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A Practical, One-Pot Synthesis of Highly Substituted Thiophenes and Benzo[*b*]thiophenes from Bromoenynes and *o*-Alkynylbromobenzenes

Verónica Guilarte, Manuel A. Fernández-Rodríguez, Patricia García-García, Elsa Hernando, and Roberto Sanz*

Departamento de Química, Área de Química Orgánica, Facultad de Ciencias, Universidad de Burgos, Pza. Misael Bañuelos s/n, 09001-Burgos, Spain

rsd@ubu.es

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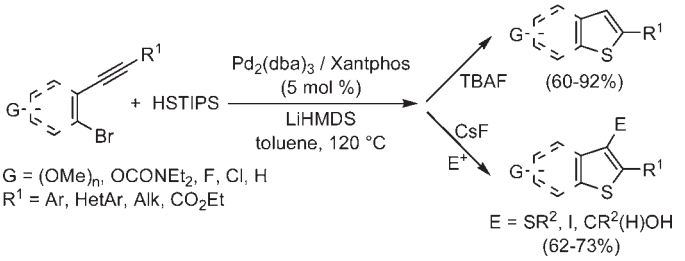
ABSTRACT



An efficient synthesis of thiophenes and benzo[*b*]thiophenes has been developed from easily available bromoenynes and *o*-alkynylbromobenzene derivatives. This novel one-pot procedure involves a Pd-catalyzed C−S bond formation using a hydrogen sulfide surrogate followed by a heterocyclization reaction. Moreover, in situ functionalization with selected electrophiles further expands the potential of this methodology to the preparation of the corresponding highly substituted sulfur heterocycles.

Thiophenes, as well as its benzofused derivative benzo[*b*]thiophenes, are basic skeletons found in new electronic materials[1] as well as in biologically active molecules.[2] Indeed, these sulfur heterocycles are essential components of clinically important drugs such as clopidogrel,[3] raloxifene,[4] and zileuton.[5] Consequently, the development of facile and convenient synthetic routes to these sulfur-based heterocycles is of high interest.[6] In particular, one of the most useful approaches to the synthesis of benzo[*b*]thiophenes involves a 5-*endo*-*dig* cyclization reaction from *o*-alkynylaryl thioether derivatives.[7] These precursors are typically

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(6) For recent examples, see: Benzothiophenes: (a) Bryan, C. S.; Braunger, J. A.; Lautens, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7064–7068. (b) Li, C.-L.; Zhang, X.-G.; Tang, R.-Y.; Zhong, P.; Li, J.-H. *J. Org. Chem.* **2010**, *75*, 7037–7040. (c) Duan, Z.; Ranjit, S.; Liu, X. *Org. Lett.* **2010**, *12*, 2430–2433. (d) Zeng, F.; Alper, H. *Org. Lett.* **2011**, *13*, 2868–2871. Thiophenes: (e) You, W.; Yan, X.; Liao, Q.; Xi, C. *Org. Lett.* **2010**, *12*, 3930–3933.

(7) Gold(I)-catalyzed: (a) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473–4475. (b) Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 4081–4083. Halonium ion promoted: (c) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *3*, 651–654. (d) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905–1909. Cupric halide promoted: (e) Lu, W.-D.; Wu, M.-J. *Tetrahedron* **2007**, *63*, 356–362. PTSA-mediated: (f) Jacubert, M.; Hamze, A.; Provot, O.; Peyrat, J.-F.; Brion, J.-D.; Alami, M. *Tetrahedron Lett.* **2009**, *50*, 3588–3592.

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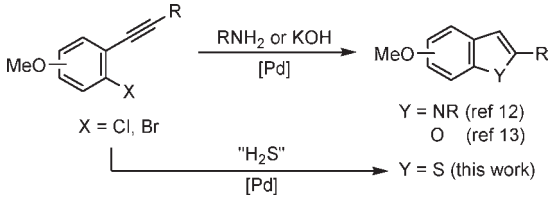
prepared by the treatment of *o*-metalated arylalkynes with electrophilic sulfur reagents[8] or S_NAr reactions.[9]

On the other hand, in recent years we have been involved in different projects on the synthesis of regioselectively functionalized heterocyclic compounds.[10] In this context, we have reported an efficient access to 3-halo-7-oxygen-functionalized benzo[*b*]thiophenes by combined *ortho*-lithiation–halocyclization strategies,[11] and we have also devised useful preparations of regioselectively alkoxy-functionalized indoles[12] and benzo[*b*]furans.[13] In this context we decided to tackle the synthesis of the corresponding oxygen-substituted benzo[*b*]thiophene derivatives, which are interesting compounds not previously described (Scheme 1). Herein we report a new, easy, and efficient access to (benzo[*b*])thiophenes through a tandem C–S coupling/heteroannulation reaction employing different hydrogen sulfide surrogates[14] and the use of a related one-pot protocol in the presence of electrophiles for the synthesis of the corresponding functionalized highly substituted (benzo[*b*])thiophenes.

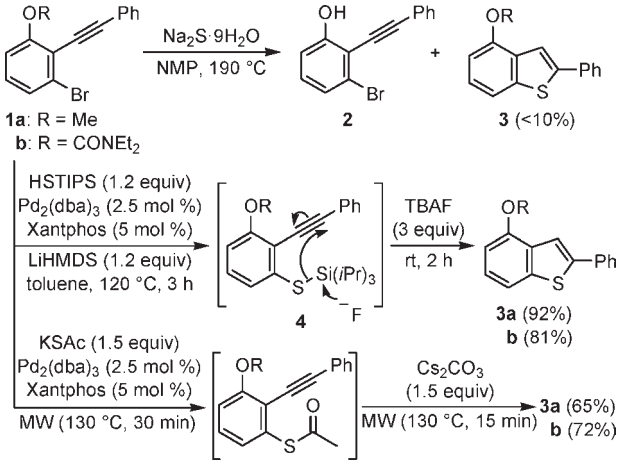
Scheme 1. Synthesis of Alkoxy-Substituted Indoles, Benzo[*b*]furans, and Benzo[*b*]thiophenes from Methoxy-Substituted 2-Alkynylhalobenzenes



Using oxygen-functionalized *o*-halo-substituted ethynylbenzenes **1a** and **1b** as model substrates, we initially considered the employment of sodium sulphide in NMP as solvent at high temperature, following the procedure described by Takimiya and co-workers.[9] However, under the reported conditions the main product in both reactions was 3-bromo-2-(phenylethynyl)phenol **2**, formed by the cleavage of the corresponding *O*-protecting group,[15] whereas the expected benzo[*b*]thiophenes **3** were obtained in less than 10% yield (Scheme 2). Alternatively, we envisioned that another entry to the benzothiophene moiety from the same starting materials **1** could entail a Pd-catalyzed C–S coupling[16] with a thiol surrogate to afford a protected arenethiol intermediate,[17] which after removal of the protecting group could undergo a subsequent heterocyclization (Scheme 2).

After screening several thiol surrogates, catalyst systems, and reaction conditions for the coupling, as well as various reagents for the deprotection step, we found two different one-pot procedures that allowed the efficient synthesis of the desired 4-oxygen-functionalized benzothiophenes. In the first protocol (method A), reactions of substrates **1a,b** with triisopropylsilanethiol (HSTIPS)[18] using the combination $Pd_2(dba)_3$/Xantphos (5 mol %)[19] in toluene at 120 °C with LiHMDS as base occurred to full conversion in less than 3 h to form silyl-protected arenethiols **4**. The following addition of an excess of tetrabutylammonium fluoride (TBAF) afforded **3a,b** in high yields (Scheme 2). The second methodology involves a cross-coupling reaction with potassium thioacetate[20] using the same catalyst system and reaction conditions, but in this case no additional base was needed. In this way, and after treatment with cesium carbonate the expected heterocycles were obtained, although prolonged reaction times (14 h) were needed for the coupling reaction. Interestingly, the later one-pot protocol could be conducted under microwave irradiation (method B) dramatically reducing the reaction times. However, lower yields were obtained compared with the first procedure (Scheme 2).

Scheme 2. Synthesis of 4-Oxygen-Functionalized Benzo[*b*]thiophenes **3a,b**: Proof of the Concept



(8) See, for instance: (a) Takimiya, K.; Kunugi, Y.; Konda, Y.; Niihara, N.; Otsubo, T. *J. Am. Chem. Soc.* **2004**, *126*, 5084–5085. (b) Okamoto, T.; Kudoh, K.; Wakamiya, A.; Yamaguchi, S. *Org. Lett.* **2005**, *7*, 5301–5304.

(9) (a) Kashiki, T.; Shinamura, S.; Kohara, M.; Miyazaki, E.; Takimiya, K.; Ideda, M.; Kuwabara, H. *Org. Lett.* **2009**, *11*, 2473–2475. (b) Shinamura, S.; Miyazaki, E.; Takimiya, K. *J. Org. Chem.* **2010**, *75*, 1228–1234.

(10) See, for instance: (a) Sanz, R.; Fernández, Y.; Castroviejo, M. P.; Pérez, A.; Fañanás, F. J. *J. Org. Chem.* **2006**, *71*, 6291–6294. (b) Sanz, R.; Guilarte, V.; García, N. *Org. Biomol. Chem.* **2010**, *8*, 3860–3864. (c) Guilarte, V.; Castroviejo, M. P.; García-García, P.; Fernández-Rodríguez, M. A.; Sanz, R. *J. Org. Chem.* **2011**, *76*, 3416–3437.

(11) Sanz, R.; Guilarte, V.; Hernando, E.; Sanjuán, A. M. *J. Org. Chem.* **2010**, *75*, 7443–7446.

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

(13) Guilarte, V.; Castroviejo, M. P.; Álvarez, E.; Sanz, R. *Beilstein J. Org. Chem.* **2011**, *7*, in press.

(14) During the preparation of this manuscript a related paper has appeared that reports the use of thiourea as a dihydrosulfide surrogate in the synthesis of thioethers and benzo[*b*]thiophenes. See: Kuhn, M.; Falk, F. C.; Paradies, J. *Org. Lett.* **2011**, *13*, 4100–4103.

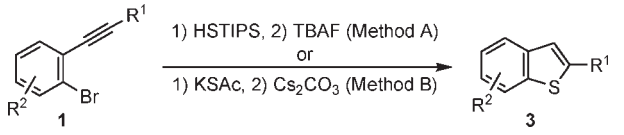
(15) For the cleavage of methoxy groups with thiolates, see: Vyvyan, J. R.; Holst, C. L.; Johnson, A. J.; Schwenk, C. M. *J. Org. Chem.* **2002**, *67*, 2263–2265.

These two sets of reaction conditions were applied in reactions of a variety of representative *o*-alkynylbromobenzenes **1** to evaluate the scope of the one-pot procedures, and the results are summarized in Table 1. Thus, benzo[*b*]thiophenes **3c**–**j** bearing phenyl, electron-deficient and electron-rich aromatic, heteroaromatic, alkenyl, alkyl, functionalized alkyl, and ester groups at the C-2 position were efficiently prepared (entries 1–15). In addition, substitution at the benzenoid moiety of substrates **1**, including halides, was also well tolerated (entries 16–21). In general, and as we previously observed with bromides **1a,b**, the protocol involving the formation of silyl-protected benzenethiols afforded the adducts **3** in higher yields. Moreover, the catalyst loading for the coupling step with HSTIPS could be reduced to 1 mol % by increasing the reaction time from 1 to 14 h without an appreciable decrease in the yield (entry 1).

Once we had demonstrated the feasibility of our tandem method for the preparation of benzo[*b*]thiophenes, we turned to our original goal, the synthesis of unknown oxygen-substituted benzo[*b*]thiophenes. Pleasingly, reactions of selected substrates **1n**–**v** possessing one or two methoxy groups on the benzene unit and different substituents at the triple bond occurred to form the desired functionalized heterocycles **3n**–**v** in high yields (entries 22–32).

Next we considered that the developed one-pot procedure could be applied as well for the synthesis of thiophenes using 1-bromo-1,3-enynes as starting materials. To test this hypothesis selected enynes **5** were prepared and reacted under the optimized conditions employing HSTIPS as a thiol surrogate. As expected, the tandem C–S coupling/heterocyclization methodology turned out to be also suitable for the synthesis of 2,3,5-trisubstituted thiophenes. As shown in Scheme 3, both aliphatic and aromatic substituents are well tolerated at the different positions of the final products **6**, which are obtained in high yields (Scheme 3).

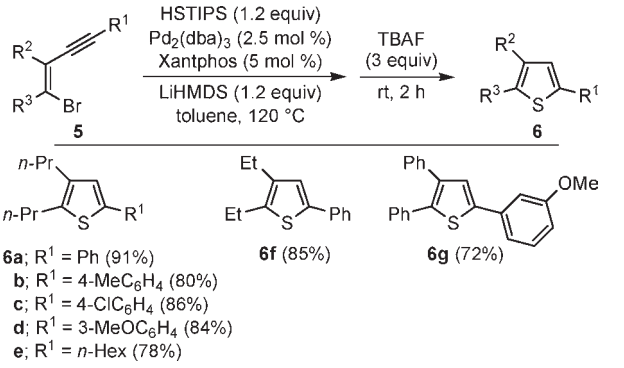
Table 1. Synthesis of 2-Substituted Benzo[*b*]thiophenes **3**[a]



entry	1	R^1	R^2	method	3[b]	yield (%)[c]
1	**1c**	Ph	H	A	**3c**	88 (87)[d]
2				B		70
3	**1d**	3-FC_6H_4	H	A	**3d**	89
4				B		62
5	**1e**	4-$MeOC_6H_4$	H	A	**3e**	66
6				B		64
7	**1f**	3-Th[e]	H	A	**3f**	77
8				B		69
9	**1g**	*c*-C_6H_9[f]	H	A	**3g**	66
10				B		59
11	**1h**	*n*-C_6H_{13}	H	A	**3h**	84
12				B		53
13	**1i**	$(CH_2)_3CN$	H	A	**3i**	86
14				B		67
15	**1j**	CO_2Et	H	B	**3j**	60
16	**1k**	3-Th[e]	6-Me	A	**3k**	75
17				B		59
18	**1l**	Ph	6-F	A	**3l**	92
19				B		72
20	**1m**	*n*-C_5H_{11}	6-Cl	A	**3m**	72
21				B		54
22	**1n**	*n*-C_5H_{11}	4-MeO	A	**3n**	80
23	**1o**	Ph	4,5-$(MeO)_2$	A	**3o**	82
24				B		68
25	**1p**	4-MeC_6H_4	4,5-$(MeO)_2$	A	**3p**	85
26	**1q**	*n*-Bu	4,5-$(MeO)_2$	A	**3q**	70
27	**1r**	3-Th[e]	4,6-$(MeO)_2$	A	**3r**	73
28	**1s**	*n*-C_6H_{13}	4,6-$(MeO)_2$	A	**3s**	70
29	**1t**	Ph	4,7-$(MeO)_2$	A	**3t**	90
30	**1u**	3-Th[e]	4,7-$(MeO)_2$	A	**3u**	71
31				B		58
32	**1v**	*n*-C_5H_{11}	4,7-$(MeO)_2$	A	**3v**	76

[a] Reactions were conducted using either method A or B. Method A: HSTIPS (1.2 equiv), $Pd_2(dba)_3$ (2.5 mol %)/Xantphos (5 mol %), LiHMDS (1.2 equiv) in toluene at 120 °C for 1–6 h, then TBAF (3 equiv) at rt for 2 h. Method B: KSAc (1.5 equiv), $Pd_2(dba)_3$ (2.5 mol %)/Xantphos (5 mol %) in toluene under MW at 130 °C for 25–60 min, then Cs_2CO_3 (1.5 equiv) under MW at 130 °C for 10–30 min. [b] Position of R^2 referred to the benzo[*b*]thiopene moiety. [c] Isolated yield after column chromatography referred to starting material **1**. [d] Reaction conducted with 1 mol % of catalyst. [e] 3-Thienyl. [f] 1-Cyclohexenyl.

Scheme 3. Synthesis of Thiophenes **6** from Bromoenynes **5**



(16) For a review, see: (a) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596–1636. For leading references, see: (b) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180–2181. (c) Fernández-Rodríguez, M. A.; Hartwig, J. F. *J. Org. Chem.* **2009**, *74*, 1663–1672.

(17) For reports about the use of different mercapto surrogates in Pd-catalyzed C–S couplings, see: (a) Itoh, M.; Mase, T. *J. Org. Chem.* **2006**, *71*, 2203–2206. (b) Yi, J.; Fu, Y.; Xiao, B.; Cui, W.-C.; Guo, Q.-X. *Tetrahedron Lett.* **2011**, *52*, 205–208.

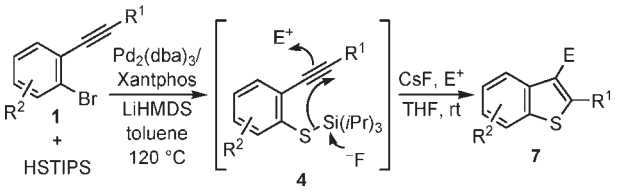
(18) For the use of HSTIPS in Pd-catalyzed C–S couplings, see: (a) Kreis, M.; Bräse, S. *Adv. Synth. Catal.* **2005**, *47*, 313–319. (b) Fernández-Rodríguez, M. A.; Hartwig, J. F. *Chem.—Eur. J.* **2010**, *16*, 2355–2359.

(19) The efficiency of the catalysts generated from $Pd_2(dba)_3$ and different phosphine ligands such as Josiphos CyPF*t*Bu (see ref 18b), XPhos, SPhos, DavePhos, and dppf for this coupling was comparable in terms of reaction rates and turnover numbers to the catalyst generated from Xantphos ligand. However, we selected Xantphos as a ligand due to its better availability.

(20) For the use of KSAc in Pd-catalyzed C–S couplings, see: (a) Lai, C.; Backes, B. J. *Tetrahedron Lett.* **2007**, *48*, 3033–3037. (b) Hoogenband, A. v. d.; Lange, J. H. M.; Bronger, R. P. J.; Stoit, A. R.; Terpstra, J. W. *Tetrahedron Lett.* **2010**, *51*, 6877–6881. (c) Park, N.; Park, K.; Jang, M.; Lee, S. *J. Org. Chem.* **2011**, *76*, 4371–4378.

On the other hand, we considered the possibility of further functionalizing the final benzothiophenes and thiophenes by adding an electrophile in the reaction sequence. At this point, it is worth noting that although the direct synthesis of 2,3-disubstituted indoles and benzofurans is easily achieved from *o*-alkynyl anilines and phenols, respectively, with organopalladium species (Cacchi reaction),[21] this methodology is inapplicable to benzothiophenes[7a] as it is not possible to obtain *o*-akynyl benzenethiols due to their high tendency to afford the corresponding 2-substituted benzothiophenes.[22] However, considering the anionic character of the reaction conditions used for the cleavage of the silyl group from intermediates **4** in the above-reported procedure, we envisaged that the preparation of 2,3-disubstituted benzo[*b*]thiophenes **7** could be possible (Scheme 4). The main requisites for the success of this idea are the simultaneous presence of a suitable electrophilic species during the cyclization step and the absence of protons from the reaction media. So, the removal of the reagents used for the C–S coupling (mainly HMDS), previous to the addition of the fluoride source and the electrophile, resulted in being compulsory.[23]

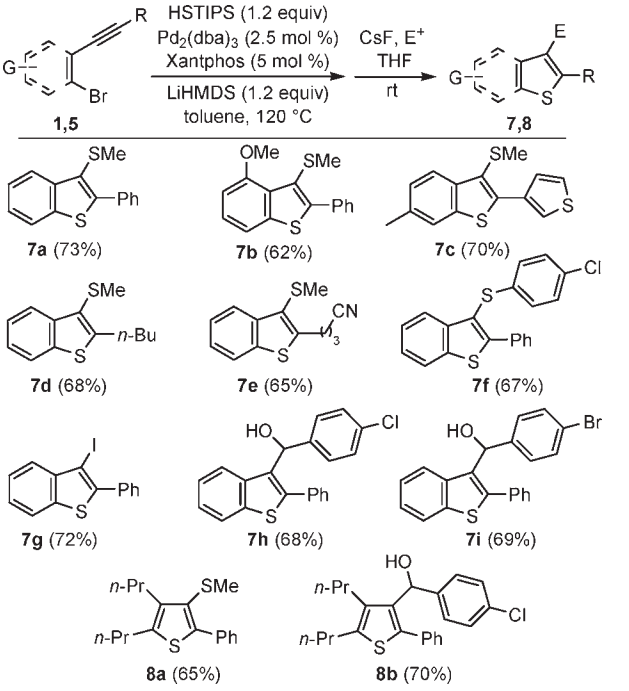
Scheme 4. Proposal for the Direct Synthesis of 2,3-Disubstituted Benzo[*b*]thiophenes **7**



After some experimentation we determined that the use of anhydrous CsF in THF were the best conditions for the introduction of electrophiles (Scheme 5).

Thus, a series of selected 3-methylthiobenzo[*b*]thiophenes **7a**–**e** could be synthesized in good yields, by performing the deprotection step of the corresponding arylthiosilanes **4** in the presence of dimethyldisulfide.[24] Aromatic disulfides as well as iodine[25] are also suitable electrophiles for this transformation (**7f,g**). Interestingly, carbon-based electrophiles such as aldehydes could also be introduced, leading to the corresponding alcohols in high yields (**7h,i**). Moreover, this methodology was efficiently applied to the synthesis of the analogous tetrasubstituted thiophenes **8a,b** from the corresponding starting bromoenynes **5**.

Scheme 5. Synthesis of 3-Functionalized Benzo[*b*]thiophenes **7** and 3-Functionalized Thiophenes **8**



In summary, we have developed an efficient route to 2-substituted benzo[*b*]thiophenes and 2,3,5-trisubstituted thiophenes through a tandem C–S coupling/heterocyclization reaction from easily available substrates. In addition, further functionalization could be introduced in the cyclization step by eletrophilic quenching leading to highly substituted sulfur heterocycles.

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Supporting Information Available. Experimental procedures and characterization data for compounds; copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671–2681.

(22) Malte, A. M.; Castro, C. E. *J. Am. Chem. Soc.* **1967**, *89*, 6770.

(23) A simple filtration through a short pad of neutral alumina gel with a hexane/Et_2O (2/1) mixture as eluent and subsequent evaporation of the solvents afforded arylthiosilanes **4**, which were not further purified.

(24) The corresponding 3-unsubstitued derivatives **3** were also formed in small variable amounts. Nevertheless, they could be separated from the 3-functionalized benzo[*b*]thiophenes **7** by column chromatography.

(25) The use of CsF for the cleavage of the S–Si bond is not necessary in this case. A direct iodine-promoted cyclization provided similar results.