Transition-Metal-Free Method for the Synthesis of Benzo[*b*]thiophenes from *o*-Halovinylbenzenes and K_2S via Direct S_NAr-Type Reaction, Cyclization, and Dehydrogenation Process

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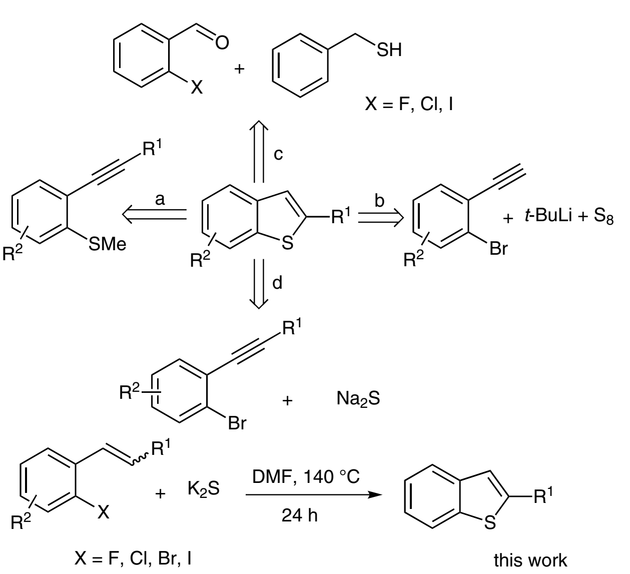
Abstract: A new, highly efficient procedure for the synthesis of benzothiophenes from easily available *o*-halovinylbenzenes and potassium sulfide has been developed. The reaction tolerated a wide range of functionalities, and various 2-substituted benzo[*b*]thiophenes are provided in the high yields in the absence of a transition-metal catalyst.

Key words: transition-metal-free, benzo[*b*]thiophenes, *o*-halovinylbenzenes, direct S_NAr-type reaction, cyclization, dehydrogenation process

Benzo[*b*]thiophenes have attracted much attention from organic chemists for many years due to their occurrence in a wide variety of pharmaceuticals and natural products possessing useful biological activities.[1] Consequently, much interest has been paid to the development of synthetic methods for benzo[*b*]thiophenes.[2–6] Most of these approaches are focused on transition-metal-catalyzed synthesis of benzo[*b*]thiophenes via constructing C–S bonds.[2] However, the need for high catalyst loading in some of these processes results in a high economic cost. And the presence of heavy transition-metal impurities in the final products also presents a major problem regarding purification. Therefore, the development of efficient and transition-metal-free processes will significantly change synthetic strategies for the assembly of benzothiophene structures. Transition-metal-free approach to benzothiophenes focus on: (1) electrophilic cyclization of *o*-alkynyl thioanisole[3] (Scheme 1, path a); (2) electrophilic cyclization reaction of *o*-bromo alkynylbenzenes with sulfur upon lithium–halogen exchange[4] (Scheme 1, path b); (3) S_NAr-type reaction, cyclization of *o*-halobenzaldehyde with benzylthiols[5] (Scheme 1, path c); (4) S_NAr-type reaction, cyclization of *o*-bromo alkynylbenzenes with sodium sulfide[6] (Scheme 1, path d). However, the reacted precursor *o*-alkynyl thioanisole and *o*-bromo alkynylbenzenes all were synthesized using transition-metal-catalyzed Sonogashira coupling reaction, and these methods are limited in drug synthesis because of contamination of heavy metal. Accordingly, the development of a facile, general, and transition-metal-free route to synthesize the benzo[*b*]thiophene ring systems from readily available starting materials would be quite attractive because of growing interest in these compounds.



Scheme 1 Approaches toward benzo[*b*]thiophene through transition-metal-free methods

During the course of our group's research into synthetic methodology involving heterocyclic compounds,[7] we unexpectedly found that in the absence of transition-metal catalyst, K_2S could couple with 2-halovinylbenzenes to produce benzo[*b*]thiophenes. To the best of our knowledge, only an analogous approach using the 2-dihalovinylbenzenes has been reported. Takimiya and coworkers reported the synthesis of [1]benzothieno[3,2-*b*][1]benzothiophene from *o*-dihalostilbenes and sodium sulfide nonahydrate in 180 °C via the direct S_NAr-type reaction, cyclization, and dehydrogenation process.[8] Unfortunately, the utility and applicability of this method suffer from the harsh reaction conditions and low yields. As a continuing interest in the synthesis of heterocyclic compounds, we want to construct various 2-substituted benzo[*b*]thiophenes using a more efficient and feasible

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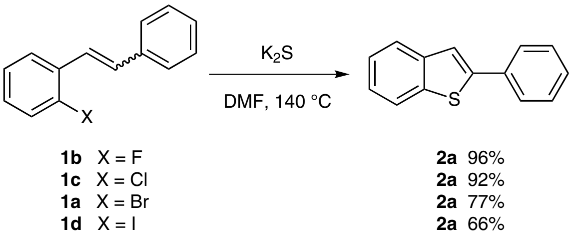
method. Herein, we report the unexpected transition-metal-free reaction of 2-halostyrenes (synthesized via Wittig reaction of phosphine ylides and aldehydes) and easily available potassium sulfide leading to 2-substituted benzo[*b*]thiophenes (Scheme 1).

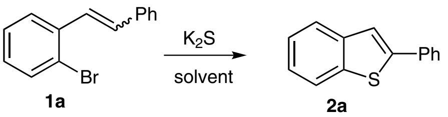
Initially, we tested the reaction of 1-bromo-2-styrylbenzene with potassium sulfide as a model example (Table 1). First, we tested different copper salts to see whether the reaction is a metal-catalyzed process (Table 1, entries 1–6). However, the control experiment results showed that the 1-bromo-2-styrylbenzene can be effectively converted into the 2-phenylbenzo[*b*]thiophene without addition of any transition metals, which implies this reaction is not catalyzed by a transition metal. Moreover, some transition metals can even prohibit the reaction. To further optimize the reaction parameters, the solvent and temperature were varied (Table 1, entries 7–12). The reaction can be accelerated by use of polar aprotic solvents and/or by elevating the reaction temperature. These experimental results indicated that K_2S acted as a nucleophile to synthesize 2-phenylbenzo[*b*]thiophene via the direct S_NAr-type reaction, cyclization, and dehydrogenation process.[8,9] Finally, the reaction was performed under air and the yield of 2-phenylbenzo[*b*]thiophene decreased slightly. Surprisingly, when the nitrogen atmosphere was replaced by oxygen, the corresponding product was obtained in a trace amount, and 78% of 1-bromo-2-styrylbenzene was recycled. We attributed this reason to potassium sulfide which could be oxidized to sulfur by oxygen. Therefore, the reaction should be performed under an inert atmosphere.

Since such a S_NAr-type reaction, cyclization, and dehydrogenation process is supposed, we then investigated the effects of fluoro, chloro, bromo, and iodo substituents on stilbenes (Scheme 2). As expected, perfect yields (96% and 92%, respectively) were obtained when 1-fluoro-2-styrylbenzene and 1-chloro-2-styrylbenzene were applied. In the reaction of 1-iodo-2-styrylbenzene, moderate yield (66%) was observed. A comparison of the reaction yields from halo-substituted styrylbenzene indicated a significant halogen dependence in the following order: F > Cl >Br > I. We believe that this observation supports the hypothesis that the benzo[*b*]thiophenes formation proceeds via the S_NAr mechanism.[4,8]



Scheme 2 Synthesis of 2-phenylbenzo[*b*]thiophenes

Table 1 Optimization of Reaction Conditions[a]

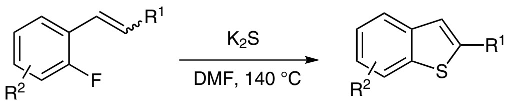


Entry	Solvent	Additive	Yield of **2a**10 (%)[b]
1	DMF	CuI	69
2	DMF	CuBr	68
3	DMF	CuCl	61
4	DMF	CuCN	71
5	DMF	$CuCl_2$	75
6	DMF	$Cu(OAc)_2$	trace
7	DMF	–	77
8	DMSO	–	73
9	NMP	–	71
10	MeCN	–	trace
11[c]	DMF	–	73
12[d]	DMF	–	58
13[e]	DMF	–	68
14[f]	DMF	–	trace

[a] Reaction conditions: **1a** (0.30 mmol), K_2S (0.90 mmol), additive (10 mol%), solvent (2 mL), N_2, 140 °C.
[b] Isolated yield.
[c] 120 °C.
[d] 100 °C.
[e] Air.
[f] O_2, 78% 1-bromo-2-styrylbenzene was recycled.

To extend the substrate scope of the cyclization reaction, various benzo[*b*]thiophenes were synthesized and submitted to the K_2S/DMF system. Table 2 listed the results obtained under the optimal reaction conditions. Initially, R^1 substituents at the terminal alkene moiety of 2-(1-alkenyl)fluorobenzenes were evaluated. The results demonstrated that both electron-rich groups such as Me, OMe, OH, or NMe_2 and electron-deficient groups such as Cl, CF_3, or CN on the phenyl ring were compatible, and the corresponding products were all obtained in high to perfect yields. For example, product **2e** and **2h** bearing the 3-hydroxylphenyl or 4-trifluoromethylphenyl group was afforded in 95% and 96% yield, respectively, via the thiolation annulation of the corresponding substrate with K_2S. Similarly, when the R^1 substituent was 1- or 2-naphthyl, the 2-(1-naphthyl)- or 2-(2-naphthyl)benzo[*b*]thiophene was obtained in excellent yield. The benzo[*b*]thiophene substituted with heterocyclic groups such as furyl, thienyl, or pyridyl could all be obtained in good to excellent yields. When we applied the method to the cyclization of alkyl- and benzyl-substituted *o*-fluorostyrene, we obtained unfavorable results. For example, *n*-butyl-, *tert*-butyl-, and benzyl-substituted *o*-fluorostyrene only afforded 42% of **2o**, 30% of **2p**, and 20% of **2q**. We attributed this reason to the lower reactivity of *o*-fluorostyrene due to the well electron-donating ability of alkyl and benzyl. However, this observation supports the hypothesis that the formation of benzo[*b*]thiophenes proceeds via a cyclic addition process. Finally, we investigated the effects of the group R^2 to the thiolation annulations of 2-(1-alkenyl)fluorobenzenes. The results indicated that electron-deficient groups promoted the reaction, but electron-rich groups hampered the reaction.

Table 2 Formation of Benzo[*b*]thiophenes from Various 2-Fluorostyrenes and K_2S[a]



1 **2**

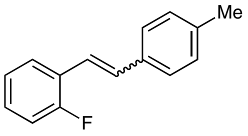
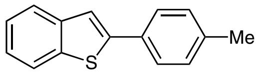
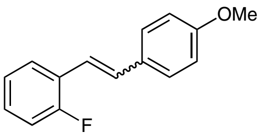
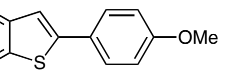
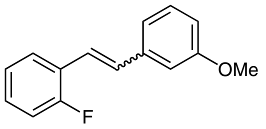
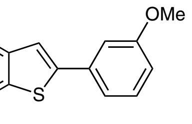
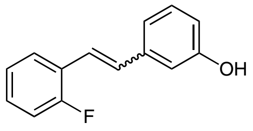
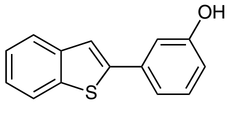
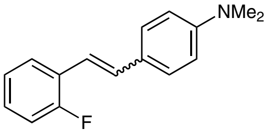
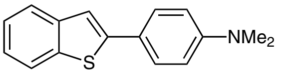
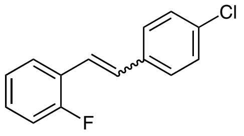
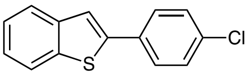
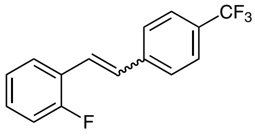
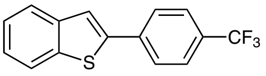
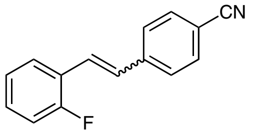
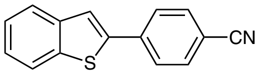
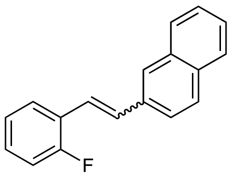
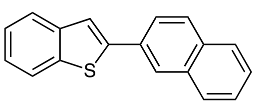
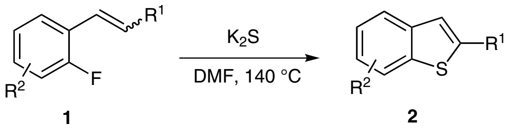
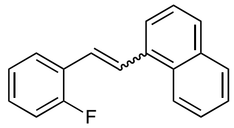
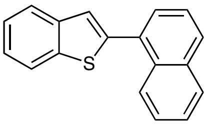
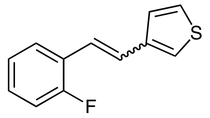
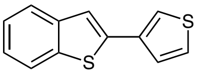
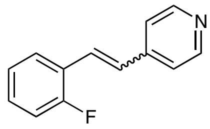
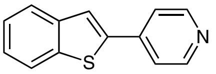
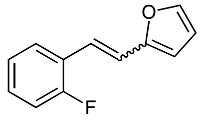
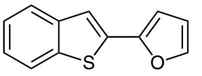
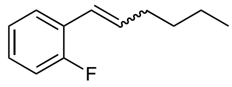
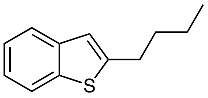
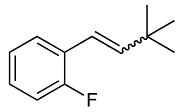
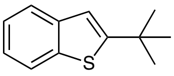
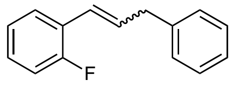
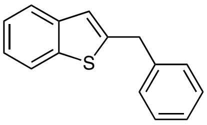
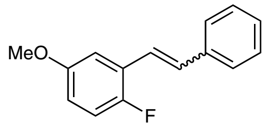
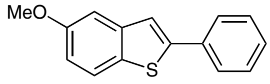
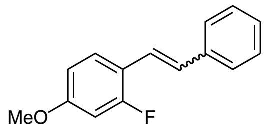
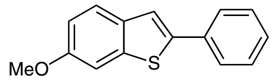
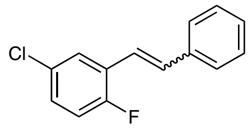
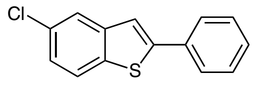
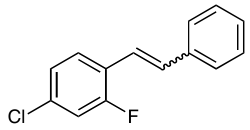
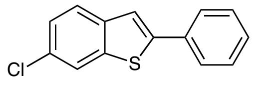
Entry	Substrate **1**	Product **2**		Yield (%)[b]
1		**2b**		92
2		**2c**		84
3		**2d**		88
4		**2e**		95
5		**2f**		93
6		**2g**		77
7		**2h**		96
8		**2i**[c]		94
9		**2j**		94

Table 2 Formation of Benzo[*b*]thiophenes from Various 2-Fluorostyrenes and K_2S[a] (continued)



Entry	Substrate **1**	Product **2**		Yield (%)[b]
10		**2k**		91
11		**2l**		90
12		**2m**		94
13		**2n**		62
14		**2o**		41
15		**2p**		30
16		**2q**		20
17		**2r**		52
18		**2s**		63
19		**2t**		90
20		**2u**		63

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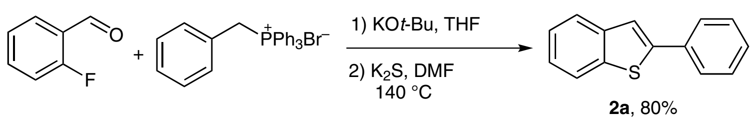
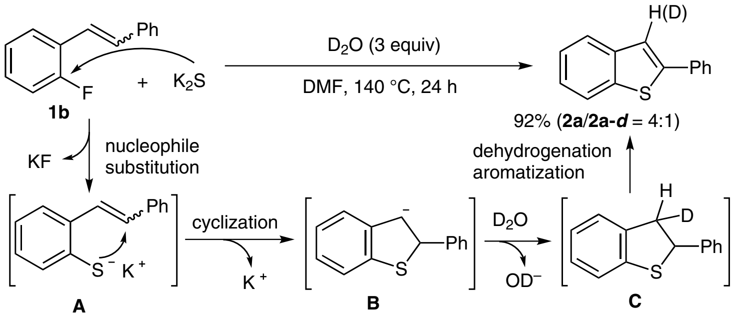
[a] Reaction conditions: **1** (0.3 mmol), K_2S (0.9 mmol), DMF (2 mL), 140 °C, under N_2 atmosphere for 24 h.

[b] Isolated yields.

[c] DMF was replaced by MeCN.



Scheme 3 One-pot reaction to synthesize 2-phenylbenzo[*b*]thiophene



Scheme 4 Possible mechanism for the reaction

To our delight, this synthetic method to synthesize benzo[*b*]thiophenes could be further extended from the initial starting material in one pot. For example, 2-fluorobenzaldehyde reacted with KO*t*-Bu and benzyltriphenylphosphonium bromide in THF for five hours, then K_2S and DMF were added, and the reaction was further stirred for 24 hours at 140 °C, and 2-phenylbenzo[*b*]thiophene was isolated in 80% yield (Scheme 3). This method could be a benign, one-pot method for synthesizing benzo[*b*]thiophenes.

A possible mechanism for the cascade reaction that leads to the formation of the benzo[*b*]thiophene ring is shown in Scheme 4. The process is initiated by the S_NAr-type reaction of K_2S to fluoro-substituted styrenes. This hypothesis is substantiated by the observation that the highest yields were obtained with fluoro-substituted styrenes, and the leaving-group activity decreases in the following order: F > Cl > Br> I. The intermediate **A**, subsequent addition to the C=C bond gave intermediate **B**. Protonation of intermediate **B** formed intermediate **C**. Subsequent dehydrogenation and aromatization of intermediate **C** gave rise to the 2-substituted benzo[*b*]thiophene product. This process was proved by the deuteration experiment. When 1-fluoro-2-styrylbenzene reacted with K_2S and D_2O in DMF, 2-phenylbenzo[*b*]thiophene was obtained in 92% yield (**2a**/**2a**-*d* = 4:1).

In summary, we have developed a simple, general, and transition-metal-free method to synthesize the benzo[*b*]thiophenes from easily utilized starting materials. This reaction features S_NAr-type reaction, cyclization, and dehydrogenation process to construct sulfur-containing heterocycles. Further studies to elucidate the mechanism and application to the synthesis of natural products are in progress.

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References and Notes

(1) (a) Berrade, L.; Aisa, B.; Ramirez, M. J.; Galiano, S.; Guccione, S.; Moltzau, L. R.; Levy, F. O.; Nicoletti, F.; Battaglia, G.; Molinaro, G.; Aldana, I.; Monge, A.; Perez-Silandes, S. *J. Med. Chem.* **2011**, *54*, 3086. (b) Venturelli, A.; Tondi, D.; Cancian, L.; Morandi, F.; Cannazza, G.; Segatore, B.; Prati, F.; Amicosante, G.; Shoichet, B. K.; Costi, M. P. *J. Med. Chem.* **2007**, *50*, 5644. (c) Romagnoli, R.; Baraldi, P. G.; Carrion, M. D.; Cara, C. L.; Preti, D.; Fruttarolo, F.; Pavani, M. G.; Tabrizi, M. A.; Tolomeo, M.; Grimaudo, S.; Cristina, A. D.; Balzarini, J.; Hadfield, J. A.; Brancale, A.; Hamel, E. *J. Med. Chem.* **2007**, *50*, 2273. (d) Witter, D. J.; Belvedere, S.; Chen, L.; Secrist, J. P.; Mosley, R. T.; Miller, T. A. *Bioorg. Med. Chem.* **2007**, *17*, 4562.

(2) For selected recent examples on transition-metal-catalyzed synthesis of benzo[*b*]thiophenes, see: (a) Sun, L.-L.; Deng, C.-L.; Tang, R.-Y.; Zhang, X.-G. *J. Org. Chem.* **2011**, *76*, 7546. (b) Kuhn, M.; Falk, F. C.; Paradies, J. *Org. Lett.* **2011**, *13*, 4100. (c) Guilarte, V.; Fernández-Rodríguez, M. A.; García-García, P.; Hernando, E.; Sanz, R. *Org. Lett.* **2011**, *13*, 5100. (d) Zeng, F.; Alper, H. *Org. Lett.* **2011**, *13*, 2868. (e) Huang, H.; Li, J.; Zhao, W.; Mei, Y.; Duan, Z. *Org. Biomol. Chem.* **2011**, *9*, 5036. (f) You, W.; Yan, X.; Liao, Q.; Xi, C. *Org. Lett.* **2010**, *12*, 3930. (g) Bryan, C. S.; Braunger, J. A.; Lautens, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 7064. (h) Newman, S. G.; Aureggi, V.; Bryan, C. S.; Lautens, M. *Chem. Commun.* **2009**, 5236. (i) Inamoto, K.; Arai, Y.; Hiroya, K.; Doi, T. *Chem. Commun.* **2008**, 5529. (j) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 4473.

(3) (a) Mehta, S.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 1652. (b) Cho, C.-H.; Neuenswander, B.; Larock, R. C. *J. Comb. Chem.* **2010**, *12*, 278. (c) Sanz, R.; Guilarte, V.; Hernando, E.; Sanjuán, A. M. *J. Org. Chem.* **2010**, *75*, 7443. (d) Cho, C.-H.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *J. Comb. Chem.* **2009**, *11*, 900. (e) Mehta, S.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 1141. (f) Ebata, H.; Miyazaki, E.; Yamamoto, T.; Takimiya, K. *Org. Lett.* **2007**, *9*, 4499. (g) Zhou, Y.; Liu, W.-J.; Ma, Y.-G.; Wang, H.-L.; Qi, L.-M.; Cao, Y.; Wang, J.; Pei, J. *J. Am. Chem. Soc.* **2007**, *129*, 12386.

(4) (a) Geng, W.-Z.; Wang, Z.-T.; Wang, H.-L.; Zhang, S.-G.; Zhang, W.-X.; Xi, Z. *Tetrahedron* **2012**, *68*, 5283. (b) Wang, Z.-T.; Geng, W.-Z.; Wang, H.-L.; Zhang, S.-G.; Zhang, W.-X.; Xi, Z. *Tetrahedron Lett.* **2011**, *52*, 6997. (c) Wang, Y.-F.; Parkin, S. R.; Watson, M. D. *Org. Lett.* **2008**, *10*, 4421. (d) Takimiya, K.; Konda, Y.; Ebata, H.; Niihara, N.; Otsubo, T. *J. Org. Chem.* **2005**, *70*, 10569. (e) Sashida, H.; Sadamori, K.; Tsuchiya, T. *Synth. Commun.* **1998**, *28*, 713.

(5) Duan, Z.-Y.; Ranjit, S.; Liu, X.-G. *Org. Lett.* **2010**, *12*, 2430.

(6) (a) Kashiki, T.; Shinamura, S.; Kohara, M.; Miyazaki, E.; Takimiya, K.; Ikeda, M.; Kuwabara, H. *Org. Lett.* **2009**, *11*, 2473. (b) Patel, M. V.; Rohde, J. J.; Gracias, V.; Kolasa, T. *Tetrahedron Lett.* **2003**, *44*, 6665.

(7) Zhang, X.-Y.; Yang, Y.; Liang, Y. *Tetrahedron Lett.* **2012**, *53*, 6406.

(8) Saito, M.; Yamamoto, T.; Osakaa, I.; Miyazaki, E.; Takimiya, K.; Kuwabara, H.; Ikeda, M. *Tetrahedron Lett.* **2010**, *51*, 5277.

(9) (a) Shaw, J. E. *J. Org. Chem.* **1991**, *56*, 3728. (b) Cogolli, P.; Maiolo, F.; Testaferri, L.; Tingoli, M.; Tiecco, M. *J. Org. Chem.* **1979**, *44*, 2642.

(10) **Benzo[*b*]thiophenes 2; General Procedure**

Under the protection of nitrogen, an oven-dried Schlenk tube was charged with K_2S (0.9 mmol, 3 equiv) and the 1-fluoro-2-styryl derivative (0.3 mmol). The tube was evacuated and backfilled with nitrogen before DMF or MeCN (2 mL) was added. The reaction mixture was stirred at 140 °C, and after 24 h was quenched with H_2O. The mixture extracted with EtOAc, and the combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, concentrated in vacuo and purified by column chromatography to afford the product.

Analytical Data for Compound 2a

white solid; isolated yield 96% (60 mg; mp 172.2–173.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.82 (d, J = 8.0 Hz, 1 H), 7.77 (d, J = 7.5 Hz, 1 H), 7.72 (d, J = 8.5 Hz, 2 H), 7.54 (s, 1 H), 7.42 (t, J = 7.8 Hz, 2 H), 7.36–7.29 (m, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.2, 140.7, 139.5, 134.3, 128.9, 128.2, 126.5, 124.5, 124.3, 123.5, 122.2, 119.4.