JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

Synthesis of Benzothiophene Derivatives by Pd-Catalyzed or Radical-Promoted Heterocyclodehydration of 1-(2-Mercaptophenyl)-2-yn-1-ols

Bartolo Gabriele,*[,†] Raffaella Mancuso,[‡] Elvira Lupinacci,[‡] Lucia Veltri,[‡] Giuseppe Salerno,[‡] and Carla Carfagna[§]

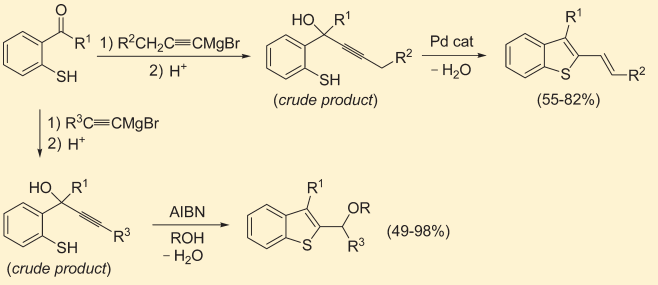
[†]Dipartimento di Scienze Farmaceutiche, Università della Calabria, 87036 Arcavacata di Rende (CS), Italy

[‡]Dipartimento di Chimica, Università della Calabria, 87036 Arcavacata di Rende (CS), Italy

[§]Dipartimento di Scienze Biomolecolari, Università di Urbino, 61029, Urbino, Italy

Supporting Information

ABSTRACT: Novel and convenient approaches to benzothiophene derivatives **3** and **5** have been developed, based on heterocyclization reactions of 1-(2-mercaptophenyl)-2-yn-1-ols **2** or **4**, respectively, readily available from alkynylation of 2-mercaptobenzaldehydes or 1-(2-mercaptophenyl) ketones **1**. In particular, 1-(2-mercaptophenyl)-2-yn-1-ols **2**, bearing a CH_2R substituent on the triple bond (R = alkyl, aryl), were conveniently converted in fair to good yields (55−82%) into (*E*)-2-(1-alkenyl)benzothiophenes **3** when allowed to react in the presence of catalytic amounts (2 mol %) of PdI_2 in conjunction with KI (KI:PdI_2 molar ratio =10) at 80−100 °C in MeCN as the solvent, through a heterocyclodehydration process. On the other hand, 2-alkoxymethylbenzothiophenes **5** were selectively obtained in fair to excellent yields (49−98%) via a radical-promoted substitutive heterocyclodehydration process, by reacting 1-(2-mercaptophenyl)-2-yn-1-ols **4** (bearing an alkyl or aryl substituent on the triple bond) in alcoholic media at 80−100 °C in the presence of a radical initiator, such as AIBN.



INTRODUCTION

Benzothiophenes are a very important class of heterocyclic compounds. The benzothiophene core is present in many natural and pharmacologically active compounds.[1] Moreover, benzothiophenes find extensive application in materials science.[2]

Several methods are known at present for the synthesis of the benzothiophene ring system starting from acyclic precursors.[3,4] Classical reactions include Bischler-type cyclizations of α-arylthio ketones to give 3-substituted benzothiophenes,[3a,b] the two-step formation of 2,3-disubstituted benzothiophenes, bearing an acyl group at C-2, from 1-(2-mercaptophenyl) ketones through S-alkylation followed by intramolecular condensation,[3c] and the benzannulation of a thiophene moiety.[3d] More recently, 2-substituted benzothiophenes have been obtained by lithiation of *S*-(2-methylphenyl) *N*,*N*,*N*′,*N*′-tetramethylphosphorodiamidothioate followed by acylation and acidic treatment.[3e] Other recently developed methods include metal-promoted annulation processes, such as the Pd-catalyzed formation of benzothiophenes from *gem*-dihalovinyl thiophenols,[4f] the acid-catalyzed heterocyclization of 2-(1-alkynyl)methylthiobenzene under MW irradiation,[4c] and the iodocyclization of suitable substrates, such as 1-[2-(methylthio)phenyl]-2-yn-1-ols.[4o]

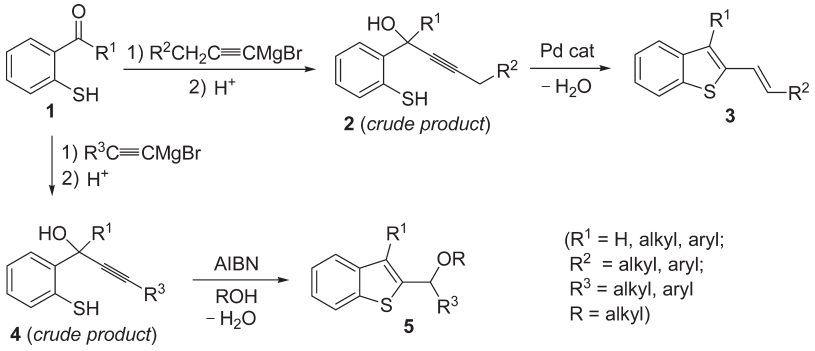
In this work, we report a novel approach to the direct synthesis of benzothiophene derivatives by heterocyclization of 1-(2-mercaptophenyl)-2-yn-1-ols **2** or **4**, readily available from alkynylation of 2-mercaptobenzaldehydes or 1-(2-mercaptophenyl) ketones **1**. We have found that, depending on the substrate substitution pattern and reaction conditions, either Pd-catalyzed heterocyclodehydration or radical-promoted substitutive heterocyclodehydration may take place, with selective formation of (*E*)-2-(1-alkenyl)benzothiophenes **3** or 2-alkoxymethylbenzothiophenes **5**, respectively, in good to high yields (Scheme 1).

RESULTS AND DISCUSSION

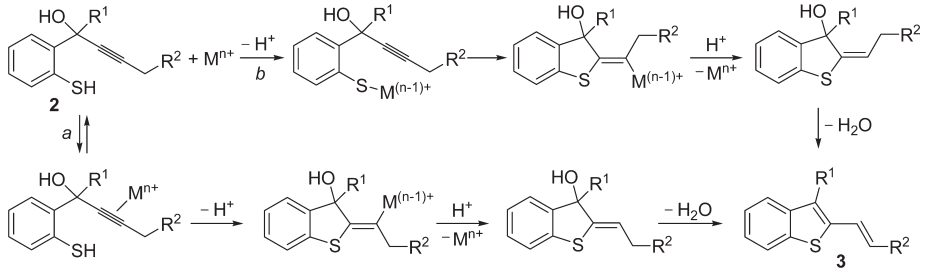
Pd-Catalyzed Heterocyclodehydration of 1-(2-Mercaptophenyl)-2-yn-1-ols 2 for the Synthesis of (*E*)-2-(1-Alkenyl)benzothiophenes 3. Metal-catalyzed heterocyclodehydration of suitably functionalized and readily available acyclic substrates is an attractive and convenient method for the regioselective synthesis of substituted heterocycles.[5] In particular, we have recently reported the formation of quinoline, furan, and pyrrole derivatives by Pd- or Cu-catalyzed heterocyclodehydration of 1-(2-aminoaryl)-2-yn-1-ols,[5f,l] 3-yne-1,2-diols,[5a,c] and N-protected 1-amino-3-yn-2-ols,[5a] respectively.

Received: July 15, 2011
Published: September 08, 2011

Scheme 1



Scheme 2



Prompted by these results, we have investigated the possibility to realize a direct synthesis of (*E*)-2-(1-alkenyl)benzothiophenes **3** by metal-catalyzed heterocyclodehydration of 1-(2-mercaptophenyl)-2-yn-1-ols **2**, according to the mechanistic hypotheses shown in Scheme 2.

In pathway a, triple bond coordination to the metal center would activate the triple bond toward the 5-exo-dig nucleophilic attack by the thiol group,[6] with formation of a vinylmetal intermediate, whose protonolysis and dehydration would lead to **3**. Alternatively, a metal sulfide species could be formed,[7] followed by triple bond insertion, protonolysis, and dehydration (pathway b).

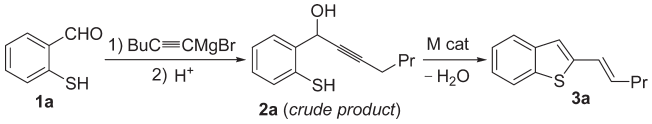
The first substrate we tested was 1-(2-mercaptophenyl)hept-2-yn-1-ol **2a** (R^2 = Pr), which was used as the crude product deriving from the alkynylation reaction of 2-mercaptobenzaldehyde **1a** with 1-hexylymagnesium bromide (see the Experimental Section for details). This substrate was allowed to react in MeCN at 100 °C in the presence of different metal species, based on Pd, Zn, Cu, and Au; the results obtained are shown in Table 1. As can be seen from Table 1, the desired product **3a** was formed with practically all the catalysts tested, thus confirming the validity of our initial work hypothesis. However, the selectivity of the process toward **3a** greatly depended on the nature of the metal complex used: in particular, the catalytic system PdI_2/KI[8] showed the highest activity (54% yield after 6 h, entry 2), while $ZnCl_2$ and CuI led to only traces amounts of **3a** (entries 4 and 6, respectively). We also run a blank experiment, in the absence of metal species, which, as expected, led to no product formation (entry 9). We accordingly carried out the next experiments, aimed at optimizing the product yield, using PdI_2/KI as the catalytic system. The results obtained by varying the KI/PdI_2 molar ratio, substrate concentration, temperature, and solvent are shown in Table 1, entries 10−22. The final optimized conditions, ensuing from this reaction parameters screening, corresponded to MeCN as the solvent with a substrate concentration of 0.02 mmol/mL of MeCN, at 80 °C for 5 h, in the presence of PdI_2 in conjunction with 10 equiv of KI.[8] Under these conditions, benzothiophene **3a** was obtained in 70% isolated yield, based on starting 2-mercaptobenzaldehyde **1a** (Table 2, entry 1).

In order to assess the generality of the process, the reaction was then extended to other differently substituted substrates. While 1-(2-mercaptophenyl)-4-phenylbut-2-yn-1-ol **2b** and 1-(2-mercaptophenyl)-5-phenylpent-2-yn-1-ol **2d** behaved similarly to **2a** (Table 2, entries 2 and 4, respectively), the other substrates tested (**2c**, **2e**−**h**) were less reactive, so the best results in terms of product yield were achieved working at 80−100 °C for 15 h (entries 3 and 5−8). In any case, the desired (*E*)-2-(1-alkenyl)benzothiophenes **3b**−**h** were selectively obtained in fair to good yields, based on the starting 2-mercaptobenzaldehyde or 1-(2-mercaptophenyl) ketones **1a**−**c** (55−82%). This synthetic result is noteworthy, also considering the well-known thiophilicity of Pd(II), which is often associated with the "poisoning effect" of the sulfur atom on palladium catalysis involving thiophenes and benzothiophenes.[9]

Radical-Promoted Substitutive Heterocyclodehydration of 1-(2-Mercaptophenyl)-2-yn-1-ols 4 for the Selective Synthesis of 2-Alkoxymethylbenzothiophenes 5. When 1-(2-mercaptophenyl)hept-2-yn-1-ol **4a** (R^3 = Bu) was allowed to react under conditions similar to those shown in entry 1 of Table 2, but in a nucleophilic solvent such as MeOH for 15 h, the reaction course changed completely, with formation of 2-(1-methoxypentyl)benzothiophene **5a** in 40% yield (Table 3, entry 1). The selective formation of **5a**, corresponding to a substitutive heterocyclization, suggested that a different reaction mechanism could take place in MeOH, possibly not involving metal catalysis. To confirm this hypothesis, a reaction without metal catalysts was carried out in MeOH as the solvent, which indeed led to the

dx.doi.org/10.1021/jo201471k |*J. Org. Chem.* 2011, 76, 8277–8286

Table 1. Heterocyclodehydration Reactions of 1-(2-Mercaptophenyl)hept-2-yn-1-ol 2a Under Different Conditions[a]



entry	metal catalyst	solvent	T (°C)	substrate concentration[b]	conversion of **2a**[c] (%)	yield of **3a**[d] (%)
1	$PdCl_2$ + 10KCl	MeCN	100	0.22	88	25
2	PdI_2 + 10KI	MeCN	100	0.22	100	54
3	$Pd(NO_3)_2 \cdot 2H_2O$	MeCN	100	0.22	59	13[e]
4	$ZnCl_2$	MeCN	100	0.22	52	3[e]
5	$CuCl_2$	MeCN	100	0.22	63	10[e]
6	CuI	MeCN	100	0.22	18	traces[e]
7	AuCl	MeCN	100	0.22	64	11[e]
8	$AuCl_3$	MeCN	100	0.22	86	24
9	none	MeCN	100	0.22	7	0
10	PdI_2 + 2KI	MeCN	100	0.22	100	46
11	PdI_2 + 20KI	MeCN	100	0.22	100	32
12	PdI_2 + 10KI	MeCN	100	0.50	100	48
13	PdI_2 + 10KI	MeCN	100	0.10	100	55
14	PdI_2 + 10KI	MeCN	100	0.05	100	58
15	PdI_2 + 10KI	MeCN	100	0.02	100	62
16	PdI_2 + 10KI	MeCN	80	0.22	100	55
17	PdI_2 + 10KI	MeCN	60	0.22	79	26
18	PdI_2 + 10KI	MeCN	80	0.02	100	67
19	PdI_2 + 2KI	MeCN	80	0.02	100	63
20	PdI_2 + 10KI	DME	100	0.22	100	45
21	PdI_2 + 10KI	DMA	100	0.22	100	45
22	PdI_2 + 10KI	dioxane	100	0.22	100	36

[a] Crude **2a** (obtained from the alkynylation reaction between 2-mercaptobenzaldehyde **1a** with 1-hexynylmagnesium bromide) was directly used as substrate without further purification (see the Experimental Section for details). Unless otherwise noted, all reactions were carried out for 6 h in the presence of 2 mol % of catalyst. [b] Millimoles of starting **1a** per milliliter of solvent. [c] Determined by GLC. [d] Isolated yield based on starting **1a**. The formation of unidentified heavy products (chromatographically immobile materials) accounted for the difference between the substrate conversion and the product yield. [e] The reaction led to a complex mixture of products.

formation of **5a** in 45% yield (Table 3, entry 2). Considering the well-known tendency of thiols to produce thiyl radicals,[10] we then verified if a radical mechanism could be at work by conducting an experiment in the presence of a radical inhibitor, such as 2,2,6,6-tetramethylpiperidinoxyl (TEMPO). No reaction occurred in the presence of TEMPO (Table 3, entry 3), which clearly indicated a free-radical mechanism for the conversion of **4a** into **5a** in MeOH as the solvent. In order to further favor the radical process leading to **5a**, the next experiment was carried out in MeOH in the presence of a classical radical initiator such as AIBN. As expected, **5a** was obtained in a higher yield with respect to the reaction carried out in MeOH alone (70% after 8 h, Table 3, entry 4), thus further confirming the involvement of a free-radical mechanism. The reaction was quite slower and less selective at 60 °C, as shown in entry 5 of Table 3, while a somewhat lower yield was obtained by working under more concentrated conditions (Table 3, entry 6).

The successful synthesis of 2-(1-methoxypentyl)benzothiophene **5a** by a simple procedure based on substitutive heterocyclodehydration of 1-(2-mercaptophenyl)hept-2-yn-1-ol **4a** opened the way to the development of a general, novel, and convenient approach to functionalized benzothiophenes, such as 2-alkoxymethylbenzothiophenes **5**, starting from readily available acyclic substrates. We accordingly tested the reactivity of other differently substituted 1-(2-mercaptophenyl)-2-yn-1-ols **4** in MeOH under radical-promoted conditions, and the results obtained are shown in Table 4, entries 1−14. As can be seen from Table 4, fair to excellent yields were obtained starting from a variety of substrates, including those bearing a highly bulky substituent on the triple bond, such as *tert*-butyl, working at 80−100 °C for 8−15 h. The reaction also worked nicely using EtOH or *i*-PrOH rather than MeOH as the reactant and solvent, as shown by entries 15−21 of Table 4.

A plausible mechanism for the formation of benzothiophenes **5** from **4** under radical conditions is shown in Scheme 3. Formation of the thiyl radical **I** followed by its intramolecular addition to the triple bond may occur, followed by ionic fragmentation of the ensuing radical species **II** to give a radical cation species **III** with elimination of HO^-.[11] Reaction of **III** with ROH and HO^- would lead to the benzylic-type radical **IV** with elimination of water. The radical chain then propagates through the reaction between **IV** and the substrate, with formation of product **5** and regeneration of the thiyl radical **I**.

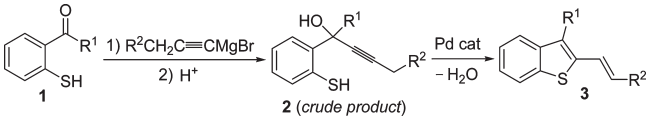
CONCLUSIONS

In conclusion, we have shown that readily available 1-(2-mercaptophenyl)-2-yn-1-ols **2** and **4**, easily obtained as crude

dx.doi.org/10.1021/jo201471k |*J. Org. Chem.* 2011, 76, 8277–8286

products from alkynylation of 2-mercaptobenzaldehydes or 1-(2-mercaptophenyl) ketones **1**, are excellent and versatile substrates for the direct synthesis of benzothiophene derivatives **3** and **5**, respectively, through novel and efficient heterocyclization processes. In particular, (*E*)-2-(1-alkenyl)benzothiophenes **3** are selectively produced in fair to good yields (55−82%) via PdI_2/KI-catalyzed heterocyclodehydration of **2** (bearing a CH_2R^2 substituent on the triple bond, R^2 = alkyl, aryl) carried out at 80−100 °C in MeCN as the solvent. On the other hand, 1-(2-mercaptophenyl)-2-yn-1-ols **4** (bearing an R^3 substituent on the triple bond, R^3 = alkyl, aryl) can also be selectively converted into 2-alkoxymethylbenzothiophenes **5** in fair to excellent yields (49−98%) when allowed to react with an alcohol (also used as the reaction medium) in the presence of AIBN, through a substitutive heterocyclodehydration process taking place under radical conditions. These novel approaches to the synthesis of benzothiophenes **3** and **5** represent convenient alternative methods with respect to the procedures reported so far for their production.[12,13]

Table 2. Synthesis of (*E*)-2-(1-Alkenyl)benzothiophenes 3 by Pd-Catalyzed Heterocyclodehydration of 1-(2-Mercaptophenyl)-2-yn-1-ols 2, Obtained by Alkynylation of 2-Mercaptobenzaldehyde or 1-(2-Mercaptophenyl) Ketones 1[a]



entry	1	R^1	R^2	2	*T* (°C)	*t* (h)	3	yield of 3[b] (%)
1	**1a**	H	Pr	**2a**	80	5	**3a**	70
2	**1a**	H	Ph	**2b**	80	5	**3b**	75
3	**1a**	H	Bn	**2c**	80	15	**3c**	55
4	**1b**	Me	Pr	**2d**	80	5	**3d**	76
5	**1b**	Me	Bn	**2e**	80	15	**3e**	70
6	**1c**	Ph	Bn	**2f**	80	15	**3f**	56
7	**1c**	Ph	Ph	**2g**	80	15	**3g**	73
8	**1c**	Ph	Pr	**2h**	100	15	**3h**	82

[a] Crude **2** [obtained from the alkynylation reaction between 2-mercaptobenzaldehyde **1a** or 1-(2-mercaptophenyl) ketones **1b,c** with 1-alkynylmagnesium bromide] was directly used as substrate without further purification (see the Experimental Section for details). All reactions were carried out in MeCN (0.02 mmol of starting **1** per mL of solvent; 0.5 mmol scale based on **1**) in the presence of 2 mol % of PdI_2 in conjunction with KI (KI:PdI_2 molar ratio = 10). Substrate conversion was quantitative in all cases. [b] Isolated yield based on starting **1**. The formation of unidentified heavy products (chromatographically immobile materials) accounted for the difference between the substrate conversion and the product yield.

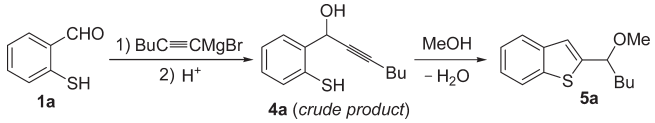
EXPERIMENTAL SECTION

General Experimental Methods. Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ solutions at 300 and 75 MHz, respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in hertz, respectively. IR spectra were taken with an FT-IR spectrometer. Mass spectra were obtained using a GC-MS apparatus at 70 eV ionization voltage. Microanalyses were carried out at our analytical laboratory. All reactions were analyzed by TLC on silica gel 60 F_{254} and by GLC 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.

Starting 2-mercaptobenzaldehyde (**1a**),[14] 2-mercaptoacetophenone (**1b**)[15] and 2-mercaptobenzophenone (**1c**)[16] were prepared according to literature procedures.

General Procedure for the Preparation of Crude 1-(2-Mercaptophenyl)-2-yn-1-ols 2 and 4. To a suspension of Mg turnings (410 mg, 16.9 mmol) in anhydrous THF (2.0 mL), maintained under nitrogen and under reflux was added pure EtBr (0.4 mL) to start the formation of the Grignard reagent. The remaining bromide was added dropwise (ca. 20 min) in THF solution (0.9 mL of EtBr in 15.0 mL of THF; total amount of EtBr added: 1.78 g, 16.3 mmol). The mixture was then allowed to reflux for additional 20 min. After cooling, the solution of EtMgBr thus obtained was transferred under nitrogen to a dropping funnel and was added dropwise to a solution of the 1-alkyne (16.3 mmol) in anhydrous THF (7.0 mL) at 0 °C with stirring. After additional stirring at 0 °C for 15 min, the mixture was allowed to warm to room

Table 3. Substitutive Heterocyclodehydration Reactions of 1-(2-Mercaptophenyl)hept-2-yn-1-ol 4a Under Different Conditions[a]

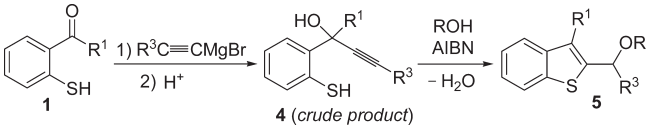


entry	radical initiator	*T* (°C)	*t* (h)	substrate concentration[b]	conversion of 4a[c] (%)	yield of 5a[d] (%)
1[e]	none	80	15	0.02	100	40
2	none	80	15	0.02	100	45
3[f]	none	80	15	0.02	23	0[g]
4	AIBN[h]	80	8	0.02	100	70
5	AIBN[h]	60	15	0.02	41	20
6	AIBN[h]	80	15	0.22	100	62

[a] Crude **4a** (obtained from the alkynylation reaction between 2-mercaptobenzaldehyde **1a** with 1-hexynylmagnesium bromide) was directly used as substrate without further purification (see the Experimental Section for details). All reactions were carried out in MeOH. [b] Millimoles of starting **1a** per milliliter of solvent. [c] Determined by GLC. [d] Isolated yield based on starting **1a**. The formation of unidentified heavy products (chromatographically immobile materials) accounted for the difference between the substrate conversion and the product yield. [e] The reaction was carried out in the presence of 2 mol % of PdI_2 in conjunction with KI (KI:PdI_2 molar ratio = 10). [f] The reaction was carried out in the presence of TEMPO (50% with respect to **4a**, w/w). [g] The reaction led to a complex mixture of products. [h] 20% with respect to **4a** (w/w).

dx.doi.org/10.1021/jo201471k |*J. Org. Chem.* 2011, 76, 8277–8286

Table 4. Synthesis of 2-Alkoxymethylbenzothiophenes 5 by Substitutive Heterocyclodehydration of 1-(2-Mercaptophenyl)-2-yn-1-ols 4, Obtained by Alkynylation of 2-Mercaptobenzaldehyde or 1-(2-Mercaptophenyl) Ketones 1, under Radical Conditions[a]



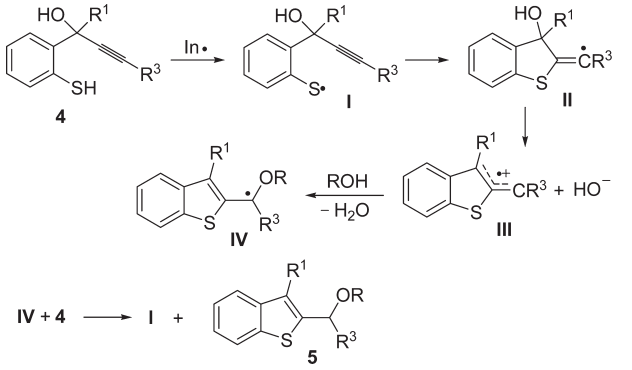
entry	1	R^1	R^3	4	R	T (°C)	t (h)	5	yield of 5[b] (%)
1	**1a**	H	Bu	**4a**	Me	80	8	**5a**	70
2	**1a**	H	Bn	**4b**	Me	80	15	**5b**	52
3	**1a**	H	Bn	**4b**	Me	100	8	**5b**	52
4	**1b**	Me	Bu	**4c**	Me	100	15	**5c**	98
5	**1b**	Me	$(CH_2)_2Ph$	**4d**	Me	100	15	**5d**	71
6	**1c**	Ph	$(CH_2)_2Ph$	**4e**	Me	100	15	**5e**	73
7	**1c**	Ph	Bn	**4f**	Me	100	15	**5f**	68
8	**1c**	Ph	Bu	**4g**	Me	100	8	**5g**	49
9	**1a**	H	Ph	**4h**	Me	80	15	**5h**	60
10	**1a**	H	*t*-Bu	**4i**	Me	100	15	**5i**	53
11	**1b**	Me	Ph	**4j**	Me	80	8	**5j**	60
12	**1b**	Me	*t*-Bu	**4k**	Me	80	8	**5k**	55
13	**1c**	Ph	Ph	**4l**	Me	100	15	**5l**	80
14	**1c**	Ph	*t*-Bu	**4m**	Me	100	8	**5m**	61
15	**1a**	H	Bu	**4a**	Et	80	15	**5a′**	63
16	**1b**	Me	Bu	**4c**	Et	80	15	**5c′**	95
17	**1c**	Ph	Bu	**4g**	Et	100	8	**5 g′**	55
18	**1a**	H	Ph	**4h**	Et	80	15	**5 h′**	54
19	**1b**	Me	Ph	**4j**	Et	80	15	**5j′**	51
20	**1b**	Me	*t*-Bu	**4k**	Et	80	8	**5k′**	58
21	**1a**	H	*t*-Bu	**4i**	*i*-Pr	80	8	**5i″**	60

[a] Crude **4** [obtained from the alkynylation reaction between 2-mercaptobenzaldehyde **1a** or 1-(2-mercaptophenyl) ketones **1b**,**c** with 1-alkynylmagnesium bromide] was directly used as substrate without further purification (see the Experimental Section for details). All reactions were carried out in ROH (0.02 mmol of starting **1** per mL of solvent, 0.5 mmol scale based on **1**) in the presence of 20% of AIBN (w/w with respect to **4**). Substrate conversion was quantitative in all cases. [b] Isolated yield based on starting **1**. The formation of unidentified heavy products (chromatographically immobile materials) accounted for the difference between the substrate conversion and the product yield.

temperature, and then it was maintained at 50 °C for 2 h and used as such at the same temperature for the next step. The 2-mercaptophenyl carbonyl compound **1** (6.52 mmol) was dissolved under nitrogen in anhydrous THF (15.0 mL) and then added dropwise to the solution of the alkynylmagnesium bromide in THF (prepared as described above) under nitrogen. After stirring at 50 °C for 2 h, the mixture was cooled to room temperature. Saturated NH_4Cl was added with stirring to achieve weakly acidic pH. After additional stirring at room temperature for 15 min, Et_2O (ca. 20 mL) was added and phases were separated. The aqueous phase was extracted with Et_2O (3 × 50 mL), and the collected organic layers were washed with brine to ca. neutral pH and eventually dried over Na_2SO_4. After filtration, the solvent was evaporated and crude products **2** or **4** were diluted with Et_2O and transferred into a volumetric flask (50 mL).

General Procedure for the Synthesis of (*E*)-2-(1-Alkenyl)-benzothiophenes 3. A 3.8 mL of the ethereal solution of **2** (obtained as described above) were evaporated, and the residue (formally deriving

Scheme 3



from 0.50 mmol of **1**) was diluted with MeCN (25 mL). To the resulting mixture were added PdI_2 (3.6 mg, 0.01 mmol) and KI (16.7 mg, 0.1 mmol), and the mixture was heated at the temperature and for the time required (see Table 2). The solvent was evaporated, and the crude products **3** were purified by column chromatography on silica gel using 95:5 hexane–Et_2O as eluent.

*2-Pent-1-enylbenzo[b]thiophene (**3a**).* Yield: 71 mg (70%, based on starting **1a**, Table 2, entry 1). Yellow solid, mp 57–59 °C. IR (KBr): ν = 3057 (w), 2960 (s), 2929 (m), 2870 (m), 1677 (w), 1457 (s), 1436 (s), 1378 (w), 1156 (w), 953 (s), 839 (m), 744 (s), 725 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.69 (m, 1 H), 7.65–7.60 (m, 1 H), 7.31–7.20 (m, 2 H), 7.02 (s, 1 H), 6.63–6.54 (m, 1 H), 6.15 (dt, J = 15.3, 7.2, 1 H), 2.24–2.13 (m, 2 H), 1.59–1.42 (m, 2 H), 0.96 (t, J = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.4, 137.8, 136.9, 133.4, 127.6, 124.5, 124.0, 122.2, 122.1, 121.5, 35.5, 22.6, 13.9, ; GC-MS: m/z = 204 (3) [$(M + 2)^+$], 203 (10), 202 (62) [M^+], 184 (4), 174 (14), 173 (100), 172 (13), 171 (19), 160 (22), 147 (9), 134 (15), 129 (32), 128 (14), 115 (14). Anal. Calcd for $C_{13}H_{14}S$ (202.32): C, 77.18; H, 6.97; S, 15.85; found C, 77.31; H, 6.95; S, 15.74.

*2-Styrylbenzo[b]thiophene (**3b**).*[4c,f] Yield: 89 mg (75% based on starting **1a**, Table 2, entry 2). Yellow solid, mp 123–125 °C. IR (KBr): ν = 2921 (m), 1447 (w), 1225 (w), 1074 (m), 948 (s), 818 (m), 740 (s), 691 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.81–7.76 (m, 1 H), 7.71–7.67 (m, 1 H), 7.55–7.48 (m, 2 H), 7.42–7.24 (m, 7 H), 6.99 (distorted d, J = 16.2, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.9, 140.2, 138.9, 136.7, 130.9, 128.8, 128.0, 126.6, 124.8, 124.5, 123.4, 123.3, 122.3, 122.2; m/z = 238 (5) [$(M + 2)^+$], 237 (20), 236 (100) [M^+], 235 (87), 234 (55), 221 (18), 203 (8), 202 (21), 189 (6), 165 (3), 134 (5), 117 (14), 104 (8), 101 (7), 89 (5), 77 (7). Anal. Calcd for $C_{16}H_{12}S$ (236.33): C, 81.31; H, 5.12; S, 13.57; found C, 81.27; H, 5.14; S, 13.59.

*2-(3-Phenylpropenyl)benzo[b]thiophene (**3c**).* Yield: 69 mg (55% based on starting **1a**, Table 2, entry 3). Yellow solid, mp 59–60 °C. IR (KBr): ν = 2947 (m), 2877 (m), 1631 (m), 1450 (m), 1385 (m), 1080 (w), 1026 (m), 949 (m), 833 (m), 749 (s), 698 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.77–7.62 (m, 2 H), 7.37–7.16 (m, 7 H), 7.07 (s, 1 H), 6.64 (distorted d, br, J = 15.7, 1 H), 6.30 (dt, J = 15.3, 6.9, 1 H), 3.57 (d, J = 6.9, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.7, 140.2, 139.5, 138.7, 132.0, 128.8, 128.6, 126.4, 125.0, 124.4, 124.3, 123.2, 122.1, 121.8, 39.2 ; GC-MS: m/z = 252 (10) [$(M + 2)^+$], 251 (24), 250 (100) [M^+], 249 (41), 235 (32), 215 (18), 202 (12), 173 (21), 171 (15), 147 (22), 128 (19), 115 (34), 91 (10), 89 (11), 77 (12). Anal. Calcd for $C_{17}H_{14}S$ (250.36): C, 81.56; H, 5.64; S, 12.81; found C, 81.51; H, 5.63; S, 12.86.

*3-Methyl-2-pent-1-enylbenzo[b]thiophene (**3d**).* Yield: 82 mg (76% based on starting **1b**, Table 2, entry 4). Yellow solid, mp 63–65 °C. IR (KBr): ν = 2957 (m), 2927 (m), 2870 (m), 1460 (m), 1435 (m), 1379 (w), 1198 (w), 1017 (w), 950 (s), 752 (s), 727 (m) cm^{-1}; ^1H NMR

dx.doi.org/10.1021/jo201471k |*J. Org. Chem.* 2011, 76, 8277–8286

(300 MHz, $CDCl_3$): δ = 7.69 (dd, J = 6.9, 1.6, 1 H), 7.56 (dd, J = 6.9, 1.6, 1 H), 7.36−7.17 (m, 2 H), 6.69 (dt, J = 15.3, 1.2, 1 H), 6.12 (dt, J = 15.3, 7.3, 1 H), 2.39 (s, 3 H), 2.21 (qd, J = 7.3, 1.2, 2 H), 1.57−1.43 (m, 2 H), 0.95 (t, J = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.3, 137.7, 136.8, 133.3, 127.5, 124.4, 123.9, 122.1, 122.0, 121.4, 35.4, 22.5, 13.7, 11.6; GC-MS: m/z = 218 (5) [$(M + 2)^+$], 217 (12), 216 (82) [M^+], 187 (100), 174 (19), 173 (18), 172 (48), 171 (37), 154 (11), 147 (24), 128 (16), 115 (19), 77 (9). Anal. Calcd for $C_{14}H_{16}S$ (216.34): C, 77.72; H, 7.45; S, 14.82; found C, 77.85; H, 7.43; S, 14.72.

*3-Methyl-2-(3-phenylpropenyl)benzo[b]thiophene (**3e**).* Yield: 93 mg (70% based on starting **1b**, Table 2, entry 5). White solid, mp 62−63 °C. IR (KBr): ν = 2918 (m), 2855 (w), 1601 (w), 1495 (m), 1464 (m), 1437 (m), 1418 (w), 957 (m), 933 (w), 752 (m), 741 (s), 727 (m), 700 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72−7.67 (m, 1 H), 7.61−7.56 (m, 1 H), 7.35−7.17 (m, 7 H), 6.76 (dt, J = 15.3, 1.2, 1 H), 6.25 (dt, J = 15.3, 6.9, 1 H), 3.58 (d, br, J = 6.9, 2 H), 2.35 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.1, 139.7, 137.8, 136.2, 131.3, 128.7, 128.5, 128.3, 126.3, 124.6, 124.0, 123.2, 122.1, 121.6, 39.5, 11.7; GC-MS: m/z = 266 (6) [$(M + 2)^+$], 265 (20), 264 (100) [M^+], 250 (13), 249 (64), 234 (11), 216 (15), 215 (10), 187 (6), 185 (5), 173 (23), 171 (22), 161 (16), 160 (12), 147 (15), 128 (16), 116 (19), 115 (95), 91 (29), 77 (13). Anal. Calcd for $C_{18}H_{16}S$ (264.38): C, 81.77; H, 6.10; S, 12.13; found C, 81.86; H, 6.08; S, 12.06.

*3-Phenyl-2-(3-phenylpropenyl)benzo[b]thiophene (**3f**).* Yield: 92 mg (56% based on starting **1c**, Table 2, entry 6). Yellow solid, mp 59−62 °C. IR (KBr): ν =1597 (w), 1489 (m), 1435 (m), 1385 (w), 1207 (m), 1153 (w), 1068 (m), 1022 (w), 949 (s), 748 (s), 694 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (dd, J = 6.9, 1.6, 1 H), 7.54−7.36 (m, 6 H), 7.33−7.14 (m, 7 H), 6.54 (distorted d, br, J = 15.3, 1 H), 6.32 (dt, J = 15.3, 7.3, 1 H), 3.48 (d, J = 7.3, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.4, 139.7, 138.2, 137.8, 134.9, 134.4, 132.2, 130.4, 128.5, 127.6, 126.3, 124.8, 124.3, 124.1, 122.9, 122.1, 39.4; GC-MS: m/z = 328 (2) [$(M + 2)^+$], 327 (14), 326 (37) [M^+], 236 (23), 235 (100), 234 (89), 221 (28), 115 (19), 91 (21). Anal. Calcd for $C_{23}H_{18}S$ (326.45): C, 84.62; H, 5.56; S, 9.82; found C, 84.71; H, 5.53; S, 9.76.

*3-Phenyl-2-styrylbenzo[b]thiophene (**3g**).* Yield: 114 mg (73% based on starting **1c**, Table 2, entry 7). Yellow solid, mp 57−59 °C. IR (KBr): ν = 2923 (m), 2850 (w), 1599 (w), 1494 (m), 1432 (m), 1318 (w), 1221 (w), 1072 (w), 951 (m), 769 (s), 692 (s), cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (dd, J = 6.9, 1.6, 1 H), 7.59−7.16 (m, 14 H), 7.04 (distorted d, J = 16.2, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.5, 138.5, 138.1, 136.9, 136.0, 134.8, 131.2, 130.5, 128.6, 127.9, 127.7, 126.6, 125.1, 124.5, 123.0, 122.1, 121.4; GC-MS: m/z = 314 (7) [$(M + 2)^+$], 313 (24), 312 (100) [M^+], 311 (40), 297 (17), 279 (5), 235 (37), 234 (46), 221 (10), 202 (11), 189 (8), 178 (4), 163 (5), 147 (3), 139 (3), 102 (3), 89 (3), 78 (28), 77 (18). Anal. Calcd for $C_{22}H_{16}S$ (312.43): C, 84.57; H, 5.16; S, 10.26; found C, 84.49; H, 5.18; S, 10.33.

*2-Pent-1-enyl-3-phenylbenzo[b]thiophene (**3h**).* Yield: 114 mg (82% based on starting **1c**, Table 2, entry 8). Pale yellow solid, mp 61−63 °C. IR (KBr): ν = 2958 (s), 2928 (s), 2870 (m), 1487 (w), 1457 (m), 1434 (s), 1206 (m), 1157 (w), 1071 (w), 1020 (w), 956 (s), 767 (s), 753 (m), 732 (s), 717 (m), 701 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78−7.72 (m, 1 H), 7.53−7.44 (m, 3 H), 7.44−7.37 (m, 3 H), 7.30−7.21 (m, 2 H), 6.53 (distorted dt, J = 15.3, 1.2, 1 H), 6.20 (distorted dt, J = 15.3, 7.3, 1 H), 2.13 (qd, J = 7.3, 1.2, 2 H), 1.44 (hexuplet, J = 7.3, 2 H), 0.91 (t, J = 7.3, 3 H);^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.6, 138.8, 137.7, 135.0, 134.3, 130.4, 128.5, 127.5, 124.6, 124.3, 122.9, 122.8, 122.0, 35.2, 22.4, 13.7; GC-MS: m/z = 280 (5) [$(M + 2)^+$], 279 (17), 278 (75) [M^+], 263 (1), 250 (12), 249 (60), 247 (18), 236 (26), 235 (100), 234 (86), 221 (33), 216 (16), 215 (20), 202 (12), 189 (9), 171 (10), 165 (5), 115 (10). Anal. Calcd for $C_{19}H_{18}S$ (278.41): C, 81.97; H, 6.52; S, 11.52; found C, 82.01; H, 6.51; S, 11.48.

General Procedure for the Synthesis of 2-Alkoxymethylbenzothiophenes 5. A 3.8 mL amount of the ethereal solution of **4** (obtained as described above) was evaporated, and the residue (formally deriving from 0.50 mmol of **1**) was diluted with ROH (R = Me, Et, *i*-Pr) (25 mL). To the resulting mixture was added AIBN (20% w/w with respect to **4**), and the mixture was heated at the temperature and for the time required (see Table 4). The solvent was evaporated, and the crude products **5** were purified by column chromatography on silica gel using as eluent: 95:5 hexane−AcOEt (**5a**, **5a′**, **5b**, **5e**, **5f**, **5g**, **5 h′**, **5k′**, **5i″**, **5j′**, **5l**, **5m**); 99:1 hexane−AcOEt (**5d**, **5i**, **5 g′**); 9:1 hexane−AcOEt (**5c**, **5c′**, **5h**, **5j**, **5k**).

*2-(1-Methoxypentyl)benzo[b]thiophene (**5a**).* Yield: 82 mg (70% based on starting **1a**, Table 4, entry 1). Yellow oil. IR (film): ν = 2956 (s), 2931 (s), 2859 (m), 2821 (m), 1458 (s), 1436 (w), 1126 (m), 1091 (s), 829 (w), 746 (m), 727 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86−7.78 (m, 1 H), 7.75 −7.68 (m, 1 H), 7.37−7.25 (m, 2 H), 7.18 (s, 1 H), 4.41 (t, J = 6.7, 1 H), 3.30 (s, 3 H), 2.03−1.88 (m, 1 H), 1.86−1.71 (m, 1 H), 1.48−1.21 (m, 4 H), 0.88 (t, J = 6.9, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.5, 139.7, 139.4, 124.1, 123.3, 122.6, 121.8, 80.2, 56.7, 37.7, 27.9, 22.5, 14.0; GC-MS: m/z = 236 (1) [$(M + 2)^+$], 235 (2), 234 (14) [M^+], 178 (13), 177 (100), 162 (12), 161 (16), 147 (12), 134 (11), 115 (7), 89 (8). Anal. Calcd for $C_{14}H_{18}OS$ (234.36): C, 71.75; H, 7.74; S, 13.68; found C, 71.77; H, 7.72; S, 13.73.

*2-(1-Methoxy-2-phenylethyl)benzo[b]thiophene (**5b**).* Yield: 70 mg (52% based on starting **1a**, Table 4, entry 2). Yellow solid, mp 63−64 °C. IR (KBr): ν = 2927 (m), 2852 (w), 1495 (w), 1456 (m), 1434 (w), 1384 (s), 1102 (s), 1079 (w), 871 (w), 842 (w), 756 (s), 727 (m), 705 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87−7.78 (m, 1 H), 7.71−7.63 (m, 1 H), 7.38−7.13 (m, 7 H), 7.04 (s, 1 H), 4.65 (t, J = 7.0, 1 H), 3.30 (s, 3 H), 3.28 (distorted dd, J = 13.9, 7.0, 1 H), 3.07 (distorted dd, J = 13.9, 7.0, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.4, 139.7, 139.3, 137.8, 129.4, 128.2, 126.4, 124.2, 123.4, 122.6, 122.2, 81.3, 56.9, 44.6; GC-MS: m/z = 270 (0.2) [$(M + 2)^+$], 269 (0.8), 268 (4) [M^+], 178 (12), 177 (100), 162 (12), 161 (14), 134 (9). Anal. Calcd for $C_{17}H_{16}OS$ (268.37): C, 76.08; H, 6.01; S, 11.95; found C, 76.13; H, 5.99; S, 11.93.

*2-(1-Methoxypentyl)-3-methylbenzo[b]thiophene (**5c**).* Yield: 122 mg (98% based on starting **1b**, Table 4, entry 4). Yellow oil. IR (film): ν = 2955 (s), 2931 (s), 2859 (m), 1460 (m), 1437 (m), 1177 (w), 1094 (s), 754 (s), 729 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84−7.78 (m, 1 H), 7.69−7.63 (m, 1 H), 7.41−7.27 (m, 2 H), 4.61 (t, J = 7.0, 1 H), 3.28 (s, 3 H), 2.38 (s, 3 H), 2.04−1.90 (m, 1 H), 1.83−1.69 (m, 1 H), 1.47−1.21 (m, 4 H), 0.88 (t, J = 6.9, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.3, 140.6, 138.9, 128.7, 124.2, 123.8, 122.6, 121.5, 76.6, 56.6, 37.7, 27.9, 22.6, 14.0, 11.9; GC-MS: m/z = 250 (1) [$(M + 2)^+$], 249 (2), 248 (12) [M^+], 192 (14), 191 (100), 176 (14), 175 (13), 161 (9), 148 (9), 147 (16), 128 (5), 115 (5). Anal. Calcd for $C_{15}H_{20}OS$ (248.38): C, 72.53; H, 8.12; S, 12.91; found C, 72.57; H, 8.10; S, 12.89.

*2-(1-Methoxy-3-phenylpropyl)-3-methylbenzo[b]thiophene (**5d**).* Yield: 105 mg (71% based on starting **1b**, Table 4, entry 5). Yellow oil. IR (film): ν = 2924 (m), 2859 (w), 2818 (w), 1496 (w), 1455 (m), 1437 (m), 1340 (w), 1178 (w), 1102 (s), 942 (w), 754 (s), 729 (m), 700 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84−7.79 (m, 1 H), 7.68−7.63 (m, 1 H), 7.40−7.24 (m, 4 H), 7.22−7.14 (m, 3 H), 4.58 (distorted dd, J = 7.7, 6.1, 1 H), 3.28 (s, 3 H), 2.82−2.63 (m, 2 H), 2.38−2.26 (m, 1 H), 2.29 (s, 3 H), 2.13−2.01 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.5, 140.7, 140.6, 138.9, 128.9, 128.5, 128.4, 125.9, 124.3, 123.8, 122.6, 121.5, 77.4, 56.6, 39.2, 31.9, 11.8; GC-MS: m/z = 298 (1) [$(M + 2)^+$], 296 (14) [M^+], 264 (1), 192 (14), 191 (100), 176 (12), 175 (11), 161 (3), 147 (14), 91 (28). Anal. Calcd for $C_{19}H_{20}OS$ (296.43): C, 76.98; H, 6.80; S, 10.82; found C, 77.01; H, 6.81; S, 10.79.

*2-(1-Methoxy-3-phenylpropyl)-3-phenylbenzo[b]thiophene (**5e**).* Yield: 131 mg (73% based on starting **1c**, Table 4, entry 6). Yellow solid, mp 62−63 °C. IR (KBr): ν = 2931 (m), 2858 (w), 1493 (w), 1442 (m), 1385 (w), 1261 (w), 1074 (s), 1026 (w), 941 (w), 748 (s),

690 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.92−7.84 (m, 1 H), 7.53−7.04 (m, 13 H), 4.55−4.44 (m, 1 H), 3.21 (s, 3 H), 2.83−2.56 (m, 2 H), 2.38−2.19 (m, 1 H), 2.16−1.98 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.3, 141.4, 140.1, 138.9, 136.0, 134.8, 129.9, 128.6, 128.4, 128.3, 127.6, 125.8, 124.6, 124.1, 123.0, 122.5, 76.6, 56.6, 39.8, 31.9; GC-MS: m/z = 360 (1) [$(M + 2)^+$], 359 (5), 358 (17) [M^+], 254 (21), 253 (100), 237 (17), 234 (10), 221 (37), 165 (12), 91 (23). Anal. Calcd for $C_{24}H_{22}OS$ (358.50): C, 80.41; H, 6.19; S, 8.94; found C, 80.45; H, 6.17; S, 8.96.

2-(1-Methoxy-2-phenylethyl)-3-phenylbenzo[b]thiophene (**5f**). Yield: 117 mg (68% based on starting **1c**, Table 4, entry 7). Yellow solid, mp 70−71 °C. IR (KBr): ν = 2921 (w), 1489 (w), 1440 (m), 1304 (s), 1333 (w), 1195 (w), 1092 (m), 974 (m), 770 (m), 757 (m), 698 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.93−7.87 (m, 1 H), 7.40−7.24 (m, 7 H), 7.22−7.15 (m, 3 H), 7.08−7.01 (m, 3 H), 4.61 (distorted dd, J = 7.5, 6.5, 1 H), 3.26 (distorted dd, J = 13.3, 6.5, 1 H), 3.18 (s, 3 H), 3.09 (distorted dd, J = 13.3, 7.5, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.2, 140.1, 138.9, 137.5, 136.8, 134.6, 129.8, 129.5, 128.4, 128.2, 127.5, 126.4, 124.6, 124.1, 123.1, 122.6, 79.0, 56.5, 44.7; GC-MS: m/z = 346 (0.1) [$(M + 2)^+$], 345 (0.5), 344 (2) [M^+], 254 (18), 253 (100), 237 (21), 221 (37), 208 (6), 165 (14), 91 (30). Anal. Calcd for $C_{23}H_{20}OS$ (344.47): C, 80.19; H, 5.85; S, 9.31; found C, 80.22; H, 5.84; S, 9.29.

2-(1-Methoxypentyl)-3-phenylbenzo[b]thiophene (**5g**). Yield: 76 mg (49% based on starting **1c**, Table 4, entry 8). Yellow oil. IR (film): ν = 2984 (m), 2858 (s), 2818 (m), 1603 (w), 1489 (m), 1456 (s), 1435 (s), 1350 (w), 1335 (m), 1251 (w), 1194 (m), 1124 (w), 1089 (m), 1030 (w), 949 (w), 768 (s), 733 (s), 701 (s), 649 (w), 603 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.88−7.82 (m, 1 H), 7.54−7.24 (m, 8 H), 4.45 (t, J = 6.8, 1 H), 3.21 (s, 3 H), 2.01−1.86 (m, 1 H), 1.85−1.70 (m, 1 H), 1.41−1.15 (m, 4 H), 0.82 (t, J = 7.0, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.7, 140.1, 138.8, 136.0, 135.1, 130.0, 128.6, 127.7, 124.5, 124.1, 123.0, 122.5, 77.5, 56.5, 38.1, 27.9, 22.5, 13.9; GC-MS: m/z = 312 (1) [$(M + 2)^+$], 311 (3), 310 (14) [M^+], 254 (18), 253 (100), 237 (16), 221 (33), 178 (3), 165 (11). Anal. Calcd for $C_{20}H_{22}OS$ (310.45): C, 77.38; H, 7.14; S, 10.33; found C, 77.35; H, 7.14; S, 10.35.

2-(Methoxyphenylmethyl)benzo[b]thiophene (**5h**). Yield: 76 mg (60% based on starting **1a**, Table 4, entry 9). Yellow solid, mp 60−61 °C. IR (KBr): ν = 2930 (m), 2830 (m), 1493 (m), 1451 (m), 1384 (w), 1338 (w), 1307 (w), 1195 (m), 1090 (s), 1026 (w), 964 (w), 833 (m), 782 (s), 715 (s), 660 (m), 641 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.80−7.72 (m, 1 H), 7.69−7.63 (m, 1 H), 7.50−7.20 (m, 7 H), 7.07 (s, 1 H), 5.52 (s, 1 H), 3.43 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.1, 140.8, 140.1, 139.4, 128.5, 128.1, 126.9, 124.1, 123.5, 122.4, 121.8, 81.9, 57.1; GC-MS: m/z = 256 (4) [$(M + 2)^+$], 255 (9), 254 (53) [M^+], 224 (20), 223 (100), 222 (21), 221 (32), 208 (9), 178 (17), 177 (19), 161 (17), 134 (9), 133 (8), 111 (15), 105 (43), 89 (21), 77 (31). Anal. Calcd for $C_{16}H_{14}OS$ (254.35): C, 75.55; H, 5.55; S, 12.61; found C, 75.56; H, 5.54; S, 12.63.

2-(1-Methoxy-2,2-dimethylpropyl)benzo[b]thiophene (**5i**). Yield: 62 mg (53% based on starting **1a**, Table 4, entry 10). Yellow solid, mp 96−97 °C. IR (KBr): ν = 2960 (m), 2925 (m), 2867 (w), 1460 (m), 1384 (s), 1187 (w), 1127 (m), 1087 (s), 966 (w), 836 (s), 759 (s), 728 (m), 676 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.85−7.78 (m, 1 H), 7.76−7.69 (m, 1 H), 7.38−7.23 (m, 2 H), 7.14 (s, 1 H), 4.07 (s, 1 H), 3.30 (s, 3 H), 1.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.9, 139.8, 139.3, 124.0, 123.8, 123.2, 123.1, 122.2, 88.9, 57.9, 35.7, 26.3; GC-MS: m/z = 236 (0.4) [$(M + 2)^+$], 235 (1), 234 (9) [M^+], 178 (12), 177 (100), 162 (12), 161 (17), 147 (4), 134 (10), 115 (2), 89 (5). Anal. Calcd for $C_{14}H_{18}OS$ (234.36): C, 71.75; H, 7.74; S, 13.68; found C, 71.71; H, 7.76; S, 13.70.

2-(Methoxyphenylmethyl)-3-methylbenzo[b]thiophene (**5j**). Yield: 81 mg (60% based on starting **1b**, Table 4, entry 11). Yellow oil. IR (film): ν = 2985 (w), 2929 (m), 2820 (m), 1493 (m), 1460 (s), 1436 (s), 1312 (m), 1187 (m), 1171 (m), 1094 (s), 1070 (s), 1029 (w), 960 (m), 732 (s), 730 (s), 700 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.79−7.74 (m, 1 H), 7.68−7.62 (m, 1 H), 7.47−7.40 (m, 2 H), 7.38−7.23 (m, 5 H), 5.70 (s, 1 H), 3.45 (s, 3 H), 2.41 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.9, 140.5, 140.3, 139.1, 128.5, 127.8, 126.7, 124.2, 123.8, 122.5, 121.6, 79.7, 57.1, 12.0; GC-MS: m/z = 270 (3) [$(M + 2)^+$], 269 (10), 268 (52) [M^+], 253 (16), 238 (18), 237 (100), 236 (12), 222 (12), 221 (18), 203 (9), 191 (21), 175 (11), 147 (15), 134 (6), 121 (8), 105 (16), 91 (10), 77 (38). Anal. Calcd for $C_{17}H_{16}OS$ (268.37): C, 76.08; H, 6.01; S, 11.95; found C, 76.12; H, 5.99; S, 11.94.

2-(1-Methoxy-2,2-dimethylpropyl)-3-methylbenzo[b]thiophene (**5k**). Yield: 68 mg (55% based on starting **1b**, Table 4, entry 12). White solid, mp 56−58 °C. IR (KBr): ν = 2965 (m), 2929 (m), 2818 (m), 1480 (w), 1460 (s), 1436 (m), 1385 (m), 1362 (s), 1264 (w), 1169 (s), 1156 (w), 1092 (s), 960 (m), 912 (w), 755 (s), 739 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.83−7.77 (m, 1 H), 7.69−7.63 (m, 1 H), 7.40−7.27 (m, 2 H), 4.28 (s, 1 H), 3.24 (s, 3 H), 2.37 (s, 3 H), 1.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.3, 139.1, 139.0, 130.0, 124.1, 123.5, 122.2, 121.3, 86.1, 57.6, 36.9, 26.5, 12.8; GC-MS: m/z = 250 (1) [$(M + 2)^+$], 249 (2), 248 (9) [M^+], 217 (1), 192 (17), 191 (100), 176 (19), 175 (17), 147 (17), 115 (4), 77 (2). Anal. Calcd for $C_{15}H_{20}OS$ (248.38): C, 72.53; H, 8.12; S, 12.91; found C, 72.55; H, 8.11; S, 12.94.

2-(Methoxyphenylmethyl)-3-phenylbenzo[b]thiophene (**5l**). Yield: 132 mg (80% based on starting **1c**, Table 4, entry 13). Yellow solid, mp 106−107 °C. IR (KBr): ν = 2994 (m), 2925 (m), 2815 (m), 1494 (m), 1440 (s), 1384 (m), 1317 (m), 1185 (m), 1133 (m), 1077 (s), 1028 (m), 970 (m), 857 (w), 771 (s), 751 (s), 700 (s), 667 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.82−7.75 (m, 1 H), 7.54−7.15 (m, 13 H), 5.54 (s, 1 H), 3.35 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.5, 141.2, 139.9, 139.3, 135.8, 134.9, 130.1, 128.7, 128.4, 127.8, 127.7, 126.6, 124.6, 124.1, 123.1, 122.4, 79.4, 56.8; GC-MS: m/z = 332 (4) [$(M + 2)^+$], 331 (16), 330 (61) [M^+], 315 (3), 300 (18), 299 (70), 298 (27), 297 (13), 253 (15), 237 (11), 222 (17), 221 (100), 208 (9), 165 (15), 149 (6), 105 (16), 77 (32). Anal. Calcd for $C_{22}H_{18}OS$ (330.44): C, 79.96; H, 5.49; S, 9.70; found C, 80.01; H, 5.47; S, 9.69.

2-(1-Methoxy-2,2-dimethylpropyl)-3-phenylbenzo[b]thiophene (**5m**). Yield: 95 mg (61% based on starting **1c**, Table 4, entry 14). White solid, mp 99−100 °C. IR (KBr): ν = 2983 (s), 2919 (m), 2868 (m), 2817 (m), 1600 (w), 1477 (m), 1459 (s), 1389 (m), 1364 (m), 1193 (w), 1179 (w), 1133 (m), 1068 (s), 963 (m), 755 (s), 735 (s), 700 (s), 654 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, J = 7.3, 1 H), 7.53−7.23 (m, 8 H), 4.22 (s, 1 H), 3.30 (s, 3 H), 0.90 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.8, 140.1, 139.1, 137.6, 135.7, 128.6, 127.5, 124.4, 123.9, 122.9, 122.1, 85.6, 57.3, 36.4, 26.6; GC-MS: m/z = 312 (0.3) [$(M + 2)^+$], 311 (0.9), 310 (4) [M^+], 254 (18), 253 (100), 237 (15), 221 (30), 208 (4), 165 (9). Anal. Calcd for $C_{20}H_{22}OS$ (310.45): C, 77.38; H, 7.14; S, 10.33; found C, 77.34; H, 7.14; S, 10.36.

2-(1-Ethoxypentyl)benzo[b]thiophene (**5a′**). Yield: 78 mg (63% based on starting **1a**, Table 4, entry 15). Yellow oil. IR (film): ν = 2955 (m), 2936 (m), 2859 (m), 1457 (m), 1438 (w), 1398 (w), 1318 (m), 1105 (m), 1087 (m), 938 (w), 872 (w), 836 (s), 750 (s), 727 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.85−7.77 (m, 1 H), 7.75−7.67 (m, 1 H), 7.37−7.25 (m, 2 H), 7.16 (s, 1 H), 4.52 (t, J = 6.9, 1 H), 3.59−3.35 (m, 2 H), 2.02−1.88 (m, 1 H), 1.87−1.71 (m, 1 H), 1.47−1.15 (m, 4 H), 1.20 (t, J = 7.1, 3 H), 0.88 (t, J = 7.1, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.5, 139.6, 139.4, 124.1, 124.0, 123.2, 122.6, 121.3, 78.3, 64.3, 37.9, 27.9, 22.5, 15.3, 14.0; GC-MS: m/z = 250 (1) [$(M + 2)^+$], 249 (3), 248 (20) [M^+], 192 (15), 191 (100), 163 (75), 161 (15), 147 (23), 135 (42), 134 (13), 115 (10), 91 (23), 89 (9). Anal. Calcd for $C_{15}H_{20}OS$ (248.38): C, 72.53; H, 8.12; S, 12.91; found C, 72.56; H, 8.11; S, 12.87.

2-(1-Ethoxypentyl)-3-methylbenzo[b]thiophene (**5c′**). Yield: 125 mg (95% based on starting **1b**, Table 4, entry 16). Colorless oil. IR (film): ν = 2957 (m), 2931 (s), 2861 (s), 1460 (m), 1438 (m), 1380 (w),

1331 (w), 1180 (w), 1089 (m), 756 (s), 729 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, J = 8.1, 1 H), 7.64 (d, J = 8.1, 1 H), 7.40−7.24 (m, 2 H), 4.70 (t, J = 6.6, 1 H), 3.57−3.31 (m, 2 H), 2.36 (s, 3 H), 2.07−1.89 (m, 1 H), 1.85−1.68 (m, 1 H), 1.49−1.18 (m, 4 H), 1.19 (t, J = 6.6, 3 H), 0.88 (t, J = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.3, 140.7, 138.8, 128.1, 124.1, 123.7, 122.5, 121.4, 76.0, 64.2, 37.9, 27.9, 22.6, 15.3, 14.0, 11.9; GC-MS: m/z = 264 (2) [$(M + 2)^+$], 263 (8), 262 (39) [M^+], 206 (26), 205 (100), 177 (85), 161 (20), 149 (42), 147 (17), 134 (20), 115 (8). Anal. Calcd for $C_{16}H_{22}OS$ (262.41): C, 73.23; H, 8.45; S, 12.22; found C, 73.27; H, 8.47; S, 12.20.

*2-(1-Ethoxypentyl)-3-phenylbenzo[b]thiophene (**5g′**).* Yield: 90 mg (55% based on starting **1c**, Table 4, entry 17). Colorless oil. IR (film): ν = 2935 (m), 2856 (s), 1457 (m), 1377 (w), 1086 (m), 768 (m), 734 (m), 701 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.88−7.80 (m, 1 H), 7.56−7.22 (m, 8 H), 4.56 (t, J = 6.7, 1 H), 3.58−3.42 (m, 1 H), 3.33−3.18 (m, 1 H), 2.03−1.87 (m, 1 H), 1.86−1.70 (m, 1 H), 1.42−1.09 (m, 4 H), 1.12 (t, J = 7.3, 3 H), 0.82 (t, J = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.8, 140.2, 138.8, 135.4, 135.2, 130.0, 128.6, 127.6, 124.4, 124.0, 122.9, 122.5, 75.6, 64.0, 38.3, 27.9, 22.4, 15.2, 13.9; GC-MS: m/z = 326 (1) [$(M + 2)^+$], 325 (3), 324 (14) [M^+], 268 (20), 267 (100), 239 (40), 221 (16), 211 (16), 178 (14), 165 (11). Anal. Calcd for $C_{21}H_{24}OS$ (324.48): C, 77.73; H, 7.46; S, 9.88; found C, 77.68; H, 7.49; S, 9.85.

*2-(Ethoxyphenylmethyl)benzo[b]thiophene (**5h′**).* Yield: 73 mg (54% based on starting **1a**, Table 4, entry 18). Yellow solid, mp. 34−35 °C. IR (KBr): ν = 2971 (m), 2890 (m), 2866 (m), 1492 (w), 1458 (s), 1433 (s), 1436 (m), 1384 (w), 1312 (w), 1216 (w), 1139 (m), 1083 (s), 1072 (s), 1009 (m), 818 (m), 756 (s), 728 (m), 701 (s), 640 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.79−7.73 (m, 1 H), 7.69−7.63 (m, 1 H), 7.49−7.43 (m, 2 H), 7.40−7.22 (m, 5 H), 7.08 (s, 1 H), 5.64 (s, 1 H), 3.68−3.54 (m, 2 H), 1.29 (t, J = 7.0, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.7, 141.3, 140.0, 139.4, 128.5, 128.0, 126.9, 124.09, 124.06, 123.5, 122.4, 121.6, 80.0, 64.9, 15.3; GC-MS: m/z = 270 (3) [$(M + 2)^+$], 269 (11), 268 (56) [M^+], 224 (32), 223 (100), 222 (20), 221 (30), 189 (8), 178 (21), 163 (11), 161 (12), 147 (6), 135 (10), 111 (12), 105 (53), 105 (53), 91 (10), 89 (21), 77 (26). Anal. Calcd for $C_{17}H_{16}OS$ (268.37): C, 76.08; H, 6.01; S, 11.95; found C, 76.11; H, 5.99; S, 11.97.

*2-(Ethoxyphenylmethyl)-3-methylbenzo[b]thiophene (**5j′**).* Yield: 72 mg (51% based on starting **1b**, Table 4, entry 19). Colorless oil. IR (KBr): ν = 2974 (m), 2917 (s), 2849 (m), 1493 (w), 1453 (m), 1436 (m), 1381 (w), 1170 (m), 1155 (m), 1087 (s), 1070 (s), 733 (s), 729 (s), 700 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, J = 7.3, 1 H), 7.63 (d, J = 7.3, 1 H), 7.48−7.41 (m, 2 H), 7.37−7.20 (m, 5 H), 5.80 (s, 1 H), 3.71−3.51 (m, 2 H), 2.39 (s, 3 H), 1.28 (t, J = 7.3, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.3, 141.1, 140.6, 139.1, 128.4, 128.2, 127.7, 126.7, 124.1, 123.8, 122.4, 121.5, 77.8, 64.8, 15.2, 12.0; GC-MS: m/z = 284 (4) [$(M + 2)^+$], 283 (13), 282 (57) [M^+], 267 (11), 238 (24), 237 (100), 236 (17), 221 (18), 205 (11), 177 (10), 149 (6), 134 (6), 115 (6), 105 (24), 77 (14). Anal. Calcd for $C_{18}H_{18}OS$ (282.40): C, 76.56; H, 6.42; S, 11.35; found C, 76.59; H, 6.41; S, 11.38.

*2-(1-Ethoxy-2,2-dimethylpropyl)-3-methylbenzo[b]thiophene (**5k′**).* Yield: 76 mg (58% based on starting **1b**, Table 4, entry 20). Yellow solid, mp 49−51 °C. IR (KBr): ν = 2964 (m), 2931 (m), 2863 (m), 2837 (m), 1479 (w), 1461 (m), 1438 (m), 1384 (m), 1316 (m), 1263 (w), 1160 (m), 1072 (s), 996 (m), 916 (w), 763 (s), 736 (m), 715 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, J = 7.3, 1 H), 7.64 (d, J = 7.3, 1 H), 7.39−7.25 (m, 2 H), 4.37 (s, 1 H), 3.52−3.38 (m, 1 H), 3.34−3.21 (m, 1 H), 2.36 (s, 3 H), 1.15 (t, J = 7.0, 3 H), 1.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.4, 140.2, 139.1, 129.4, 123.9, 123.5, 122.1, 121.3, 83.7, 64.9, 36.9, 26.5, 15.1, 12.8; GC-MS: m/z = 264 (0.5) [$(M + 2)^+$], 263 (2), 262 (8) [M^+], 206 (14), 205 (100), 177 (61), 149 (31), 147 (12), 134 (16), 115 (6). Anal. Calcd for $C_{16}H_{22}OS$ (262.41): C, 73.23; H, 8.45; S, 12.22; found C, 73.26; H, 8.44; S, 12.19.

*2-(1-Isopropoxy-2,2-dimethylpropyl)benzo[b]thiophene (**5i′**).* Yield: 79 mg (60% based on starting **1a**, Table 4, entry 21). Yellow solid, mp. 83−84 °C. IR (KBr): ν = 2970 (s), 2929 (m), 2866 (m), 1462 (m), 1304 (s), 1315 (w), 1185 (w), 1125 (m), 1060 (s), 1031 (w), 937 (w), 868 (w), 834 (m), 751 (s), 728 (m), 719 (w), 684 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.83−7.77 (m, 1 H), 7.73−7.67 (m, 1 H), 7.36−7.23 (m, 2 H), 7.11 (s, 1 H), 4.28 (s, 1 H), 3.54 (heptuplet, J = 6.6, 1 H), 1.12 (d, J = 6.6, 3 H), 1.11 (d, J = 6.6, 3 H), 0.99 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.9, 139.7, 139.4, 123.9, 123.6, 123.0, 122.4, 122.1, 83.5, 69.6, 35.5, 26.4, 23.3, 20.8; GC-MS: m/z = 264 (1) [$(M + 2)^+$], 263 (1), 262 (5) [M^+], 205 (26), 164 (12), 163 (100), 147 (5), 135 (22), 115 (2), 91 (11). Anal. Calcd for $C_{16}H_{22}OS$ (262.41): C, 73.23; H, 8.45; S, 12.22; found C, 73.27; H, 8.44; S, 12.19.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^1H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: b.gabriele@unical.it.

■ ACKNOWLEDGMENT

Financial support from the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR, Rome, Italy), and from the University of Calabria (Rende, Italy) is gratefully acknowledged (Progetto di Ricerca d'Interesse Nazionale PRIN 2008A7P7YJ).

■ REFERENCES

(1) For recent representative examples, see: (a) Li, L.; Mathieu, M.-C.; Denis, D.; Therien, A. G.; Wang, Z. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 734–737. (b) Li, L.; Berthelette, C.; Chateauneuf, A.; Ouellet, M.; Sturino, C. F.; Wang, Z. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7440–7443. (c) Santillan, A.; McClure, K. J.; Allison, B. D.; Lord, B.; Boggs, J. D.; Morton, K. L.; Everson, A. M.; Nepomuceno, D.; Letavic, M. A.; Lee-Dutra, A.; Lovenberg, T. W.; Carruthers, N. I.; Grice, C. A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6226–6230. (d) Vangveravong, S.; Taylor, M.; Xu, J.; Cui, J.; Calvin, W.; Babic, S.; Luedtke, R. R.; Mach, R. H. *Bioorg. Med. Chem.* **2010**, *18*, 5291–5300. (e) Mourey, R. J.; Burnette, B. L.; Brustkern, S. J.; Daniels, J. S.; Hirsch, J. L.; Hood, W. F.; Meyers, M. J.; Mnich, S. J.; Pierce, B. S.; Saabye, M. J.; Schindler, J. F.; South, S. A.; Webb, E. G.; Zhang, J.; Anderson, D. R. *J. Pharmacol. Exp. Ther.* **2010**, *333*, 797–807. (f) Davis, R. L.; Kahraman, M.; Prins, T. J.; Beaver, Y.; Cook, T. G.; Cramp, J.; Cayanan, C. S.; Gardiner, E. M. M.; McLaughlin, M. A.; Clark, A. F.; Hellberg, M. R.; Shiau, A. K.; Noble, S. A.; Borchardt, A. J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3361–3366. (g) Moree, W. J.; Jovic, F.; Coon, T.; Yu, J.; Li, B.-F.; Tucci, F. C.; Marinkovic, D.; Gross, R. S.; Malany, S.; Bradbury, M. J.; Hernandez, L. M.; O'Brien, Z.; Wen, J.; Wang, H.; Hoare, S. R. J.; Petroski, R. E.; Sacaan, A.; Madan, A.; Crowe, P. D.; Beaton, G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2316–2320. (h) Shao, H.; Li, D.; Yang, Y.; Guo, H.-F.; Liu, Z.-Y.; Si, S.-Y.; Yang, Z.; Li, Z.-R. *J. Enzyme Inhib. Med. Chem.* **2010**, *25*, 282–289. (i) Wang, S.; Beck, R.; Blench, T.; Burd, A.; Buxton, S.; Malic, M.; Ayele, T.; Shaikh, S.; Chahwala, S.; Chander, C.; Holland, R.; Merette, S.; Zhao, L.; Blackney, M.; Watts, A. *J. Med. Chem.* **2010**, *53*, 1465–1472.

(2) For recent representative examples, see: (a) Kovarova, A.; Svoboda, J.; Novotna, V.; Glogavora, M.; Salamonczyk, M.; Pociecha, D.; Gorecka, E. *Liq. Cryst.* **2010**, *37*, 1501–1513. (b) Luyksaar, S. I.; Migulin, V. A.; Nabatov, B. V.; Krayushkin, M. M. *Russ. Chem. Bull.* **2010**, *59*, 446–451. (c) Jung, K. H.; Kim, K. H.; Lee, D. H.; Jung, D. S.; Park, C. E.; Choi, D. H. *Org. Electron.* **2010**, *11*, 1584–1593. (d) Uemura, T.;

Hirose, Y.; Uno, M.; Takimiya, K.; Takeya *J. Appl. Phys. Expr.* **2009**, *2*, article number 111501. (e) Pu, S.; Li, M.; Liu, G.; Le, Z. *Aust. J. Chem.* **2009**, *62*, 464–474. (f) Pu, S.; Li, M.; Fan, C.; Liu, G.; Shen, L. *J. Mol. Struct.* **2009**, *919*, 100–111. (g) Um, M.-C.; Kwak, J.; Hong, J.-P.; Kang, J.; Yoon, D. Y.; Lee, S. H.; Lee, C.; Hong, J.-I. *J. Mater. Chem.* **2008**, *18*, 4698–4703. (h) Yamaguchi, T.; Uchida, K.; Irie, M. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 644–652. (i) Lo, C.; Adenier, A.; Maurel, F.; Aaron, J. J.; Kozmik, V.; Svoboda, J. *Synth. Met.* **2008**, *158*, 6–24. (j) Gao, P.; Beckmann, D.; Tsao, H. N.; Feng, X.; Enkelmann, V.; Pisula, W.; Muellen, K. *Chem. Commun.* **2008**, 1548–1550. (k) Keshtov, M. L.; Mal'tsev, E. I.; Lypenko, D. A.; Brusentseva, M. A.; Sosnovyi, M. A.; Il'ina, M. N.; Vasnev, V. A.; Peregudov, A. S.; Petrovskii, P. V.; Vannikov, A. V.; Khokhlov, A. R. *Polym. Sci. Ser. A* **2008**, *50*, 18–24. (l) Kurfurst, M.; Kozmik, V.; Svoboda, J.; Novotna, V.; Glogarova, M. *Liq. Cryst.* **2008**, *35*, 21–31.

(3) (a) Werner, E. G. G. *Rec. Trav. Chim. Pays-Bas* **1949**, *68*, 509–519. (b) Capozzi, G.; Melloni, G.; Modena, G. *J. Chem. Soc. C* **1970**, 2621–2625. (c) Mayer, F.; Mombour, A.; Lassmann, W.; Werner, W.; Landmann, P.; Schneider, E. *Liebigs Ann. Chem.* **1931**, *488*, 259–296. (d) Terpstra, J. W.; Van Lausen, A. M. *J. Org. Chem.* **1986**, *51*, 230–238. (e) Watanabe, M.; Date, M.; Kawanishi, K.; Akiyoshi, R.; Furukawa, S. *J. Heterocycl. Chem.* **1991**, *28*, 173–176.

(4) (a) Gonzalez, J. P.; Edgar, M.; Elsegood, M. R. J. *Org. Biomol. Chem.* **2011**, *9*, 2294–2305. (b) Li, C.-L.; Zhang, X.-G.; Fang, R.-Y.; Zhong, P.; Li, J.-H. *J. Org. Chem.* **2010**, *75*, 7037–7040. (c) Jacubert, M.; Provot, O.; Peyrat, J.-F.; Hamze, A.; Brion, J.-D.; Alami, M. *Tetrahedron* **2010**, *66*, 3775–3787. (d) Hussain, M.; Malik, I.; Villinger, A.; Langer, P. *Synlett* **2009**, 2691–2695. (e) Gopinath, P.; Nilaya, S.; Debi, T. R.; Ramkumar, V.; Muraleedharan, K. M. *Chem. Commun.* **2009**, 7131–7133. (f) Bryan, C. S.; Braunger, J. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7064–7068. (g) Capperucci, A.; Degl'Innocenti, A.; Nocentini, T.; Pollicino, S. *J. Sulfur Chem.* **2009**, *30*, 319–326. (h) Toguem, S.-M. T.; Hussain, M.; Malik, I.; Villinger, A.; Langer, P. *Tetrahedron Lett.* **2009**, *50*, 4962–4964. (i) Jacubert, M.; Hamze, A.; Provot, O.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2009**, *50*, 3588–3592. (j) Jeong, H. J.; Yoon, U. Y.; Jang, S. H.; Yoo, U.-A.; Kim, S. N.; Truong, B. T.; Shin, S. C.; Yoon, Y.-J.; Singh, O. M.; Lee, S.-G. *Synlett* **2007**, 1407–1410. (k) Kobayashi, K.; Fujita, S.; Hase, M.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 763–767. (l) Barluenga, J.; Vazquez-Villa, H.; Merino, I.; Ballesteros, A.; Gonzalez, J. M. *Chem.—Eur. J.* **2006**, *12*, 5790–5805. (m) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473–4475. (n) Barluenga, J.; Vazquez-Villa., H.; Ballesteros, A.; Gonzalez, J. M. *Adv. Synth. Catal.* **2005**, *347*, 526–530. (o) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2003**, *5*, 4377–4380. (p) Yang, S. M.; Shie, J. J.; Fang, J. M.; Nandy, S. K.; Chang, H. Y.; Lu, S. H.; Wang, G. *J. Org. Chem.* **2002**, *67*, 5208–5215. (q) Cabiddu, M. G.; Cabiddu, S.; Cadoni, E.; Demontis, S.; Fattuoni, C.; Melis, S. *Tetrahedron* **2002**, *58*, 4529–4533. (r) Kim, S. K.; Yang, J.; DiNinno, F. *Tetrahedron Lett.* **1999**, *40*, 2909–2912. (s) Afxantidis, J.; Bouchry, N.; Aune, J. P. *J. Mol. Catal. A: Chem.* **1995**, *102*, 49–58. (t) Liebeskind, L. S.; Wang, J. Y. *J. Org. Chem.* **1993**, *58*, 3350–3356. (u) Buchwald, S. L.; Qun, F. *J. Org. Chem.* **1989**, *54*, 2793–2797.

(5) For representative examples, see: (a) Gabriele, B.; Plastina, P.; Vetere, M. V.; Veltri, L.; Mancuso, R.; Salerno, G. *Tetrahedron Lett.* **2010**, *51*, 3565–3567. (b) Gabriele, B.; Mancuso, R.; Lupinacci, E.; Salerno, G.; Veltri, L. *Tetrahedron* **2010**, *66*, 6156–6161. (c) Gabriele, B.; Veltri, L.; Mancuso, R.; Plastina, P.; Salerno, G.; Costa, M. *Tetrahedron Lett.* **2010**, *51*, 1663–1665. (d) Egi, M.; Azechi, K.; Akai, S. *Org. Lett.* **2009**, *11*, 5002–5005. (e) Aponick, A.; Li, C.-Y.; Malinge, J.; Marques, E. F. *Org. Lett.* **2009**, *11*, 4624–4627. (f) Gabriele, B.; Mancuso, R.; Lupinacci, E.; Spina, R.; Salerno, G.; Veltri, L.; Dibenedetto, A. *Tetrahedron* **2009**, *65*, 8507–8512. (g) Yada, Y.; Miyake, Y.; Nishibayashi, Y. *Organometallics* **2008**, *27*, 3614–3617. (h) Gabriele, B.; Mancuso, R.; Salerno, G.; Lupinacci, E.; Ruffolo, G.; Costa, M. *J. Org. Chem.* **2008**, *73*, 4971–4977. (i) Gabriele, B.; Mancuso, R.; Salerno, G.; Plastina, P. *J. Org. Chem.* **2008**, *73*, 756–759. (j) Hayes, S. J.; Knight, D. W.; Menzies, M. D.; O'Halloran, M.; Tan, W.-F. *Tetrahedron Lett.* **2007**, *48*, 7709–7712. (k) Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. *J. Org. Chem.* **2007**, *72*, 9278–9282. (l) Gabriele, B.; Mancuso, R.; Salerno, G.; Ruffolo, G.; Plastina, P. *J. Org. Chem.* **2007**, *72*, 6873–6877. (m) Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. *Adv. Synth. Catal.* **2006**, *348*, 1101–1109. (n) Gabriele, B.; Mancuso, R.; Salerno, G.; Veltri, L. *Chem. Commun.* **2005**, 271–273. (o) Knight, D. W.; Sharland, C. M. *Synlett* **2004**, 119–121. (p) Sakai, M.; Sasaki, M.; Tanino, K.; Miyashita, M. *Tetrahedron Lett.* **2002**, *43*, 1705–1708. (q) McDonald, F. E.; Zhu, H. Y. H. *Tetrahedron* **1997**, *53*, 11061–11068. (r) McDonald, F. E.; Gleason, M. M. *J. Am. Chem. Soc.* **1996**, *118*, 6648–6659. (s) McDonald, F. E.; Connolly, C. B.; Gleason, M. M.; Towne, T. B.; Treiber, K. D. *J. Org. Chem.* **1993**, *58*, 6952–6953. (t) Wakabayashi, Y.; Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3655–3661. (u) Utimoto, K.; Miwa, H.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277–4278.

(6) For recent representative reviews on heterocyclization reactions induced by triple bond activation by a metal center, see: (a) Yamamoto, T.; Gridnev, I. D.; Patil, N. T.; Jin, T. *Chem. Commun.* **2009**, 5075–5087. (b) Luo, P.; Tang, R.; Zhong, P.; Li, J. *Chin. J. Org. Chem.* **2009**, *29*, 1924–1937. (c) Kirsch, S. F. *Synthesis* **2008**, 3183–3204. (d) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847–7870. (e) Weibel, J.-M.; Blanc, A.; Pale, P. *Chem. Rev.* **2008**, *108*, 3149–3173. (f) Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem. Rev.* **2008**, *108*, 3174–3198. (g) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885–3903. (h) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442. (i) Gabriele, B.; Salerno, G.; Costa, M. *Top. Organomet. Chem.* **2006**, *18*, 239–272. (j) Wolfe, J. P.; Thomas, J. S. *Curr. Org. Chem.* **2005**, *9*, 625–655. (k) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198. (l) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309. (m) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079–3160. (n) Gabriele, B.; Salerno, G.; Costa, M. *Synlett* **2004**, 2468–2483. (o) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101–4111. (p) Gabriele, B.; Salerno, G. PdI_2. In *e-EROS (Electronic Encyclopedia of Reagents for Organic Synthesis)*; Crich, D., Ed.; John Wiley & Sons: Chichester, 2006. (q) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *J. Organomet. Chem.* **2003**, *687*, 219–228.

(7) For recent leading examples of reactions involving metal sulfide intermediates, see:(a) Ananikov, V. P.; Zalesskiy, S. S.; Kachala, V. V.; Beletskaya, I. P. *J. Organomet. Chem.* **2011**, *696*, 400–405. (b) Ananikov, V. P.; Gayduk, K. A.; Orlov, N. V.; Beletskaya, I. P.; Khrustalev, V. N.; Antipin, M. Y. *Chem.—Eur. J.* **2010**, *16*, 2063–2071. (c) Ananikov, V. P.; Gayduk, K. A.; Beletskaya, I. P.; Khrustalev, V. N.; Antipin, M. Y. *Eur. J. Org. Chem.* **2009**, 1149–1161. (d) Ananikov, V. P.; Gayduk, K. A.; Beletskaya, I. P.; Khrustalev, V. N. *Chem.—Eur. J.* **2008**, *14*, 2420–2434. (e) Beletskaya, I. P.; Ananikov, V. P. *Eur. J. Org. Chem.* **2007**, 3431–3444. (f) Ananikov, V. P.; Orlov, N. V.; Beletskaya, I. P.; Khrustalev, V. N.; Antipin, M. Y.; Timofeeva, T. V. *J. Am. Chem. Soc.* **2007**, *129*, 7252–7253.

(8) The use of KI was needed in order to solubilize PdI_2 by forming the PdI_4^{2-} anion. As we already observed in other cases, the excess of KI tended to stabilize the anionic complex. For recent examples on the use of the PdI_2/KI system in heterocycles synthesis, see refs 5a−5c, 5f, 5h,5i, 5k−5n, 6i, 6n, 6p, 6q and (a) Gabriele, B.; Veltri, L.; Salerno, G.; Mancuso, R.; Costa, M. *Adv. Synth. Catal.* **2010**, *352*, 3355–3363. (b) Gabriele, B.; Mancuso, R.; Salerno, G.; Ruffolo, G.; Costa, M.; Dibenedetto, A. *Tetrahedron Lett.* **2009**, *50*, 7330–7332. (c) Della Cà, N.; Campanini, F.; Gabriele, B.; Salerno, G.; Massera, C.; Costa, M. *Adv. Synth. Catal.* **2009**, *351*, 2423–2432. (d) Gabriele, B.; Mancuso, R.; Salerno, G. *J. Org. Chem.* **2008**, *73*, 7336–7341. (e) Gabriele, B.; Plastina, P.; Salerno, G.; Mancuso, R.; Costa, M. *Org. Lett.* **2007**, *9*, 3319–3322. (f) Gabriele, B.; Plastina, P.; Salerno, G.; Mancuso, R. *Synthesis* **2006**, 4247–4251. (g) Gabriele, B.; Salerno, G.; Fazio, A.; Veltri, L. *Adv. Synth. Catal.* **2006**, *348*, 2212–2222. (h) Gabriele, B.; Salerno, G.; Veltri, L.; Mancuso, R.; Li, Z.; Crispini, A.; Bellusci, A. *J. Org. Chem.* **2006**, *71*, 7895–7898. (i) Bacchi, A.; Costa, M.; Della Cà, N.; Gabriele, B.; Salerno, G.; Cassoni, S. *J. Org. Chem.* **2005**, *70*, 4971–4979. (j) Gabriele, B.; Plastina, P.; Salerno, G.; Costa, M. *Synlett* **2005**, 935–938. (k) Gabriele, B.; Salerno, G.; Plastina, P. *Lett. Org. Chem.* **2004**, *1*, 134–136. (l) Costa, M.; Della Cà, N.; Gabriele, B.; Massera, C.; Salerno, G.; Soliani, M. *J. Org. Chem.* **2004**, *69*, 2469–2477. (m) Gabriele, B.; Salerno, G.; Plastina, P.; Costa, M.; Crispini, A. *Adv. Synth. Catal.* **2004**, *346*, 351–358. (n) Bacchi, A.; Costa, M.; Della Cà, N.; Fabbricatore, M.; Fazio, A.; Gabriele, B.; Nasi, C.;

Salerno, G. *Eur. J. Org. Chem.* **2004**, 574–585. (o) Gabriele, B.; Salerno, G.; Fazio, A. *J. Org. Chem.* **2003**, *68*, 7853–7861. (p) Gabriele, B.; Salerno, G.; Fazio, A.; Pittelli, R. *Tetrahedron* **2003**, *59*, 6251–6259. (q) Gabriele, B.; Veltri, L.; Salerno, G.; Costa, M.; Chiusoli, G. P. *Eur. J. Org. Chem.* **2003**, 1722–1728. (r) Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. *J. Org. Chem.* **2003**, *68*, 601–604. (s) Bacchi, A.; Costa, M.; Gabriele, B.; Pelizzi, G.; Salerno, G. *J. Org. Chem.* **2002**, *67*, 4450–4457. (t) Gabriele, B.; Salerno, G.; Veltri, L.; Costa, M.; Massera, C. *Eur. J. Org. Chem.* **2001**, 4607–4613. (u) Gabriele, B.; Salerno, G.; Fazio, A. *Org. Lett.* **2000**, *2*, 351–352. (v) Gabriele, B.; Salerno, G.; De Pascali, F.; Costa, M.; Chiusoli, G. P. *J. Org. Chem.* **1999**, *64*, 7693–7699. (w) Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* **1999**, *64*, 7687–7692. (x) Chiusoli, G. P.; Costa, M.; Gabriele, B.; Salerno, G. *J. Mol. Catal.* **1999**, *143*, 297–310. (y) Fazio, A.; Gabriele, B.; Salerno, G. *Tetrahedron* **1999**, *55*, 485–502. (z) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *Tetrahedron Lett.* **1999**, *40*, 989–990.

(9) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: Oxford, 2000; pp 233, 260.

(10) For recent reviews on reactivity of thiols, see: (a) Koval', I. V. *Russ. J. Org. Chem.* **2007**, *43*, 319–346. (b) Koval', I. V. *Russ. J. Org. Chem.* **2005**, *41*, 631–648. For a recent review on thiol-mediated radical cyclization, see:(c) Majumdar, K. C.; Debnath, P. *Tetrahedron* **2008**, *64*, 9799–9820.

(11) For some other examples of radical cation formation induced by an initial thiyl radical addition, see: (a) Crich, D.; Mo, X.-S. *J. Am. Chem. Soc.* **1997**, *119*, 249–250. (b) Gabriele, B.; Mancuso, R.; Salerno, G. *Eur. J. Org. Chem.* **2010**, 3459–3464. (c) For a literature overview on ionic fragmentation of radical intermediates to give radical cations, see: Crich, D.; Shirai, M.; Brebion, F.; Rumthao, S. *Tetrahedron* **2006**, *62*, 6501–6518.

(12) (*E*)-2-(1-Alkenyl)benzothiophenes **3** have been mainly prepared by coupling, condensation, or olefination reactions starting from the corresponding functionalized benzothiophene precursors; for recent examples, see: (a) Aloui, F.; Moussa, S.; Hassine, B. B. *Tetrahedron Lett.* **2011**, *52*, 572–575. (b) Zhing, M.; Zhou, J.; Kan, J.; Wang, M.; Su, W.; Hong, M. *Chem. Commun.* **2010**, *46*, 5455–5457. (c) Fu, Z.; Huang, S.; Su, W.; Hong, M. *Org. Lett.* **2010**, *12*, 4992–4995. (d) Tseng, N.-W.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 1809–1811. (e) Zhao, J.; Huang, L.; Cheng, K.; Zhang, Y *Tetrahedron Lett.* **2009**, *50*, 2758–2761. (f) Hussein, M.; Malik, I.; Villinger, A.; Langer, P. *Synlett* **2009**, 2691–2695. (g) Chintareddy, V. R.; Wadhwa, K.; Verkade, J. G. *J. Org. Chem.* **2009**, *74*, 8118–8132. (h) Maehara, A.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1159–1162. (i) Um, M.-C.; Hong, J.-P.; Kang, J.; Yoon, D. Y.; Lee, S. H.; Hong, J.-I.; Jang, J.; Kim, J.-J. *New J. Chem.* **2008**, *32*, 2006–2010. (j) Choi, H.; Lee, J. K.; Song, K.; Kang, S. O.; Ko, J. *Tetrahedron* **2007**, *63*, 3115–3121. (k) Buszek, K. R.; Brown, N. *Org. Lett.* **2007**, *9*, 707–710. (l) Chu, L.-T.; Yu, P.-C.; Wu, B.-J.; Liao, Y.-C.; Chou, C.-H. *Heterocycles* **2007**, *71*, 165–173. (m) Hopf, H.; Hucker, J.; Ernst, L. *Eur. J. Org. Chem.* **2007**, 1891–1904. (n) Choi, H.; Lee, J. K.; Song, K.; Kang, S. O.; Ko, J. *Tetrahedron* **2007**, *63*, 3115–3121. (o) Yamano, Y.; Fujita, Y.; Mizuguchi, Y.; Nakagawa, K.; Okano, T.; Ito, M.; Wada, A. *Chem. Pharm. Bull.* **2007**, *55*, 1365–1370. (p) Sato, K.; Katayama, Y.; Yamagishi, T.; Arai, S. *J. Heterocycl. Chem.* **2006**, *43*, 177–181. (q) Modzelewska, A.; Pettit, C.; Achanta, G.; Davidson, N. E.; Huang, P.; Khan, S. R. *Bioorg. Med. Chem.* **2006**, *14*, 3491–3495. (r) Palmer, B. D.; Thompson, A. M.; Booth, R. J.; Dobrusin, E. M.; Kraker, A. J.; Lee, H. H.; Lunney, E. A.; Mitchell, L. H.; Ortwine, D. F.; Smaill, J. B.; Swan, L. M.; Denny, W. A. *J. Med. Chem.* **2006**, *49*, 4896–4911. (s) Paizs, C.; Katona, A.; Retey, J. *Chem.—Eur. J.* **2006**, *12*, 2739–2744. A few methods based on heterocyclization reactions have also been developed: see, for example, refs 4c and 4f.

(13) Only a few examples are reported in the literature on the synthesis of 2-alkoxymethylbenzothiophenes **5**, mainly based on alkylation of the corresponding alcoholic derivatives: (a) Voskressensky, L. G.; Kovaleva, S. A.; Borisova, T. N.; Listratova, A. V.; Varlamov, A. V.; Eresko, A. B.; Tolkunov, V. S.; Tolkunov, S. V. *Tetrahedron* **2010**, *66*, 9421–9430. (b) Voskressensky, L. G.; Borisova, T. N.; Listratova, A. V.; Sorokina, E. A.; Tolkunov, S. V.; Varlamov, A. V. *Russ. Chem. Bull.* **2007**, *56*, 1041–1048. (c) Yarovenko, V. N.; Es'kov, A. A.; Semenov, S. L.; Zavarzin, I. V.; Kadentsev, V. I.; Kalik, M. A.; Krayushkin, M. M.; Strokach, Y. P.; Valova, T. M.; Golotyuk, Z. O.; Barachevsky, V. A. *Russ. Chem. Bull.* **2005**, *54*, 2697–2700. To the best of our knowledge, no methods are known so far for the synthesis of **5** by heterocyclization of acyclic precursors.

(14) Toste, F. D.; Lough, A. J.; Still, I. W. J. *Tetrahedron Lett.* **1995**, *36*, 6619–6622.

(15) Topolski, M. *J. Org. Chem.* **1995**, *60*, 5588–5594.

(16) Schellenberg, K. A.; Westheimer, F. H. *J. Org. Chem.* **1965**, *30*, 1859–1862.