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Direct Synthesis of Diverse 2-Aminobenzo[*b*]thiophenes via Palladium-Catalyzed Carbon−Sulfur Bond Formation Using $Na_2S_2O_3$ as the Sulfur Source

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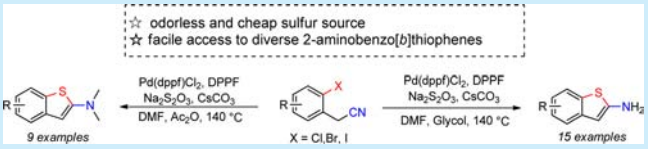
Supporting Information

ABSTRACT: A novel and direct synthesis of various 2-aminobenzo[*b*]thiophenes has been developed. The reactions were catalyzed by a combination of $Pd(dppf)Cl_2$ and dppf using odorless and cheap $Na_2S_2O_3$ as the sulfur source. This strategy allowed us to synthesize important 2-aminobenzo[*b*]-thiophene scaffold more efficiently and conveniently.



Benzo[*b*]thiophene is an important privileged structure which can provide potent and selective ligands for a range of different biological targets. It is widely used in the development of bioactive compounds, including estrogen receptor antagonists,[1] acetyl-CoA carboxylase inhibitors,[2] HIV-1 reverse transcriptase inhibitors,[3] antidepressants,[4] and tubulin polymerization inhibitors.[5] Among them, 2-aminobenzo[*b*]thiophene and its derivatives played an important role.[2b,5a] Moreover, it also served as a key intermediate in the synthesis of clinically used raloxifene and analogues.[1b,c] Given the significance of bioactive benzo[*b*]-thiophenes, there has been an increasing interest in the search for novel methodologies for the synthesis of benzo[*b*]-thiophene and its derivatives (Figure 1).[6]

In fact, 2-aminobenzo[*b*]thiophene was synthesized in an overall yield of 48% via five steps from thiosalicylic acid.[7] Knochel and co-workers obtained 2-aminobenzo[*b*]thiophene by treating benzo[*b*]thiophen-2-ylmagnesium chloride with LiHMDS under harsh conditions.[8] It was also reported that the Willgerodt−Kindler reaction was applied to synthesize 2-aminobenzo[*b*]thiophenes generally in a low yield (4−47%), while the substituted functional group on the motif was limited to nitro.[9] Hopkinson and Lee-Ruff prepared 2-aminobenzo[*b*]-thiophenes from benzaldehyde and *N*,*N*-dimethylthioforma-mide treated with LDA at −78 °C,[10] and the Lilly research laboratories followed this method to synthesize a variety of substituted 2-aminobenzo[*b*]thiophenes in the development of raloxifene and its analogues.[1b] However, these methods generally could not circumvent the disgusting smell, harsh reaction conditions, low yields, and complicated or tedious procedures (Scheme 1). Because of all the problems mentioned above, the development of concise and novel strategies for the synthesis of 2-aminobenzo[*b*]thiophene and its derivatives is considered of high practical value. Herein we report a novel access to synthesize various substituted 2-aminobenzo[*b*]-thiophenes using $Na_2S_2O_3$ as the sulfur source.

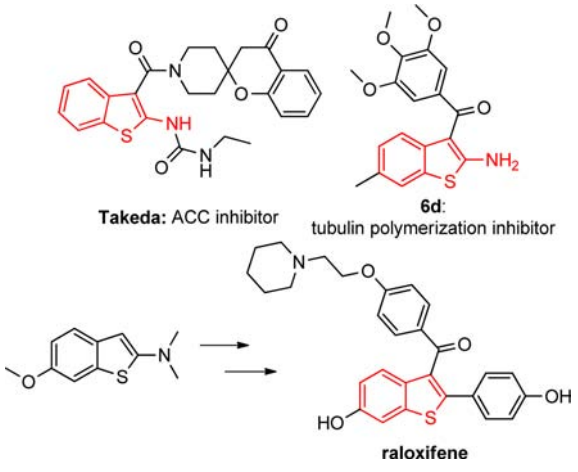


Figure 1. Bioactive molecules containing benzo[*b*]thiophenes.

Recently, $Na_2S_2O_3$ is gaining more and more attention in the methodologies for the synthesis of organosulfur compounds. In 2007, Ma and co-workers used $Na_2S_2O_3$ as sulfur source to prepare 1,2-allenyl sulfones.[11] Jiang and co-workers reported metal-catalyzed intramolecular or intermolecular double C−S bond formation by using $Na_2S_2O_3$ as the sulfurating reagent.[12] Considering the results reported in the literatures, we envisaged that the source of the sulfur in 2-aminobenzo[*b*]thiophenes could be transferred from $Na_2S_2O_3$ with the help of desired metal catalysts.

Previously, we reported the construction of various privileged structures such as functionalized naphthalenes[13] and inden-ones[14] from 2-bromophenylacetonitrile. Here we began our investigation with an attempt to treat 2-bromophenylacetoni-trile with $Na_2S_2O_3{\cdot}5H_2O$ in DMF at 140 °C in the presence of $Pd(dppf)Cl_2$ and dppf. Gratifyingly, the desired product 2-

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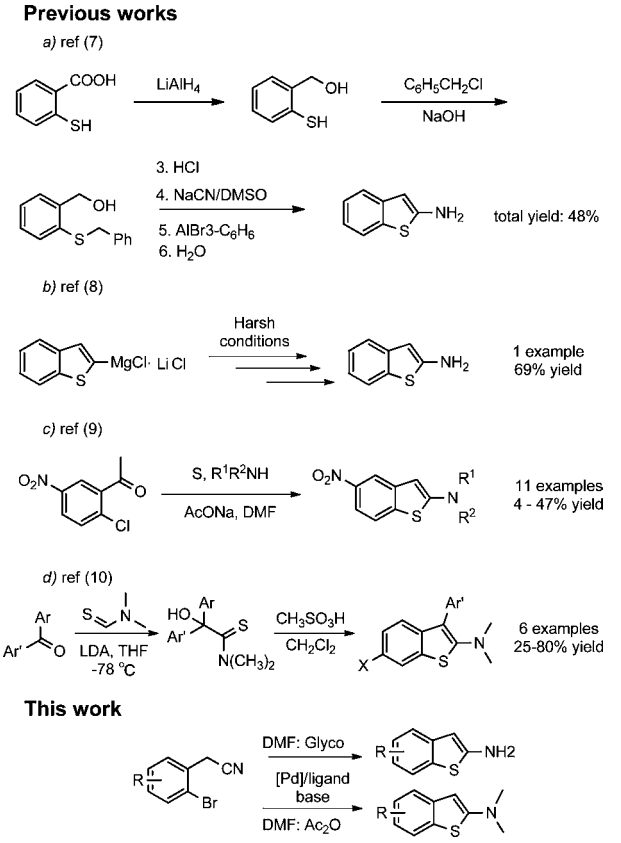
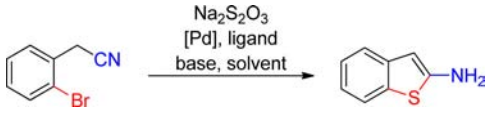
Scheme 1. Synthesis of 2-Aminobenzo[*b*]thiophenes



aminobenzo[*b*]thiophene was isolated in 36% yield (Table 1, entry 1). A screen of different Palladium catalysts indicated that $Pd(dppf)Cl_2$ was the best choice (Table 1, entries 1−3). After that, we tried several approches to enhance the solubility of $Na_2S_2O_3{\cdot}5H_2O$, and the results showed that the yield was slightly improved when tetrabutylammonium bromide (TBAB, 0.03 mmol) and H_2O (0.2 mL) were added (Table 1, entry 7 vs entries 4−6). Other bases including K_2CO_3, KOAc, and tBuOK were proven to be ineffective under the same conditions (Table 1, entries 8−10 vs entry 7). Further attempts to search for a better ligand than dppf also failed (Table 1, entries 11 and 12). We then tested different solvent systems, and the application of DMF (4 mL) and ethylene glycol (0.2 mL) gave the title product in a yield of 50% (Table 1, entry 13). To our delight, the yield of the product was elevated to 64% when the amount of dppf was increased to 15 mol %. The temperature also has great impact on the reaction, and the yield was decreased to 20% when we lowered the temperature to 120 °C (Table 1, entry 19).

With the optimized conditions in hand (5 equiv of $Na_2S_2O_3{\cdot}5H_2O$, 10 mmol % of $Pd(dppf)Cl_2$, 15 mmol % of dppf, 3 equiv of Cs_2CO_3, 4 mL of DMF, 0.2 mL of ethylene glycol), we explored the scope and generality of this method. As shown in Scheme 2, substituted groups including fluoro, chloro, methoxy, and trifluoromethyl were all well tolerated during the reaction to give the corresponding products, respectively. Meanwhile, substrates with chloro or iodo substitution on *ortho*-position furnished lower yields compared with *o*-bromo substituent (Scheme 2, **1b**). All 2-bromophenylacetonitriles with a fluoro group on C4, C5, or C6, respectively, gave the desired products in 46−50% yields (Scheme 2, **2b**, **3b**, **4b**). 6-Methyl-substituted compound **5b** could be obtained in 60% yield (Scheme 2, **5b**).

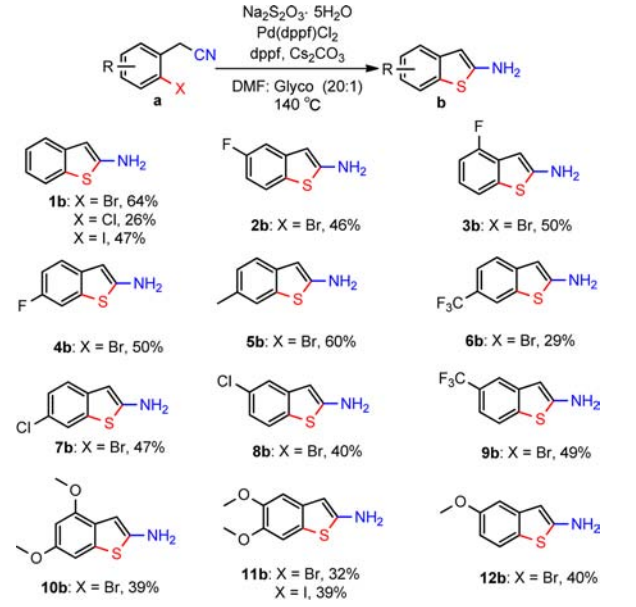
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (0.05 mmol)	ligand (0.025 mmol)	base (3 equiv)	solvent	yield[b] (%)
1	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMF	36
2	$Pd(OAc)_2$	dppf	Cs_2CO_3	DMF	17
3	$Pd(MeCN)_2Cl_2$	dppf	Cs_2CO_3	DMF	21
4	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMF[e]	29
5	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMF[f]	28
6	$Pd(dppf)Cl_2$[c]	dppf	Cs_2CO_3	DMF[e]	33
7	$Pd(dppf)Cl_2$[c]	dppf	Cs_2CO_3	DMF[f]	43
8	$Pd(dppf)Cl_2$[c]	dppf	K_2CO_3	DMF[f]	24
9	$Pd(dppf)Cl_2$[c]	dppf	KOAc	DMF[f]	trace
10	$Pd(dppf)Cl_2$[c]	dppf	tBuOK	DMF[f]	trace
11	$Pd(dppf)Cl_2$[c]	JohnPhos	Cs_2CO_3	DMF[f]	17
12	$Pd(dppf)Cl_2$[c]	$P(tBuO)_3$	Cs_2CO_3	DMF[f]	30
13	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMF[g]	50
14	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMF[h]	trace
15	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	DMSO[g]	17
16	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	NMP[g]	42
17	$Pd(dppf)Cl_2$	dppf	Cs_2CO_3	glycol	trace
18	**$Pd(dppf)Cl_2$**	**dppf**[d]	**Cs_2CO_3**	**DMF**[g]	**64**
19	$Pd(dppf)Cl_2$	dppf[d]	Cs_2CO_3	DMF[g]	20[i]

[a]Reaction conditions: 2-bromophenylacetonitrile (0.5 mmol), $Na_2S_2O_3{\cdot}5H_2O$ (2.5 mmol), [Pd] (0.05 mmol), ligand (0.025 mmol), base (1.5 mmol), solvent (4.0 mL), 140 °C, sealed tube, argon atmosphere, 12 h. [b]Isolated yield. [c]TBAB (0.03 mmol). [d]Dppf (0.075 mmol). [e]H_2O (0.4 mL). [f]H_2O (0.2 mL). [g]Glycol (0.2 mL). [h]DETA (0.2 mL). [i]120 °C.

Scheme 2. Synthesis of Diverse 2-Aminobenzo[*b*]thiophenes[a,b]



[a]Reaction conditions: **a** (0.5 mmol), $Na_2S_2O_3{\cdot}5H_2O$ (2.5 mmol), $Pd(dppf)Cl_2$ (0.05 mmol), dppf (0.075 mmol), Cs_2CO_3 (1.5 mmol), DMF (4.0 mL), glycol (0.2 mL), 140 °C, sealed tube, argon atmosphere, 12 h. [b]Isolated yield.

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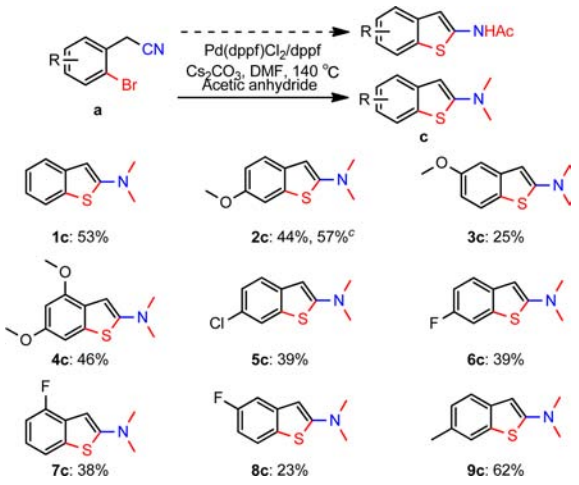
Differently, 4-(trifluoromethyl)-2-bromophenylacetonitrile gave the corresponding product **6b** in 29% yield (Scheme 2, **6b**), while substrate bearing a trifluoromethyl substitution on C5 gave the corresponding compound **9b** in 49% yield (Scheme 2, **9b**). Furthermore, 4- or 5-chloro-substituted substrates provided the corresponding products in 47% or 40% yield, respectively (Scheme 2, **7b**, **8b**). To investigate the effect of electron-donating groups, substrates bearing one or two methoxyl substituents were tested and the desired products were successfully isolated in 32−40% yields (Scheme 2, **10b**, **11b**, **12b**).

Despite the moderate yields reported herein, this strategy with an odorless, easy to handle, and one-step procedure is still a big step forward in the development of the synthesis of 2-aminobenzo[*b*]thiophenes. Considering that the scaffold might be unstable under the optimized conditions, we attempted to exchange the glycol with acetic anhydride in order to get the protected acetamide of benzo[*b*]thiophenes. Unexpectedly, 2-(dimethylamino)benzo[*b*]thiophenes were isolated in moderate yields (Scheme 3). It is worth noting that compound **2c**, an

Scheme 3. Synthesis of Diverse 2-(Dimethylamino)benzo[*b*]thiophenes[a,bc]



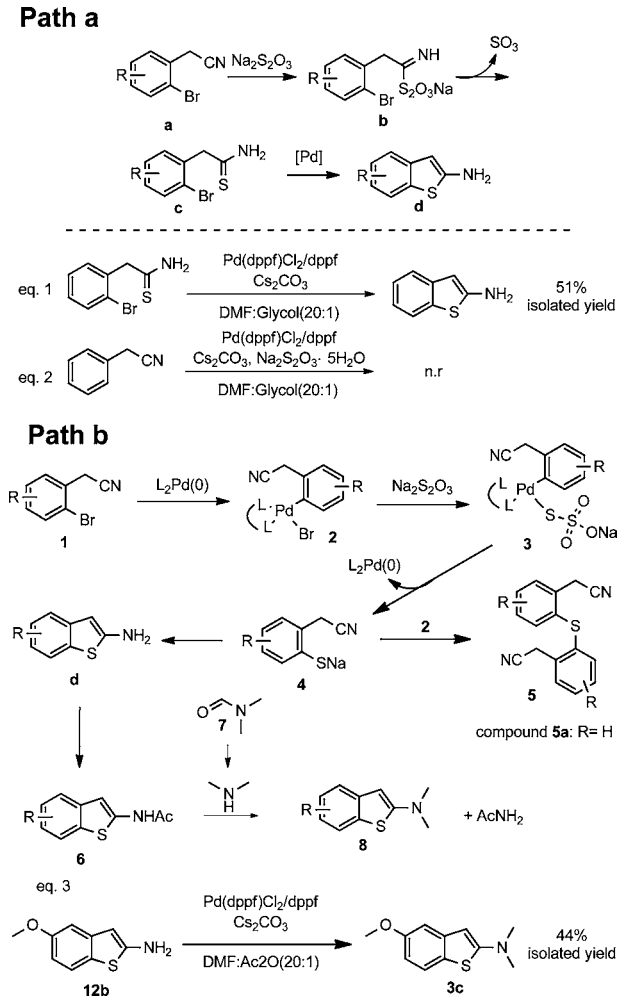
[a]Reaction conditions: **a** (0.5 mmol), $Na_2S_2O_3{\cdot}5H_2O$ (2.5 mmol), $Pd(dppf)Cl_2$ (0.05 mmol), dppf (0.075 mmol), Cs_2CO_3 (1.5 mmol), DMF (4.0 mL), Ac_2O (0.2 mL), 140 °C, sealed tube, argon atmosphere, 12 h. [b]Isolated yield. [c]The procedure was scaled up to 5 mmol.

alternative key intermediate of raloxifene, could be prepared in one step through this method with a 44% yield. However, the substrate with a methoxy substituent on the C5 position gave the product **3c** with a 20% yield. Further investigation proved that fluorine and chlorine were well tolerated under the reaction conditions. In addition, compound **4c** bearing two methoxy substituents on C4, C6 and compound **9c** with a methyl substituent on C6 could be obtained in good yield.

To highlight the efficiency and practicability of the strategy, we successfully scaled up the procedure to 5 mmol and obtained 595 mg of **2c** after 12 h in 57% isolated yield (Scheme 3). In addition, it was reported that 2-aminobenzo[*b*]thiophene could be easily transformed to 2-bromobenzo[*b*]thiophene by using $NaNO_2$, HBr, and CuBr in water.[15]

On the basis of the above results, two plausible mechanisms are proposed and outlined in Scheme 4. To investigate the possibility of path a, some tentative experiments were

Scheme 4. Proposed Mechanisms



examined. First, the treatment of (2-bromophenyl)-thioacetamide under the standard conditions with glycol added successfully gave 2-aminobenzo[*b*]thiophene in 51% yield (eq 1). However, the attempt to prepare phenylthioacetamide from phenylacetonitrile under standard conditions with glycol failed (eq 2). Therefore, path a could not be the proper one. Another mechanism was proposed as path b. In path b, after an oxidative addition of $L_2Pd(0)$ to compound **1** to form complex **2**, a ligand exchange with $Na_2S_2O_3$ was assumed to give complex **3**, which could then provide intermediate **4** and $L_2Pd(0)$ via reductive elimination. The intramolecular condensation of compound **4** would furnish 2-aminobenzo[*b*]-thiophene **d**. On the other hand, the intermediate **4** might react with complex **2** to give the side product **5**. The formation of **5** was confirmed by isolation of compound **5a**. Furthermore, we assumed that compound **6** might be formed when Ac_2O was added. When it is heated, the DMF could provide dimethylamine, with which the compound **6** could undergo a nucleophilic addition and an elimination to give product **8**. This step was proved by successfully transferring compound **12b** to **3c** in 44% isolated yield under the standard conditions (eq 3).

In conclusion, we have developed a novel and direct method for the synthesis of multiple 2-aminobenzo[*b*]thiophenes. The advantages of this method include the odorless sulfur source, easy-handling procedure, and wide scope. Furthermore, 2-

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aminobenzo[*b*]thiophenes as important building blocks or bioactive compounds should make this approach attractive for chemists. Further studies in order to extend this methodology are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of new compounds (^{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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Notes

The authors declare no competing financial interest.

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