Chemical Papers
https://doi.org/10.1007/s11696-018-0640-2

ORIGINAL PAPER

New strategy for the synthesis of 3-ethynyl-2-(thiophen-2-yl)benzo[b]thiophene derivatives

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Received: 2 May 2018 / Accepted: 13 November 2018

Abstract
Pd-catalyzed coupling reactions like the Sonogashira coupling reaction are very useful tools for the formation of new carbon–carbon bonds under mild reaction conditions. Coupling reactions are also used for elaboration of organic compounds in drug and material discovery. Terminal alkynes have a very critical role in Sonogashira coupling reaction. Therefore, design and synthesis of new terminal alkynes are very important for the preparation of organic compounds. In the present study, a novel alkyne 3-ethynyl-2-(thiophen-2-yl)benzo[b]thiophene **13** was synthesized, and it was tested for Sonogashira coupling reaction with different iodoaryl compounds. It was investigated whether our terminal alkyne **13** having a special construction might be a useful precursor for the synthesis of potentially active organic molecules.

Keywords Alkynes · Benzothiophenes · Sonogashira coupling reaction · C–C bond formation reactions

Introduction

Heteroaromatic compounds have a very important role in discovery and development of new drug and material candidates due to their interesting properties (Brasholz et al. 2009; Katritzky et al. 1998; Kivrak and Larock 2010). They have been used as anti-parasitic (Coa et al. 2015), antibacterial (Pathak et al. 2012; Shakdofa et al. 2014), anti-cancer (Rahmouni et al. 2016), anti-fungal (Pathak et al. 2012), anti-inflammatory (Kazemizadeh et al. 2016), and antioxidant (Richardson et al. 2009) drugs. In addition, conjugated heterocyclic compounds have been used in solar cells, transistor, LEDs, biosensors, sensors, and electrochromic devices.

Thiophenes and benzothiophenes are well-known five-membered heterocyclic compounds present in organic chemistry. Their core is present in many natural and pharmacologically active compounds (Scheme 1). They have been used for the treatment of a variety of diseases. For example, Raloxifene **1** (Meixner et al. 2017; Weiser et al. 2017), Zileuton **2** (Sarret et al. 2017), and Sertaconazole **3** (Croxtall and Plosker 2009) are commercially available drugs. Raloxifene is used for the treatment of breast cancer. Moreover, Raloxifene has less side effects than Tamoxifen which has similar biological activities (Vogel et al. 2006). Moreover, the stability of thiophenes and benzothiophenes **4** plays an important role in increasing and preparing different types molecules for the material (Guo et al. 2018) and pharmaceutical areas. Recently, we also reported the novel biological activities of alkynyl-substituted benzothiophene derivatives (Algso et al. 2018). It was investigated whether benzothiophene derivatives have a high antibacterial activity against *S. aureus* ATCC 25923. Moreover, they may also be used for the treatment of fungal diseases.

Benzothiophenes are generally obtained from intramolecular cyclization and Claisen rearrangement reactions. For example, benzothiophenes were regioselectively synthesized via intramolecular cyclization reaction of *o*-alkinylthioanisoles (Sun et al. 2011). Recently, Mohanakrishnan et al. published a new method for the synthesis of benzothiophene and dibenzothiophene from thiophenes and 2,5-dimethoxy-THF using Lewis acid catalyst (Rafiq et al. 2014).

Organic reactions including cyclization reactions, condensation reactions, oxidation reaction, etc., have been used for the synthesis of organic molecules. Therefore,

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11696-018-0640-2) contains supplementary material, which is available to authorized users.

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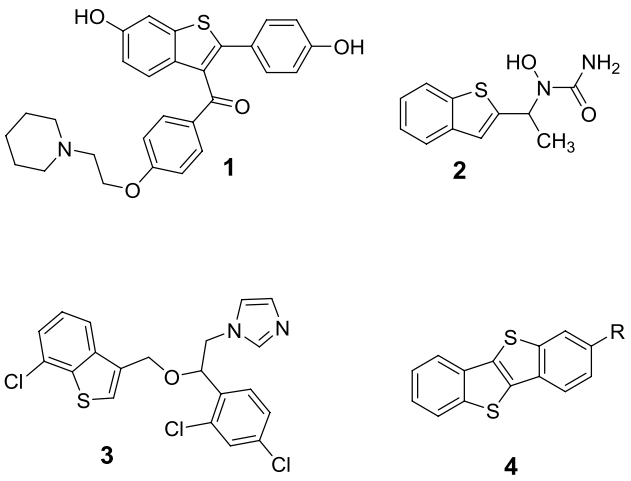
Published online: 19 November 2018



Scheme 1 The structures of Raloxifene **1**, Zileton **2**, Sertaconazole **3** and benzothieno-benzothiophene **4**

many scientists have been tried to find easy and effective methodologies for the formation of novel compounds. In the last decades, coupling reactions were mostly applied for the synthesis of organic molecules via a new carbon–carbon bond formation. One of the important coupling reactions is the palladium-catalyzed Sonogashira coupling reaction discovered in 1975. Sonogashira coupling reaction needs very easy reaction conditions such as, lower temperature, shorter reaction time and higher yields. Palladium-catalyzed Sonogashira coupling reaction needs a terminal alkyne and halo-substituted aromatics. Therefore, terminal alkynes are very important for the formation of a new C–C bond in designed molecules.

In the present study, a novel terminal alkyne-substituted benzothiophene was synthesized using electrophilic cyclization reactions and palladium-catalyzed coupling reaction. Then, our terminal alkyne was tested for Sonogashira coupling reaction using different halo-substituted aromatics, heteroaromatics and polyaromatics in the presence of Pd catalyst.

Experimental section

General information

All organic compounds were analyzed by ^{1}H and ^{13}C NMR. ^{1}H and ^{13}C NMR spectra which were recorded on an Agilent NMR (400 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from an internal TMS (trimethylsilane) reference. Coupling constants (*J*) are reported in hertz (Hz). In addition, spin multiplicities are presented by the following symbols: s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Flash chromatography was performed using thick-walled glass columns and 'flash grade' silica 60 (Merck 230–400 mesh). Commercially prepared 0.25 mm silica gel plates (Silica gel 60, F254) was used for thin layer chromatography (TLC) and visualization was affected by short wavelength UV lamp. Solvents, reagents, and chemicals used for reactions were purchased from commercial suppliers. All commercially available reagents were used directly without purification unless otherwise stated. The inert atmosphere was created by slight positive pressure (ca. 0.1 psi) of argon. All the glasswares were dried before using for reactions.

Synthesis of trimethyl((2-(methylthio)phenyl) ethynyl)silane (6)

To a stirred mixture of the 2-iodothioanisole **5** (2.5 mol, 620 mg), THF (8 mL), ethynyltrimethylsilane (3 mol, 303 mg), triethylamine (12.4 mol, 1.72 mL), $PdCl_2(PPh_3)_2$ (0.06 mol, 42.1 mg) was added CuI (0.06 mol, 11.4 mg) under Argon atmosphere. The resulting mixture was stirred at room temperature for 12 h. Then, the mixture was quenched with water (30 mL), then extracted with DCM (3 × 30 mL). The organic phase was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuum, and the residue was purified by column chromatography over silica gel with hexane to afford trimethyl((2-(methylthio)phenyl)ethynyl)silane (**6**) as a light yellow oil in an 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 7.43 (dd, *J* = 7.7, 1.5 Hz; 1H), 7.27 (td, *J* = 7.5, 1.5 Hz; 1H), 7.11 (d, *J* = 7.4 Hz; 1H), 7.05 (td, *J* = 7.5, 1.2 Hz; 1H), 2.46 (s, 3H), 0.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 132.7, 129.1, 124.1, 123.9, 121.1, 102.3, 101.4, 15.0, 0.13; IR (ATR) ν_{max} (cm^{-1}): 3060, 2981, 2921, 2891, 2155 (C ≡ C), 1436, 1248 (Si–CH_3), 838, 748, 685 (S–C). The spectral data were in agreement with those reported previously for this compound (Chen et al. 2014; Algso et al. 2018).

Synthesis of 1-ethynyl-2-(methylsulfanyl)benzene (7)

To a stirred mixture of **6** (500 mg, 2.27 mol), methanol (60 mL), and THF (20 mL) K_2CO_3 (939 mg, 6.81 mol) was added. The mixture was stirred at room temperature for 60 min. The reaction mixture extracted with EtOAc (3 × 15 mL). The organic extracts were dried over anhydrous $MgSO_4$ and filtered. The solvents was removed under vacuum, and the residue was purified by column chromatography over silica gel with hexane to afforded 1-ethynyl-2-(methylsulfanyl)benzene **(7)** as yellow oil in an 91% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 7.6, 1.5 Hz; 1H), 7.30 (td, *J* = 8.2, 1.4 Hz; 1H), 7.15 (d, *J* = 8.0 Hz; 1H), 7.08 (td, *J* = 8.5, 1.0 Hz; 1H), 3.5 (s, 1H, alkyne), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 133.1, 129.3, 124.2,

124.1, 120.1, 83.7, 81.0, 60.3; IR (ATR) ν_{max} (cm^{-1}): 3058, 2982, 3281 (≡ C–H), 2920, 2102 (C ≡ C), 1433, 748, 615 (S–C); HRMS calcd for C_9H_9S, 149.0425 $[M+H]^+$ found 149.0248 $[M+H]^+$. The spectral data were in agreement with those reported previously for this compound (Chen et al. 2014; Algso et al. 2018).

Synthesis of 2-((2-(methylthio) phenyl)ethynyl) thiophene 10

Method A: to a solution of 2-bromothiophene **9** (456.4 mg, 2.8 mol) in 1,4-dioxane (6 mL), CuI (32.4 mg, 0.17 mmol), $PdCl_2(PhCN)_2$ (65.2 mg, 0.17 mol) 1-ethynyl-2-(methylsulfanyl)benzene **7** (3.0 mol, 444 mg), diisopropylamine (1.38 g, 13.7 mol), and P(*t*-Bu)$_3$ (52.9 mg, 0.33 mol) were successively added at room temperature under argon. The mixture was stirred at room temperature for 12 h, and then extracted with DCM (3 × 20 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuum, and the residue was purified by column chromatography over silica gel with Hexane/EtOAc (10:1) to afford 2-((2-(methylthio) phenyl)ethynyl)thiophene (**10**) as orange oil in an **77**% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.7 Hz; 1H), 7.36–7.30 (m, 3H), 7.19 (d, *J* = 8,0 Hz; 1H), 7.13 (td, *J* = 8.0, 1.1 Hz; 1H), 7.04 (m, 1H), 2.53 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 132.3, 132.2, 129.1, 127.8, 127.3, 124.4, 124.3, 123.2, 121.1, 90.7, 89.2, 15.3; IR (ATR) ν_{max} (cm^{-1}): 3086, 2912, 2981, 2200 (C ≡ C), 1431, 753, 699 (S–C); HRMS calcd for $C_{13}H_{11}S_2$, 231.0302 $[M+H]^+$ found 231.0313 $[M+H]^+$. The spectral data were in agreement with those reported previously for this compound (Lu and Wu 2007; Algso et al. 2018).

Method B: to a mixture of 2-iodothiophene (707 mg, 3.37 mol), 1-ethynyl-2-(methylsulfanyl)benzene **7** (500 mg, 3.37), DMF (6 mL), $PdCl_2(PPh_3)_2$ (118 mg, 0.17 mol), and triethylamine (1.9 mL, 13.7 mol) at 0 °C under argon gas CuI (32.1 mg, 0.17 mmol) was successively added. The mixture was stirred at room temperature for 4 h. The mixture was extracted with ether (3 × 20 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuum, and the residue was purified by column chromatography over silica gel with Hexane/EtOAc (10:1) to afford compound **10** as orange oil in a 71% yield.

Synthesis of 3-iodo-2-(thiophen-2-yl)benzo[b] thiophene (11)

To a solution of 2-((2-(methylthio) phenyl)ethynyl) thiophene (**10**) (230 mg, 1 mol) in CH_2Cl_2 (10 mL) I_2 (762 mg, 3 mol) was added at room temperature. After stirring for 30 min, the saturated aqueous solution of $Na_2S_2O_3$ was added subsequently into the reaction mixture and extracted with EtOAc (3 × 20 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuum, and the residue was purified by column chromatography over silica gel with hexane/EtOAc (19:1) to afford 3-iodo-2-(thiophen-2-yl)benzo[b]thiophene **(11)** as light yellow solid in a 99% yield. 7.82 (d, *J* = 8.1 Hz; 1H), 7.75 (d, *J* = 9.1 Hz; 1H), 7.62 (dd, *J* = 4.0, 1.1 Hz; 1H), 7.48-7.44 (m, 2H), 7.39 (td, *J* = 8.0, 1.2 Hz; 1H), 7.17 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 138.1, 136.0, 135.9, 128.8, 127.5, 127.4, 126.4, 125.9, 125.8, 122.0, 79.5; IR (ATR) ν_{max} (cm^{-1}): 699, 815, 1419, 2912, 2981, 3086; HRMS calcd for $C_{12}H_7S_2$, 341.9034 $[M]^+$ found; 341.9059 $[M]^+$ (Algso et al. 2018).

Synthesis of trimethyl((2-(thiophen-2-yl)benzo[b] thiophen-3-yl)ethynyl)silane 12

To a stirred mixture of the 3-iodo-2-(thiophen-2-yl)benzo[*b*] thiophene **11** (0.7 mol, 239.5 mg), dimethylformamide (DMF) (7.5 mL), ethynyltrimethylsilane (0.75 mol), triethylamine (3.0 mL), $PdCl_2(PPh_3)_2$ (0.035 mol, 24.5 mg) under argon atmosphere CuI (0.035 mol, 6.6 mg) was added. The resulting mixture was stirred at room temperature for 12 h. Then, the reaction mixture was quenched with water (30 mL) and extracted with DCM (3 × 30 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuum, and the residue was purified by column chromatography over silica gel with Hexane/EtOAc (19/1) to afford trimethyl((2-(thiophen-2-yl) benzo[b]thiophen-3-yl)ethynyl)silane **12** in a 89% yield as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 10,0 Hz; 1H), 7.74 (d, *J* = 8.0 Hz; 1H), 7.68 (d, *J* = 4.0 Hz; 1H), 7.47-7.41 (m, 2H), 7.36 (td, *J* = 8.0, 0.9 Hz; 1H), 7.14-7.11 (m, 1H), 0.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 140.9, 136.8, 136.4, 127.4, 127.2, 127.0, 125.6, 125.3, 123.4, 122.0, 112.9, 104.1, 99.2, 0.13; IR (ATR) ν_{max} (cm^{-1}): 2958, 2148, 1438, 1247, 909, 839, 756, 696; HRMS calcd for $C_{17}H_{17}S_2Si$, 313.0541 $[M+H]^+$ found; 313.0537 $[M+H]^+$(Algso et al. 2018).

Synthesis of 3-ethynyl-2-(thiophen-2-yl)benzo[*b*] thiophene (13)

To a solution of trimethyl((2-(thiophen-2-yl)benzo[b]thiophen-3-yl)ethynyl)silane (**12**) (56 mg, 0.17 mol) in methanol (15 mL) and THF (5 mL) K_2CO_3 (74.3 mg, 0.53 mol) was added at room temperature for 1 h. When the starting compound was gone, solvents were removed under reduced pressure and the residue was extracted with DCM. The solvent was removed under vacuum, and the residue was purified by column chromatography over silica gel with Hexane/EtOAc (19/1) to afford 3-ethynyl-2-(thiophen-2-yl) benzo[b]thiophene (**13**) as a red oil in a 83% yield. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.91 (d, J=8.0 Hz; 1H), 7.77-7.70 (m, 2H), 7.48–7.34 (m, 3H), 7.16–7.10 (m, 1H), 3.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 140.1, 136.9, 136.0, 127.7, 127.4, 127.1, 125.7, 125.4, 123.2, 122.1, 111.8, 85.8, 78.3; IR (ATR) ν_{max} (cm^{-1}): 3286, 3101, 2922, 2851, 2095, 1940, 1791, 1438, 1189, 752, 690, 647, 584; HRMS calcd for $C_{14}H_9S_2$, 241.0146 $[M+H]^+$ found; 241.0139 $[M+H]^+$ (Algso et al. 2018).

General procedure of Sonogashira cross-coupling reaction between compound 13 and aryl iodide (14A–H)

To a stirred mixture of the terminal alkyne **13** (0.7 mol), dimethylformamide (DMF) (7.5 mL), aryl iodide compound (0.75 mol), triethylamine (3.0 mL), $PdCl_2(PPh_3)_2$ (0.035 mol) under argon atmosphere CuI was added (0.035 mmol). The resulting mixture was stirred at room temperature for 10 h. Then, the reaction mixture was quenched with water (30 mL) and extracted with EtOAc (3 × 30 mL). The organic layer was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuum, and the residue was purified by column chromatography over silica gel with Hexane–EtOAc.

Compound 14A

The terminal alkyne (**13**) 170 mg (0.7 mol), dimethylformamide (DMF) (7.5 mL), iodobenzene, 142.8 mg (0.75 mol), triethylamine (3.0 mL), $PdCl_2(PPh_3)_2$, 24.5 mg (0.035 mol), and CuI 7 mg (0.035 mmol) were employed to afford 68% yield as yellow-green solid of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J=7.4 Hz; 1H), 7.77 (d, J=8.0 Hz; 1H), 7.74–7.70 (m, 2H), 7.66 (d, J=3.7 Hz; 1H), 7.49–7.37 (m, 6H), 7.13–7.15 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8; 140.2, 137.0, 136.5, 131.8, 128.8, 128.7, 127.5, 127.2, 127.16, 125.7, 125.3, 123.5, 123.3, 122.2, 113.0, 97.9, 84.2; IR (ATR) ν_{max} (cm^{-1}): 3063, 2980, 2922, 2199, 1438, 1237, 746, 684; HRMS: calcd for $C_{20}H_{13}S_2$, 317.0419 $[M+H]^+$ found, 317.0457 $[M+H]^+$.

Compound 14B

The terminal alkyne (**13**), 170 mg (0.7 mol), dimethylformamide (DMF) (7.5 mL), 4-iodotoluene, 152.6 mg (0.75 mol), triethylamine (3.0 mL), $PdCl_2(PPh_3)_2$, 24.5 mg (0.035 mol), and CuI, 6.66 mg (0.035 mmol) were employed to afford 80% yield as yellow solid of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J=8.0 Hz; 1H), 7.76 (d, J=7.9 Hz; 1H), 7.66 (d, J=3.8 Hz; 1H), 7.60 (d, J=8.0 Hz; 2H), 7.48–7.36 (m, 3H), 7.24 (d, J=7.9 Hz; 2H), 7.15–7.12 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 139.8, 139.0, 137.0, 136.6, 131.7, 129.5, 127.4, 127.04, 127.01, 125.6, 125.2, 123.3, 122.1, 120.4, 113.1, 98.2, 83.6, 21.8; IR (ATR) ν_{max} (cm^{-1}): 3069, 2981, 2918, 1437, 807, 752; HRMS: calcd for $C_{21}H_{15}S_2$, 331.0615 $[M+H]^+$ found 331.0699 $[M+H]^+$.

Compound 14C

The terminal alkyne (**13**), 170 mg (0.7 mmol), dimethylformamide (DMF) (7.5 mL), 4-iodoaniline, 153 mg (0.75 mol), triethylamine (3.0 mL), $PdCl_2(PPh_3)_2$, 24.5 mg (0.035 mmol), and CuI, 7 mg (0.035 mmol) were employed to afford 55% yield as yellow solid of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 10.0 Hz; 1H), 7.76 (d, J = 9.6 Hz; 1H), 7.65 (dd, J=3.7 Hz, 1.12 Hz; 1H), 7.51 (d, J=8.7 Hz; 2H), 7.47–7.35 (m, 3H), 7.14–7.11 (m, 1H), 6.70 (d, J = 8.7 Hz; 2H), 3.9 (brs, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 140.9, 138.8, 136.9, 136.8, 133.2, 127.4, 126.8 (including 2C), 125.6, 125.2, 123.4, 122.1, 115.1, 113.6, 112.8, 98.9, 82.2; IR (ATR) ν_{max} (cm^{-1}): 3648, 3378.68, 2956, 2922, 2194, 1603, 1614, 1288, 1174, 906, 825, 729, 696; HRMS:calcd for $C_{20}H_{14}S_2$, 332.0568 $[M+H]^+$ found 332.0559 $[M+H]^+$.

Compound 14D

The terminal alkyne (**13**), 170 mg (0.7 mol), dimethylformamide (DMF) (7.5 mL), 2-iodothioanisole, 175 mg (0.75 mol), triethylamine (3.0 mL), $PdCl_2(PPh_3)_2$, 24.5 mg (0.035 mol), and CuI, 7 mg (0.035 mmol) were employed to afford 93% yield as yellow solid of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.0 Hz; 1H), 7.75 (d, J = 7.96 Hz; 1H) 7.72 (dd, J = 3.7 Hz, 1.08 Hz; 1H), 7.66 (dd, J = 7.7 Hz, 1.32 Hz;1H), 7.49–7.33 (m, 4H) 7.27–7.24 (m, 1H), 7.22–7.11 (m, 2H),2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 141.0, 136.9, 136.5, 132.64, 130.0, 129.2, 127.6, 127.3, 127.2, 125.7, 125.5, 124.6, 124.5, 123.8, 122.1, 121.7, 113.0, 95.1, 90.5, 15.52; IR (ATR) ν_{max} (cm^{-1}): 3054, 2919, 2197, 1433, 1069, 745, 691; HRMS: calcd for $C_{21}H_{15}S_3$, 363.0336 $[M+H]^+$ found 363.0335 $[M+H]^+$.

Compound 14E

The terminal alkyne (**13**), 170 mg (0.7 mol), dimethylformamide (DMF) (7.5 mL), 4-iodoanisole, 163 mg (0.75 mol), triethylamine (3.0 mL), $PdCl_2(PPh_3)_2$ (24.5 mg, 0.035 mol), and CuI 7 mg (0.035 mmol) were employed to afford 80% yield as yellow-green solid of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 10.2 Hz; 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.66–7.63 (m, 3H), 7.45–7.35 (m, 3H), 7.14–7.11 (m, 1H), 6.96 (d, J = 14.4 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 140.8, 139.4, 136.9, 136.7, 133.3, 127.4, 127.0, 126.9, 125.6, 125.2, 123.4,

122.9, 115.6, 114.4, 113.3, 98.1, 82.9, 55.6; IR (ATR) ν_{max} (cm^{-1}): 3099, 3050, 2970, 2836, 2537, 2199, 1603, 1455, 1299, 1248, 1169, 1022, 834, 753, 689; HRMS: calcd for $C_{21}H_{14}OS_2$, 346.0486 $[M]^+$, found 346.0488 $[M]^+$.

Compound 14F

The terminal alkyne (**13**), 168 mg (0.7 mol), dimethylformamide (DMF) (7.5 mL), 2-iodothiophene, 147 mg (0.75 mol), triethylamine (3.0 mL), $PdCl_2(PPh_3)_2$, 24.5 mg (0.035 mol), and CuI 7 mg (0.035 mol) were employed to afford 74% yield as yellow-green solid of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, $J = 10.0$ Hz, 1H), 7.7 (d, $J = 10.0$ Hz; 1H), 7.65–7.63 (d, $J = 3.8$, 1.2 Hz, 1H), 7.48–7.42 (m, 3H), 7.41–7.36 (m, 2H) 7.15–7.09 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 140.4, 136.9, 136.4, 132.4, 128.1, 127.53, 127.50, 127.3, 127.2, 125.7, 125.4, 123.5, 123.3, 122.2, 112.6, 91.2, 88.0; IR (ATR) ν_{max} (cm^{-1}): 3112, 2980, 2809, 2199, 1670, 1508, 755, 700; HRMS: calcd for $C_{18}H_{10}S_3$ $[M]^+$, 321.9945; found 321.9948 $[M]^+$.

Compound 14G

The terminal alkyne (**13**), 168.2 mg (0.7 mol), dimethylformamide (DMF) (7.5 mL), 5-iodofuran-2-carbaldehyde, 155 mg (0.75 mol), triethylamine (3.0 mL), $PdCl_2(PPh_3)_2$, 24.5 mg (0.035 mol), and CuI, 7 mg (0.035 mmol) were employed to afford 63% yield as orange solid of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.90 (d, $J = 6.08$ Hz; 1H), 7.75(d, $J = 0.76$ Hz, 1H), 7.63 (d, $J = 6.08$ Hz; 1H), 7.45–7.42 (m, 2H), 7.40–7.35 (m, 1H), 7.30 (d, $J = 3.8$ Hz, 1H), 7.13–7.10 (m,1H), 6.89 (d, $J = 3.7$ Hz; 1H); ^{13}C NMR (100 MH, $CDCl_3$) δ 177.5, 152.8, 142.8, 142.1, 140.2, 136.8, 135.8, 127.83, 127.80, 127.78, 127.77, 126.0, 125.6, 123.1, 122.2, 117.7, 110.7, 91.5, 86.4; IR (ATR) ν_{max} (cm^{-1}): 359, 3113, 2981, 2808, 2199, 1670, 1506, 1386, 966, 761, 700; HRMS: calcd for $C_{19}H_{10}O_2S_2$ $[M]^+$, 334.0122; found 334.0167 $[M]^+$.

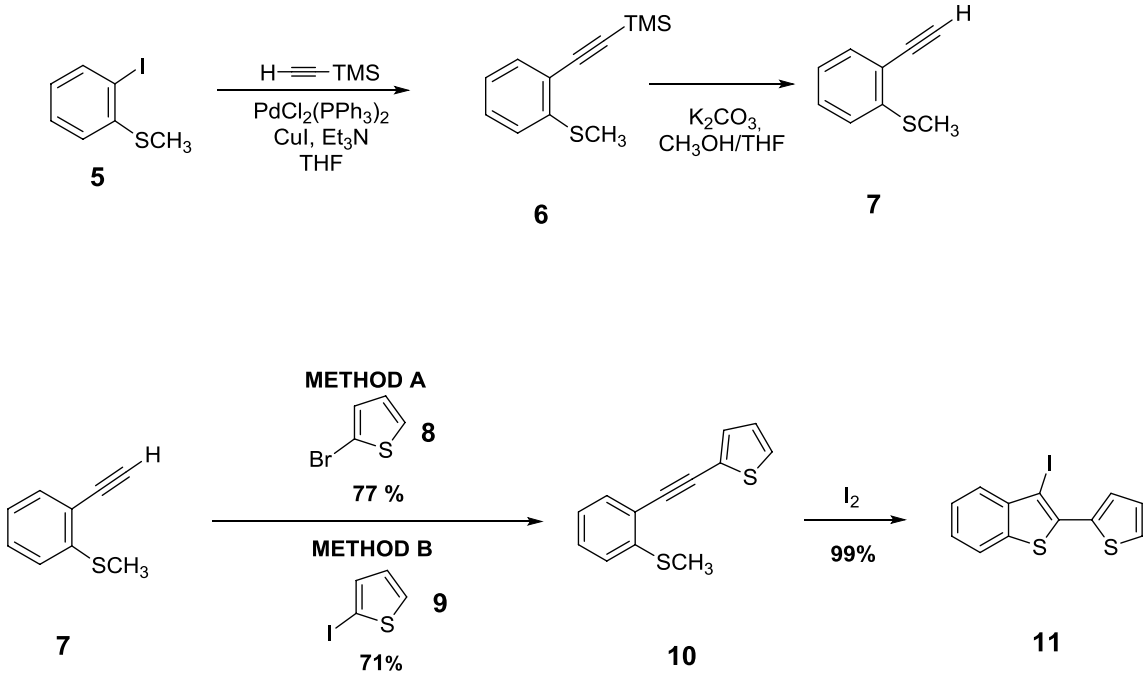
Compound 15

The terminal alkyne (**13**), 168.2 mg (0.7 mol), dimethylformamide (DMF) (7.5 mL), 3-iodo-2-(thiophen-2-yl) benzo[*b*]thiophene (**11**), 239.55 mg (0.75 mol), triethylamine (3.0 mL), $PdCl_2(PPh_3)_2$, 24.5 mg (0.035 mol), and CuI, 6.66 mg (0.035 mmol) were employed to afford 34% yield as yellow-green solid of the indicated product **15**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, $J = 7.4$ Hz, 2H), 7.78 (d, $J = 8$ Hz; 2H), 7.73 (dd, $J = 4.0$ Hz, 1.16 Hz; 2H), 7.50–7.45 (m, 4H), 7.40 (td, $J = 8.04$ Hz, 1.24 Hz; 2H), 7.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 140.9, 137.3, 136.2, 127.8, 127.7, 127.5, 126.0, 125.7, 123.44, 123.4, 122.3, 82.6, 78.9; IR (ATR) ν_{max} (cm^{-1}): 3063, 2980, 2922, 2136, 1437, 1061, 748, 685; HRMS:calcd for $C_{28}H_{14}S_4$, 477.9978; found 477.9971.

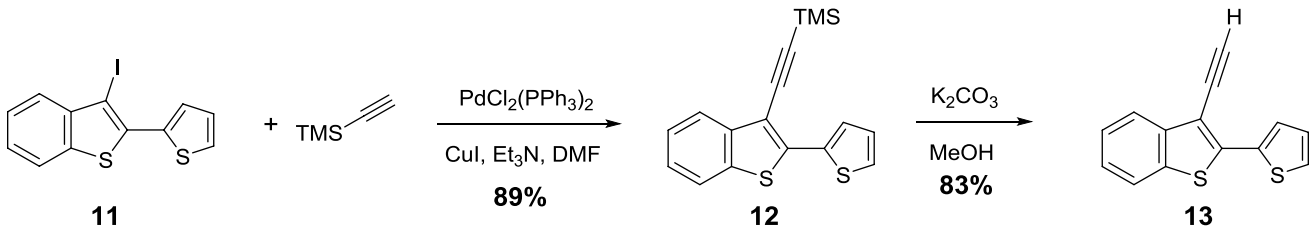
Results and discussion

First, 2-iodothioanisole **5** was allowed to react with trimethylsilylacetylene for the preparation of 2-ethynyltrimethylsilane **6** via palladium-catalyzed Sonogashira coupling reaction. The standard Sonogashira coupling condition was applied for the synthesis of **6** $Pd(PPh_3)_2Cl_2$ which was used as a catalyst in the presence of CuI under basic (Et_3N) reaction medium. After isolation of compound **6**, 2-ethynylthioanisole **7** was obtained from the desilylation reaction of 2-ethynyltrimethylsilane **6** with potassium carbonate in methanol. When compound **7** was allowed to undergo coupling reaction with 2-bromothiophene in the presence of $PdCl_2(PhCN)_2$, CuI, $(t\text{-}Bu)_3P$ in Dioxane at room temperature for 12 h, desired compound **10** was isolated in **77%** yield. Fascinatingly, 2-iodothiophene was used for the synthesis of **10** in the presence of Pd catalyst at room temperature, only the self-coupling reaction of terminal alkyne was formed. If the temperature was decreased to 0 °C, desired compound **10** was obtained in **72%** yield (Scheme 2). In the last decades, electrophilic cyclization reactions have gained big importance for the synthesis of novel five- or six-membered heterocyclic compounds (Kumar et al. 2017; Yaragorla et al. 2017; Miao et al. 2017) such as indoles, benzothiophenes, and benzofurans. Recently, Zora et al. investigated a novel methodology for the synthesis of iodo-substituted pyrazoles via electrophilic cyclization under mild reaction conditions (Zora et al. 2011). For electrophilic cyclization reactions, moleculer iodine, monoiodochloride (ICl) and PhSeCl were used as electrophiles in a variety of organic solvents (Togo and Iida 2006; Yue and Larock 2004). Previous studies displayed that CH_2Cl_2 (DCM) and chloroform were among the most employed solvents for those kinds of cyclizations. Mild and nontoxic moleculer iodine was mostly used as electrophile which catalyzed various organic reactions with high efficiency and selectivity. In the light of the knowledge, when **10** was reacted with molecular iodine in DCM for 2 h at RT, a expected product 3-iodo-2-(thiophen-2-yl)benzo[*b*]thiophene (**11**) was obtained in good yield (99%) (Scheme 2).

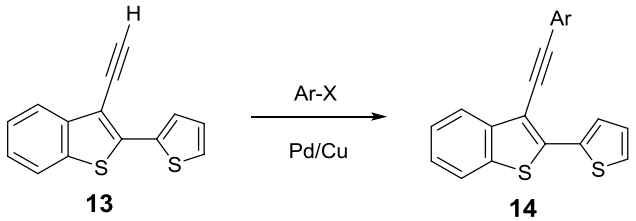
For the synthesis of our designed terminal alkyne **13**, intermediate **11** was allowed to react with ethynyltrimethylsilane for the formation of compound **12** which isolated in 89% yields via Sonogashira coupling reaction. Then, protecting TMS groups were removed using desilyation reaction with potassium carbonate in methanol to give the new benzothiophene-substituted terminal alkyne **13** (Scheme 3).



Scheme 2 Synthesis of 3-iodo-2-(thiophen-2-yl)benzo[*b*]thiophene (**11**)



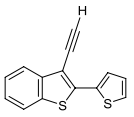
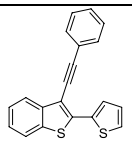
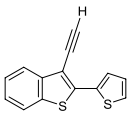
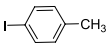
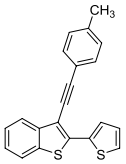
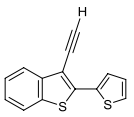
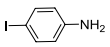
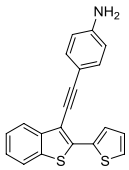
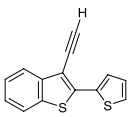
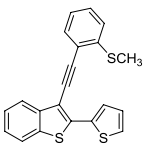
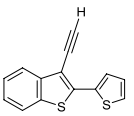
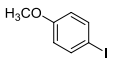
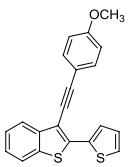
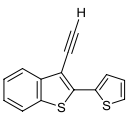
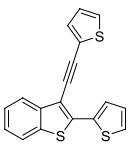
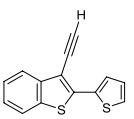
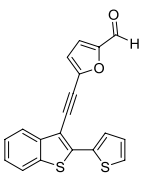
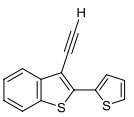
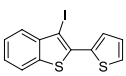
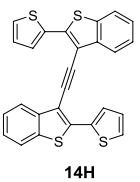
Scheme 3 Synthesis of terminal alkyne **13**



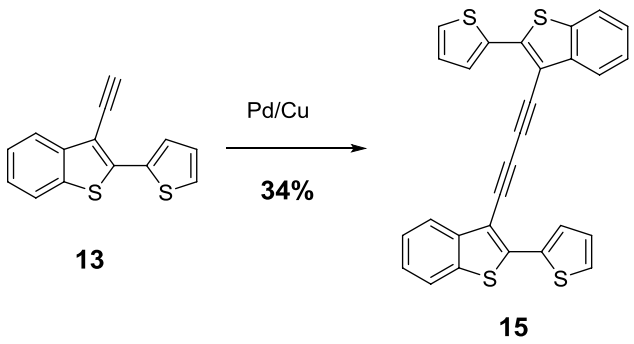
Scheme 4 Coupling reaction between terminal alkyne **13** and iodoaryl derivatives

After isolation and characterization of our terminal alkyne precursor **13**, the coupling properties were investigated using Sonogashira reaction in the presence of Pd catalyst (Scheme 4). As seen in Table 1, a variety of 3-alkynylic benzothiophene derivatives (**14 A–H**) were synthesized from coupling reaction. When **13** was allowed to react with iodobenzene in the presence of $Pd(PPh_2)_2Cl_2$ and CuI in DMF/Et_3N at RT, **14A** was obtained in 68% yield (Table 1). If the same reaction condition was applied for the synthesis of **14B**, the isolated yield was found as 79% yield. When the effect of heteroaromatic compounds were tested using 2-iodothiophene and 2-iodofuran, the 74% yield of **14F** and 63% yield of **14G** was found, respectively. Notably, **12C** was obtained in moderate yield (55%). Interestingly, the reaction between 2-thioanisole and terminal alkyne **13** gave the highest yield as 93% yield. It was also tested for coupling reaction for poly-heteroaromatic compounds like compound **11**, dibenzothiophene-substituted alkyne (Table 1, Entry 8) was not obtained. When our standard reaction condition was used for the formation of compound 14H, we obtained only self-coupling product **15** in 34% yield (Scheme 5). As a result, Sonogashira cross-coupling reaction was found to be general for a wide range of our terminal alkyne **13** and tolerated the presence of aromatic, poly-aromatic and heteroaromatic

Table 1 Synthesized alkyne derivative **14** via Sonogashira coupling reaction

Entry	Terminal Alkyne	Aryl iodide	Product	yield, %
1	 **13**		 **14A**	68
2	 **13**		 **14B**	80
3	 **13**		 **14C**	55
4	 **13**		 **14D**	93
5	 **13**		 **14E**	80
6	 **13**		 **14 F**	74
7	 **13**		 **14G**	63
8[a]	 **13**		 **14H**	0

[a]Only the self-coupling product was isolated after Sonogashira reaction



Scheme 5 Self-coupling product **15**

moieties with electron-withdrawing and electron-donating substituents (Table 1).

Conclusions

Pd-catalyzed coupling reactions have been used for the synthesis of important organic molecules via a new C–C bond formation. Sonogashira cross-coupling reaction also plays a critical role in the synthesis of alkynyl-substituted organic molecules. Terminal alkynes have a very critical role in Sonogashira coupling reaction, so the design of new terminal alkyne could be very important for Sonogashira coupling reaction. In this work, we have investigated a user-friendly methodology for the synthesis of novel alkynyl-substituted benzothiophene derivatives using Pd-catalyzed Sonogashira coupling reaction under mild reaction conditions. In the first part of study, a novel alkyne **13** was synthesized and characterized. Then, it was tested for coupling reactions with a variety of aryl iodide derivatives including aromatics, heteroaromatics and polyaromatics. As a result, it was found that our terminal alkyne **13** might be a useful precursor for the synthesis of potentially active novel organic molecules via coupling reactions in future studies.

Acknowledgements The authors thank The Scientific and Technological Research Council of Turkey (Project no: 115Z020) for providing financial support for obtaining reactant and reagents, and Van Yüzüncü Yil University (Project no: FBA-2017-6007) for providing financial support for obtaining solvents, glasswares and salts. We thank University of Duhok for the scholarship given to Muheb A.S. Algso. The authors would also like to acknowledge networking contribution by the COST Action CM1407.

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