH$_2$CH$_3$), 150.2 (C-2), 146.7 (C-3), 144.8 (C-5), 117.2 (CN), 114.3 (C-4), 56.2 (CO$_2$*CH*$_2$CH$_3$), 20.1 (CO$_2$CH$_2$*CH*$_3$), 11.2 (CH$_3$). Anal. Calcd for $C_9H_9NO_2S$ (195.24): C, 55.37; H, 4.65; N, 7.17. Found: C, 55.40; H, 4.62; N, 7.15. Mass (ESI) *m/z* (%) 195.02.
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18. *Ethyl 4-cyano-3-methyl-5-[(trimethylsilyl)ethynyl]thiophene-2-carboxylate* (**4**): Under N$_2$, an oven dried round-bottomed flask was charged with bis(triphenylphosphine)palladium(II) chloride (0.023 mmol, 16.4 mg, 5 mol %), copper(I) bromide (0.023 mmol, 3.35 mg, 5 mol %), compound **2** (0.467 mmol, 150 mg), trimethylsilyl acetylene (0.514 mmol, 0.073 mL), and diisopropylamine (100 μL). The mixture was heated to 50 °C in THF–CH$_3$OH (20: 1, 10 mL) for 20 h. After cooling to rt, the mixture was poured into water (5 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layer was dried with Na$_2$SO$_4$ and evaporated to give a mixture of the desired product **4** and by-products **3** and **7** (ratio 3:2:2). The products were separated by column chromatography on silica gel using *n*-hexane/ethyl acetate (90:10) to give the desired product **4** in 30% yield (41 mg), deiodinated thiophene **7**[14] in 20% yield (18 mg), and homocoupled 2,2′-bithiophene **3**[13] in 20% yield (36 mg). Evaporation of the solvent gave product **4** as a yellow solid, mp = 103–105 °C; $\nu_{\max}$(KBr) = 3123 (br), 2227, 1712, 1266, 1183, 811 cm^{-1}; δ_{H} (300 MHz, CDCl$_3$) 4.42–4.32 (m, 2H, CO$_2$*CH*$_2$CH$_3$), 2.63 (s, 3H, C*H*$_3$), 1.42–1.35 (m, 3H, CO$_2$CH$_2$*CH*$_3$), 0.30 [s, 9H, Si(C*H*$_3$)$_3$]; δ_{C} (75 MHz, CDCl$_3$) 170 (*CO*$_2$CH$_2$CH$_3$), 152.7 (C-2), 145.1 (C-3), 141.9 (C-5), 116.1 (CN), 94.2 (*CH*-TMS), 87.4 (C-4), 75.3 (Ar-*CH*), 61.0 (CO$_2$*CH*$_2$CH$_3$), 15.4 (CO$_2$CH$_2$*CH*$_3$), 9.6 (CH$_3$), 4.7 [Si(C*H*$_3$)$_3$]. Anal. Calcd for $C_{14}H_{17}NO_2SSi$ (291.44): C, 57.70; H, 5.88; N, 4.81. Found: C, 57.72; H, 4.84; N, 4.79. Mass (ESI) *m/z* (%) 291.1.
19. *4-Cyano-5-ethynyl-3-methylthiophene-2-carboxylic acid* (**5**): To a solution of **4** (0.14 mmol, 40 mg) in THF–CH$_3$OH (2:1, 5 mL), a 20% aq solution of NaOH was added (20 μL) and the solution stirred at 50 °C for 5 h. After cooling to rt the mixture was acidified with concentrated HCl and then extracted into ethyl acetate (3 × 10 mL). The combined organic layer was dried with Na$_2$SO$_4$ and the solvent evaporated to yield a brownish solid. The crude product was crystallized to afford α-ethynyl substituted thiophene **5** as a shiny yellow solid in 65% yield (20 mg), mp = 131–133 °C; $\nu_{\max}$(KBr) = 3305 (br), 2105, 1760, 1419, 1275, 1109, 875 cm^{-1}; δ_{H} (300 MHz, CDCl$_3$) 10.50 (br s, 1H, COOH), 3.12 (s, 1H, CH), 2.59 (s, 3H, C*H*$_3$), δ_{C} (75 MHz, CDCl$_3$) 162.0 (*COO*H), 150.6 (C-2), 146.9 (C-3), 145.5 (C-5), 115.0 (CN), 86.1 (C-4), 74.3 (CH), 72.0 (Ar-*CH*), 4.1 (CH$_3$). Anal. Calcd for $C_9H_5NO_2S$ (191.21): C, 56.53; H, 2.64; N, 7.33. Found: C, 56.55; H, 2.67; N, 7.30. Mass (ESI) *m/z* (%) 192.3 (M+H).
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23. *Ethyl 4-cyano-5-(4-methoxyphenyl)-3-methylthiophene-2-carboxylate* (**6**): In a dry round-bottomed flask, compound **2** (0.5 mmol, 160 mg), *p*-methoxyphenylboronic acid (1.0 mmol, 153 mg), Pd(dppf)Cl$_2$ (0.1 mmol, 30 mg), and triethylamine (0.3 mmol, 30 mg) in dry toluene (5 mL) were stirred under a N$_2$ atmosphere at 85 °C for 16 h. After cooling to rt, the mixture was washed with a 5% solution of aq NaHCO$_3$ (5 mL) and ethyl acetate (20 mL). After stirring at rt for 30 min, the mixture was acidified with a 3 M aq solution of HCl and extracted into ethyl acetate (3 × 15 mL). The combined organic layer was dried with Na$_2$SO$_4$, the solvent evaporated, and the residue was purified by flash chromatography, eluent *n*-hexane/ethyl acetate (70:30) to give the desired cross-coupled product **6** in 71% yield (107 mg) as a light-brown solid, mp = 107–108 °C; $\nu_{\max}$(KBr) = 2982, 1740, 1631, 1495, 1192, 890, 757 cm^{-1}; δ_{H} (300 MHz, CDCl$_3$) 7.77 (d, ^3J = 8.2 Hz, 1H, phenyl), 7.52 (d, ^3J = 8.2 Hz, 1H, phenyl), 7.14 (d, ^3J = 8.2 Hz, 1H, phenyl), 6.98 (d, ^3J = 8.2 Hz, 1H, phenyl), 4.32 (q, ^3J = 6.2 Hz, 2H, CO$_2$*CH*$_2$CH$_3$), 3.78 (s, 3H, O*CH*$_3$), 2.60 (s, 3H, CH$_3$), 1.32 (t, *J* = 6.2 Hz, 3H, CO$_2$CH$_2$*CH*$_3$); δ_{C} (75 MHz, CDCl$_3$) 161.3 (*C*–OCH$_3$), 160.5 (*CO*$_2$CH$_2$CH$_3$), 156.2 (C-5), 152.2 (C-2), 147.8 (C-3), 129.5, 127.2, 125.4, (3 × C phenyl), 115.0 (C-4), 114.3 (2 × C phenyl), 108.8 (CN), 61.4 (CO$_2$*CH*$_2$CH$_3$), 55.8 (O*CH*$_3$), 14.2 (CO$_2$CH$_2$*CH*$_3$), 7.7 (CH$_3$). Anal. Calcd for $C_{16}H_{15}NO_3S$ (301.36): C, 63.77; H, 5.02; N, 4.65. Found: C, 63.74; H, 5.05; N, 4.62. Mass (ESI) *m/z* (%) 301.32.