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Synthesis of Regioselectively Functionalized Benzo[*b*]thiophenes by Combined *ortho*-Lithiation−Halocyclization Strategies

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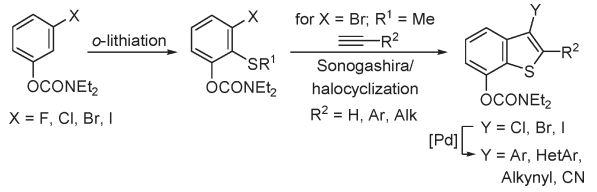

An efficient synthesis of 3-halo-7-oxygen-functionalized benzo[*b*]thiophenes bearing different substituents at C-2 has been developed from *N*,*N*-diethyl *O*-3-halophenylcarbamates. The key steps are an *ortho*-lithiation reaction, which gives rise to 3-halo-2-sulfanylphenol derivatives, and a electrophilic cyclization. The subsequent functionalization of the prepared halobenzothiophenes allows the access of a wide variety of 2,3,7-regioselectively functionalized benzo[*b*]thiophenes in good overall yields.

Molecules containing the benzo[*b*]thiophene nucleus show a wide spectrum of biological activities[1] and are also useful as functional materials.[2] So, the development of efficient and selective methodologies for the construction of diversely functionalized benzothiophenes is of considerable importance in organic synthesis.[3] In this context, the preparation of 7-hydroxybenzothiophene derivatives has proved to be difficult, and only a few reports have appeared that use thiophene derivatives to build up the benzenoid moiety in several steps.[4]

On the other hand, the electrophilic cyclization of alkynes bearing tethered heteroatom nucleophiles has emerged as a useful method for the synthesis of heterocycles, such as benzofurans, furans, benzopyrans, indoles, isoquinolines, or isochromenes.[5] By using this methodology, Flynn and co-workers[6] as well as Larock and co-workers[7] have reported the preparation of 2,3-disubstituted benzo[*b*]thiophenes by treatment of alkyl *o*-(1-alkynyl)phenyl sulfides with electrophilic reagents such as I_2, Br_2, NBS, and PhSeCl. Later on, Wu and Lu described the same halocyclization by using cupric halides as electrophilic partners.[8]

In recent years, we have been involved in the development of suitable methodologies for the synthesis of regioselectively functionalized heterocyclic compounds.[9] In this context, we have reported an efficient access to 2,3-dihalophenol derivatives,[10] and we have used these interesting functionalized scaffolds as starting materials for the preparation of 4-functionalized-benzo[*b*]furans,[10] 4- and 7-alkoxyindoles,[11] and 4-halo-1*H*-indoles.[12] Considering the interest in the synthesis of regioselectively functionalized benzo[*b*]thiophenes and the scarcity of methods for preparing these heterocyclic compounds with oxygen substituents at C-7, we reasoned that a Sonogashira coupling followed by a halocyclization reaction would provide the corresponding 3-halo-7-oxygen-functionalized benzo[*b*]thiophenes from 3-halo-2-methylsulfanylphenol derivatives. These intermediates could be accessible from *O*-3-halophenyl carbamates by *o*-lithiation and trapping with disulfides (Scheme 1).

Herein, we report an efficient entry to regioselectively 2,3,7-functionalized benzo[*b*]thiophenes from *m*-halophenols using the *O*-carbamate-directed metalation and the halocyclization methodologies as key steps.

Our studies started by checking the possibility of accessing 3-halo-2-methylsulfanylphenol derivatives **3** by the reaction of lithiated carbamates **2**, derived from *O*-3-halophenyl *N*,*N*-diethyl carbamates **1** through selective *o*-lithiation processes according to our reported methodology,[10,11] with dimethyl

(1) See, for instance: (a) Yu, L.; Liu, H.; Li, W.; Zhang, F.; Luckie, C.; van Breemen, R. B.; Thatcher, G. R. J.; Bolton, J. L. *Chem. Res. Toxicol.* **2004**, *17*, 879–888. (b) 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) See, for instance: (a) Ohsita, J.; Lee, K.-H.; Kimura, K.; Kunai, A. *Organometallics* **2004**, *23*, 5622–5625. (b) Ebata, H.; Miyazaki, E.; Yamamoto, T.; Takimiya, K. *Org. Lett.* **2007**, *9*, 4499–4502.

(3) For some recent examples, see: (a) Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 4081–4083. (b) Bryan, C. S.; Braunger, J. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7064–7068. (c)

(4) (a) Samanta, S. S.; Ghosh, S. C.; De, A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2683–2685. (b) Ghosh, S. C.; De, A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3705–3708.

(5) For leading references, see: (a) Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406–2409. (b) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292–10296. (c) Mehta, S.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 1652–1658. For a recent review, see: Rodríguez, F.; Fañanás, F. J. In *Handbook of Cyclization Reactions*; Ma, S., Ed.; Wiley: Weinheim, 2010; Vol. 2, p 951.

(6) (a) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *3*, 651–654. (b) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2003**, *5*, 4377–4380.

(7) (a) Larock, R. C.; Yue, D. *Tetrahedron Lett.* **2001**, *42*, 6011–6013. (b) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905–1909.

(8) Lu, W.-D.; Wu, M.-J. *Tetrahedron* **2007**, *63*, 356–362.

(9) (a) Barluenga, J.; Fañanás, F. J.; Sanz, R.; Marcos, C. *Chem.—Eur. J.* **2005**, *11*, 5397–5407. (b) Sanz, R.; Miguel, D.; Martínez, A.; Pérez, A. *J. Org. Chem.* **2006**, *71*, 4024–4027. (c) Sanz, R.; Fernánez, Y.; Castroviejo, M. P.; Pérez, A.; Fañanás, F. J. *J. Org. Chem.* **2006**, *71*, 6291–6294. (d) Sanz, R.; Escribano, J.; Pedrosa, M. R.; Aguado, R.; Arnáiz, F. J. *Adv. Synth. Catal.* **2007**, *349*, 713–718. (e) Sanz, R.; Guilarte, V.; Castroviejo, M. P. *Synlett* **2008**, 3006–3010. (f) Sanz, R.; Miguel, D.; Rodríguez, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7354–7357.

(10) Sanz, R.; Castroviejo, M. P.; Fernández, Y.; Fañanás, F. J. *J. Org. Chem.* **2005**, *70*, 6548–6551.

(11) Sanz, R.; Castroviejo, M. P.; Guilarte, V.; Pérez, A.; Fañanás, F. J. *J. Org. Chem.* **2007**, *72*, 5113–5118.

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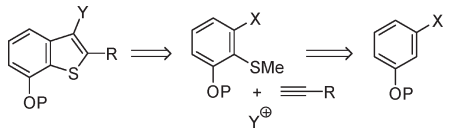
SCHEME 1. Retrosynthetic Analysis of 3-Halo-7-oxygen-Functionalized Benzo[*b*]thiophenes



SCHEME 2. Synthesis of *O*-3-Halo-2-sulfanylphenyl *N*,*N*-Diethylcarbamates 3

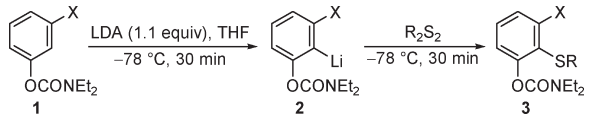


TABLE 1. Preparation of 3-Halo-2-sulfanylphenol Derivatives 3 from *O*-3-Halophenyl *N*,*N*-Diethylcarbamates 1

entry	starting material	X	disulfide (R)	product	yield [a](%)
1	**1a**	F	Me	**3aa**	79
2	**1b**	Cl	Me	**3ba**	83
3	**1c**	Br	Me	**3ca**	81
4	**1d**	I	Me	**3da**	70[b]
5	**1c**	Br	$PhCH_2$	**3cb**	79
6	**1c**	Br	$(4\text{-}MeOC_6H_4)CH_2$	**3cc**	77
7	**1c**	Br	Ph	**3cd**	77
8	**1c**	Br	$2\text{-}BrC_6H_4$	**3ce**	82

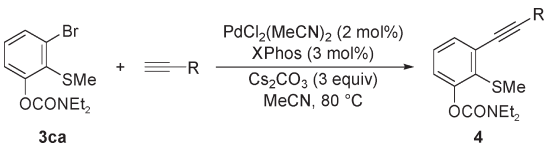
[a]Isolated yield of **3** after column chromatography. [b]Isolated with ca. 10% of *O*-2-methylsulfanylphenyl *N*,*N*-diethylcarbamate.

disulfide as a model sulfur-containing electrophilic reagent (Scheme 2 and Table 1, entries 1−4).

High yields of the corresponding 1,2,3-trifunctionalized benzene derivatives **3aa**−**da** were obtained. Whereas clean reactions were observed for carbamates **1a**−**c**, a small amount of the deiodinated carbamate was formed in the case of *O*-3-iodophenyl carbamate **1d** (Table 1, entry 4). Thus, we decided to investigate the scope of this process regarding the disulfide moiety by using *O*-3-bromophenyl carbamate **1c** as starting material due to potential further transformations through the bromine atom. In addition to dimethyl disulfide, benzylic and aromatic disulfides properly react with lithiated carbamate **2c** affording the corresponding benzyl- or arylsulfanyl-functionalized carbamates **3cb**−**ce** in high yields (Table 1, entries 5−8).

Having in mind the proposed retrosynthetic analysis for the synthesis of functionalized benzothiophenes (Scheme 1), our next goal was the introduction of the alkynyl moiety through a Sonogashira reaction. Several terminal alkynes bearing aromatic (Table 2, entries 1 and 2), heteroaromatic (entry 3), aliphatic (entries 4 and 5), alkenyl (entry 6), as well as trialkylsilyl substituents (entry 7) were effectively coupled with *O*-3-bromo-2-methylsulfanylphenyl *N*,*N*-diethyl carbamate **3ca** by using cesium carbonate as base and $PdCl_2(MeCN)_2$/XPhos as catalyst.[13] Under these catalytic conditions, *O*-3-alkynyl-2-methylsulfanylphenyl carbamates **4** were obtained in high yields (Table 2). However, when we used 2-propyn-1-ol as the alkyne partner for the Sonogashira coupling, 3-bromo-2-methylsulfanylphenol was obtained instead of the expected alkyne (entry 8).[14] Finally, when we used iodocarbamate **3da** as starting material (entries 9 and 10), under standard Sonogashira conditions,[15] the expected alkynes were also formed though they could not be isolated in pure form.

TABLE 2. Preparation of *o*-Alkynylthioanisoles 4 from 3ca



entry	R	time (h)	product	yield[a] (%)
1	Ph	2	**4a**	77
2	$4\text{-}MeOC_6H_4$	2	**4b**	72
3	3-Thienyl	3	**4c**	70
4	$n\text{-}C_5H_{11}$	2.5	**4d**	91
5	$n\text{-}C_6H_{13}$	3	**4e**	86
6	$c\text{-}C_6H_9$[b]	2	**4f**	71
7[c]	$i\text{-}Pr_3Si$	45	**4g**	77
8	CH_2OH	19	—[d]	—
9[e]	Ph	2.5	**4a**	78[f]
10[e]	*n*-Bu	2.5	**4h**	70[f]

[a]Isolated yield after column chromatography based on starting material **3ca**. [b] 1-Cyclohexenyl. [c]Carried out at 45 °C. [d]3-Bromo-2-methylsulfanylphenol was obtained in 71% yield. [e]Iodocarbamate **3da** was used as starting material and the Sonogashira coupling was carried out in DMF by using $PdCl_2(PPh_3)_2$ and CuI as catalysts and Et_2NH as base. [f]The final compound was not completely pure probably due to the fact that the starting carbamate **3da** could not be obtained in pure form.

With a reliable procedure to access methylthio-functionalized carbamates **4**, we then decided to check the ability of these substrates to undergo the halocyclization reaction in the presence of iodine. Pleasantly, we found that treatment of **4** with a slight excess of I_2 (1.5 equiv) in CH_2Cl_2 afforded 7-(*N*,*N*-diethylcarbamoyloxy)-3-iodo-2-substituted benzo[*b*]thiophenes **5** in high yields (Table 3, entries 1−6). Reactions proceeded at room temperature in a few hours, and only alkyne **4f**, bearing an alkenyl group, gave rise to a moderate yield of the corresponding benzothiophene **5f** (entry 5). In the same way, exposure of alkynes **4** to electrophiles like NBS and PhSeCl afforded 2,3-disubstituted benzo[*b*]thiophenes **6** and **7**, respectively, in high yields (entries 7−13), though reaction times were longer than in the case of iodocyclization reactions. Whereas silyl-functionalized carbamate **4g** smoothly undergoes iodocyclization without desilylation (entry 6), it did not undergo any reaction under treatment with NBS and starting material was recovered (entry 10). In addition, 3-chlorobenzo[*b*]thiophenes **8** could also be obtained in high yields by the reaction of *o*-alkynylthioanisole derivatives **4a** and **4d** with $CuCl_2$ in refluxing acetonitrile (Table 3, entries 14 and 15).[8]

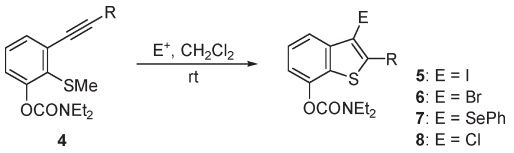
Having seen the generality of this strategy for the synthesis of 7-(*N*,*N*-diethylcarbamoyloxy)-3-halobenzo[*b*]thiophenes substituted with aryl, heteroaryl, and alkyl groups at the C-2 position, we also prepared the benzothiophene derivative **5h** with no substituent at C-2 by desilylation of **5g** with TBAF (Scheme 3). In order to introduce further functionalization on the benzothiophene ring, the silyl-substituted alkyne **4g** was desilylated with TBAF affording almost quantitatively the terminal alkyne **4i**, which under treatment with *n*-BuLi and further addition of diphenyl disulfide gave rise to the phenylthio-functionalized alkyne **4j** (Scheme 3). This

(13) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993–5996.

(14) The carbamate group undergoes alkaline hydrolysis in the presence of the alkynol and Cs_2CO_3.

(15) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.

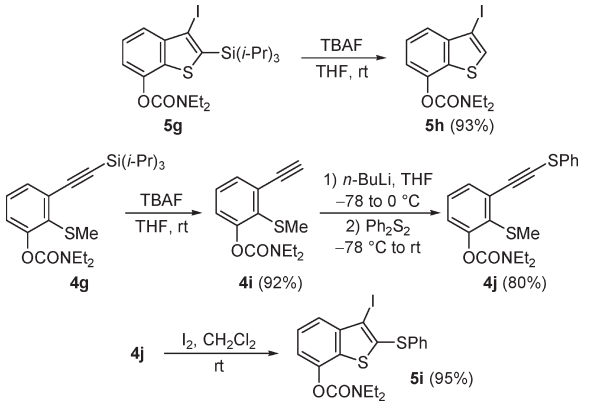
TABLE 3. Electrophilic Cyclization of Carbamates 4 to 7-Oxy-Functionalized 2,3-Disubstituted Benzo[*b*]thiophenes 5−8



entry	starting material (R)	electrophile (E^+)	time (h)	product	E	yield[a] (%)
1	**4a** (Ph)	I_2	4	**5a**	I	90
2	**4b** (4-$MeOC_6H_4$)	I_2	3	**5b**	I	91
3	**4c** (3-Thienyl)	I_2	3	**5c**	I	77
4	**4e** (*n*-C_6H_{13})	I_2	3	**5e**	I	92
5	**4f** (*c*-C_6H_9)[b]	I_2	3	**5f**	I	56
6	**4g** (*i*-Pr_3Si)	I_2	3	**5g**	I	83
7	**4a** (Ph)	NBS	16	**6a**	Br	91
8	**4c** (3-Thienyl)	NBS	16	**6c**	Br	80
9	**4d** (*n*-C_5H_{11})	NBS	16	**6d**	Br	76
10	**4g** (*i*-Pr_3Si)	NBS	16			—[c]
11	**4a** (Ph)	PhSeCl	16	**7a**	SePh	79
12	**4c** (3-Thienyl)	PhSeCl	16	**7c**	SePh	75
13	**4d** (*n*-C_5H_{11})	PhSeCl	16	**7d**	SePh	74
14[d]	**4a** (Ph)	$CuCl_2$	2.5	**8a**	Cl	90
15[d]	**4d** (*n*-C_5H_{11})	$CuCl_2$	2.5	**8d**	Cl	87

[a]Isolated yield of benzo[*b*]thiophenes **5**−**8** after column chromatography. [b]1-Cyclohexenyl. [c]Starting material **4g** was recovered. [d]Carried out in MeCN at reflux.

SCHEME 3. Synthesis of 3-Iodobenzo[*b*]thiophenes 5h,i

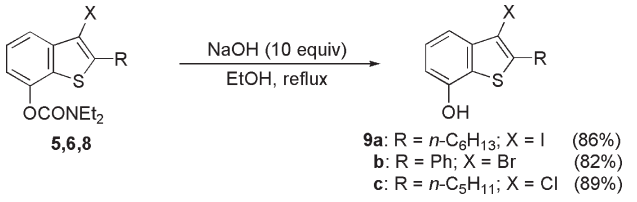


carbamate derivative also underwent the iodocyclization reaction in a quantitative manner affording the 3-iodo-2-phenylthiobenzo[*b*]thiophene **5i** (Scheme 3).

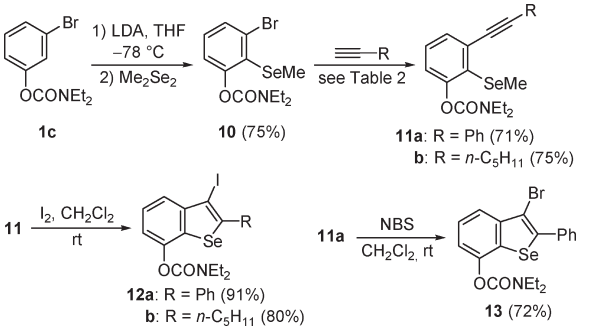
Taking into account that the carbamoyl group could be easily removed by alkaline hydrolysis,[16] the treatment of some of the prepared carbamates with excess of NaOH in refluxing ethanol allowed us the isolation of 3-halo-7-hydroxybenzothiophenes **9** in high yields (Scheme 4).

On the other hand, it has been also reported that benzo[*b*]selenophenes could be accessed by electrophilic cyclization from *o*-(alkynyl)methylseleno derivatives.[17] However, the required starting 2-iodoselenoanisoles have been prepared in low yields by a two-step approach from *o*-iodoanilines.[18] Taking advantage of our combined strategy for the synthesis of benzothiophenes, we decided to apply it to the preparation of related benzoselenophenes (Scheme 5). In this way, metalation

SCHEME 4. Synthesis of 7-Hydroxybenzo[*b*]thiophenes 9



SCHEME 5. Synthesis of 3-Halobenzo[*b*]selenophenes 12 and 13 from *O*-3-Bromophenyl *N*,*N*-Diethylcarbamate 1c

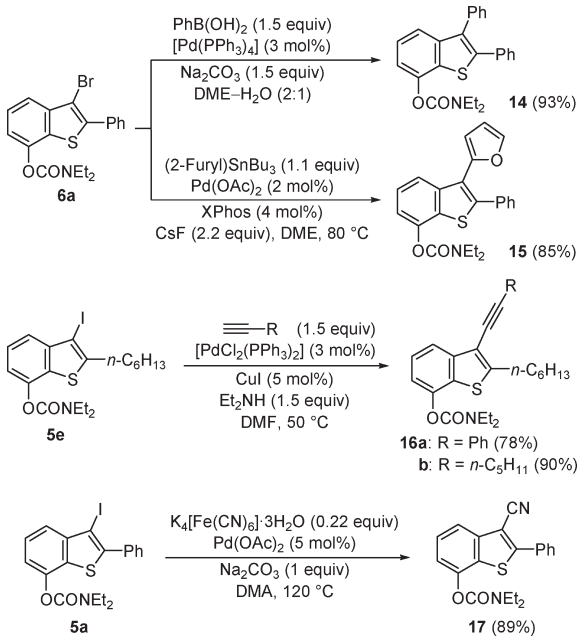


of 3-bromocarbamate **1c** with LDA and subsequent addition of dimethyl diselenide gave rise to *O*-3-bromo-2-methylselenophenyl *N*,*N*-diethylcarbamate **10** in good yield. Its coupling with two different terminal alkynes under the same conditions used for the analogous carbamates **3** afforded alkynes **11**. These substrates efficiently undergo halocyclization reactions upon treatment with I_2 or NBS leading to high yields of 3-halobenzo[*b*]selenophenes **12** and **13** functionalized with a *N*,*N*-diethylcarbamoyloxy group at the C-7 position (Scheme 5).

Finally, we decided to explore the synthetic utility of the obtained 3-halobenzo[*b*]thiophene derivatives **5** and **6** as precursors of other 3-substituted benzothiophenes using Pd-catalyzed reactions (Scheme 6). Due to the interest of multiple

(16) See, for instance: Mabic, S.; Vaysse, L.; Benezra, C.; Lepoittevin, J.-P. *Synthesis* **1999**, 1127–1134.
(17) Kesharwani, T.; Worlikar, S. A.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 2307–2312.
(18) Luxen, A.; Christiaens, L. *Tetrahedron Lett.* **1982**, *23*, 3905–3908.

SCHEME 6. Further Transformations of 3-Halobenzo[*b*]thiophenes 5 and 6



arylated benzo[*b*]thiophene derivatives,[19] we synthesized 2,3-diarylbenzothiophenes **14** and **15**, which could be obtained in high yields from 3-bromobenzothiophene **6a** by Suzuki[20] and Stille[21] couplings, respectively. A Sonogashira cross-coupling allowed the preparation of 3-alkynylbenzothiophenes **16a**,**b** from iodo derivative **5e**. Finally, 3-cyanobenzothiophene **17** could be obtained under ligand-free Pd-catalysis by treatment of **5a** with potassium ferricyanide.[22]

In summary, we have developed an efficient route to regioselectively functionalized benzo[*b*]thiophenes using the *o*-metalation and halocyclization methodologies as the key steps. The hydroxy-substituted benzothiophene moiety is an important scaffold in biologically active compounds.

Experimental Section

Typical Procedure for the Synthesis of *O*-2-Alkyl(aryl)thio-3-halophenyl *N*,*N*-Diethylcarbamates 3. Synthesis of *O*-3-Bromo-2-(methylthio)phenyl *N*,*N*-Diethylcarbamate (3ca; Table 1, Entry 3). *n*-BuLi (8.25 mL of a 1.6 M solution in hexane, 13.2 mmol) was added to a solution of *i*-Pr_2NH (1.85 mL, 13.2 mmol) in THF (48 mL) at 0 °C. After 30 min at 0 °C, the LDA solution was cooled to −78 °C, and carbamate **1c** (3.25 g, 12 mmol) was added. The resulting solution was stirred for 30 min at −78 °C, and then dimethyl disulfide (1.27 mL, 14.4 mmol) was added. After 30 min at low temperature, the reaction mixture was allowed to reach rt and quenched with H_2O. The aqueous phase was extracted with Et_2O (3 × 30 mL), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The resulting material was purified by column chromatography (eluent: hexane/EtOAc, 10/1) on silica gel to afford **3ca** (3.09 g, 81%) as a white solid: R_f 0.42 (hexane/EtOAc, 4/1); mp 46−48 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.47 (m, 1H), 7.16 (t, J = 7.9 Hz, 1H), 7.12−7.07 (m, 1H), 3.48 (q, J = 7.1 Hz, 2H), 3.37 (q, J = 7.1 Hz, 2H), 2.35 (d, J = 0.6 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 154.2 (C), 153.8 (C), 131.3 (C), 130.4 (CH), 130.2 (CH), 122.6 (CH), 42.4 (CH_2), 42.2 (CH_2), 18.4 (CH_3), 14.2 (CH_3), 13.3 (CH_3); EI-LRMS m/z 319 (M^+ + 2, 10), 317 (M^+, 9), 270 (4), 138 (6), 100 (100), 72 (38); HRMS calcd for $C_{12}H_{16}BrNO_2S$ 317.0085, found 317.0085.

Typical Procedure for the Synthesis of *O*-3-Alkynyl-2-(methylthio)phenyl *N*,*N*-Diethylcarbamates 4. Synthesis of *O*-3-(4-Methoxyphenyl)ethynyl-2-(methylthio)phenyl *N*,*N*-Diethylcarbamate (4b; Table 2, Entry 2). A mixture of **3ca** (318 mg, 1 mmol), $PdCl_2(MeCN)_2$ (5.2 mg, 0.02 mmol), XPhos (14.3 mg, 0.03 mmol), and Cs_2CO_3 (977 mg, 3 mmol) in anhydrous MeCN (2 mL) was stirred under N_2 at rt for 25 min. Then, 4-methoxyphenylacetylene (194 μL, 1.5 mmol) was added, and the reaction was stirred at 85 °C for 3 h (the complete consumption of starting material was monitored by GC−MS). After cooling of the reaction mixture, EtOAc and water were added. The separated aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc, 9/1) to afford **4b** (265 mg, 72%) as a brown oil: R_f 0.34 (hexane/EtOAc, 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.48 (m, 2H), 7.42 (dd, J = 7.7, 1.4 Hz, 1H), 7.26 (t, J = 7.7 Hz, 1H), 7.10 (dd, J = 7.7, 1.4 Hz, 1H), 6.93−6.86 (m, 2H), 3.82 (s, 3H), 3.60−3.50 (m, 2H), 3.49−3.40 (m, 2H), 2.50 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H), 1.22 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.8 (C), 153.9 (C), 153.0 (C), 133.1 (2 × CH), 132.0 (C), 130.02 (CH), 129.97 (C), 128.6 (CH), 122.9 (CH), 115.2 (C), 114.0 (2 × CH), 94.5 (C), 86.7 (C), 55.3 (CH_3), 42.3 (CH_2), 42.1 (CH_2), 18.3 (CH_3), 14.2 (CH_3), 13.4 (CH_3); EI-LRMS m/z 369 (M^+, 27), 322 (5), 207 (12), 100 (100), 72 (31); HRMS calcd for $C_{21}H_{23}NO_3S$ 369.1399, found 369.1400.

Typical Procedure for the Synthesis of *O*-3-Halo-2-substituted Benzo[*b*]thiophene-7-yl *N*,*N*-Diethylcarbamates 5 and 6. *O*-3-Iodo-2-phenylbenzo[*b*]thiophene-7-yl *N*,*N*-diethylcarbamate (5a; Table 3, Entry 1). Iodine (190 mg, 0.75 mmol) was added to a solution of **4a** (169 mg, 0.5 mmol) in anhydrous CH_2Cl_2 (2.5 mL) at rt. The resulting mixture was stirred for 4 h (complete cyclization was monitored by GC−MS). Saturated aqueous $Na_2S_2O_3$ solution (10 mL) was added, and the separated aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc, 9/1) to afford **5a** (202 mg, 90%) as a white solid: R_f 0.27 (hexane/EtOAc, 9/1); mp 74−76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75−7.66 (m, 3H), 7.58−7.43 (m, 4H), 7.34 (dd, J = 7.8, 0.9 Hz, 1H), 3.58−3.49 (m, 2H), 3.48−3.38 (m, 2H), 1.35 (t, J = 7.0 Hz, 3H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 153.1 (C), 145.6 (C), 143.9 (C), 142.5 (C), 134.5 (C), 131.8 (C), 130.1 (2 × CH), 129.1 (CH), 128.6 (2 × CH), 126.2 (CH), 123.2 (CH), 118.0 (CH), 79.4 (C), 42.7 (CH_2), 42.3 (CH_2), 14.4 (CH_3), 13.5 (CH_3); EI-LRMS m/z 451 (M^+, 26), 323 (6), 195 (10), 152 (14), 100 (100), 72 (30); HRMS calcd for $C_{19}H_{18}INO_2S$ 451.0103, found 451.0106.

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Supporting Information Available: Typical experimental procedures and spectroscopic data for all compounds and a copy of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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