Palladium-catalysed direct synthesis of benzo[*b*]thiophenes from thioenols†

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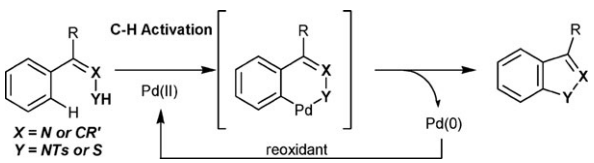
The one-pot conversion of thioenols into benzo[*b*]thiophenes was achieved by using a simple palladium catalyst such as $PdCl_2$ or $PdCl_2$(cod).

Multi-substituted benzo[*b*]thiophenes are of considerable importance, as they exhibit various biological activities[1] and also provide useful properties in materials science.[2] A number of methods to synthesise this class of compounds have been reported in recent years,[3] most of which involve the cyclisation of benzenethiol derivatives. However, facile and versatile methods to access multi-substituted benzo[*b*]thiophenes are still limited. Furthermore, catalytic cyclisation approaches using transition metals for the construction of the benzo[*b*]thiophene skeleton, which would provide a more efficient and practical route, are extremely rare in the literature, presumably due to catalyst poisoning by sulfur. Only a few reports of this nature have appeared,[4] in which Au[4a] or Pd[4b] catalysts have been employed to effect C–S bond formation.

In connection with our studies on the synthesis of heterocyclic compounds *via* transition metal-catalysed reactions,[5] we recently developed an efficient method for the construction of indazoles *via* a palladium-catalysed C–H activation/intramolecular amination sequence (Scheme 1, X = N, Y = NTs).[5a] In this context, we became interested in whether this intramolecular C–H amination process could be extended to C–S bond formation to prepare sulfur-based heterocycles, such as benzo[*b*]thiophenes (Scheme 1, X = CR′, Y = S).

Initial studies to determine the optimal reaction conditions were performed using 1,2,2-triphenylethenethiol (**1a**) as a substrate (Table 1). Despite extensive screening of a range of



Scheme 1 A strategy for the synthesis of heterocycles *via* palladium-catalysed C–H activation followed by intramolecular carbon–heteroatom bond formation.

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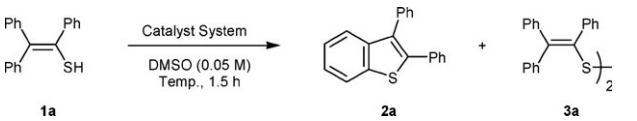
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for thioenols and benzo[*b*]thiophenes. See DOI: 10.1039/b811362a

Table 1 Optimisation of the reaction conditions

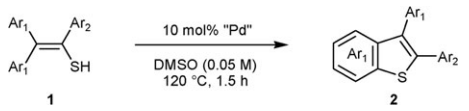


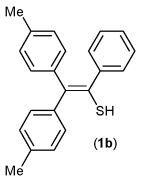
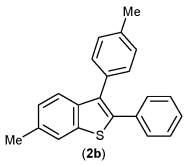
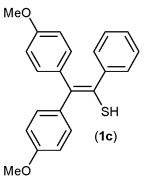
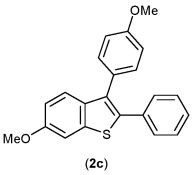
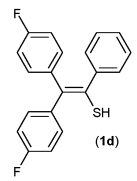
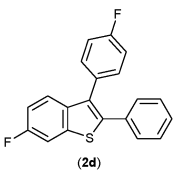
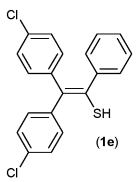
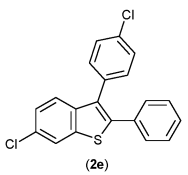
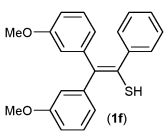
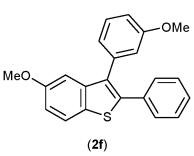
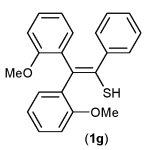
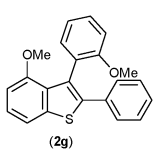
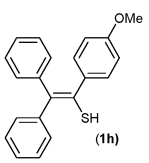
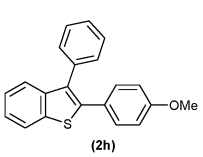
			Yield (%)[a]		
Entry	Catalyst system	Temp./°C	**2a**	**3a**	**1a**
1	50 mol% $Pd(OAc)_2$/ 100 mol% $Cu(OAc)_2$	80	19	2	0
2	25 mol% $Pd(OAc)_2$/ 100 mol% $Cu(OAc)_2$	80	8	21	0
3	25 mol% $Pd(OAc)_2$	80	22	10	10
4	25 mol% $Pd(OAc)_2$	120	27	37	0
5	25 mol% $Pd(TFA)_2$	120	21	36	Trace
6	25 mol% $Pd(PPh_3)_4$	120	Trace	0	59
7	25 mol% $PdCl_2$	120	75	Trace	0
8	25 mol% $PdCl_2$(cod)	120	80	<3	0
9	10 mol% $PdCl_2$	120	82	2	0
10	10 mol% $PdCl_2$(cod)	120	85	2	0
11	None	120	Trace	11	63
12	10 mol% $NiCl_2$	120	Trace	14	14
13	10 mol% $PtCl_2$	120	8	23	0
14	10 mol% $RuCl_3$[b]	120	13	32	0
15	10 mol% AuCl	120	4	46	0

[a] Isolated yield. [b] *n*-Hydrate (*n* = 1–3).

catalytic systems (palladium/reoxidant combinations) and solvents, the desired 2,3-diphenylbenzo[*b*]thiophene (**2a**) was not obtained in a satisfactory yield (up to 12% yield with 25 mol% of palladium source). However, to our surprise, further optimisation revealed that this palladium-catalysed cyclisation proceeded more efficiently in the *absence* of reoxidants. Namely, the reaction of **1a** using 25 mol% of $Pd(OAc)_2$ and 100 mol% of $Cu(OAc)_2$ as a catalyst system in DMSO at 80 °C resulted in the formation of **2a** in only an 8% yield (Table 1, entry 2), while the use of $Pd(OAc)_2$ as the sole catalyst delivered **2a** in a 22% yield (Table 1, entry 3). Increasing the reaction temperature to 120 °C gave a slightly better result (Table 1, entry 4). From subsequent examinations of various palladium sources, $PdCl_2$ and $PdCl_2$(cod) proved to be the best catalysts (Table 1, entries 9 and 10); 10 mol% of palladium efficiently catalysed this cyclisation, producing **2a** in high yields (82 and 85%, respectively).[6] DMSO is crucial for high conversion in this process.[6] Interestingly, disulfide **3a** was observed in almost all cases, yields of which were dependent on the reaction conditions employed. Essentially none of the desired product, **2a**, was obtained in the absence of a

Table 2 Benzo[*b*]thiophene synthesis from symmetrically-substituted thiols[a]



Entry	Starting material	Product	Yield (%)[b] $PdCl_2$	Yield (%)[b] $PdCl_2$(cod)
1	 (**1b**)	 (**2b**)	77	81
2	 (**1c**)	 (**2c**)	74	74
3	 (**1d**)	 (**2d**)	72	78
4	 (**1e**)	 (**2e**)	85	89
5	 (**1f**)	 (**2f**)	72	63
6	 (**1g**)	 (**2g**)	<16	<13
7	 (**1h**)	 (**2h**)	89	78

[a] Reagents: **1** (1 equiv.), "Pd" (10 mol%) and DMSO (0.05 M). [b] Isolated yield.

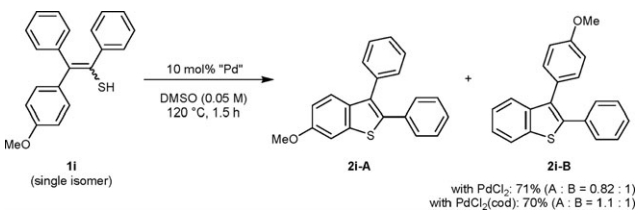
palladium catalyst (Table 1, entry 11). Furthermore, other metal salts, such as $NiCl_2$, $PtCl_2$, $RuCl_3$ and AuCl, were not effective catalysts (Table 1, entries 12–15).

Intrigued by this benzo[*b*]thiophene ring formation, we next investigated the scope of the reaction by employing several kinds of thioenol, **1** (Table 2). In the case of substrates that had identical Ar_1 substituents ('symmetric' substrates), substituted 2,3-diarylbenzo[*b*]thiophenes **2** were generally obtained in good to high yields from the corresponding 4,4′- and 3,3′-substituted thioenols, **1** (Table 2, entries 1–5). No regioisomers, such as 3-(3-methoxyphenyl)-7-methoxy-2-phenylbenzo[*b*]thiophene, were observed in the reaction of the substrate with methoxy groups at the 3- and 3′-positions (**1f**) (Table 2, entry 5). In contrast, a satisfactory result was not obtained from the reaction of **1g**, which had an *ortho*-methoxy group on each Ar_1 (Table 2, entry 6). In addition, 2-anisoyl-3-phenylbenzo[*b*]thiophene (**2h**) was obtained in high yield (Table 2, entry 7). The formation of a small amount of the corresponding disulfide was observed in some cases (Table 2, entries 1, 2, 3 and 6).

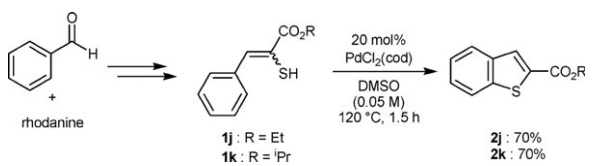
The reaction of a substrate that had only one methoxy-substituted benzene ring ('dissymmetric' substrate) was also examined using our optimal reaction conditions. Despite the starting thioenol, **1i**, being a single isomer, the cyclised product obtained was a mixture of two benzo[*b*]thiophenes, **2i-A** and **2i-B**, suggesting that the *E*/*Z*-isomerisation of the thioenol could be occurring relatively easily during this process (Scheme 2).

The reaction conditions developed above were also successfully applied to the cyclisation of another class of substrates, **1j** and **1k**, which were readily prepared from rhodanine and benzaldehyde. As a result, 2-alkoxycarbonylbenzo-[*b*]thiophenes **2j** and **2k** were obtained in high yields, although a relatively high catalyst loading was necessary for the best conversion (Scheme 3).

Although extensive mechanistic studies have not yet been conducted, we believe that this palladium-catalysed cyclisation proceeds *via* the formation of disulfide **3** (Fig. 1). DMSO itself,[7] or in combination with a variety of acidic co-reagents,[8] has been known to mediate the transformation of thiols to



Scheme 2 The reaction of 'dissymmetric' substrate **1i**.



Scheme 3 The synthesis of 2-alkoxycarbonylbenzo[*b*]thiophenes.

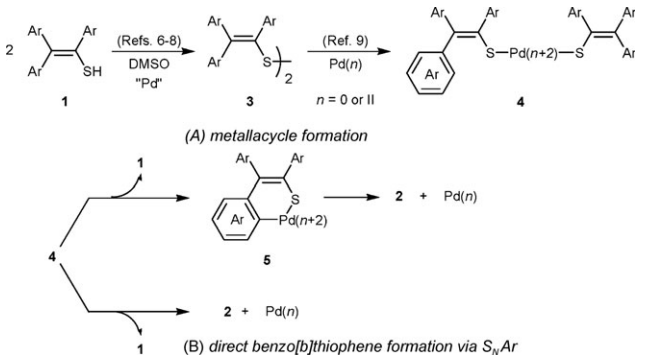
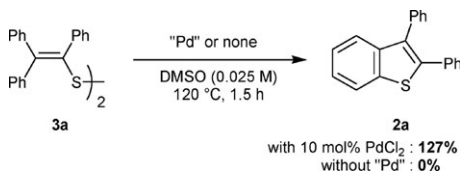


Fig. 1 A plausible reaction mechanism.



Scheme 4 The conversion of disulfide **3a** into benzo[*b*]thiophene **2a**.

disulfides. The palladium catalyst may also be involved in this oxidation step because the heating of **1a** in DMSO in the *absence* of palladium resulted in the formation of disulfide **3a** in only an 11% yield (Table 1, entry 11).[8a,b,9] Disulfide **3**, formed from the corresponding thioenol, **1**, undergoes oxidative addition to palladium, leading to complex **4**.[10] Electrophilic attack of the aryl ring, either at the palladium centre (Fig. 1; path A, **4** to **5**) or at the sulfur atom (path B, **4** to **2**), may occur next. From the former pathway, the formation of six-membered palladacycle **5**, followed by reductive elimination, provides benzo[*b*]thiophene **2**. The direct formation of **2**, along with starting thioenol **1** and reduced palladium, occurs in the latter pathway. Direct C–H activation of thioenol **1** is unlikely, although we cannot completely rule out this mechanism at present.

The above-proposed mechanism complements the following observations: (1) the formation of a small amount of disulfide compound was observed in most cases, (2) oxidants are *not* necessary for this process and (3) isolated disulfide **3a** can be converted into benzo[*b*]thiophene **2a** in the presence of a palladium catalyst (Scheme 4).[11,12]

In summary, we have developed a novel method for the direct synthesis of multi-substituted benzo[*b*]thiophenes through the unprecedented palladium-catalysed cyclisation of thioenols. The procedure presented here employs a simple catalyst system, in which $PdCl_2$ or $PdCl_2$(cod) is the sole metal source required, and where additional redox-active reagents are not necessary. For this transformation, we postulate a reaction mechanism in which palladium might be playing a dual role, both in the formation of disulfides and in the subsequent cyclisation. This direct high-yielding and atom-economical procedure for the synthesis of benzo[*b*]thiophenes will find applications in a range of areas, including medicinal and materials chemistry. Further investigations to expand the substrate scope, as well as to clarify the precise reaction mechanism, are now in progress.

Notes and references

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6 The use of a reduced amount of palladium catalyst, such as 5 mol% $PdCl_2$, led to a decreased yield (44% of **2a** along with 27% of **3a**). See the ESI† for the detailed results of screening.

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11 Interestingly, Pd(0) has no catalytic activity for this transformation; only 4% of **2a**, along with 92% of recovered **3a**, was obtained in the presence of 20 mol% $Pd_2(dba)_3$.

12 Either Pd(0) and Pd(II), Pd(II) and Pd(IV), or both mechanisms can be operating during this process. Detailed mechanistic studies are currently under way.