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Synthesis of benzo[*b*]thiophenes by electrophilic cyclization

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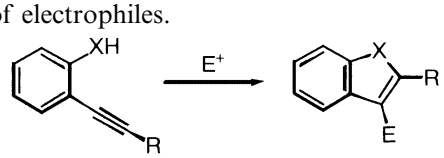
Abstract—2,3-Disubstituted benzo[*b*]thiophenes are readily prepared in excellent yields under very mild reaction conditions by the Pd/Cu-catalyzed cross-coupling of commercially available *o*-iodothioanisole and terminal alkynes, followed by electrophilic cyclization by I_2, Br_2, NBS, *p*-$O_2NC_6H_4SCl$ or PhSeCl. © 2001 Published by Elsevier Science Ltd.

Benzo[*b*]thiophenes are of great current interest because of their common occurrence in nature and their considerable biological activity.[1] A number of synthetic approaches to this class of compounds have been introduced in recent years.[2] One common approach to heterocycles that has been utilized for the synthesis of benzofurans[3] and indoles[4] has been electrophilic cyclization of the corresponding 2-(1-alkynyl)phenols or -anilines (Eq. (1)). Our recent interest in the preparation of these same heterocycles by the Pd-catalyzed annulation of alkynes[5] has encouraged us to look at an analogous approach to the benzo[*b*]thiophene ring system. Although many transition metals, including Pd, are often incompatible with sulfur-containing substrates, we were nevertheless encouraged to examine the possibility of preparing benzo[*b*]thiophenes by a strategy involving a palladium-catalyzed coupling, followed by electrophilic cyclization. Flynn and co-workers have recently reported the synthesis of benzo[*b*]thiophenes by a related process involving the iodocyclization of *o*-(1-alkynyl)phenyl benzyl sulfides (Eq. (2)).[6] Unfortunately, the preparation of these sulfides required several synthetic steps from commercially available starting materials and the yields are not particularly good. Furthermore, the scope of the cyclization step has not been examined. We wish to report a much more efficient approach to benzo[*b*]thiophenes involving the Pd/Cu-catalyzed coupling of *o*-iodothioanisole and terminal alkynes, followed by electrophilic cyclization by a range of electrophiles.



(1)

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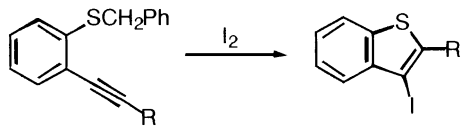
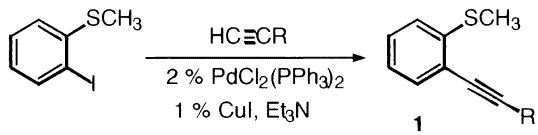


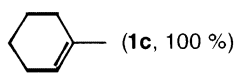
(2)

The sulfur-containing arylalkynes required for our approach are readily prepared by the Sonogashira coupling[7] of commercially available *o*-iodothioanisole (5 mmol) and terminal alkynes (6 mmol) using a catalyst consisting of 2 mol% $PdCl_2(PPh_3)_2$ and 1 mol% CuI in the presence of Et_3N (12.5 ml) as solvent at room temperature for 3 h (Eq. (3)). The yields of this process range from 93 to 100% and this procedure should accommodate considerable functionality.



(3)

R = *n*-C_8H_{17} (**1a**, 93 %), (b) Ph (**1b**, 100 %),



Since Flynn and co-workers had previously established that analogous benzyl sulfides undergo facile iodocyclization, we first examined the reaction of our thiomethyl-containing alkynes **1a–c** (0.25 mmol in 3 ml of CH_2Cl_2) with I_2 (2.0 equiv. in 2 ml of CH_2Cl_2). We were pleased to see that our methyl sulfides reacted in less than 10 min at room temperature to afford the 3-iodobenzo[*b*]thiophenes in 97–100% yields (Eq. (4)). Clearly, the benzyl leaving group is not critical to this cyclization. Virtually no difference in the rates of reaction or the overall yields were observed using alkynes

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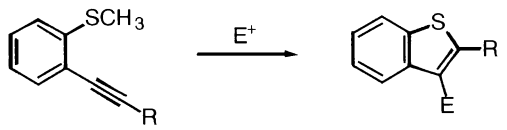
bearing a long-chain alkyl group (**1a**), an aryl group (**1b**) or a vinylic group (**1c**).



(4)

Alkyne	E^+	% Yield
1a	I_2	100
1b	–	100
1c	–	97
1a	Br_2	91
1b	–	92
1c	–	–
1c	NBS	74
1a	p-$O_2NC_6H_4SCl$	70
1b	–	97
1c	–	95
1a	PhSeCl	91
1b	–	100
1c	–	97

This approach to benzo[*b*]thiophenes has been extended to a range of other readily available electrophiles (Eq. (4)). We were pleased to find that Br_2 reacts in 10 min or less with the alkynes **1a** and **1b** to afford the corresponding 3-bromobenzo[*b*]thiophenes in 91 and 92% yields, respectively. We were not too surprised to find that the bromocyclization of the olefinic substrate **1c** failed to provide any of the desired 3-bromobenzo[*b*]thiophene. Presumably, Br_2 addition to the carbon–carbon double bond is occurring faster than cyclization. Fortunately, alkyne **1c** reacts cleanly at room temperature with 1.2 equiv. of *N*-bromosuccinimide (NBS) to afford the desired 3-bromo derivative in 74% yield, although the reaction takes 2 days.

Since arylsulfenyl and -selenyl chlorides often react with olefins and acetylenes in much the same way that halogens do, we have examined the reactivity of p-$O_2NC_6H_4SCl$ and PhSeCl in our cyclizations. Both electrophiles (1.5 equiv.) react in 10 min or less at room temperature in CH_2Cl_2 to produce the corresponding benzo[*b*]thiophenes in yields of 70–100% (Eq. (4)). Only the long chain alkyl-substituted alkyne **1a** gives a yield of less than 91%. In this particular example, some product of the addition of the arylsulfenyl chloride across the carbon–carbon triple bond was actually observed, thus accounting for the lower yield of the benzo[*b*]thiophene.

Mechanistically, we believe that these cyclizations proceed by *anti* attack of the electrophile and the sulfur of the thiomethyl group on the alkyne to produce a sulfonium salt, which undergoes methyl group removal via S_N2 displacement by nucleophiles present in the reaction mixture. In most cases, the nucleophile is presumably the halide remaining in solution. Clearly, the methyl group is as easily removed as the benzyl group of Flynn and co-workers. Virtually all electrophiles react with each of these substituted alkynes at about the same rate and almost all yields are above 90%.

We believe that this approach to 2,3-disubstituted benzo[*b*]thiophenes should prove quite useful in synthesis, particularly when one considers that there are many ways to transform the resulting halogen, sulfur and selenium functional groups into other substituents. For example, the resulting heterocyclic iodides should be particularly useful as intermediates in many palladium-catalyzed processes, like Sonagashira, Suzuki and Stille cross-coupling processes.

Acknowledgements

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References

1. (a) Bradley, D. A.; Godfrey, A. G.; Schmid, C. R. *Tetrahedron Lett.* **1999**, *40*, 5155; (b) Pinny, K. G.; Bounds, A. D.; Dubgenab, K. M.; Mocharla, V. P.; Pettit, G. R.; Bai, R.; Hamel, E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1081; (c) Magarian, R. A.; Overacre, L. B.; Singh, S.; Meyer, K. L. *Curr. Med. Chem.* **1994**, *1*, 61; (d) Bryant, H. U.; Dere, W. H. *Proc. Soc. Exp. Biol. Med.* **1998**, *217*, 45; (e) Su, T.; Naughton, M. A. H.; Smyth, M. S.; Rose, J. W.; Arfsten, A. E.; McCowan, J. R.; Jakubowski, J. A.; Wyss, V. L.; Ruterbories, K. J.; Sall, D. J.; Scarborough, R. M. *J. Med. Chem.* **1997**, *40*, 4308.
2. (a) Tony, Y. Z.; O'Toole, J.; Proctor, C. S. *Sulfur Rep.* **1999**, *22*, 1; (b) Pelkey, E. T. *Prog. Heterocyclic Chem.* **1999**, *11*, 102; (c) Bianchini, C.; Meli, A. *Synlett* **1997**, 643; (d) Russell, R. K.; Press, J. B. *Compr. Heterocyclic Chem. II* **1996**, *2*, 679; (e) Irie, M.; Uchida, K. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 985; (f) Gallagher, T.; Pardoe, D. A.; Porter, R. A. *Tetrahedron Lett.* **2000**, *41*, 5415; (g) McDonald, F. E.; Burova, S. A.; Huffman, Jr., L. G. *Synthesis* **2000**, 970.
3. (a) Larock, R. C.; Harrison, L. W. *J. Am. Chem. Soc.* **1984**, *106*, 4218; (b) Cacchi, S. *J. Organomet. Chem.* **1999**, *576*, 42; (c) Arcadi, A.; Cacchi, S.; Giancarlo, F.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432; (d) Cacchi, S.; Fabrizi, G.; Moro, L. *Tetrahedron Lett.* **1998**, *39*, 5101; (e) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280; (f) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915.
4. (a) Yasuhara, A.; Kanamori, Y.; Kaneko, M.; Numata, A.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, *4*, 529; (b) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001; (c) Cacchi, S.; Fabrizi,

G.; Marinelli, F.; Moro, L.; Pace, P. *Synlett* **1997**, *12*, 1363.
5. For reviews, see: (a) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111; (b) Larock, R. C. In *Palladium-Catalyzed Annulation*; Tsuji, J., Ed.; Elsevier Press: Lausanne, Switzerland, 1999; pp. 111–124; (c) Larock, R. C. *Pure Appl. Chem.* **1999**, *71*, 1435.
6. Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *5*, 651.
7. (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds. Perspectives in organopalladium chemistry for the XXI century. Wiley-VCH: Weinheim, 1998; Chapter 5, pp. 203–229; (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.