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Advanced Synthesis & Catalysis

Multicomponent Synthesis of Benzothiophen-2-acetic Esters by a Palladium Iodide Catalyzed *S*-cyclization – Alkoxycarbonylation Sequence

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Abstract: A catalytic carbonylative approach to the multicomponent synthesis of benzothiophene derivatives from simple building blocks [1-(2-(methylthio)phenyl)prop-2-yn-1-ols, carbon monoxide, and an alcohol)] is presented. It is based on an *S*-cyclization-demethylation-alkoxycarbonylation-reduction sequence promoted by the PdI_2/KI catalytic system, occurring under relatively mild conditions (40 atm, 80 °C, 15 h). Benzothiophene-2-acetic esters are obtained in moderate to good yields (35–70%) starting from variously substituted substrates in combination with different alcohols as external nucleophiles (17 examples).

Keywords: benzothiophenes; carbonylation; *S*-cyclization; multicomponent reaction; palladium

Introduction

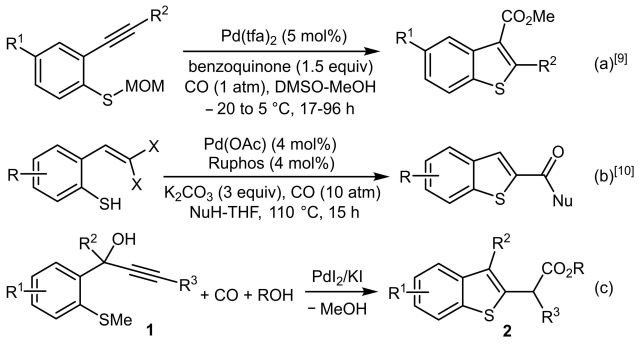
Benzothiophenes are among the most important heterocyclic derivatives. The benzothiophene nucleus is present in many natural products and pharmaceuticals. These molecules have shown important bioactivities, including anti-cancer, antifungal, anti-diabetic, estrogen receptor modulation, and leukotriene synthesis inhibition activities.[1] Benzothiophene derivatives are also very useful substrates in organic synthesis. In fact, they can be employed for the preparation of new compounds that find application in the pharmaceutical field as well as in materials science.[2] Accordingly, the development of novel strategies for the synthesis of benzothiophenes (based, in particular, on catalytic reactions) is of particular importance and interest.[3]

Catalytic processes are known to convert simple and readily available starting materials into high value added functionalized molecules, including heterocycles. In this contest, metal-catalyzed carbonylative heterocyclization processes have been playing a major role. With these reactions it is possible to simultaneously activate the organic substrate and carbon monoxide to give the final carbonylated derivative in one step.[4]

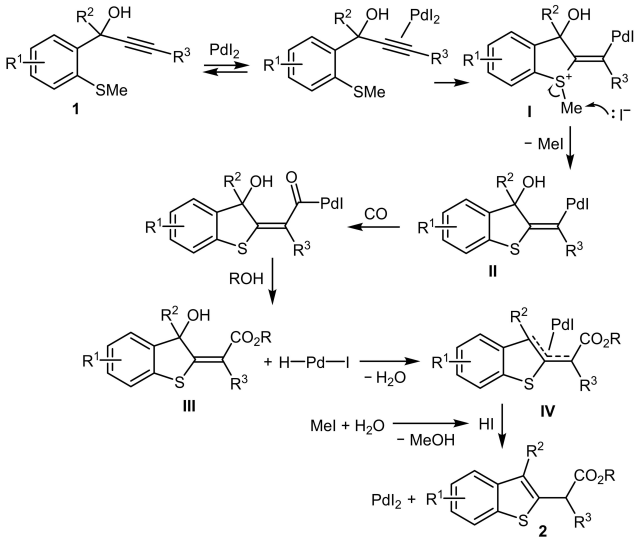
Compared to the huge number of examples of carbonylative *O*- and *N*-heterocyclizations known so far,[5,6] carbonylative *S*-heterocyclizations have been reported in a limited number of cases.[4] This is mainly due to the well-known "poisoning" effect that the sulfur atom may exert on the metal catalyst.[7] In addition, sulfur-containing substrates can be unstable when the reaction is carried out in the presence of an external oxidant (as in oxidative carbonylations).[8] Nevertheless, some important carbonylative *S*-cyclization processes have been reported in the literature. These include: the synthesis of benzothiophene-3-carboxylic esters from MOM-protected 2-alkynylthio-

phenols (Scheme 1a);[9] the preparation of benzothiophene-2-carboxylic derivatives from 2-(2,2-dihalovinyl)thiophenols (Scheme 1b);[10] and the synthesis of thiophene-3-carboxylic esters from 1-(methylthio)-3-yn-2-ols.[8]

To the best of our knowledge, no approach has been reported to date for the direct carbonylative synthesis of benzothiophene-2-acetic esters from an acyclic precursor,[11] in spite of the importance of these derivatives.[12] In this work, we wish to fill this gap, by reporting the palladium iodide-catalyzed synthesis of alkyl benzothiophene-2-acetates **2** starting from 1-(2-(methylthio)phenyl)prop-2-yn-1-ols **1**, CO, and an alcohol (Scheme 1c).



Scheme 1. (a, b) Previuosly reported[9,10] carbonylative *S*-cyclization reactions to benzothiophene derivatives and (c) *This work:* Synthesis of benzothiophene-2-acetic esters **2** by palladium iodide-catalyzed carbonylative *S*-cyclization of 1-(2-(methylthio)phenyl)prop-2-yn-1-ols **1**.



Scheme 2. Mechanistic hypothesis for the formation of benzothiophene-2-acetic esters **2** by PdI_2/KI-catalyzed carbonylation of 1-(2-(methylthio)phenyl)prop-2-yn-1-ols **1**.

Results and Discussion

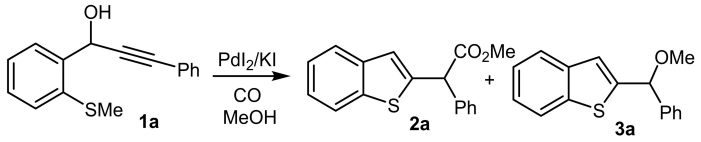
Our work hypothesis for the carbonylative synthesis of benzothiophene-2-acetates **2** from 1-(2-(methylthio)-phenyl)prop-2-yn-1-ols **1** (Scheme 1c) was based on the use of the catalytic system PdI_2/KI. This catalyst has been successfully employed by our group for promoting a variety of carbonylative heterocyclizations.[4]

As shown in Scheme 2, in the present case, an initial *S*-cyclization would lead to sulfonium intermediate **I**. *S*-demethylation by the iodide anion would give complex **II** together with methyl iodide. Alkoxycarbonylation of **II** then affords 2-(3-hydroxybenzo[*b*]thiophen-2(3*H*)-ylidene)acetate intermediate **III** and a palladium hydride species (H–Pd–I). The allylalcoholic moiety of **III** undergoes reduction by H–Pd–I to give π-allylpalladium complex **IV** with elimination of water.[13] Protonolysis of **IV** by HI eventually affords the desired product **2**. HI is formed by the reaction of MeI (previously obtained by iodide attack to **I**) with water (Scheme 2; anionic iodide ligands are omitted for clarity).

To assess our work hypothesis, we synthesized 1-(2-(methylthio)phenyl)-3-phenylprop-2-yn-1-ol **1a** ($R^1 = R^2 = H$, $R^3 = Ph$) by alkynylation of 2-(methylthio)benzaldehyde, and used it as model substrate to optimize reaction conditions.

The first experiment was carried out in MeOH as the solvent (**1a** concentration, 0.10 mmol per mL of MeOH), at 100 °C for 15 h, under 30 atm of CO, and in the presence of PdI_2 (10 mol%) and an excess of KI (2 equiv., to promote sulfur demethylation). However, under these conditions, mainly substrate decomposition was observed, and the desired product, methyl 2-(benzo[*b*]thiophen-2-yl)-2-phenylacetate **2a**, was formed only in traces (Table 1, entry 1). A detectable yield of **2a** (8%) could be observed when using a larger excess of KI (3 equiv.) (Table 1, entry 2). The yield improved to 26% with 15 equiv. of KI (Table 1, entry 3) and to 40% with 30 equiv. of KI (Table 1, entry 4). Under the last conditions, small amounts of 2-(methoxy(phenyl)methyl)benzo[*b*]thiophene **3a**,[14] deriving from annulative methoxylation without CO incorporation, were also detected (2% and 5%, respectively). With 30 equiv. of KI, the yield of **2a** dropped to ca. 25% when the process was performed under more concentrated or diluted conditions (Table 1, entries 5 and 6, respectively). On the other hand, the **2a** yield increased to 50–55% when performing the process under higher CO pressures (Table 1, entries 7 and 8) or at a lower temperature (Table 1, entry 9). The final optimized conditions therefore corresponded to an **1a** concentration = 0.10 mmol/mL of MeOH, at 80 °C for 15 h under 40 atm of CO and in the presence of 10 mol% PdI_2 and 30 equiv. of KI. Under these conditions, **2a** was isolated with an acceptable yield of

Table 1. PdI_2/KI-catalyzed carbonylation of 1-(2-(methylthio)phenyl)-3-phenylprop-2-yn-1-ol **1a** under different conditions.[a]



Entry	KI/**1a**/PdI_2 molar ratio	*T* [°C]	Substrate concentration[b]	P_{CO} [atm]	Substrate conversion[c]	Yield of **2a** [%][d]	Yield of **3a** [%][d]
1	20:10:1	100	0.10	30	30	traces	0
2	50:10:1	100	0.10	30	42	8	0
3	150:10:1	100	0.10	30	75	26	2
4	300:10:1	100	0.10	30	91	40	5
5	300:10:1	100	0.22	30	91	25	1
6	300:10:1	100	0.05	30	90	24	4
7	300:10:1	100	0.10	40	92	50	4
8	300:10:1	100	0.10	60	98	52	5
9	300:10:1	80	0.10	30	92	55	traces
10	300:10:1	80	0.10	40	100	70	0
11	300:20:1	80	0.10	40	41	23	0
12[e]	300:10:1	80	0.10	40	100	0	0

[a] Unless otherwise noted, all reactions were carried out in MeOH as the solvent for 15 h.
[b] Mmol of **1a** per mL of MeOH.
[c] Determined by isolation of unreacted **1a** from the reaction mixture.
[d] Isolated yield based on starting **1a**.
[e] The reaction was carried out with $PdCl_2$ and KCl in place of PdI_2 and KI, and led to the formation of (2-(1-methoxy-3-phenylprop-2-yn-1-yl)phenyl)(methyl)sulfane **4a** in 54% isolated yield.

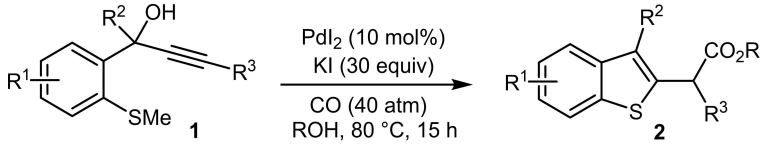
70%, with formation of traces of byproduct **3a** (Table 1, entry 10). With a lower catalyst loading (5 mol%), the process was significantly less efficient, as shown in Table 1, entry 11. Interestingly, the use of $PdCl_2$/KCl in place of PdI_2/KI did not lead to the formation of **2a**, and the substrate was converted into its methyl ether **4a** in 54% yield, (Table 1, entry 12). This latter result clearly shows the importance of the iodide anions for the success of the carbonylative process leading to **2a**, according to the mechanistic hypothesis shown in Scheme 2.

To verify the generality of the process, we then applied the optimized conditions to differently substituted substrates; the results obtained are shown in Table 2. The presence of an electron-donating group at the *para* position of the phenyl group bonded to the triple bond (Me, *t*-Bu, or OMe) led to the corresponding methyl benzothiophene-2-acetic esters **2b–d** in 66–68% yields (Table 2, entries 2–4). A halogen atom such as bromine or chlorine on the phenyl substituent was compatible as well, the corresponding benzothiophene derivatives being formed in 64–65% yields (Table 2, entries 5–7). The reaction of substrates **1h–j**, bearing a methyl or methoxy substituent on the aromatic ring in different positions with respect to the methylthio group, was also successful (Table 2, entries 8–10).

The yields tended to be lower when the substrate presented a tertiary rather than secondary alcoholic group. This is exemplified by the reaction of 2-(2-(methylthio)phenyl)-4-phenylbut-3-yn-2-ol **1k** (R^1 = H, R^2 = Me, R^3 = Ph), which was converted into a mixture of methyl 2-(3-methylbenzo[*b*]thiophen-2-yl)-2-phenylacetate **2k** and 2-(methoxy(phenyl)methyl)-3-methylbenzo[*b*]thiophene **3k**[14] (45% and 18% yields, respectively; Table 2, entry 11). This is likely due to the steric effect exerted by the R^2 substituent, which tends to make less efficient the CO insertion into intermediate **II** (see Scheme 2). With 1-(2-(methylthio)phenyl)-1,3-diphenylprop-2-yn-1-ol **1l** (R^1 = H, R^2 = R^3 = Ph), the yield of the corresponding methyl benzothiophene-2-acetate **2l** was 50% (Table 2, entry 12). Unfortunately, when the triple bond was substituted with an alkyl group, such as butyl (substrate **1m**), the product yield was modest (yield of **2m**, 35%; Table 2, entry 13). On the other hand, a heteroaromatic ring, such as 3-thienyl (substrate **1n**), led to a good yield of the corresponding product **2n** (68%; Table 2, entry 14).

The reaction also worked nicely when a higher alcohol was employed as solvent and external nucleophile. The results obtained with **1a** in EtOH, PrOH, and *i*-PrOH are shown in Table 2, entries 15-17. With these alcohols, the substrate conversion rate was slower with respect to MeOH, so the reaction time was increased to 24 h. As can be seen from entries 15–17, the product yield depended on the nucleophilicy of the alcohol, the lowest yield (51%) being obtained with

Table 2. Synthesis of benzothiophene-2-acetic esters **2** by PdI_2/KI-catalyzed carbonylation of 1-(2-(methylthio)phenyl)prop-2-yn-1-ols **1**.[a]



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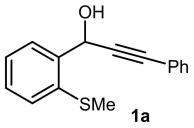
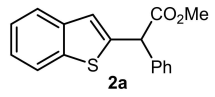
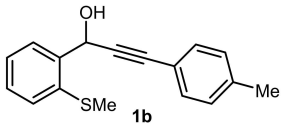
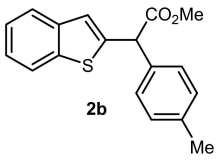
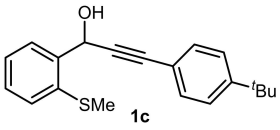
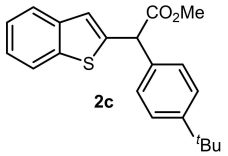
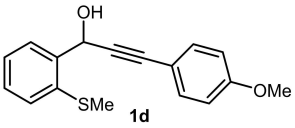
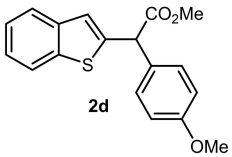
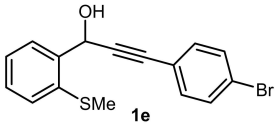
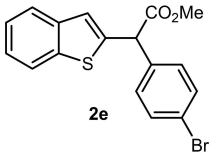
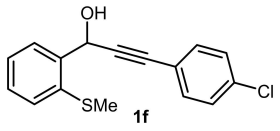
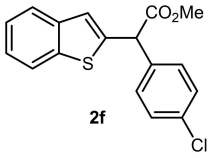
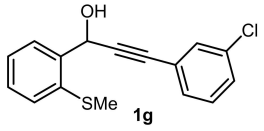
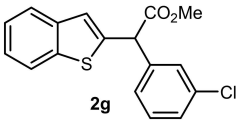
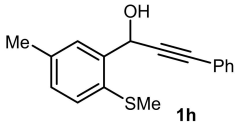
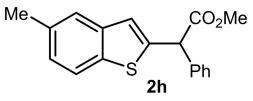
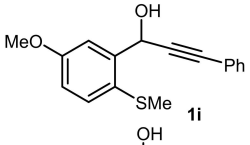
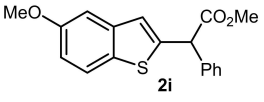
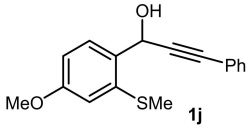
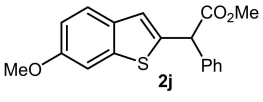
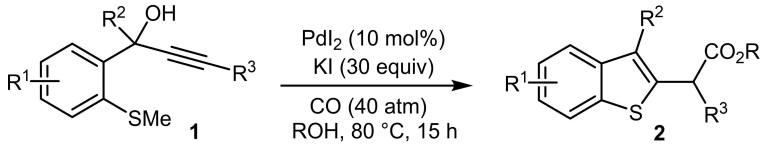
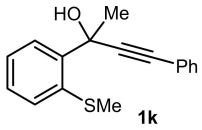
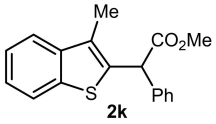
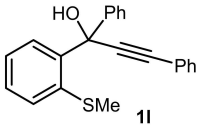
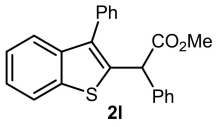
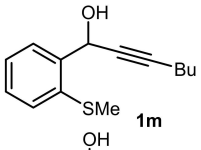
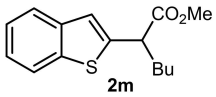
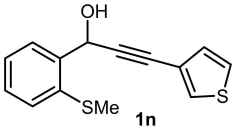
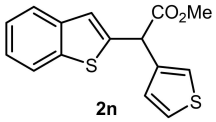
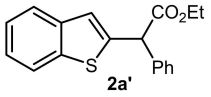
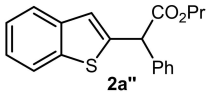
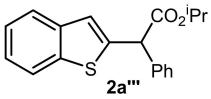
1		MeOH		70
2		MeOH		68
3		MeOH		67
4		MeOH		66
5		MeOH		65
6		MeOH		65
7		MeOH		64
8		MeOH		64
9		MeOH		66
10		MeOH		65

Table 2. continued



Entry	1	ROH	2	Yield of 2 [%][b]
11[c]		MeOH		45
12		MeOH		50
13		MeOH		35
14		MeOH		68
15[d]	1a	EtOH		66
16[d]	1a	PrOH		61
17[d]	1a	*i*-PrOH		51

[a] Unless otherwise noted, all reactions were carried out in ROH as the solvent (0.10 mmol of **1** per mL of ROH) at 80 °C for 15 h under 40 atm of CO, in the presence of PdI_2 (10 mol%) and KI (30 equiv.). Substrate conversion was quantitative in all cases.
[b] Isolated yield based on starting **1**.
[c] The reaction also led to the formation of 2-(methoxy(phenyl)methyl)-3-methylbenzo[*b*]thiophene **3 k** (18%).
[d] The reaction was carried out for 24 h.

the most sterically hindered isopropanol (Table 2, entry 17).[15]

Conclusion

In conclusion, we have reported a carbonylative approach to the synthesis of benzothiophene-2-acetic esters starting from readily available 1-(2-(methylthio) phenyl)prop-2-yn-1-ols, under the catalysis of palladium iodide in the presence of an excess of potassium iodide.

The catalytic process takes place through an ordered sequence of steps, involving *S*-cyclization (by intramolecular nucleophilic attack by the thiomethyl group to the triple bond coordinated to the Pd(II) center) followed by iodide-promoted demethylation and alkoxycarbonylation. This leads to a 2-(3-hydroxybenzo[*b*]thiophen-2(3*H*)-ylidene)acetate intermediate and an H–Pd–I complex. The formation of a π-allylpalladium complex then takes place, from which the final product is formed by protonolysis.

Our method therefore represents a direct carbonylative approach to benzothiophene-2-acetic esters (an important class of heterocycles, with several applications) from acyclic precursors.

Experimental Section

General Experimental Methods

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ at 300 MHz or 500 MHz and 75 MHz or 125 MHz, respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. IR spectra were taken with an FT-IR spectrometer. Mass spectra were obtained using a GC-MS apparatus at 70 eV ionization voltage (normal resolution) and by electrospray ionization mass spectrometry (ESI-MS) (high resolution) with a UHD accurate-mass Q-TOF spectrometer equipped with a Dual AJS ESI source working in positive mode or negative mode, and were recorded in the 150–1000 *m/z* range. The flow-rate was 0.4 mL/min and the column temperature was set to 30 °C. The eluents were formic acid-water (0.1:99.9, v/v) (phase A) and formic acid–acetonitrile (0.1:99.9, v/v) (phase B). The following gradient was employed: 0–10 min, linear gradient from 5% to 95% B; 10–15 min, washing and reconditioning of the column to 5% B. Injection volume was 10 µL. The eluate was monitored through MS TIC. The LC–MS experimental conditions were as follows: N_2 was employed as desolvation gas at 300 °C and a flow rate of 9 L/min. The nebulizer was set to 45 psig. The Sheat gas temperature was set at 350 °C and a flow of 12 L/min. A potential of 3.5 kV was used on the capillary for positive ion mode or 2.6 kV for negative ion mode. The fragmentor was set to 175 V. All reactions were analyzed by TLC on silica gel 60 F_{254} and by GLC-MS using a gas chromatograph and capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase. Column chromatography was performed on silica gel 60 (70–230 mesh). Evaporation refers to the removal of solvent under reduced pressure.

Preparation of Substrates 1

1-(2-(Methylthio)phenyl)prop-2-yn-1-ols **1a–n** were prepared by alkynylation of 2-(methylthio)benzaldehydes, 1-(2-(methylthio)phenyl)ethan-1-one, and (2-(methylthio)phenyl)(phenyl) methanone, as described in the Supporting Information.

General Procedure for the Synthesis of Benzothiophen-2-Acetic Esters 2

A 50 mL stainless-steel autoclave was charged in the presence of air with PdI_2 (11.0 mg, 0.031 mmol), KI (1.54 g, 9.3 mmol), and substrate **1** (0.31 mmol; **1a**, 79.0 mg; **1b**, 83.0 mg; **1c**, 96.5 mg; **1d**, 88.0 mg; **1e**, 103.5 mg; **1f**, 90.0 mg; **1g**, 89.5 mg; **1h**, 83.0 mg; **1i**, 88.5 mg; **1j**, 88.0 mg; **1k**, 83.5 mg; **1l**, 103.0 mg; **1m**, 73.0 mg; **1n**, 81.0 mg) in ROH (3.1 mL). The autoclave was sealed, purged at room temperature several times with CO with stirring (5 atm), and finally pressurized with CO (40 atm). After being stirred at 80 °C for 15 h (ROH = MeOH) or 24 h (ROH = EtOH, PrOH, *i*-PrOH), the autoclave was cooled, degassed and opened. The solvent was evaporated and the products **2a–n** were purified by column chromatography on silica gel using as eluent 99:1 hexane-AcOEt.

Synthesis of Methyl 2-(Benzo[*b*]Thiophen-2-yl)-2-Phenylacetate 2a in Larger Scale

A 50 mL stainless-steel autoclave was charged in the presence of air with PdI_2 (42.5 mg, 0.118 mmol), KI (5.9 g, 35.4 mmol), and 1-(2-(methylthio)phenyl)-3-phenylprop-2-yn-1-ol **1a** (300 mg, 1.18 mmol;) in MeOH (11.8 mL). The autoclave was sealed, purged at room temperature several times with CO with stirring (5 atm), and finally pressurized with CO (40 atm). After being stirred at 80 °C for 15 h, the autoclave was cooled, degassed and opened. The solvent was evaporated and the products were purified by column chromatography on silica gel using as eluent 99:1 hexane-AcOEt (Yield: 230 mg, 69% based on starting **1a**).

Methyl 2-(benzo[*b*]thiophen-2-yl)-2-phenylacetate (2a): Yield: 61.4 mg, starting from 79.0 mg of **1a** (70%) (Table 2, entry 1). Yellow solid, mp = 73–74 °C. IR (KBr): *v* = 1736 (s), 1458 (w), 1435 (m), 1296 (w), 1204 (m), 1157 (m), 1011 (w), 995 (w), 748 (m), 725 (w), 702 (w); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.76–7.72 (m, 1H, aromatic), 7.70–7.67 (m, 1H, aromatic), 7.45–7.25 (m, 2H, aromatic), 7.38–7.33 (m, 2H, aromatic), 7.33–7.24 (m, 3H, aromatic), 7.21 (s, 1H at C-3), 5.27 (s, 1H, C*H*CO_2Me), 3.78 (s, 3H, CO_2Me); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.7, 141.9, 139.9, 139.4, 137.7, 128.8, 128.4, 128.0, 124.3, 124.2, 123.5, 123.0, 122.1, 52.9; GC-MS (EI, 70 eV): *m/z* = 282 (M^+, 25), 223 (100), 221 (31), 178 (12); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $[C_{17}H_{14}NaO_2S]^+$: 305.0607, found: 305.0621.

Ethyl 2-(benzo[*b*]thiophen-2-yl)-2-phenylacetate (2a′): Yield: 61.0 mg, starting from 79.1 mg of **1a** (66%) (Table 2, entry 15). Yellow solid, mp = 59–60 °C. IR (KBr): *v* = 1736 (s), 1458 (w), 1435 (w), 1296 (w), 1150 (m), 1026 (m), 748 (w), 725 (w), 702 (w); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.77–7.73 (m, 1H, aromatic), 7.71–7.67 (m, 1H, aromatic), 7.46–7.42 (m, 2H, aromatic), 7.38–7.24 (m, 5H, aromatic), 7.22 (s, 1H at C-3), 5.25 (s, 1H, C*H*CO_2Et), 4.30–4.19 (m, 2H, C$H_2$$CH_3$), 1.28 (t, *J* = 7.1, 3H, Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.2, 142.1, 139.9, 139.4, 137.9, 128.8, 128.3, 127.8, 124.24, 124.17, 123.4, 122.9, 122.1, 61.7, 53.1, 14.1; GC-MS (EI, 70 eV): *m/z* = 296 (M^+, 22), 223 (100), 221 (27), 178 (13); HRMS (ESI-TOF) *m/z*: $[M-H]^-$ calcd for $[C_{18}H_{15}O_2S]^-$: 295.0798, found: 295.0796.

Propyl 2-(benzo[*b*]thiophen-2-yl)-2-phenylacetate (2a''): Yield: 59.0 mg, starting from 79.0 mg of **1a** (61%) (Table 2, entry 16). Yellow solid, mp = 72–74 °C. IR (KBr): *v* = 1736 (s), 1596 (w), 1574 (w), 1458 (w), 1435 (m), 1319 (w), 1296 (w), 1204 (m), 1157 (s), 1011 (m), 748 (m), 725 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.77–7.72 (m, 1 H, aromatic), 7.70–7.66 (m, 1 H, aromatic), 7.46–7.41 (m, 2H, aromatic), 7.37–7.23 (m, 5H, aromatic), 7.22 (s, 1H at C-3), 5.26 (s, 1H, C*H*CO_2Pr), 4.18–4.09 (m, 2 H, C$H_2$$CH_2$$CH_3$), 1.67 (sextuplet, *J* = 7.3, 2H, CH_2C$H_2$$CH_3$), 0.90 (t, *J* = 7.3, 3 H, $CH_2$$CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.3, 142.1, 140.0, 139.4, 138.0, 128.8, 128.4, 127.9, 124.3, 124.2, 123.5, 123.0, 122.1, 67.3, 53.2, 21.9, 10.3; GC-MS (EI, 70 eV): *m/z* = 310 (M^+, 10), 223 (100), 221 (27), 178 (12); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $[C_{19}H_{19}O_2S]^+$: 311.1100, found: 311.1100.

Isopropyl 2-(benzo[*b*]thiophen-2-yl)-2-phenylacetate (2a'''): Yield: 49.0 mg, starting from 78.9 mg of **1a** (51%) (Table 2, entry 17). Yellow solid, mp = 67–68 °C. IR (KBr): *v* = 1728 (s),

1458 (w), 1373 (w), 1296 (w), 1204 (m), 1103 (s), 748 (w); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.78–7.72 (m, 1H, aromatic), 7.72–7.65 (m, 1H, aromatic), 7.49–7.21 (m, 7H, aromatic), 7.20 (s, 1 H at C-3), 5.21 (s, 1H, C*H*CO_2^iPr), 5.16–5.03 (m, 1H, C*H*Me_2), 1.35–1.17 [m, 6H, CH(C*H*$_3$)$_2$]; ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.7, 142.3, 140.0, 139.4, 138.0, 128.7, 128.3, 127.8, 124.2, 124.1, 123.4, 122.9, 122.1, 69.3, 53.4, 21.7, 21.6; GC-MS (EI, 70 eV): *m/z* = 310 (M^+, 17), 223 (100), 221 (24), 178 (11); HRMS (ESI-TOF) *m/z*: $[M-H]^-$ calcd for $[C_{19}H_{17}O_2S]^-$: 309.0955, found: 309.0953.

Methyl 2-(benzo[*b*]thiophen-2-yl)-2-(*p*–tolyl)acetate (2 b): Yield: 62.5 mg, starting from 83.0 mg of **1 b** (68%) (Table 2, entry 2). Yellow solid, mp = 56–57 °C. IR (KBr): *v* = 1736 (s), 1512 (w), 1458 (w), 1435 (w), 1304 (w), 1204 (w), 1157 (s), 995 (w), 826 (m), 748 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.75–7.72 (m, 1H, aromatic), 7.69–7.66 (m, 1H, aromatic), 7.33–7.24 (m, 4H, aromatic), 7.20 (s, 1H at C-3), 7.18–7.14 (m, 2H, aromatic), 5.23 (s, 1H, C*H*CO_2Me), 3.77 (s, 3H, CO_2Me), 2.23 (s, 3H, *p*-Me); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.9, 142.3, 140.0, 139.4, 137.7, 134.8, 129.5, 128.2, 124.3, 124.2, 123.5, 122.9, 122.1, 52.6, 52.5, 21.1; GC-MS (EI, 70 eV): *m/z* = 296 (M^+, 25), 237 (100), 221 (39); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $[C_{18}H_{17}O_2S]^+$: 297.0944, found: 297.0990.

Methyl 2-(benzo[*b*]thiophen-2-yl)-2-4-(*tert*-butyl)phenyl) acetate (2 c): Yield: 70.5 mg, starting from 96.5 mg of **1 c** (67%) (Table 2, entry 3). Yellow solid, mp = 66–68 °C. IR (KBr): *v* = 1744 (s), 1512 (w), 1458 (w), 1435 (w), 1204 (m), 1157 (s), 1018 (w), 841 (w), 748 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.75 (d, *J* = 7.9, 1 H, aromatic), 7.71–7.67 (m, 1 H, aromatic), 7.39–7.33 (m, 4 H, aromatic), 7.33–7.24 (m, 2 H, aromatic), 7.22 (s, 1 H at C-3) 5.25 (s, br, 1H, C*H*CO_2Me), 3.78 (s, 3H, CO_2Me), 1.30 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.9, 150.8, 142.1, 139.9, 139.4, 134.7, 127.9, 125.7, 124.24, 124.15, 123.4, 122.9, 122.1, 52.61, 52.54, 34.5, 31.3; GC-MS (EI, 70 eV): *m/z* = 338 (M^+, 32), 279 (100), 249 (18), 223 (27), 118 (11); HRMS (ESI-TOF) *m/z*: $[M-H]^-$ calcd for $[C_{21}H_{21}O_2S]^-$: 337.1268, found: 337.1268.

Methyl 2-(benzo[*b*]thiophen-2-yl)-2-(*p*-methoxyphenyl) acetate (2 d): Yield: 64.1 mg, starting from 88.0 mg of **1 d** (66%) (Table 2, entry 4). Yellow solid, mp = 69–70 °C. IR (KBr): *v* = 1736 (s), 1612 (w), 1512 (m), 1458 (w), 1435 (m), 1304 (w), 1250 (s), 1157 (s), 1034 (m), 833 (m), 748 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.75–7.72 (m, 1H, aromatic), 7.69–7.66 (m, 1H, aromatic), 7.37–7.23 (m, 4H, aromatic), 7.19 (s, 1H at C-3), 6.90–6.85 (m, 2H, aromatic), 5.21 (s, 1H, C*H*CO_2Me), 3.79 (s, 3H, OMe), 3.77 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.9, 159.3, 142.5, 139.9, 139.4, 129.9, 129.5, 124.3, 124.2, 123.5, 122.8, 122.1, 114.2, 55.3, 52.6, 52.2; GC-MS (EI, 70 eV): *m/z* = 312 (M^+, 18), 253 (100), 221 (14); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $[C_{18}H_{16}NaO_3S]^+$: 335.0712, found: 335.0732.

Methyl 2-(benzo[*b*]thiophen-2-yl)-2-(4-bromophenyl)acetate (2 e): Yield: 73.0 mg, starting from 103.5 mg of **1 e** (65%) (Table 2, entry 5). Yellow solid, mp = 42–44 °C. IR (KBr): *v* = 1736 (s), 1489 (w), 1435 (w), 1204 (w), 1157 (m), 1011 (w), 748 (m); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.79–7.63 (m, 2H, aromatic), 7.52–7.40 (m, 2H, aromatic), 7.36–7.15 (m, 5H, aromatic), 5.22 (s, 1H, C*H*CO_2Me), 3.78 (s, 3H, CO_2Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.2, 141.1, 139.9, 139.3, 136.7, 131.9, 130.1, 124.4, 123.5, 123.1, 122.13, 122.08, 52.8, 52.3; GC-MS (EI, 70 eV): *m/z* = 362 [$(M+2)^+$, 26], 360 (M^+, 26), 303 (75), 301 (78), 221 (100), 111 (17); HRMS (ESI-TOF) *m/z*: $[M-H]^-$ calcd for $[C_{17}H_{12}BrO_2S]^-$: 358.9747, found: 358.9749.

Methyl 2-(benzo[*b*]thiophen-2-yl)-2-(4-chlorophenyl)acetate (2 f): Yield: 64.1 mg, starting from 90.0 mg of **1 f** (65%) (Table 2, entry 6). Yellow solid, mp = 40–42 °C. IR (KBr): *v* = 1736 (s), 1489 (w), 1435 (w), 1204 (w), 1157 (m), 1096 (w), 1011 (w), 826 (w), 748 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.75 (d, *J* = 7.9, 1H, aromatic), 7.72–7.68 (m, 1H, aromatic), 7.39–7.34 (m, 2 H, aromatic), 7.34–7.26 (m, 4H, aromatic), 7.20 (s, 1 H at C-3), 5.22 (s, 1H, C*H*CO_2Me), 3.79 (s, 3H, CO_2Me); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.3, 141.3, 139.9, 139.3, 136.2, 133.9, 129.8, 129.0, 124.4, 123.5, 123.1, 122.2, 52.2; GC-MS (EI, 70 eV): *m/z* = 318 [$(M+2)^+$, 9], 316 (M^+, 24), 257 (100), 221 (70), 111 (13); HRMS (ESI-TOF) *m/z*: $[M-H]^-$ calcd for $[C_{17}H_{12}ClO_2S]^-$: 315.0252, found: 315.0254.

Methyl 2-(benzo[*b*]thiophen-2-yl)-2-(3-chlorophenyl)acetate (2 g): Yield: 63.0 mg, starting from 89.5 mg of **1 g** (64%) (Table 2, entry 7). Yellow solid, mp = 67–69 °C. IR (KBr): *v* = 1736 (s), 1597 (w), 1574 (w), 1435 (m), 1319 (w), 1296 (w), 1204 (m), 1157 (s), 1011 (w), 748 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.76 (d, *J* = 7.7, 1H, aromatic), 7.73–7.69 (m, 1 H, aromatic), 7.43 (s, br, 1H, aromatic), 7.35–7.27 (m, 5H, aromatic), 7.23 (s, 1 H at C-3), 5.23 (s, 1H, C*H*CO_2Me), 3.79 (s, 3H, CO_2Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.1, 140.9, 139.9, 139.5, 139.3, 134.6, 130.0, 128.5, 128.2, 126.6, 124.4, 123.6, 123.2, 122.1, 52.8, 52.5; GC-MS (EI, 70 eV): *m/z* = 318 [$(M+2)^+$, 11], 316 (M^+, 29), 257 (100), 221 (72), 189 (6), 110 (11); HRMS (ESI-TOF) *m/z*: $[M-H]^-$ calcd for $[C_{17}H_{12}ClO_2S]^-$: 315.0252, found: 315.0256.

Methyl 2-(5-methylbenzo[*b*]thiophen-2-yl)-2-phenylacetate (2 h): Yield: 59.0 mg, starting from 83.0 mg of **1 h** (64%) (Table 2, entry 8). Yellow solid, mp = 59–61 °C. IR (KBr): *v* = 1736 (s), 1450 (m), 1211 (w), 1157 (m), 995 (w), 880 (w), 802 (w), 756 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.61 (d, *J* = 8.1, 1H, aromatic), 7.48 (s, 1H, aromatic), 7.45–7.37 (m, 2H, aromatic), 7.37–7.26 (m, 3H, aromatic), 7.13 (s, 1H, aromatic), 7.09 (d, *J* = 8.2, 1H, aromatic), 5.24 (s, 1H, C*H*CO_2Me), 3.77 (s, 3H, CO_2Me), 2.42 (s, 3H, Me at C-5); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.7, 141.9, 139.7, 137.8, 137.1, 134.0, 128.8, 128.4, 127.9, 126.0, 123.4, 122.7, 121.8, 53.0, 52.7, 21.4; GC-MS (EI, 70 eV): *m/z* = 296 (M^+, 30), 237 (100), 222 (36), 221 (40), 202 (5), 189 (3), 111 (4); HRMS (ESI-TOF) *m/z*: $[M-H]^-$ calcd for $[C_{18}H_{15}O_2S]^-$: 295.0798, found: 295.0801.

Methyl 2-(5-methoxylbenzo[*b*]thiophen-2-yl)-2-phenylacetate (2 i): Yield: 64.0 mg, starting from 88.5 mg of **1 i** (66%) (Table 2, entry 9). Yellow solid, mp = 87–89 °C. IR (KBr): *v* = 1736 (s), 1605 (m), 1458 (m), 1435 (m), 1219 (m), 1157 (s), 1026 (w), 702 (w); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.60 (d, *J* = 8.8, 1H, aromatic), 7.47–7.28 (m, 5H, aromatic), 7.17–7.11 (m, 2H, aromatic), 6.93 (dd, *J* = 8.8, 2.0, 1H, aromatic), 5.24 (s, 1H, C*H*CO_2Me), 3.83 (s, 3H, OMe), 3.78 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.7, 157.5, 143.1, 140.4, 137.7, 132.3, 128.8, 128.3, 127.9, 122.9, 122.8, 114.4, 105.7, 55.5, 53.0, 52.7; GC-MS (EI, 70 eV): *m/z* = 312 (M^+, 35), 253 (100), 238 (8), 221 (26), 165 (10); HRMS (ESI-TOF) *m/z*: $[M-H]^-$ calcd for $[C_{18}H_{15}O_3S]^-$: 311.0747, found: 311.0747.

Methyl 2-(6-methoxylbenzo[*b*]thiophen-2-yl)-2-phenylacetate (2j): Yield: 63.0 mg, starting from 88.0 mg of **1j** (65%) (Table 2, entry 10). Yellow solid, mp = 42–44 °C. IR (KBr): ν = 1736 (s), 1497 (w), 1458 (w), 1435 (m), 1319 (m), 1196 (m), 1157 (m), 1011 (m), 756 (m); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.60–7.53 (m, 1H, aromatic), 7.46–7.26 (m, 5 H, aromatic), 7.22 (d, J = 2.4, 1H, aromatic), 7.10 (s, 1H at C-3), 6.93 (dd, J = 8.7, 2.4, 1H, aromatic), 5.23 (s, 1H, C*H*CO_2Me), 3.83 (s, 3H, OMe), 3.78 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 171.8, 157.4, 141.4, 139.1, 137.9, 133.4, 128.8, 128.4, 127.9, 124.1, 122.6, 114.4, 104.7, 65.9, 55.6, 52.9; GC-MS (EI, 70 eV): *m/z* = 312 (M^+, 25), 253 (100), 221 (18), 209 (24); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $[C_{18}H_{17}O_3S]^+$: 313.0893, found: 313.0891.

Methyl 2-(3-methylbenzo[*b*]thiophen-2-yl)-2-phenylacetate (2k): Yield: 41.7 mg, starting from 83.5 mg of **1k** (45%) (Table 2, entry 11). Yellow oil. IR (film): ν = 1736 (s), 1458 (w), 1435 (m), 1319 (m), 1227 (w), 1196 (m), 1157 (m), 1011 (w), 756 (m), 725 (m), 702 (w); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.75 (dist d, J = 7.4, 1H, aromatic), 7.64 (dist d, J = 7.4, 1H, aromatic), 7.46–7.19 (m, 7H, aromatic), 5.43 (s, 1H, C*H*CO_2Me), 3.77 (s, 3H, CO_2Me), 2.35 (s, 3H, Me at C-3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.0, 140.1, 139.0, 137.7, 135.2, 129.1, 128.8, 128.3, 127.7, 124.2, 123.9, 122.2, 121.6, 52.6, 51.0, 11.9; GC-MS (EI, 70 eV): *m/z* = 296 (M^+, 20), 237 (100), 147 (7), 115 (9); HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $[C_{18}H_{16}NaO_2S]^+$: 319.0763, found: 319.0765.

Methyl 2-phenyl-2-(3-phenylbenzo[*b*]thiophen-2-yl)acetate (2l): Yield: 56.0 mg, starting from 103.0 mg of **1l** (50%) (Table 2, entry 12). Colorless oil. IR (film): ν = 1736 (s), 1597 (w), 1435 (m), 1312 (w), 1196 (m), 1157 (m), 1011 (m), 756 (m), 702 (m); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.84–7.81 (m, 1H, aromatic), 7.81–7.77 (m, 1H, aromatic), 7.54–7.40 (m, 5H, aromatic), 7.35–7.25 (m, 7H, aromatic), 5.34 (s, 1H, C*H*CO_2Me), 3.72 (s, 3H, CO_2Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.1, 139.6, 139.3, 138.3, 137.4, 136.0, 134.8, 130.1, 128.7, 128.2, 127.9, 127.6, 124.6, 124.2, 123.2, 122.1, 52.6, 51.2; GC-MS (EI, 70 eV): *m/z* = 358 (M^+, 32), 299 (59), 221 (100); HRMS (ESI-TOF) *m/z*: $[M-H]^-$ calcd for $[C_{23}H_{17}O_2S]^-$: 357.0955, found: 357.0948.

Methyl 2-(benzo[*b*]thiophen-2-yl)hexanoate (2m): Yield: 28.5 mg, starting from 73.0 mg of **1m** (35%) (Table 2, entry 13). Yellow oil. IR (film): ν = 1736 (s), 1458 (w), 1435 (w), 1219 (m), 1165 (m), 1018 (w), 772 (m), 748 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.77 (d, J = 7.9, 1H, aromatic), 7.69 (d, J = 7.9, 1H, aromatic), 7.35–7.24 (m, 2H, aromatic), 3.90 (t, J = 7.7, 1H, C*H*CO_2Me), 3.71 (s, 3H, CO_2Me), 2.17–2.07 (m, 1H, CHC*H*H), 1.97–1.87 (m, 1H, CHCH*H*), 1.42–1.25 (m, 4 H, $CH_2CH_2CH_3$), 0.89 (t, J = 7.0, 3 H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 173.3, 142.6, 139.5, 124.3, 124.1, 123.3, 122.2, 122.07, 122.06, 52.3, 47.7, 33.9, 29.6, 22.4, 13.8; GC-MS (EI, 70 eV): *m/z* = 262 (M^+, 21), 206 (15), 203 (19), 174 (9), 161 (10), 147 (100), 115 (12); HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $[C_{15}H_{19}O_2S]^+$: 263.1100, found: 263.1100.

Methyl 2-(benzo[*b*]thiophen-2-yl)-2-(thiophen-3-yl)acetate (2n): Yield: 61.0 mg, starting from 81.0 mg of **1n** (68%) (Table 2, entry 14). Yellow solid, mp = 144–146 °C. IR (KBr): ν = 1736 (s), 1458 (w), 1435 (m), 1319 (w), 1304 (w), 1196 (w), 1157 (m), 1080 (w), 1011 (w), 748 (m), 725 (w); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.80–7.72 (m, 1H, aromatic), 7.72–7.65 (m, 1H, aromatic), 7.37–7.10 (m, 6H, aromatic), 5.37 (s, 1H, C*H*CO_2Me), 3.79 (s, 3H, CO_2Me); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.4, 141.6, 139.9, 139.4, 137.6, 127.7, 126.1, 124.33, 124.29, 123.5, 123.3, 122.8, 122.2, 52.7, 48.5; GC-MS (EI, 70 eV): *m/z* = 288 (M^+, 24), 229 (100), 227 (11), 184 (19); HRMS (ESI-TOF) *m/z*: $[M-H]^-$ calcd for $[C_{15}H_{11}O_2S]^-$: 287.0206, found: 287.0208.

(2-(1-Methoxy-3-phenylprop-2-yn-1-yl)phenyl)(methyl)-sulfane (4a): Yield: 45 mg, starting from 79.0 mg of **1a** (54%) (Table 1, entry 12). Yellow oil. IR (KBr): ν = 2222 (w), 1589 (m), 1443 (m), 1319 (m), 1273 (w), 1188 (m), 1080 (s), 988 (m), 756 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.79 (d, J = 7.2, 1H, aromatic), 7.52–7.46 (m, 2H, aromatic), 7.37–7.27 (m, 5H, aromatic), 7.26–7.21 (m, 1H, aromatic), 5.71 (s, 1H, C*H*OMe), 3.54 (s, 3H, OMe), 2.50 (s, 3 H, SMe); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 137.7, 137.2, 131.8, 129.1, 128.5, 128.3, 127.9, 127.5, 125.7, 122.6, 87.7, 86.5, 70.8, 56.3, 17.0; GC-MS (EI, 70 eV): *m/z* = 268 (M^+, absent), 253 (100), 238 (28), 221 (35), 189 (8), 161 (15), 111 (16).

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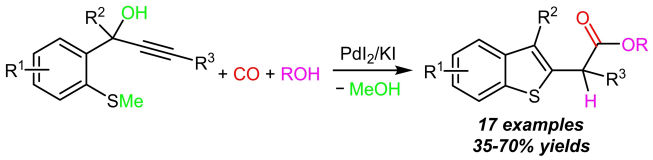
RESEARCH ARTICLE

Multicomponent Synthesis of Benzothiophen-2-acetic Esters by a Palladium Iodide Catalyzed *S*-cyclization – Alkoxycarbonylation Sequence



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