ChemPubSoc Europe

DOI: 10.1002/chem.201501828

CHEMISTRY
A European Journal
Full Paper

C–H Functionalization

# Diversity-Oriented Synthesis of Substituted Benzo[*b*]thiophenes and Their Hetero-Fused Analogues through Palladium-Catalyzed Oxidative C–H Functionalization/Intramolecular Arylthiolation

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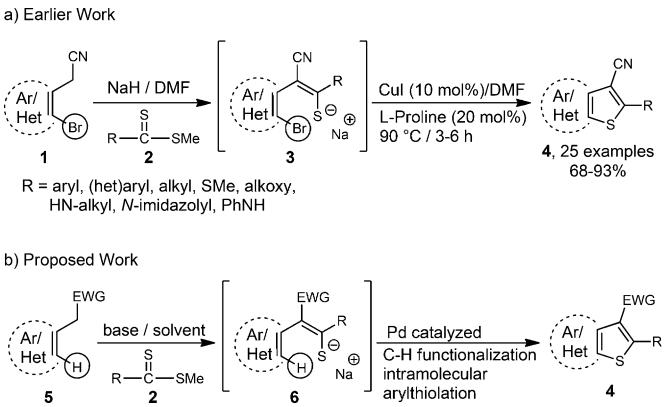
*Dedicated to Professor Paul Knochel on the occasion of his 60th birthday*

**Abstract:** An efficient, high yielding route to multisubstituted benzo[*b*]thiophenes has been developed through palladium-catalyzed intramolecular oxidative C–H functionalization–arylthiolation of enethiolate salts of $\alpha$-aryl-$\beta$-(het)aryl/alkyl-$\beta$-mercaptoacrylonitriles/acrylates or acrylophenones. The overall strategy involves a one-pot, two-step process in which enethiolate salts [generated in situ through base-mediated condensation of substituted arylacetonitriles, deoxybenzoins, or arylacetates with (het)aryl (or alkyl) dithioates] are subjected to intramolecular C–H functionalization–arylthiolation under the influence of a palladium acetate (or palladium chloride)/cupric acetate catalytic system and tetrabutylammonium bromide as additive in *N*,*N*-dimethylformamide (DMF) as solvent. In a few cases, the yields of benzo[*b*]thiophenes were better in a two-step process by employing the corresponding enethiols as substrates. In a few examples, $Pd(OAc)_2$ (or $PdCl_2$) catalyst in the presence of oxygen was found to be more efficient than cupric acetate as reoxidant, furnishing benzothiophenes in improved yields by avoiding formation of side products. The method is compatible with a diverse range of substituents on the aryl ring as well as on the 2- and 3-positions of the benzothiophene scaffold. The protocol could also be extended to the synthesis of a raloxifene precursor and a tubulin polymerization inhibitor in good yields. The versatility of this newly developed method was further demonstrated by elaborating it for the synthesis of substituted thieno-fused heterocycles such as thieno[2,3-*b*]thiophenes, thieno[2,3-*b*]indoles, thieno[3,2-*c*]pyrazole, and thieno[2,3-*b*]pyridines in high yields. A probable mechanism involving intramolecular electrophilic arylthiolation via either a Pd-S adduct or palladacycle intermediate has been proposed on the basis of experimental studies.

## Introduction

Substituted benzo[*b*]thiophenes represent an important class of heterocyclic compounds because they exhibit a broad range of biological activities and provide useful properties in material science.[1a,b,2] The benzo[*b*]thiophene ring system and its derivatives are the core structures of numerous drug molecules,[1a,b] such as clinically used raloxifene,[3a–c] arzoxifene,[3d] and zileuton.[3e–f] Consequently, the synthesis of this privileged structure has attracted much attention in recent years and many efficient methods have been developed.[1,2,4] Most of these approaches rely upon electrophilic cyclization reactions of *o*-alkynylbenzenethiol derivatives.[1a,5,6] Recently, transition-metal-catalyzed C–heteroatom bond-forming cross-coupling reactions have also been developed, which provide more efficient, practical, and straightforward approaches for the construction of benzo-fused heterocycles.[1a,7] In this context, we have also recently described an efficient one-pot synthesis of substituted benzo[*b*]thiophenes **4** and their hetero analogues involving sequential base-mediated condensation of substituted 2-bromo-het(aryl)acetonitriles **1** with a range of dithioesters **2** and other thiocarbonyl variants, followed by $Cu^{I}$-catalyzed intramolecular




**Scheme 1.** a) Previous and b) present synthesis of benzo[*b*]thiophenes.

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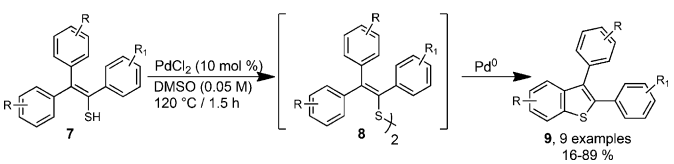
*Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201501828.*

C–S arylation of the resulting thioenolate intermediates **3** in situ (Scheme 1a).[1a]

In a continuation of these studies, we became intrigued with the idea of whether benzo[*b*]thiophenes **4** could be synthesized by an alternate strategy involving direct catalytic oxidative intramolecular C–H functionalization–arylthiolation of thioenol precursors such as **6**, which do not bear a 2-bromo substituent (obtained by condensation of active methylene precursors **5** with dithioates). This would eliminate the requirement of *o*-bromo (or halo) substituent in **1**, thus opening up a much wider range of more readily accessible precursors for benzo[*b*]thiophene synthesis (Scheme 1b). The development of novel transition-metal-catalyzed methods for selective functionalization of a C–H bond (also called cross dehydrogenative coupling[8c]) continues to be an area of intense research.[8] In contrast to traditional metal-catalyzed cross-coupling reactions employing prefunctionalized substrates such as aryl/vinyl halides/triflates, precursors, which proceed by oxidative insertion and elimination mechanism, direct C–H functionalization provides a simpler synthetic strategy from C–H aryl/vinyl precursors without requiring any prefunctionalization and proceeds through a completely different mechanism.[8] Whereas intermolecular C–H functionalization of five- and six-membered heterocycles has been studied extensively,[8,9] many examples of intramolecular aryl C–H functionalization[8c,10] leading to a wide range of benzoheterocycles such as carbazoles,[11] indazoles,[12] benzimidazoles,[13] benzoxazoles,[14] benzotriazole,[15] dibenzofurans,[16] and indoles[17] have been reported only recently. However, in contrast to C–H amination and etherification reactions, catalytic C–H thiolation still represents a challenge because of the long-standing reputation that sulfur has for catalyst poisoning. Inamoto[18a] and others[18b] have recently reported the synthesis of substituted benzothiazoles[18] through palladium-catalyzed intramolecular oxidative C–H functionalization–arylthiolation of thiobenzanilides. The same group also described earlier a direct synthesis of 2,3-bis(aryl)benzo[*b*]thiophenes **9** through an intramolecular palladium ($PdCl_2$) catalyzed cyclization of 1,2,2-triarylethenethiols **7** in the presence of dimethyl sulfoxide (DMSO) (Scheme 2).[19] The reaction was shown to proceed through palladium-catalyzed oxidative disulfide formation (i.e., **8**) and subsequent Pd-catalyzed intramolecular cyclization to benzothiophenes, without involving a direct C–H functionalization. However, the generality and scope of the reaction was limited to the synthesis of a few 1,2-diarylbenzo[*b*]thiophenes. We herein disclose a novel one-pot, two-step diversity-oriented synthesis of highly functionalized benzo[*b*]thiophenes and their hetero-fused analogues by palladium-catalyzed oxidative intramolecular C–H functionalization–arylthiolation of thioenolates that are generated in situ (Scheme 1). The reaction can tolerate a broad array of substituents and functionalities at various positions of the benzothiophene skeleton. The methodology has also been extended to the synthesis of a raloxifene precursor and a tubulin polymerization inhibitor. A possible mechanism for the formation of benzo[*b*]thiophenes from thioenolates (or thioenol) through this catalytic intramolecular thiolation process has also been proposed based on the results of experimental studies.



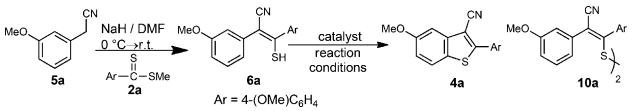

**Scheme 2.** Synthesis of benzo[*b*]thiophenes by Inamoto and co-workers.

## Results and Discussion

Initial studies were performed on enethiol **6a** (prepared by reaction of 3-methoxyphenylacetonitrile **5a** with 4-methoxyphenyldithioate **2a** in the presence of sodium hydride in *N*,*N*-dimethylformamide (DMF)) for optimization of reaction conditions leading to benzo[*b*]thiophene **4a** (Table 1). Extensive screening of palladium-based catalysts along with reoxidants, solvents, and reaction conditions revealed that benzo[*b*]thiophene **4a** was obtained in good yields in the presence of either $Pd(OAc)_2$ or $PdCl_2$ catalyst (20 mol%) at 120–130 °C within 6–7 h, in combination with $Cu(OAc)_2$ (1 equiv) as reoxidant, in either DMF or DMSO as solvent, under $N_2$ atmosphere (entries 1–4). Addition of $Bu_4NBr$ (2 equiv) further facilitated the process and the reaction was complete at lower temperature (90 °C) within 4–5 h, furnishing benzo[*b*]thiophene **4a** in comparable yields (entries 5–8). It was also observed that decreasing the concentration of $Bu_4NBr$ (20 mol%) did not affect the yield of **4a** under similar conditions (entries 9–12). On the other hand, decreasing the catalytic loading (entries 13–14) or reoxidant concentration (entries 15–16) resulted in lower yield of **4a** even after prolonged reaction time. Subsequently, we found that this transformation also proceeds in the presence of $Pd(OAc)_2$ (or $PdCl_2$) catalyst under oxygen atmosphere at 120–130 °C, yielding **4a** in high yields (entries 17–20). Examination of other palladium sources such as $Pd(PPh_3)_4$ and $Pd(TFA)_2$ did not give satisfactory results. Other metal catalysts such as $AuCl_3$, $RuCl_3$, $NiCl_2$, and $PtCl_2$ were also found to be ineffective in this reaction.

Having established the optimal reaction conditions for the conversion of enethiol **6a** into benzo[*b*]thiophene **4a**, we then wanted to develop a one-pot reaction by generating enethiolate **6a′** in situ from **5a** and dithioate **2a** (in the presence of NaH and DMF) and their direct conversion into benzothiophene **4a** (Table 2). To our delight, **4a** was obtained in comparable yields under these conditions (entry 1). We therefore performed most of the reactions in a one-pot, two-step process by using the $Pd(OAC)_2/Cu(OAC)_2$ catalytic system (Method A); however, in a few cases the yields of benzo[*b*]thiophenes **4** obtained by using this procedure were low, therefore some of the benzothiophenes were synthesized directly from enethiols **6** in improved yields by using a two-step process (Method B; Table 2, entries 6, 15, and 20). In a few examples, with substrates carrying alkyl or polymethoxy substituents, cleavage and acetoxylation of products were observed in the presence of cupric acetate reoxidant, resulting in lower yields of benzothiophenes **4**. Therefore, these reactions were performed by subjecting the corresponding thioenols **6** to oxidative cycliza-

**Table 1.** Optimization studies for the synthesis of benzo[*b*]thiophene **4a** from enethiol **6a**.



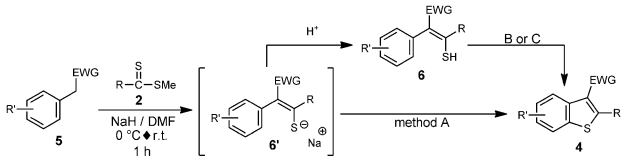

| Entry | Catalyst (mol %) | Reaction conditions | *T* [°C] | *t* [h] | Yield [%] **4a** | **10a** |
|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ (20)/ $Cu(OAc)_2$ (1 equiv) | $DMF/N_2$ | 130 | 6 | 88 | – |
| 2 | $Pd(OAc)_2$ (20)/ $Cu(OAc)_2$ (1 equiv) | $DMSO/N_2$ | 120 | 7 | 77 | 10 |
| 3 | $PdCl_2$ (20)/ $Cu(OAc)_2$ (1 equiv) | $DMF/N_2$ | 130 | 6 | 87 | – |
| 4 | $PdCl_2$ (20)/ $Cu(OAc)_2$ (1 equiv) | $DMSO/N_2$ | 120 | 7 | 76 | 12 |
| 5 | $Pd(OAc)_2$ (20)/ $Cu(OAc)_2$ (1 equiv)/ $Bu_4NBr$ (2 equiv) | $DMF/N_2$ | 90 | 4 | 90 | – |
| 6 | $Pd(OAc)_2$ (20)/ $Cu(OAc)_2$ (1 equiv)/ $Bu_4NBr$ (2 equiv) | $DMSO/N_2$ | 90 | 5 | 80 | 11 |
| 7 | $PdCl_2$ (20)/ $Cu(OAc)_2$ (1 equiv)/ $Bu_4NBr$ (2 equiv) | $DMF/N_2$ | 90 | 5 | 89 | – |
| 8 | $PdCl_2$ (20)/ $Cu(OAc)_2$ (1 equiv)/ $Bu_4NBr$ (2 equiv) | $DMSO/N_2$ | 90 | 5 | 79 | 10 |
| 9 | $Pd(OAc)_2$ (20)/ $Cu(OAc)_2$ (1 equiv)/ $Bu_4NBr$ (20) | $DMF/N_2$ | 90 | 5 | 91 | – |
| 10 | $Pd(OAc)_2$ (20)/ $Cu(OAc)_2$ (1 equiv)/ $Bu_4NBr$ (20) | $DMSO/N_2$ | 90 | 5 | 78 | 12 |
| 11 | $PdCl_2$ (20)/ $Cu(OAc)_2$ (1 equiv)/ $Bu_4NBr$ (20) | $DMF/N_2$ | 90 | 5 | 90 | – |
| 12 | $PdCl_2$ (20)/ $Cu(OAc)_2$ (1 equiv)/ $Bu_4NBr$ (20) | $DMSO/N_2$ | 90 | 5 | 77 | 10 |
| 13 | $Pd(OAc)_2$ (10)/ $Cu(OAc)_2$ (1 equiv)/ $Bu_4NBr$ (20) | $DMF/N_2$ | 90 | 10 | 81 | – |
| 14 | $PdCl_2$ (10)/ $Cu(OAc)_2$ (1 equiv)/ $Bu_4NBr$ (20) | $DMF/N_2$ | 90 | 10 | 80 | – |
| 15 | $Pd(OAc)_2$ (20)/ $Cu(OAc)_2$ (50)/ $Bu_4NBr$ (20) | $DMF/N_2$ | 90 | 15 | 75 (25)[a] | – |
| 16 | $PdCl_2$ (20)/ $Cu(OAc)_2$ (50)/ $Bu_4NBr$ (20) | $DMF/N_2$ | 90 | 15 | 70 (30)[a] | – |
| 17 | $Pd(OAc)_2$ (20) | $DMF/O_2$ | 130 | 3 | 91 | – |
| 18 | $Pd(OAc)_2$ (20) | $DMSO/O_2$ | 120 | 4 | 89 | – |
| 19 | $PdCl_2$ (20) | $DMF/O_2$ | 130 | 3 | 90 | – |
| 20 | $PdCl_2$ (20) | $DMSO/O_2$ | 120 | 4 | 90 | – |

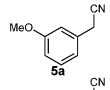
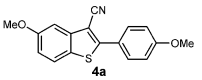
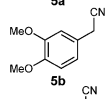
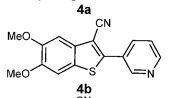
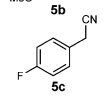
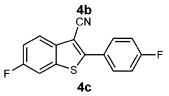
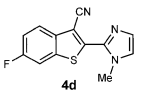
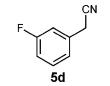
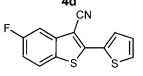
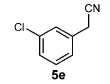
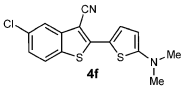
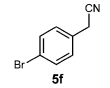
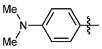
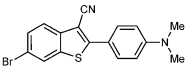
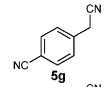
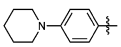
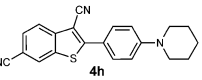
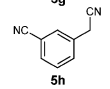
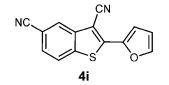
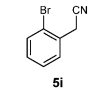
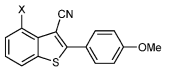
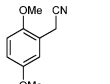
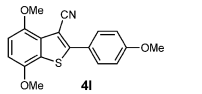
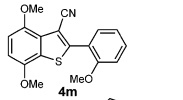
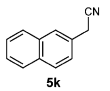
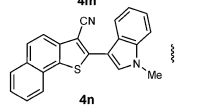
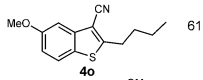
[a] Yields in parenthesis are recovered starting enethiol **6**.

tion in the presence of $Pd(OAc)_2$ or $PdCl_2$ under an oxygen atmosphere (Method C; Table 2, entries 14 and 16 and 18).

With optimized reaction conditions in hand for the one-pot synthesis of benzo[*b*]thiophene **4a** through palladium-catalyzed oxidative-intramolecular arylthiolation of enethiolate **6a**′ from **5a** and **2a**, we then examined the scope of this new method with respect to substituent compatibility at different positions of the benzo[*b*]thiophene scaffold (Table 2). Both electron-donating and electron-withdrawing substituents on the benzene ring of the arylacetonitriles were tolerated, yielding benzo[*b*]thiophenes **4b–d** in high yields (entries 2–4). However, thioenolate **6e**′ (from 3-fluorophenylacetonitrile **5d** and the dithioate **2e**), having an electron-withdrawing fluorine atom *para* to the cyclization position, failed to furnish the desired 5-fluorbenzo[*b*]thiophene **4e**, yielding only an intractable reaction mixture (entry 5). On the other hand, intramolecular cyclization of 3-chlorophenylacetonitrile **5e** with dithioate **2f** under identical conditions (Method A) afforded the corresponding 5-chloro-2-(5-dimethylaminothienyl)-3-cyanobenzo[*b*]thiophene (**4f**) in 67% yield, which could be increased to 76% by using the two-step procedure (Method B; entry 6). Similarly, the corresponding 6-bromo analogue **4g** was obtained in high yield by subjecting the corresponding 4-bromophenylacetonitrile **5f** to intramolecular arylthiolation with **2g** under similar conditions without formation of any cross-coupled side products (entry 7). Synthesis of 5-chloro and 6-bromobenzo[*b*]thiophenes **4f–g** is significant for further functionalization of benzothiophene nucleus through transition-metal-catalyzed cross-coupling reactions. Similarly, an electron-withdrawing nitrile group at the 4-position in **5g** was also tolerated, affording the corresponding 6-cyanobenzo[*b*]thiophene **4h** in excellent yield on condensation with dithioate **2h** and subsequent Pd-catalyzed cyclization under identical conditions (entry 8). However, attempted catalytic cyclization of 3-cyanophenylacetonitrile **5h** with dithioate **2i** did not provide the expected 5-cyanothiophene **4i** and afforded only a complex mixture of products (entry 9). These studies, along with the result shown in Table 2, entry 5 demonstrate that the presence of an electron-withdrawing group *para* to the cyclization position inhibits the formation of benzo[*b*]thiophenes. Interestingly, attempted synthesis of 4-bromobenzothiophene **4j** from 2-bromophenylacetonitrile **5i** and **2a** under similar conditions yielded only benzothiophene **4k**, formed by intramolecular cross-coupling, and no trace of **4j** was obtained from the reaction mixture (entry 10). The results shown in Table 2, entries 1, 2, and 6 also demonstrate the regioselectivity of the cyclization process, because no trace of the corresponding 7-substituted benzothiophenes were isolated from the reaction mixture, which may be due to steric crowding at the cyclization position. The steric effect of the substituents was further evident from the examples presented in Table 2, entries 11 and 12. Thus, whereas the corresponding 2,5-bis(methoxy)phenylacetonitrile (**5j**) yielded 4,7-bis(methoxy)benzo[*b*]thiophene (**4l**) in 59% yield on cyclization with 4-methoxyphenyldithioate (**2a**) (entry 11), the intramolecular cyclization of **5j** with the corresponding 2-methoxyphenyldithioate (**2j**) afforded the sterically crowded benzo[*b*]thiophene **4m** in only 25% yield under similar conditions (entry 12). The reaction could also be elaborated for the synthesis of 2,3-substituted naphtha[*b*]thiophene **4n** by employing 2-naphthylacetonitrile precursor **5k** and indole 3-dithioate **2k** (entry 13). The results presented in Table 2, entries 1–13 further illustrate the diverse range of (het)aryl substituents that could be introduced at the 2-position of benzothiophene derivatives. Similarly, treatment of phenylacetonitrile

**Table 2.** Synthesis of benzothiophene **4**.




| Entry | 5 | 2, R | Method[a] | Product | Yield [%] |
|---|---|---|---|---|---|
| 1 |  5a |  2a | A |  4a | 85 |
| 2 |  5b |  2b | A |  4b | 70 |
| 3 |  5c |  2c | A |  4c | 76 |
| 4 | 5c |  2d | A |  4d | 82 |
| 5 |  5d |  2e | A/ B/ C |  4e | 0 |
| 6 |  5e |  2f | A / B |  4f | 67,[b] 76[c] |
| 7 |  5f |  2g | A |  4g | 81 |
| 8 |  5g |  2h | A |  4h | 82 |
| 9 |  5h |  2i | A/ B/ C |  4i | 0 |
| 10 |  5i |  2a | A |  **4j**, X = Br **4k**, X = H | 0 90 |
| 11 |  5j |  2a | A |  4l | 59 |
| 12 | 5j |  2j | A |  4m | 25 |
| 13 |  5k |  2k | A |  4n | 84 |
| 14 | 5a |  2l | A /B /C |  4o | 61,[b] 63,[c] 76[d] |
| 15 |  5l |  2a | A / B |  4p | 65,[b] 80[c] |
| 16 |  5m |  2l | A /B /C |  4q | 50,[a] 45,[c] 78[d] |
| 17 |  5n |  2m | A |  4r | 76 |
| 18 |  5o |  2a | A / B |  4s | 68,[b] 79[c] |
| 19 |  5p |  2i | A |  4t | 77 |

[a] Reaction conditions: Method A: **5** (1.0 mmol), **2** (1.0 mmol) and NaH (1.0 mmol) in DMF (6 mL), stirred for 1 h; $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1.0 mmol), $Bu_4NBr$ (20 mol%) added and heated to 90 °C for 4–6 h; Method B: crude **6** (1.0 mmol), $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1.0 mmol), $Bu_4NBr$ (20 mol%) in DMF (3 mL) heated to 90 °C for 4–6 h; Method C: crude **6** (1.0 mmol), $Pd(OAc)_2$ (20 mol%) in DMF (3 mL) heated under $O_2$ atm at 90 °C for 8–10 h. [b] Yield from Method A. [c] Yield from Method B. [d] Yield from Method C.

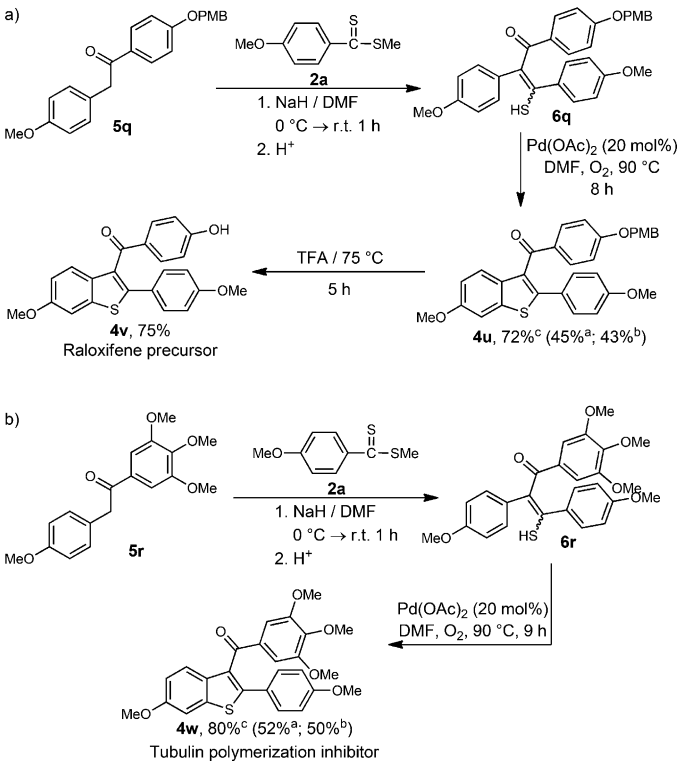
**5a** with an alkyldithioate such as *n*-butyldithioate **2l** under one-pot conditions afforded the corresponding 2-(*n*-butyl)-3-cyanobenzothiophene (**4o**) in 60% yield (Method A), which could not be improved further, when the corresponding thioenol **6o** was subjected to intramolecular thiolation under the two-step procedure (Method B), probably because of acetoxylation of alkyl side chain with cupric acetate. However, **4o** was obtained in higher yield (76%), when thioenol **6o** was cyclized in the presence of $PdCl_2$ under an oxygen atmosphere (Method C) (entry 14).

Further diversity at the 3-position of benzo[*b*]thiophene was introduced by employing deoxybenzoins as active methylene partners for the synthesis of 3-aroylbenzo[*b*]thiophenes (Table 2, entries 15–17). Thus 3-(3-methoxybenzoyl)-2-(4-methoxyphenyl)-5-methoxybenzo[*b*]thiophene (**4p**) was obtained in 65% yield in the presence of $Pd(OAc)_2$–cupric acetate catalysis under one-pot conditions (Method A), whereas direct cyclization of thioenol **6p** furnished **4p** in 80% yield (Method B) (entry 15). Similarly, the corresponding 2-(*n*-butyl)-3-benzoyl- and 2-(*n*-propylthio)-3-(4-methoxybenzoyl)benzothiophenes **4q** and **4r** could also be obtained in good yields by utilizing *n*-butylthioate **2l** and bis(*n*-propyl)trithiocarbonate (**2m**), respectively, as thiocarbonyl precursors (entries 16–17). The results presented in Table 2, entries 18 and 19 show the introduction of a carboalkoxy group at the 3-position of benzo[*b*]-thiophenes by employing phenyl acetates **5o** and **5p** as active

methylene partners with (het)aryl dithioates **2a** and **2i** under similar conditions, thus affording the corresponding benzo[*b*]-thiophenes-3-carboxylates **4s** and **4t** in good yields (entries 18 and 19).

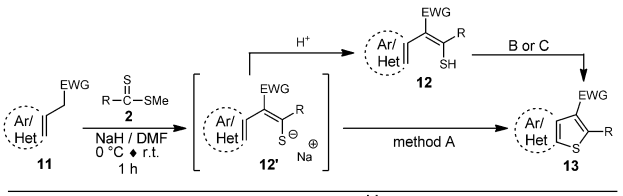
Further versatility of this efficient protocol was demonstrated by the synthesis of raloxifene precursor[20] **4v** and tubulin polymerization inhibitor[21] **4w** (Scheme 3). Thus, when the appropriate PMB-protected 4-hydroxy-4′-methoxydeoxybenzoin **5q** and the trimethoxy analogue **5r** were subjected to intramolecular thiolation with dithioester **2a** in the presence of the $Pd(OAc)_2/Cu(OAC)_2$ catalytic system (Method A or B), the desired benzo[*b*]thiophenes **4u** or **4w** were obtained in only moderate yields (Scheme 3); however, by using oxygen as reoxidant (Method C), benzothiophenes **4u** and **4w** were obtained in higher yields (Scheme 3). Subsequent deprotection of the PMB group in **4u** with TFA furnished the raloxifene precursor **4v** in 75% yield (Scheme 3).

With the successful implementation of the present intramolecular C–H arylthiolation methodology for the synthesis of substituted benzo[*b*]thiophenes (Table 2), we next conceived of extending this protocol for construction of hetero-fused thiophene frameworks[22] as depicted in Table 3. It should be noted that although transition-metal-catalyzed intermolecular C–H functionalization of five- and six-membered heterocycles has been investigated extensively,[8,9] to our knowledge, the corresponding intramolecular version of this protocol (such as C–H amination, C–H thiolation, C–H oxygenation) leading to pyrrole-, thieno-, or furano-fused heterocycles has not been reported. Several thieno-fused heterocycles such as thienothiophenes and indolo-fused thiophenes are known to display optoelectronic and charge-conducting properties, besides a broad range of biological activity.[22,23] We therefore subjected a few of the selected (het)arylacetonitriles such as 3-thienyl- **11a**, 3-indolyl- **11b**, 5-pyrazolyl- **11c**, and 3-pyridyl- **11d** derivatives to Pd-catalyzed intramolecular C–H thiolation with vari-




**Scheme 3.** a) Synthesis of raloxifene precursor **4v**. b) Synthesis of tubulin polymerization inhibitor **4w**.

**Table 3.** Synthesis of hetero-fused thiophenes **13**.




| Entry | 1 | 2, R | Method[a] | Product | Yield [%] |
|---|---|---|---|---|---|
| 1 | **11a** | **2c** | A | **13a** | 80 |
| 2 | **11a** | **2d** | A | **13b** | 73 |
| 3 | **11b** | **2k** | A | **13c** | 78 |
| 4 | **11b** | **2d** | A | **13d** | 77 |
| 5 | **11c** | **2b** | A | **13e** | 74 |
| 6 | **11d** | **2n** | A / B | **13f** | 64,[b] 77[c] |
| 7 | **11e** | **2e** | A | **13g** | 85 |
| 8 | **11f** | **2i** | A | **13h** | 72 |
| 9 | **11g** | **2o** | A /B | **13i** | 56,[b] 82[c] |
| 10 | **11h** | **2l** | A / C | **13j** | 41,[b] 76[d] |

[a] Reaction conditions: Method A: **11** (1.0 mmol), **2** (1.0 mmol) and NaH (1.0 mmol) in DMF (6 mL), stirred for 1 h; $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1.0 mmol), $Bu_4NBr$ (20 mol%) added and heated to 90 °C for 4–6 h; Method B: crude **13** (1.0 mmol), $Pd(OAc)_2$ (20 mol%), $Cu(OAc)_2$ (1.0 mmol), $Bu_4NBr$ (20 mol%) in DMF (3 mL) heated to 90 °C for 4–6 h; Method C: crude **13** (1.0 mmol), $Pd(OAc)_2$ (20 mol%) in DMF (3 mL) heated under $O_2$ atm at 90 °C for 8–10 h.[b] Yield from Method A. [c] Yield from Method B. [d] Yield from Method C.

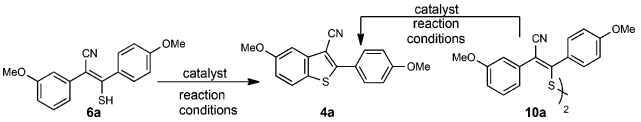
ous (het)ary/alkyldithioesters under previously described one-pot conditions (Method A), which afforded the corresponding cyano-substituted thieno-fused heterocycles **13a–f** in high yields (Table 3, entries 1–6). Similarly, the results presented in entries 7–10 depict examples of hetero-fused thiophenes **13g–h** and **13i–j**, bearing a (2-thienoyl) or a carboethoxy functionality respectively at the 3-position, which were obtained in good yields from the corresponding heterocyclic active methylene precursors **11e–h**, respectively, and the relevant dithioesters by following the standard procedure.

## Mechanistic Studies

Although a detailed mechanistic understanding of the reaction has yet to be established, a few observations are noteworthy in view of the mechanism suggested by Inamoto,[19] which proceeds through the involvement of a disulfide intermediate. Interestingly, in most of the reactions conducted in DMSO as solvent, the corresponding disulfide **10a** was isolated as a minor product in varying amounts (Table 1, entries 2, 4, 6, 8, 10, and 12), whereas in DMF as solvent, we not able to observe formation of disulfide **10a** in any of the reactions (Table 1). When thioenol **6a** was treated with 20 mol% of either $Pd(OAc)_2$ or $PdCl_2$ under a nitrogen atmosphere in the absence of any reoxidant, benzothiophene **4a** was formed in low yields with recovery of starting **6a** (Table 4, entries 1–3). When the reaction of **6a** was performed in the presence of $PdCl_2$ under Inamoto's conditions[19] in DMSO or DMF as solvent, **4a** was isolated in only moderate yields even after prolonged heating (Table 4, entries 4 and 5). On the other hand, thioenol **6a** was recovered unchanged when it was treated with cupric acetate (10 mol% or 1 equiv) under a nitrogen atmosphere in the absence of palladium catalyst (entries 6 and 7). However, when **6a** was reacted with cupric acetate (10 mol%) in the presence of oxygen or TBHP, in either DMF or DMSO, the corresponding disulfide **10a** was formed as the sole product in high yield with no trace of benzothiophene **4a** (entries 8 and 9). These observations show that cupric acetate alone is not sufficient to convert thioenol **6a** into disulfide **10a** and the reaction requires an oxidant. Furthermore, attempted conversion of pure disulfide **10a** into benzothiophene **4a** with either $Pd(OAc)_2$ or $PdCl_2$ (20 mol%) under a nitrogen atmosphere in either DMF or DMSO as solvent in the absence of any reoxidant, resulted in only low conversion (25–30%) with recovery of a large amount of disulfide **10a** (entries 10 and 11). Attempted reaction of disulfide **10a** under Inamoto's conditions also afforded only modest yield of benzothiophene **4a** along with unreacted **10a** (entry 12). However, when **10a** reacted with $Pd(OAc)_2$ (or $PdCl_2$) under an oxygen atmosphere or in the presence of cupric acetate (1 equiv) and $Bu_4NBr$ (20 mol%) in either DMF or DMSO, benzothiophene **4a** was formed in high yields (entries 13–16). These studies reveal that both palladium(II) catalyst and a reoxidant (cupric acetate or oxygen) are essential to convert disulfide **10a** into benzothiophene **4a**.

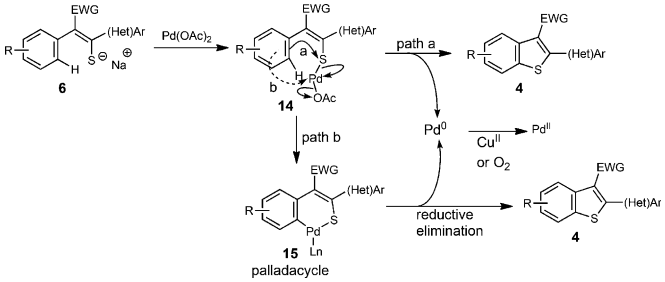
On the basis of these experimental studies and on the precedent of similar processes, a possible mechanistic pathway for the formation of benzo[*b*]thiophenes **4** from the corresponding thioenols **6** or enolates **6′** in DMF solvent is outlined in Scheme 4. Thus, the reaction of thioenol (or thioenolate) with $Pd(OAc)_2$ or $PdCl_2$ leads to formation of Pd–S adduct **14**. Subsequent attack of the aryl ring on the sulfur atom in **14**, similar to electrophilic substitution, furnishes benzo[*b*]thiophene **4** with concurrent release of reduced palladium species followed by rearomatization (Pathway A). Alternatively, the aromatic ring attacks the palladium center in **14** to afford palladacycle inter-

**Table 4.** Mechanistic studies for the formation of benzo[*b*]thiophene **4a** from **6a**.




| Entry | Substrate | Catalyst (mol%) | Reaction conditions | *T* [°C] | *t* [h] | Yield [%] **4a** | **10a** |
|---|---|---|---|---|---|---|---|
| 1 | **6a** | $Pd(OAc)_2$ (20) | $DMSO/N_2$ | 120 | 24 | 40 (55)[a] | 5 |
| 2 | **6a** | $Pd(OAc)_2$ (20) | $DMF/N_2$ | 130 | 24 | 40 (60)[a] | – |
| 3 | **6a** | $PdCl_2$ (20) | $DMF/N_2$ | 130 | 24 | 35 (65)[a] | – |
| 4[b] | **6a** | $PdCl_2$ (10) | $DMF/N_2$ sealed tube | 120 | 24 | 45 (55)[a] | – |
| 5[b] | **6a** | $PdCl_2$ (10) | $DMSO/N_2$ sealed tube | 120 | 24 | 50 (35)[a] | 15 |
| 6 | **6a** | $Cu(OAc)_2$ (1 equiv) | $DMF/N_2$ | 130 | 24 | – | – |
| 7 | **6a** | $Cu(OAc)_2$ (10) | $DMF/N_2$ | 130 | 24 | – | – |
| 8 | **6a** | $Cu(OAc)_2$ (10) | $DMF/O_2$ | 130 | 6 | – | 79 |
| 9 | **6a** | $Cu(OAc)_2$ (10)/ TBHP (1 equiv) | DMF | 90 | 5 | – | 77 |
| 10 | **10a** | $Pd(OAc)_2$ (20)/ $Bu_4NBr$ (20) | $DMF/N_2$ | 90 | 15 | 30 (70)[a,c] | – |
| 11 | **10a** | $Pd(OAc)_2$ (20)/ $Bu_4NBr$ (20) | $DMSO/N_2$ | 90 | 15 | 25 (75)[a,c] | – |
| 12 | **10a** | $PdCl_2$ (10) | $DMSO/N_2$ sealed tube | 120 | 18 | 55 (45)[a,c] | – |
| 13 | **10a** | $Pd(OAc)_2$ (20)/ $Bu_4NBr$ (20) | $DMF/O_2$ | 90 | 6 | 92 | – |
| 14 | **10a** | $Pd(OAc)_2$ (20)/ $Bu_4NBr$ (20) | $DMSO/O_2$ | 90 | 7 | 90 | – |
| 15 | **10a** | $Pd(OAc)_2$ (20)/ $Cu(OAc)_2$ (1 equiv)/ $Bu_4NBr$ (20) | $DMF/N_2$ | 90 | 7 | 91 | – |
| 16 | **10a** | $Pd(OAc)_2$(20)/ $Cu(OAc)_2$ (1 equiv)/ $Bu_4NBr$ (20) | $DMSO/N_2$ | 90 | 7 | 90 | – |

[a] Yields in parenthesis are recovered starting enethiol **6**. [b] Inamoto et al. conditions. [c] Yields of the product remain unchanged even at higher temperature (120 °C) and prolonged heating.




**Scheme 4.** Proposed mechanism for formation of benzo[*b*]thiophene **4** from enethiolate **6**.

mediate **15** followed by reductive elimination leading to benzothiophene **4** and reduced Pd(0) species, which is reoxidized to $Pd^{II}$ in the presence of oxidants such as oxygen or cupric acetate. This electrophilic cyclization mechanism is further supported by the failure of arylacetonitrles **5d** and **5h** bearing an electron-withdrawing group (fluorine or nitrile) at the 3-position, to afford benzothiophenes **4e** or **4i**, because of reduced electron density at the site of cyclization (Table 2, entries 5 and 9).

The proposed mechanism is supported by the following observations: 1) failure to isolate a disulfide intermediate in any of the reactions that are conducted in DMF as solvent. 2) low yields of benzothiophenes obtained in the presence of $Pd^{II}$ catalyst alone in the absence of any reoxidant or under Inamoto's conditions (Table 4, entries 1–5). 3) an electron-withdrawing group such as fluorine or CN in the *meta*-position (*para* to the site of C–S bond formation) completely inhibits the formation of benzothiophene (Table 2, entries 5 and 9). 4) Cupric acetate alone is not sufficient to convert thioenol into disulfide and the reaction requires a reoxidant such as oxygen or TBHP. However, further mechanistic studies are needed to unravel the precise reaction mechanism involved this process.

## Conclusion

We have developed an effective Pd-catalyzed oxidative intramolecular C–H functionalization–arylthiolation approach for substituted benzothiophenes, which is an important structural motif that is prevalent in natural and designed compounds displaying interesting biological and physical properties. Unlike, our previous benzothiophene synthesis[1a] via 2-bromo(het)arylacetonitriles, this protocol requires simple precursors without any 2-halo substitution. Furthermore, the method also allows for the synthesis of benzothiophenes carrying an acyl or carboalkoxy functionality, from readily accessible deoxybenzoins and (het)aryl acetates. This substitution pattern could not be achieved through copper-catalyzed cross-coupling reaction, because of the difficulty of accessing the desired 2-bromo-substituted deoxybenzoins and (het)aryl acetates, which were not accessible for copper-catalyzed cross coupling reaction. This atom economical and straightforward catalytic thiolation has a broad functional group tolerance, and forms the benzothiophenes in good to excellent yields. The use of $Bu_4NBr$ greatly enhanced the transformation, which enabled the process to be performed efficiently at lower temperature. The observation that oxygen can also be used in place of $Cu(OAc)_2$, broadens the substrate scope of this reaction by increasing the number of compatible functional groups. Advantages of our procedure include the simplicity of operation, high regioselectivity and use of readily accessible, inexpensive starting materials. The utility of the method was further demonstrated by the high yield synthesis of a raloxifene precursor and a tubulin polymerization inhibitor (Scheme 3). Furthermore, this catalytic intramolecular C–H functionalization–arylthiolation approach could also be extended to the synthesis of thieno-fused heterocycles from enethiol precursors bearing a five- or six-membered heterocycles such as thiophene, indole, pyrazole, and pyridine derivatives (Table 3). To our knowledge, there are no examples of transition-metal-catalyzed intramolecular C–H functionalization–(het)arylcyclization (such as C–H amination, etherification or thiolation) on five- or six-membered heterocycles leading to fused heterocycles. Further investigation to understand the precise reaction mechanism, as well as to apply this protocol for the construction of other sulfur-based heterocycles is underway.

## Experimental Section

**Synthesis of 3-mercapto-2-(3-methoxyphenyl)-3-(4-methoxyphenyl)acrylonitrile (6a)**: A solution of **5a** (147 mg, 1.0 mmol) in anhydrous DMF (3 mL) was added to a stirred suspension NaH (60% suspension in mineral oil, 80 mg, 2.0 mmol) in DMF (5 mL) at 0 °C. After further stirring for 10 min, a solution of 4-methoxyphenyldithioate (**2a**; 198 mg, 1.0 mmol) in DMF (2 mL) was added at 0 °C. The reaction mixture was stirred for 1 h at r.t. (monitored by TLC), then diluted with sat. $NH_4Cl$ solution (25 mL), extracted with EtOAc (3×25 mL), and the combined organic layer was washed with water (3×25 mL), brine (2×25 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (EtOAc/hexane) to give pure **6a** (158 mg, 95%) as a yellow solid. M.p. 77–79 °C; $R_f$ 0.3 (1:4 EtOAc/hexane); $^1$HNMR (400 MHz, $CDCl_3$): $\delta = 7.59$ (d, $J = 7.6$ Hz, 2H), 7.38 (t, $J = 7.6$ Hz, 1H), 7.14 (d, $J = 7.6$ Hz, 1H), 7.09 (s, 1H), 6.97 (d, $J = 8.0$ Hz, 2H), 6.95–6.93 (m, 1H), 3.89 (s, 1H), 3.86 (s, 3H), 3.85 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 161.4$, 160.3, 154.1, 136.0, 131.7, 130.4, 129.9, 121.3, 118.7, 115.2, 114.35, 114.32, 106.5, 55.6 ppm; IR (neat): $\tilde{\nu} = 2580$, 2202, 1601, 1508, 1247, 1042, 830 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}NO_2S$: 298.0902 $[M+H]^+$; found: 298.0894.

**Palladium-catalyzed intramolecular oxidative arylthiolation of enethiol 6a: Synthesis of 5-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene-3-carbonitrile (4a)**: $Pd(OAc)_2$ (44 mg, 0.2 mmol), $Cu(OAc)_2$ (182 mg, 1.0 mmol), and $Bu_4NBr$ (65 mg, 0.2 mmol) were added to a solution of **6a** (297 mg, 1.0 mmol) in anhydrous DMF (6 mL) and the reaction mixture was heated at 90 °C with continuous stirring for 4 h (reaction monitored by TLC). The reaction mixture was diluted with sat. aq $NH_4Cl$ (25 mL), extracted with EtOAc (3×25 mL), and the combined organic layer was washed with water (3×25 mL), brine (2×25 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (EtOAc/hexane) to give pure benzo[*b*]thiophene **4a** (210 mg, 92%) as a white solid. M.p. 112–114 °C; $R_f$ 0.7 (EtOAc/hexane, 1:4); $^1$H NMR (400 MHz, $CDCl_3$): $\delta = 7.84$ (d, $J = 8.8$ Hz, 2H), 7.66 (d, $J = 8.8$ Hz, 1H), 7.34 (d, $J = 2.4$ Hz, 1H), 7.07–7.01 (m, 3H), 3.92 (s, 3H), 3.89 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta = 161.5$, 159.0, 156.2, 140.8, 129.7, 129.4, 124.4, 123.2, 116.7, 115.8, 114.9, 104.1, 100.7, 55.9, 55.6 ppm; IR (neat): $\nu = 2218$, 1598, 1258, 1185, 823 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{17}H_{14}NO_2S$: 296.0745 $[M+H]^+$; found: 296.0735.

### General procedure for the synthesis of substituted benzo[*b*]-thiophenes 4a–w and hetero-fused thiophenes 13a–j

**One-pot procedure (Method A)**: The corresponding (het)arylacetonitrile, deoxybenzoin or (het)arylacetates **5a–r** or **11a–h** (1.0 mmol) in DMF (2 mL) was added dropwise to a stirring suspension of NaH (60% suspension in mineral oil, 80 mg, 2.0 mmol) in DMF (2 mL) at 0 °C. After further stirring for 10 min, a solution of the relevant dithioester **2a–l**, **2n–o** or trithiocarbonate **2m** (1.0 mmol) in DMF (2 mL) was added to the reaction mixture at 0 °C, followed by fur-

ther stirring for 1 h at ambient temperature. After complete consumption of starting materials (monitored by TLC), $Pd(OAc)_2$ (44 mg, 0.2 mmol), $Cu(OAc)_2$ (182 mg, 1.0 mmol), and $Bu_4NBr$ (65 mg, 0.2 mmol) were added and the reaction mixture was heated at 90 °C with continuous stirring for 4–6 h (monitored by TLC). The reaction mixture was diluted with sat. aq $NH_4Cl$ (25 mL), extracted with EtOAc (3×25 mL), and the combined organic layer was washed with water (3×25 mL), brine (2×25 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure to give the crude products, which were purified by column chromatography over silica gel (EtOAc/hexane).

**Two-step procedure from enethiols 6 (Method B)**: All the desired enethiols **6e–f**, **6i**, **6o–q**, **6s**, **6u**, **6w**, **12f**, and **12i–j** were prepared in nearly quantitative yields from the respective arylacetonitriles, deoxybenzoin or aryl acetates (1.0 mmol), and the corresponding dithioesters (1.0 mmol), by following a similar procedure to that described for the preparation of enethiol **6a**. These crude enethiols were used as such for the next step without further purification. The crude enethiols **6e–f**, **6i**, **6o–q**, **6s**, **6u**, **6w**, **12f**, and **12i–j** (1.0 mmol) were subjected to intramolecular arylthiolation in the presence of $Pd(OAc)_2$ (44 mg, 0.2 mmol), $Cu(OAc)_2$ (182 mg, 1.0 mmol), and $Bu_4NBr$ (65 mg, 0.2 mmol) in DMF (6 mL) at 90 °C for 8–10 h (monitored by TLC) by following a similar procedure and work-up to that described for the synthesis of benzo[*b*]thiophene **4a**. The benzo[*b*]- and hetero-fused thiophenes **4f**, **4o–q**, **4s**, **4u**, **4w**, **13f**, and **13i**, thus obtained, were further purified by column chromatography over silica gel (EtOAc/hexane).

**Two-step procedure with oxygen as reoxidant (Method C)**: $Pd(OAc)_2$ (44 mg, 0.2 mmol) was added to a solution of crude enethiol **6o**, **6q**, **6u**, **6w**, and **12j** (1.0 mmol), prepared as described above in DMF (5 mL), and the reaction mixture was heated at 90 °C under $O_2$ atmosphere with continuous stirring for 8–12 h (monitored by TLC). The reaction mixture was diluted with sat. aq $NH_4Cl$ (25 mL), extracted with EtOAc (3×25 mL), and the combined organic layer was washed with water (3×25 mL), brine (2×25 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure. The crude products were purified by column chromatography over silica gel (EtOAc/hexane). Spectral and analytical data of representative benzo[*b*]thiophenes and the corresponding hetero-fused thiophenes are given below.

**5-Chloro-2-(5-(dimethylamino)thiophen-2-yl)benzo[*b*]thiophene-3-carbonitrile (4f)**: Obtained from acetonitrile **5e** and dithioester **2f** as a brown solid (141 mg, 67% by Method A; 160 mg, 76% by Method B). M.p.193–195 °C; $R_f$ 0.7 (EtOAc/hexane, 1:4); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.72 (d, $J$ = 2.0 Hz, 1H), 7.56 (d, $J$ = 6.0 Hz, 1H), 7.54 (d, $J$ = 1.6 Hz, 1H), 7.25 (dd, $J$ = 8.4, 2.0 Hz, 1H), 5.89 (d, $J$ = 8.4 Hz, 1H), 3.07 ppm (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 163.2, 151.3, 140.9, 133.2, 132.6, 131.6, 130.8, 125.4, 122.9, 121.0, 116.2, 116.0, 103.0, 42.5 ppm; IR (neat): $\tilde{\nu}$ = 2921, 2197, 1700, 1633, 1548, 1194, 911 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{15}H_{12}ClN_2S_2$: 319.0130 and 321.0101 $[M+H]^+$; found: 319.0120 and 320.9992.

**2-(4-(Piperidin-1-yl)phenyl)benzo[*b*]thiophene-3,6-dicarbonitrile (4h)**: Obtained from acetonitrile **5g** and dithioester **2h** by Method A as an orange solid (198 mg, 82%). M.p. 212–214 °C; $R_f$ 0.8 (EtOAc/hexane, 1:4); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.08 (d, $J$ = 0.8 Hz, 1H), 7.94 (d, $J$ = 8.4 Hz, 1H), 7.85 (d, $J$ = 8.8 Hz, 2H), 7.70 (dd, $J$ = 8.4, 1.2 Hz, 1H), 6.96 (d, $J$ = 8.8 Hz, 2H), 3.39–3.37 (m, 4H), 1.71–1.69 ppm (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 160.1, 153.4, 143.0, 136.3, 129.7, 128.9, 126.6, 122.6, 119.3, 118.8, 115.3, 114.7, 108.7, 98.8, 48.8, 25.5, 24.5 ppm; IR (neat): $\tilde{\nu}$ = 2224, 2209, 1603, 1485, 1314, 1166, 803 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{21}H_{18}N_3S$: 344.1221 $[M+H]^+$; found: 344.1216.

**4,7-Dimethoxy-2-(4-methoxyphenyl)benzo[*b*]thiophene-3-carbonitrile (4l)**: Obtained from acetonitrile **5j** and dithioester **2a** by Method A as a yellow liquid (130 mg, 59%). $R_f$ 0.6 (EtOAc/hexane, 1:4); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.51 (d, $J$ = 8.8 Hz, 2H), 7.00 (d, $J$ = 8.8 Hz, 2H), 6.93 (d, $J$ = 2.8 Hz, 1H), 6.87 (d, $J$ = 2.8 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.80 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 161.0, 153.6, 151.2, 131.8, 131.6, 127.8, 123.0, 116.7, 116.1, 113.9, 113.5, 112.8, 107.8, 56.4, 56.0, 55.4 ppm; IR (neat): $\tilde{\nu}$ = 2937, 2204, 1602, 1494, 1225, 1020 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{18}H_{16}NO_3S$: 326.0851 $[M+H]^+$; found: 326.0835.

**(2-Butylbenzo[*b*]thiophen-3-yl)(phenyl)methanone (4q)**: Obtained from deoxybenzoin **5m** and dithioester **2l** as a brown liquid (75 mg, 50% by Method A; 62 mg, 45% by Method B; 115 mg, 78% by Method C). $R_f$ 0.6 (EtOAc/hexane, 2:8); $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta$ = 8.01–7.99 (m, 1H), 7.76–7.74 (m, 2H), 7.72–7.67 (m, 1H), 7.55 (t, $J$ = 8.0 Hz, 2H), 7.38–7.29 (m, 3H), 2.78 (t, $J$ = 7.6 Hz, 2H), 1.58 (quin, $J$ = 7.6 Hz, 2H), 1.22 (quin, $J$ = 7.6 Hz, 2H), 0.76 ppm (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta$ = 192.9, 150.3, 138.2, 137.9, 137.2, 133.6, 131.5, 129.1, 128.9, 124.8, 124.4, 122.5, 122.3, 33,1, 28.6, 21.4, 13.3 ppm; IR (neat): $\tilde{\nu}$ = 2925, 1650, 1434, 1230, 1167, 1069, 755 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{19}H_{19}OS$: 295.1157 $[M+H]^+$; found: 295.1156.

**Methyl 2-(furan-2-yl)benzo[*b*]thiophene-3-carboxylate (4t)**: Obtained from acetate **5p** and dithioester **2m** by Method A as a brown liquid (132 mg, 77%). $R_f$ 0.6 (EtOAc/hexane, 2:8); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.51 (d, $J$ = 1.2 Hz, 1H), 7.42–7.36 (m, 4H), 6.69 (d, $J$ = 0.8 Hz, 1H), 6.50 (dd, $J$ = 3.2, 1.6 Hz, 1H), 3.68 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 168.4, 150.1, 143.8, 136.3, 135.7, 133.6, 129.6, 128.8, 128.7, 128.4, 128.3, 113.4, 111.7, 52.5 ppm; IR (neat): $\nu$ = 1718, 1535, 1430, 1289, 1196, 1012, 739 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{14}H_{11}O_3S$: 259.0429 $[M+H]^+$; found: 259.0428.

**(4-(4-Methoxybenzyloxy)phenyl)(6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)methanone (4u)**: Obtained from deoxybenzoin **5q** and dithioester **2a** as a brown liquid (63 mg, 45% by Method A; 60 mg, 43% by Method B; 101 mg, 72% by Method C). $R_f$ 0.4 (EtOAc/hexane, 3:7); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.77 (d, $J$ = 8.8 Hz, 2H), 7.52 (d, $J$ = 8.8 Hz, 1H), 7.35 (d, $J$ = 8.8 Hz, 2H), 7.32–7.29 (m, 3H), 6.95 (dd, $J$ = 9.2, 2.4 Hz, 1H), 6.90 (d, $J$ = 8.8 Hz, 2H), 6.83 (d, $J$ = 8.8 Hz, 2H), 6.76 (d, $J$ = 8.8 Hz, 2H), 4.97 (s, 2H), 3.88 (s, 3H), 3.81 (s, 3H), 3.75 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 193.4, 163.1, 159.9, 159.8, 157.8, 142.6, 140.2, 134.1, 132.5, 130.8, 130.7, 130.4, 129.4, 128.2, 126.2, 124.2, 114.9, 114.6, 114.2, 104.7, 70.1, 55.8, 55.44, 55.39 ppm; IR (neat): $\tilde{\nu}$ = 3057, 1652, 1560, 1404, 1064, 852 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{31}H_{27}O_5S$: 511.1579 $[M+H]^+$; found: 511.1598.

**Deprotection of 4p with TFA—synthesis of (4-hydroxyphenyl)(6-methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)methanone (4v)**: Compound **4u** 100 mg, 0.2 mmol) was dissolved in trifluoroacetic acid (5 mL) and heated to reflux for 5 h (monitored by TLC). The reaction mixture was poured in ice-cold water and extracted with $CH_2Cl_2$ (3×25 mL) and the combined organic layer was washed with water (3×25 mL), brine (2×25 mL), dried ($Na_2SO_4$), and concentrated. The crude products were purified by silica gel column chromatography (EtOAc/hexane) to give pure **4v** (57 mg, 75%) as a yellow oil. $R_f$ 0.2 (EtOAc/hexane, 8:2); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.71 (d, $J$ = 8.8 Hz, 2H), 5.52 (d, $J$ = 8.8 Hz, 1H), 7.34–7.31 (m, 3H), 6.95 (dd, $J$ = 9.2, 2.4 Hz, 1H), 6.75 (d, $J$ = 8.8 Hz, 2H), 6.68 (d, $J$ = 8.8 Hz, 2H), 5.78 (br s, 1H), 3.88 (s, 3H), 3.74 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 193.5, 160.4, 159.9, 157.8, 143.0, 140.2, 134.1, 132.8, 130.7, 130.5, 129.8, 126.2, 124.2, 115.4, 115.0, 114.2, 104.7, 55.8, 55.4 ppm; IR (neat): $\tilde{\nu}$ = 3450–3057, 2919, 1651,

1473, 1255, 1160, 1044, 749 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{23}H_{19}O_4S$: 391.1004 $[M+H]^+$; found: 391.0997.

**(6-Methoxy-2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)(3,4,5-trimethoxyphenyl)methanone (4w)**: Obtained from deoxybenzoin **5r** and dithioester **2a** as an off-white solid (76 mg, 52% by Method A; 70 mg, 50% by Method B; 117 mg, 80% by Method C). M.p. 118–120 °C (lit. 116–118 °C);[21a] $R_f$ 0.5 (EtOAc/hexane, 3:7); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.64 (d, *J* = 8.8 Hz, 1H), 7.33–7.30 (m, 3H), 7.07 (s, 2H), 7.01 (dd, *J* = 9.2 Hz, 2.4 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H), 3.83 (s, 3H), 3.75 (s, 3H), 3.73 ppm (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 193.1, 160.1, 157.9, 152.9, 143.9, 142.8, 140.3, 134.1, 132.5, 130.5, 130.1, 126.3, 124.4, 115.1, 114.3, 107.7, 104.7, 61.0, 56.3, 55.8, 55.4 ppm; IR (neat): $\tilde{\nu}$ = 1634, 1525, 1355, 1166, 1008, 853 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{26}H_{25}O_6S$: 465.1372 $[M+H]^+$; found: 465.1386.

**2-(1-Methyl-1*H*-imidazol-2-yl)thieno[2,3-*b*]thiophene-3-carbonitrile (13b)**: Obtained from acetonitrile **11a** and dithioester **2d** by Method A as an orange solid (145 mg, 73%). M.p. 78–80 °C; $R_f$ 0.3 (EtOAc/hexane, 2:3); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.53 (d, *J* = 5.2 Hz, 1H), 7.38 (d, *J* = 5.2 Hz, 1H), 7.23 (s, 1H), 7.10 (s, 1H), 3.88 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 145.7, 144.4, 137.8, 130.6, 130.5, 124.3, 122.1, 119.2, 114.6, 102.4, 35.0 ppm; IR (neat): $\tilde{\nu}$ = 2920, 2216, 1371, 1280, 751 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{11}H_8N_3S_2$: 246.0160 $[M+H]^+$; found: 246.0158.

**8-Methyl-2-(1-methyl-1*H*-indol-3-yl)-8*H*-thieno[2,3-*b*]indole-3-carbonitrile (13c)**: Obtained from acetonitrile **11b** and dithioester **2k** by Method A as a yellow solid (156 mg, 78%). M.p. 187–189 °C; $R_f$ 0.53 (EtOAc/hexane, 3:7); $^1$H NMR (400 MHz, $[D_6]$DMSO): $\delta$ = 8.01 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.40–7.35 (m, 2H), 7.32–7.26 (m, 2H), 3.94 (s, 3H), 3.92 ppm (s, 3H); $^{13}$C NMR (100 MHz, $[D_6]$DMSO): $\delta$ = 141.5, 140.3, 140.2, 136.8, 129.6, 125.0, 123.0, 122.6, 120.7, 120.0, 119.8, 119.6, 119.2, 117.8, 116.3, 110.8, 110.6, 106.4, 94.1, 32.9, 32.2 ppm; IR (neat): $\tilde{\nu}$ = 2202, 1478, 1330, 1135, 736 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{21}H_{16}N_3S$: 342.1065 $[M+H]^+$; found: 342.1054.

**1,3-Diphenyl-5-(pyridin-3-yl)-1*H*-thieno[3,2-*c*]pyrazole-6-carbonitrile (13e)**: Obtained from acetonitrile **11c** and dithioester **2b** by Method A as an off-white solid (108 mg, 74%). M.p. 217–219 °C; $R_f$ 0.3 (EtOAc/hexane, 2:3); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.78 (br s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.97–7.94 (m, 2H), 7.79–7.76 (m, 2H), 7.62–7.57 (m, 2H), 7.55–7.48 (m, 4H), 7.47–7.41 ppm (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 157.5, 151.5, 148.8, 145.0, 143.9, 138.6, 135.5, 131.1, 129.5, 129.2, 129.1, 128.8, 126.1, 124.2, 124.14, 124.11, 119.5, 113.4, 92.5 ppm; IR (neat): $\tilde{\nu}$ = 2218, 1510, 1458, 1158, 758 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{23}H_{15}N_4S$: 379.1017 $[M+H]^+$; found: 379.1011.

**2-(1-Methyl-1*H*-pyrrol-2-yl)thieno[2,3-*b*]pyridine-3-carbonitrile (13f)**: Obtained from acetonitrile **11d** and dithioester **2n** as a gray crystalline solid (130 mg, 64% by Method A, 156 mg, 77% by Method B). M.p. 129–131 °C; $R_f$ 0.4 (EtOAc/hexane, 2:3); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.61 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.17 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.45 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.92–6.89 (m, 2H), 6.31 (dd, *J* = 3.6, 2.4 Hz, 1H), 3.89 ppm (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 158.9, 147.9, 146.1, 132.5, 129.8, 128.5, 124.0, 121.3, 115.5, 115.0, 109.9, 99.6, 36.3 ppm; IR (neat): $\tilde{\nu}$ = 2212, 1458, 1187, 1063, 737 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{13}H_{10}N_3S$: 240.0595 $[M+H]^+$; found: 240.0592.

**(2-(Furan-2-yl)thieno[2,3-*b*]pyridin-3-yl)(thiophen-2-yl)methanone (13h)**: Obtained from deoxybenzoin **11f** and dithioester **2e** by Method A as a brown liquid (136 mg, 85%). $R_f$ 0.4 (EtOAc/hexane, 1:1); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.61 (dd, *J* = 5.6, 1.6 Hz, 1H), 8.17 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.45 (dd, *J* = 8.0, 4.4 Hz, 1H), 7.22 (dd, *J* = 5.6, 1.2 Hz, 1H), 7.04 (dd, *J* = 4.0, 1.6 Hz, 1H), 6.92–6.90 (m, 2H), 6.86 (dd, *J* = 5.6, 3.6 Hz, 1H), 6.31 ppm (dd, *J* = 4.0, 3.2 Hz, 1H); $^{13}$C NMR (100 MHz, $[D_6]$DMSO): $\delta$ = 186.2, 157.9, 148.2, 145.3, 131.6, 130.4, 129.8, 129.4, 128.5, 128.3, 123.2, 121.9, 114.8, 111.3, 109.3 ppm; IR (neat): $\tilde{\nu}$ = 3057, 1652, 1404, 1216, 1064, 852 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{16}H_{10}NO_2S_2$: 312.0153 $[M+H]^+$; found: 312.0136.

**Ethyl 2-(benzo[*d*][1,3]dioxol-5-yl)-8-methyl-8*H*-thieno[2,3-*b*]indole-3-carboxylate (13i)**: Obtained from acetate **11g** and dithioester **2o** as a pale-yellow solid (98 mg, 56% by Method A, 143 mg, 82% by Method B). M.p. 118–120 °C; $R_f$ 0.6 (EtOAc/hexane, 2:8); $^1$H NMR (400 MHz, $[D_6]$DMSO): $\delta$ = 8.18 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.34–7.30 (m, 1H), 7.20–7.01 (m, 1H), 7.09 (t, *J* = 1.2 Hz, 1H), 6.99 (s, 2H), 6.10 (s, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 1.20 ppm (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $[D_6]$DMSO): $\delta$ = 163.3, 147.4, 146.9, 141.6, 141.1, 140.5, 127.6, 123.5, 122.5, 121.1, 120.8, 120.7, 120.4, 119.3, 110.2, 109.7, 107.9, 101.3, 60.3, 32.0, 13.8 ppm; IR (neat): $\tilde{\nu}$ = 1686, 1537, 1475, 1357, 1167, 926 $cm^{-1}$; HRMS (ESI): *m/z* calcd for $C_{21}H_{18}NO_4S$: 380.0957 $[M+H]^+$; found: 380.0965.

## Acknowledgements

We thank Professor C. N. R. Rao, FRS, for encouragement and support of our research, JNCASR and the Council of Scientific and Industrial Research (CSIR, New Delhi) for financial assistance, and CSIR-SRF (to A.A. and S.V.K) and the Indian National Science Academy, New Delhi, for an INSA Senior Scientist position (to H.I.).

**Keywords:** C–H activation · cyclization · oxidation · sulfur heterocycles · synthetic methods

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Received: May 10, 2015
Published online on October 2, 2015