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PALLADIUM CATALYZED SYNTHESES OF DIBENZOTHIOPHENES BY RING-CLOSURE OF 2-IODINATED DIARYL THIOETHER

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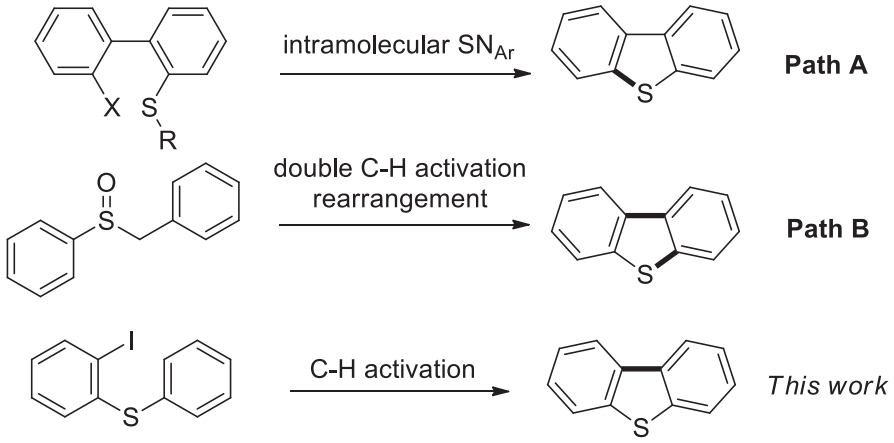
Abstract – An efficient ring-closure of 2-iodinated diaryl thioethers at the presence of palladium catalyst to form dibenzothiophene is described. After the best condition was set up as $Pd_3(dba)_2$ as the catalyst, anhydrous $Cu(OAc)_2$ as additive, $PivONa{\cdot}H_2O$ as base, DMF as solvent, a series of dibenzothiophenes could be successfully obtained through this protocol in moderate to excellent yields.

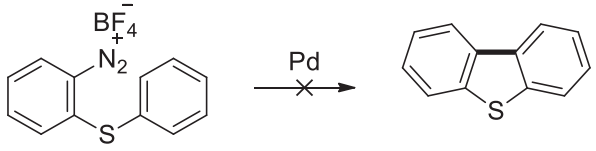
Heterocyclic compounds is a very important class of organic compounds, no matter natural or artificial ones, many heterocyclic compounds have potential pharmacological activity. Of them, dibenzothiophene (DBT) is a fused aromatic tricyclic system can be isolated from high-boiling petroleum derivatives originally.[1] However, because of the sufficient availability, DBTs have been explored to a much less extent than other related analogues such as carbazole or dibenzofurans. In fact, only a few reports of to construct the skeleton of dibenzothiophene are presented in literature. The oldest one was sulfur insertion to biphenyl at the presence of anhydrous aluminum chloride at 250 ^{o}C in spite of in low yields.[2] Intriguingly, using aryne produced by lithiation by perilous *tert*-butyllithium and a suitable electrophile, Sanz furnished a series of functional dibenzothiophenes.[3] In order to avoid the poisoning the tramsition-metal catalysis, using Negishi coupling and subsequent SN_{Ar} reaction Kienle gave an alternative strategy to form dibenzothiophenes.[4] Using similar Suzuki biphenyl forming strategy, Golding and Jepsen disclosed microwave-mediated intramolecular SN_{Ar} substitution to prepare dibenzothiophenes.[5] Regardless of the structural uniquity, under the initiation of triethylboran, a radical reduction of 2-(2-iodophenyl)phenylthio derivatives by Bu_3SnH giving dibenzothiophene was also efficient.[6] A palladium-catalyzed double C–H bond activation and thio-rearrangement, a series of polysubstituted dibenzothiophenes could be provided in moderate yields.[7] Actually, a brilliant C–H bond activation and then thiolation, several 2-brominated diaryl thioethers could be obtained. Based on these diaryl thioethers, Saravanan gave a short report of palladium catalyzed intramolecular annulations to

afford dibenzothiophenes in good yields.[8] Other miscellaneous methods can be found in literature as well.[9] Despite these advancements, there are still some drawbacks such as using sensitive organometallic reagents or expensive organoboranes, confinements in substrates, limited applicability, being lack of expandability or unsteady yields. As a continuation in searching efficient and cost-effective methods to build different heterocycles,[10] we envisaged a palladium-catalyzed C–H bond activation/ring-closure to form dibenzothiophene based on 2-diazonium tetrafluoroborate of diaryl thioether.



Scheme 1. Major present pathways of synthesis of dibenzothiophene

At first, as an expansion of our previous protocol,[10e] we were strongly interested in the palladium catalyzed denitrogenation/ C–H bond activation/ring-closure to form dibenzothiophene based on 2-diazonium tetrafluoroborate of diaryl thioether, however, after changes in palladium, base, solvent, this attempt of ring-closure route was proved fruitless.

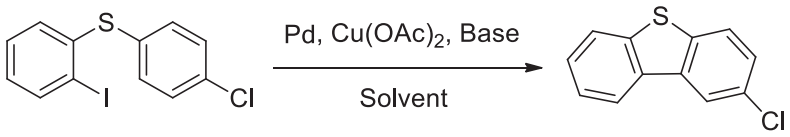


Scheme 2. Attempt in synthesis of dibenzothiophene from 2-diazonium tetrafluoroborate of diaryl thioether

Thereafter, a literature survey revealed that there was no such a ring-closure report from 2-iodinated diaryl thioether at all. So, through a simple Sandmeyer reaction, the diazonium group could be transformed into corresponding iodo derivatives smoothly. Next we checked the possibility of ring-closure method based on the obtained (4-chlorophenyl) (2-iodophenyl) thioether at the condition of $PdCl_2(MeCN)_2$ as catalyst and Cs_2CO_3 as base. First of all, in order to prevent the poisoning of palladium catalyst, 20% equivalent of anhydrous $Cu(OAc)_2$ was used as additive. At first we found that the nature of reaction solvents seems to be crucial for this reaction. In non polar solvents such as dichloromethane (**Table 1**, entry 1) and toluene (**Table 1**, entry 2), and more polar solvents such as THF (**Table 1**, entry 2),

acetonitrile (**Table 1**, entry 3), there was no desired product at all. To our pleasure, in DMF, only after 4.5 hours, a yield of 59% was obtained. Next, the different palladium catalysts were screened. Subsequent experiments revealed that $PdCl_2(MeCN)_2$, $Pd(OAc)_2(PPh_3)_2$ and $Pd(OAc)_2$ gave more or less yields under same other conditions (**Table 1**, entries 5-7). $Pd(OCOCF_3)_2$, which has strong electron withdrawing counter-ion, a higher yield of 2-chlorodibenzothiophene than the previous ones could be obtained (**Table 1**, entry 8). At last, we tried to alter base, inorganic base K_2CO_3 (**Table 1**, entry 9) didn't gave a positive yield. Delightfully, if $PivONa·H_2O$ was used as base (**Table 1**, entry 10), the best result was given. Finally, we set up the optimized reaction conditions that are DMF as solvent, 20% molar ratio $Pd_3(dba)_2$ as catalyst, 20% molar ratio anhydrous $Cu(OAc)_2$ as additive, $C_5H_{11}NaO_3$ as base at refluxing temperature (**Table 1**, entry 11).

Table 1. Screening condition of ring-closure of 4-chlorophenyl-2'-iododiphenyl thioether

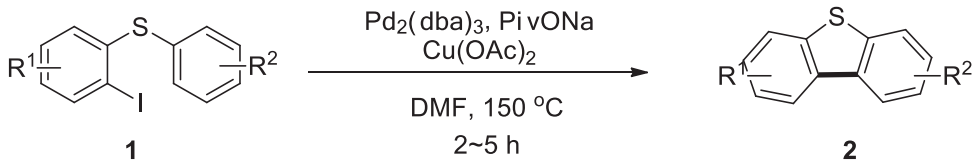


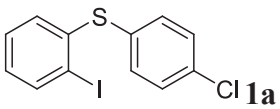
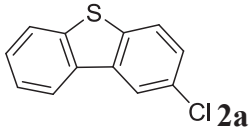
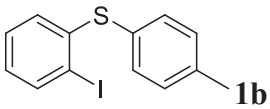
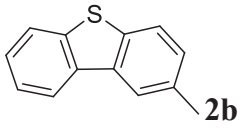
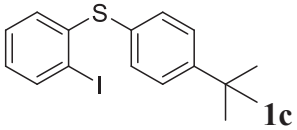
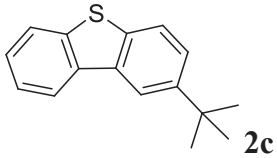
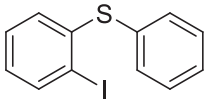
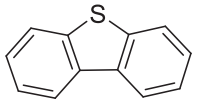
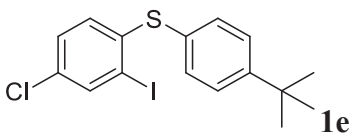
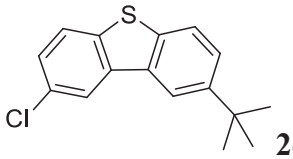
Entry	Solvent	Base	Additive	Catalyst	T (°C)	Time（h）	Yields (%)[b]
1	DCM	Cs_2CO_3	$Cu(OAc)_2$	$PdCl_2(MeCN)_2$	39.8	72	0
2	toluene	Cs_2CO_3	$Cu(OAc)_2$	$PdCl_2(MeCN)_2$	110	49	0
3	THF	Cs_2CO_3	$Cu(OAc)_2$	$PdCl_2(MeCN)_2$	66	72	0
4	MeCN	Cs_2CO_3	$Cu(OAc)_2$	$PdCl_2(MeCN)_2$	82	54	0
5	DMF	Cs_2CO_3	$Cu(OAc)_2$	$PdCl_2(MeCN)_2$	150	4.5	59
6	DMF	Cs_2CO_3	$Cu(OAc)_2$	$Pd(OAc)_2(PPh_3)_2$	150	12.5	50
7	DMF	Cs_2CO_3	$Cu(OAc)_2$	$Pd(OAc)_2$	150	4	54
8	DMF	Cs_2CO_3	$Cu(OAc)_2$	$Pd(OCOCF_3)_2$	150	4.5	68
9	DMF	Cs_2CO_3	$Cu(OAc)_2$	$Pd_2(dba)_3$	150	2	71
10	DMF	K_2CO_3	$Cu(OAc)_2$	$Pd_2(dba)_3$	150	2	64
11	DMF	$PivONa·H_2O$	$Cu(OAc)_2$	$Pd_2(dba)_3$	150	2	82

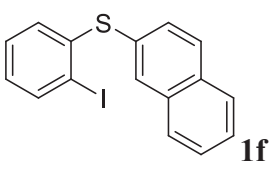
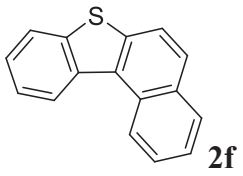
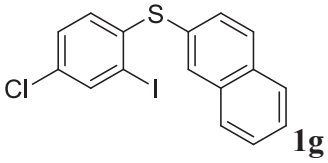
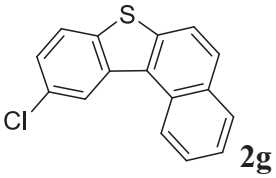
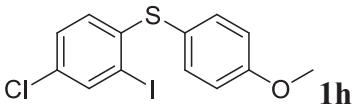
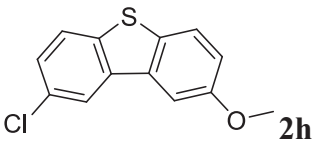
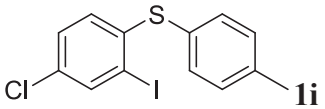
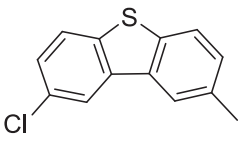
[a] Reaction conditions: unless otherwise noted, substrate (0.58 mmol, 1 equiv.), palladium catalyst (0.116 mmol, 0.2equiv.), anhydrous $Cu(OAc)_2$ (0.116 mmol, 0.2equiv.), base (0.58 mmol, 1 equiv.), solvent (5 mL). [b] Isolated yields.

Having established optimized reactions conditions, we next examined the scope of our protocol for the synthesis of a variety of substituted dibenzothiophene, as shown in Table 2. Altogether 9 examples (Table 2) with different substituents, including halo (Table 2, entry 1), *t*-butyl (Table 2, entry 5), and methyl or methoxy (Table 2, entry 3) groups were subjected to this protocol to afford diarylbenzothiophenes in fairly good yields. It is worth noting that if naphthyl was included, tetracyclic structure of benzo[*b*]naphtho[*1,2-d*]thiophene could be obtained efficiently (Table 2, entries 6-7). As for the variations of R^1, two kinds of substituents have been tested. As for the variations of R^2, electron-neutral (Table 2, entries 2-4, 9), electron-donating (Table 2, entry 8) and electron-deficient (Table 2, entry 1) groups were good substrates for this reaction. Thus, all the products in our reactions listed in Table 2 were easily characterized on the basis of physical and spectral data and also by comparison with authentic samples.

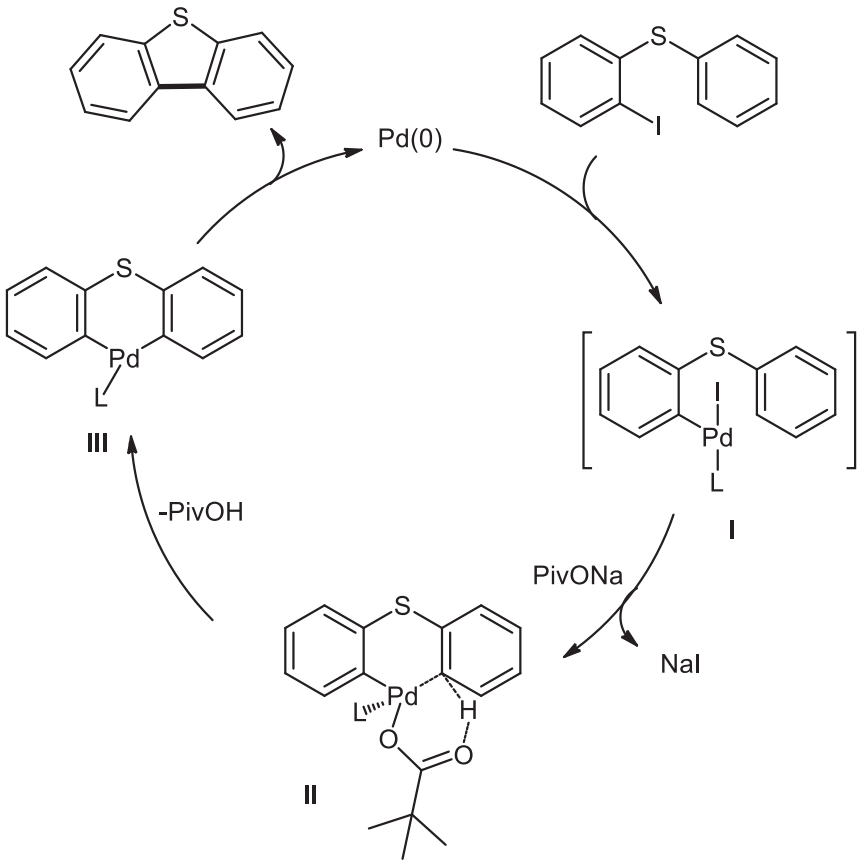
Table 2. Pd-Catalyzed synthesis of substituted dibenzothiophenes



Entry	Substrate	Product	Yield (%)[a]
1	 **1a**	 **2a**	82
2	 **1b**	 **2b**	80
3	 **1c**	 **2c**	84
4	 **1d**	 **2d**	81
5	 **1e**	 **2e**	77

6	 **1f**	 **2f**	53
7	 **1g**	 **2g**	52
8	 **1h**	 **2h**	92
9	 **1i**	 **2i**	86

[a] Isolated yields.



Scheme 3. A plausible mechanism of Pd-catalyzed synthesis of substituted dibenzothiophenes

A plausible mechanism of this intramolecular cyclization is given in **Scheme 3**. The conversion commenced with the oxidative-addition of Pd (0) to give intermediate **I**. A replacement of iodo ion by

$PivO^-$ anion would happen. With the help of bulky *tert*-butyl group, the complex would be more soluble than using normal inorganic base. And then the C–H bond is activated and then PivOH is released. Subsequent reductive elimination gives the dibenzothiophenes and and regenerates Pd (0) for next catalytic cycle.

In conclusion, we have expanded our palladium catalyzed ring-closure methodologies to synthesize different heterocycles. In this case, using *ortho* iodo diaryl thioether, we have established the optimized conditions is that $Pd_3(dba)_2$ as the catalyst, anhydrous $Cu(OAc)_2$ as additive, sodium pivalate hydrate as base, DMF as solvent. At best conditions, we have obtained 9 different dibenzothiophenes which were confirmed by NMR. Our method merits as such advantages, high yield, short reaction time, cost-effectiveness and versatility in substrates.

EXPERIMENTAL SECTION

All the solvents and commercially available reagents were purchased from commercial sources and used directly. ^1H NMR and ^{13}C NMR were recorded in $CDCl_3$ at room temperature on the Bruker NMR spectrometers (DRX 500) if not noted otherwise. The chemical-shifts scale is based on internal TMS and the coupling constants, *J* are reported in Hertz (Hz). Standard flash chromatography was employed to purify the crude reaction mixture using 200–300 mesh silica gel (Tsingdao Ocean Company, Tsingdao, China) under a positive nitrogen pressure.

General procedure for the preparation of dibenzothiophenes from the 2-iodinated diphenylthioethers using $Pd_3(dba)_2$: Under argon flush, a flask was charged with the substrates of diaryl thioethers (0.58 mmol), DMF (10 mL), $Pd_3(dba)_2$ (105 mg, 0.115 mmol), $Cu(OAc)_2$ (23 mg, 0.115 mmol) and sodium pivalate hydrate (72 mg, 0.58 mmol), and then the mixture was maintained at 150 °C with stirring for 5 h under argon atmosphere. After completion by TLC analysis, the reaction mixture was diluted with EtOAc and water. The aqueous phase was extracted with EtOAc twice and the combined organic phases were washed with brine and dried over $MgSO_4$. Then solvent was evaporated under vacuum and the crude product was purified by column chromatography on silica gel, eluting with a mixture of petroleum ether and EtOAc to give dibenzothiophenes. Yields are listed in Table 2.

2-Chlorodibenzothiophene 2a: white solid, mp 123-124 ºC; ^1H NMR (500 MHz, DMSO-d_6) δ: 8.51 (d, J = 1.5 Hz, 1H), 8.43 (d, J = 7.0 Hz, 1H), 8.03-8.07 (m, 2H), 7.50-7.56 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 139.91, 137.59, 137.15, 134.56, 130.39, 128.21, 127.40, 125.41, 125.12, 123.61, 123.08, 122.27.

2-Methyldibenzothiophene 2b: white solid, mp 81-82 ºC, Lit.[11] 81-82ºC; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.31-8.32 (m, 1H), 8.17 (s, 1H), 7.99-8.00 (m, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.48-7.50 (m, 2H), 7.34 (d, J = 8.0 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 139.39, 136.04, 135.68, 135.39, 134.58, 128.94, 127.40, 125.09, 123.51, 123.14, 122.53, 122.36, 21.50.

2-*tert*-Butyldibenzothiophene 2c: white solid, mp 63-64 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.15-8.18 (m, 2H), 7.81-7.83 (m, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.51 (dd, J = 8.5, 2.0 Hz, 1H), 7.41-7.44 (m, 2H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 147.73, 139.91, 136.55, 135.83, 135.44, 126.49, 124.90, 124.20, 122.90, 122.33, 121.45, 117.87, 34.88, 31.70.

Dibenzothiophene 2d: white solid, mp 99-100 ºC, Lit.[11] 99.7 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.14-8.16 (m, 2H), 7.83-7.85 (m, 2H), 7.44-7.46 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 139.46, 135.57, 126.72, 124.37, 122.83, 121.60.

2-*tert*-Butyl-8-chlorodibenzothiophene 2e: white solid, mp 60-61 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.13 (d, J = 2.0 Hz, 1H), 8.09 (d, J = 1.5 Hz, 1H), 7.72-7.77 (m, 2H), 7.54 (dd, J = 8.5, 2.0 Hz, 1H), 7.37 (dd, J = 8.5, 2.5 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$ δ: 148.10, 137.99, 137.31, 137.21, 134.46, 130.51, 126.69, 125.61, 123.86, 122.45, 121.37, 118.07, 34.91, 31.65.

Benzo[*b*]naphtho[1,2-*d*]thiophene 2f: white solid, mp 138-140 ºC, Lit.[12] 140 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.00 (d, J =8.5 Hz, 1H), 8.85 (d, J = 8.0 Hz, 1H), 7.99-8.03 (m, 2H), 7.87-7.92 (m, 2H), 7.71-7.75 (m, 1H), 7.56-7.61 (m, 2H), 7.48-7.51 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ:139.78, 138.66, 136.76, 131.98, 130.70, 129.48, 129.09, 127.89, 127.17, 125.26, 124.93, 124.85, 124.76, 123.25, 123.23, 121.11.

Benzo[*b*]naphtho[1,2-*d*]-8-chlorothiophene 2g: white solid, mp 129-130 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.86 (d, J =8.5 Hz, 1H), 8.78 (d, J =2.0 Hz, 1H), 8.00 (d, J =8.5 Hz, 1H) 7.85-7.89 (m, 3H), 7.73 (td, J = 7.0, 1.5 Hz, 1H), 7.57-7.60 (m, 1H), 7.44 (dd, J = 8.5, 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 139.74, 137.87, 137.82, 131.93, 131.04, 130.47, 129.56, 128.56, 128.19, 127.52, 125.48, 125.22, 124.48, 123.99, 122.89, 120.95.

2-Methoxy-8-chlorodibenzothiophene 2h: white solid, mp 97-98 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.05 (d, J =2.0 Hz, 1H), 7.69-7.74 (m, 2H), 7.54 (d, J =2.5 Hz, 1H), 7.38 (dd, J =8.5, 2.0 Hz, 1H), 7.10 (dd, J =9.0, 2.0 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 157.82, 138.68, 136.83, 135.59, 132.08, 130.42, 126.90, 123.96, 123.60, 121.45, 116.77, 104.81, 55.73;

2-Methyl-8-chlorodibenzothiophene 2i: CAS: white solid, mp 112-113 ºC; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.44 (s, 1H), 8.25 (s, 1H), 8.02 (d, J =8.5 Hz, 1H), 7.90 (d, J =8.0 Hz, 1H), 7.51 (d, J =8.5 Hz, 1H), 7.37 (d, J =8.0 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 1.38.50, 137.59, 137.51, 135.42, 135.29, 130.80, 130.16, 127.80, 125.72, 123.84, 123.70, 122.71, 22.00.

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