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Iodine catalyzed cross-dehydrogenative C–S coupling by C(sp^2)–H bond activation: Direct access to aryl sulfides from aryl thiols

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A novel, efficient and unprecedented green protocol for the formation of C–S bond has been developed under metal-free conditions. This protocol involves the synthesis of aryl sulfides through the cross-dehydrogenative coupling of readily available aryl thiols with electron-rich species under solvent-free conditions and the corresponding aryl sulfides are obtained in high to quantitative yields. A catalytic amount of inexpensive and non-toxic iodine drives the reaction and no exclusion of air and expensive ligands are required.

Introduction

The upsurge in interest in the cross-dehydrogenative coupling reactions for the construction of C–C and C–X (X = hetero atom) bonds *via* C–H activation has been creating a renaissance[1] because of the emergence of the concepts of *"atom economy"*[2] and *"green chemistry"*.[3] Over several years, a plethora of new synthetic methods have been developed for the construction of complex molecules via cross-dehydrogenative coupling reaction between two C–H/C–H and X–H centers. Such couplings avoid wearisome and sustained pre-activation of C–H and X–H bonds, providing an alternative to traditional cross-coupling reactions. Among all cross-dehydrogenative coupling reactions, the formation of C–S bond is of utmost importance and fundamentally challenging in modern organic synthesis.

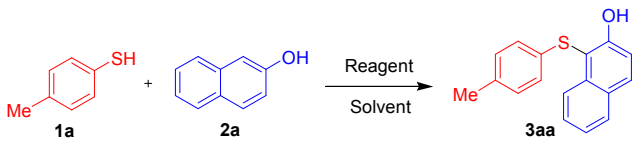
Aryl sulfides are ubiquitous structural motifs that frequently occur in many natural products, in pharmaceutically active compounds and in materials science.[4] Many drugs having aryl sulfide unit in their core structure are employed to treat Alzheimer's, Parkinson's, cancer, malarial, inflammatory and HIV diseases.[5] Among various thioethers, 2-arylsulfenylphenol containing compounds display biological and pharmaceutical activities, such as glycine transporter-1(GlyT-1) inhibitions, and 4-hydroxy-3-(arylthio)-2*H*-chromen-2-ones exhibit antibacterial and analgesic activities.[6] Over several years, numerous transition metal-catalyzed cross-coupling reactions of aryl thiols and disulfides with aryl halides, boronic acids and triflates involving palladium,[7] copper,[8] nickel,[9] iron,[10] cobalt[11] and rhodium,[12] and by direct C–H bond activation of arenes with aryl thiols as well,[13] have been powerful tools for the synthesis of aryl sulfides. Despite of the merits of these methods, some of them suffer from limitations such as pre-fuctionalization of both the coupling partners, and need for expensive, air sensitive and/or toxic metal catalysts. Metal contamination is a serious issue in the pharmaceutical industry. These aryl sulfides are also synthesized by the cross-coupling of thiols with aryl Grignard/aryl zinc reagents.[14]

Direct C–H functionalization for the synthesis of aryl sulfides under metal-free conditions is more practical and economical. In these protocols, different thiolating/sulfenylating regents[15] such as aryl sulfonyl hydrazides,[15a-c] arylsulfonyl chlorides,[15d,e] sodium sulfinates,[15e-g] diaryldisulfides[15h-o] and 1-(substituted phenylthio)-pyrrolidine-2,5-diones[15p] have been employed. These methods require an additional step for the synthesis of sulfenylating reagents. Synthesis of aryl sulfides *via* C–H functionalization using aryl thiols as sulfenylating agent under metal-free conditions have been less studied.[16] In the pharmaceutical industry, reactions under metal-free conditions are desired because of the low threshold residual tolerence of metals. Because of importance of such compounds, it is a challenging task to develop a novel, efficient and environmentally friendly approach for the synthesis of aryl sulfides directly from thiophenols. Herein, we report an efficient, metal-free and novel route for the synthesis of aryl sulfides by direct C–H bond functionalization with the umpolung strategy of aryl thiols in the presence of inexpensive and environmentally friendly iodine under *solvent-free* conditions.

Results and discussion

We initiated our investigation for the direct sulfenylation of electron-rich species by selecting the reactants 4-methylthiophenol (**1a**) and 2-naphthol (**2a**) in a model reaction. In a preliminary attempt, the reaction was performed with tetrabutylammonium iodide (TBAI)/*tert*-butyl hydroperoxide (TBHP) in CH_2Cl_2 at room temperature and the desired product **3aa** was obtained in a trace amount (Table 1, entry 1). To our delight, when the reaction was carried out in presence of I_2/H_2O_2 in CH_2Cl_2 at room temperature, the product **3aa** was obtained in 32 h in 83% yield (Table 1, entry 2). Switching of the oxidant to DMSO resulted in the formation of the product in 86% yield (Table 1, entry 3). When we used the reagent systems potassium iodide (KI)/DMSO and TBAI/DMSO, the reactions were inefficient in producing the aryl sulfide **3aa** (Table 1, entries 4 and 5). Among the oxidants used, DMSO gave this product in maximum yield. We further investigated the reaction to probe the effect of solvents and temperature using I_2/DMSO. The reaction in CH_3CN at 80 °C for 3 h furnished the aryl sulfide **3aa** in 84%

Table 1. Optimization of reaction conditions.[a]



1a 2a 3aa

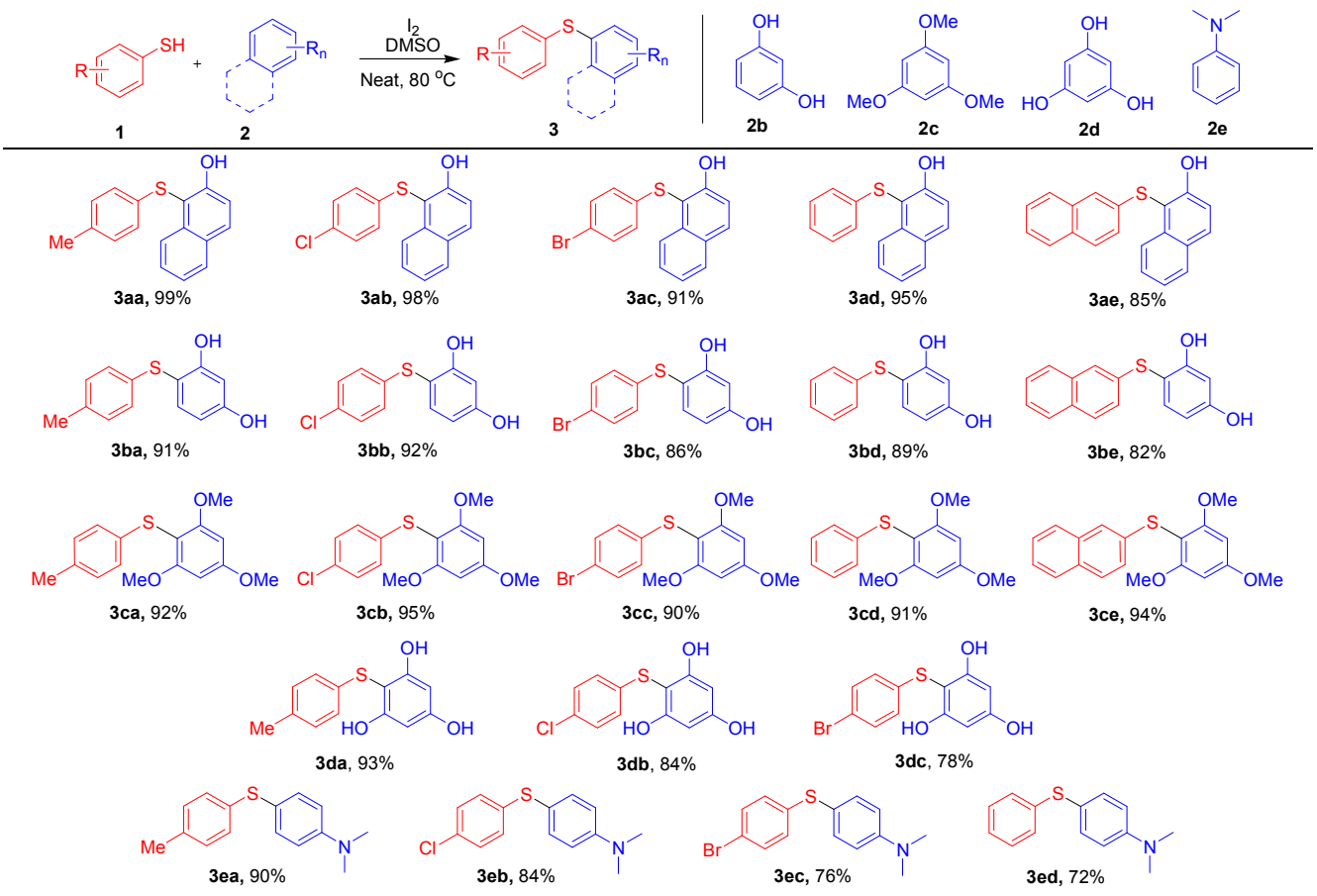
Entry	Reagent	Solvent	Temp	Time	Yield (%)
1	TBAI/TBHP	CH_2Cl_2	rt	24 h	trace
2	I_2/H_2O_2	CH_2Cl_2	rt	32 h	83
3	I_2/DMSO	CH_2Cl_2	rt	28 h	86
4	KI/DMSO	CH_2Cl_2	rt	24 h	-
5	TBAI/DMSO	CH_2Cl_2	rt	24 h	-
6	I_2/DMSO	CH_3CN	80 °C	3 h	84
7	I_2/DMSO	THF	80 °C	4 h	54
8	I_2/DMSO	EtOH	80 °C	4 h	43
9	I_2/DMSO	H_2O	100 °C	4 h	47
10	I_2/DMSO	Toluene	100 °C	2 h	75
11	I_2/DMSO	DMF	100 °C	4 h	-
12	I_2/DMSO	EtOAc	80 °C	3 h	91
13	I_2/DMSO	DCE	80 °C	2 h	98
14	I_2/DMSO	Neat	80 °C	3 h	99
15	I_2	Neat	80 °C	3 h	-

[a] Conditions: **1a** (0.75 mmol), **2a** (0.5 mmol), iodine reagent (0.05 mmol), oxidant (1.5 mmol). [b] Yields of isolated products.

yield (Table 1, entry 6). However, **3aa** was obtained in lower yield when the solvent was changed to THF, EtOH or H_2O (Table 1, entries 7–9). The reaction in toluene at 100 °C gave the aryl sulfide **3aa** in 2 h in 75% yield (Table 1, entry 10), and that in DMF did not yield any product (Table 1, entry 11). An increase in the yield of the product was observed when the reaction was carried out in EtOAc (Table 1, entry 12). Shifting of solvent to DCE further facilitated the reaction to furnish aryl sulfide **3aa** in 98% yield (Table 1, entry 13). To avoid the environmentally harmful chlorinated solvents, we performed the reaction under solvent free-conditions. To our surprise, we obtained the desired aryl sulfide **3aa** in maximum yield (99%) (Table 1, entry 14). The reaction was inefficient in the absence of oxidant with a catalytic amount of iodine (Table 1, entry 15), indicating that the oxidant is necessary for the progress of the reaction.

Thus I_2/DMSO system at 80 °C under solvent-free conditions emerged as the optimal set of conditions for subsequent studies. With the optimized condition in hand, we first explored the scope of the reaction with respect to aryl thiols **1a-e** with 2-naphthol (**2a**). Aryl thiols having electron withdrawing halo groups at the 4-position and parent thiophenol, as well as bulky substrates such as 2-naphthalenethiol, were able to react with 2-naphthol to give the corresponding products **3aa**–**3ae** in 3 h in excellent yields. Besides 2-naphthol, phenol derivatives and methoxy-benzenes **2b-d** participated well in this protocol to afford aryl sulfides in

Table 2. Substrate scope. [a]



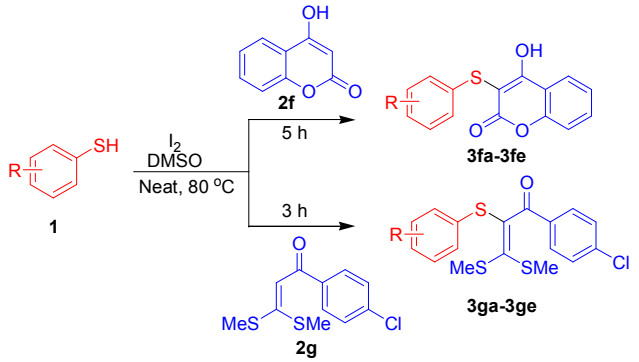
1 2 3 2b 2c 2d 2e

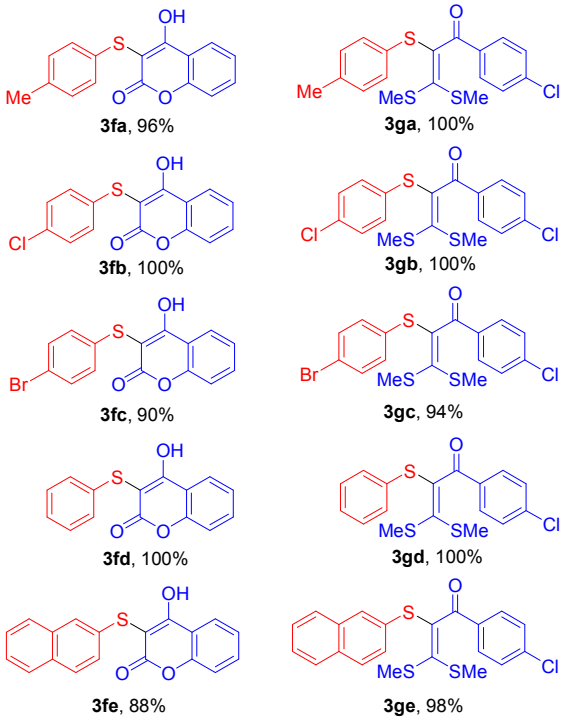
[a] Conditions: **1** (0.5 mmol; and 0.75 mmol in the case of **2a**), **2a-e** (0.5 mmol), iodine (0.05 mmol), DMSO (1.5 mmol).

high to excellent yields (Table 2). We further tested this method with the carbon nucleophile *N,N*-dimethylaniline (**2e**) bearing an amino functionality and the reaction proceeded cleanly in each case to provide the corresponding aryl sulfides **3ea**–**3ed** in good yield.

On the basis of promising results obtained in the case of electron-rich arenes **2a-e**, we have further extended this strategy to show the functional group tolerance. For this purpose, we carried out the reactions of different aryl thiols with 4-hydroxycoumarin (**2f**) and dithioacetal derivative **2g** under aforementioned conditions (Table 3). It is noteworthy that the compounds **2f,g** were well tolerated in this transformation. In the case of coumarin **2f** the reactions reached completion in 5 h and the corresponding aryl sulfides **3fa**–**3fe** were obtained in 88-100% yields, whereas those of dithioacetal **2g** are faster and the reactions reached completion in 3 h to furnish the corresponding aryl sulfides **3ga**–**3ge**, in excellent yields ranging from 94-100%.

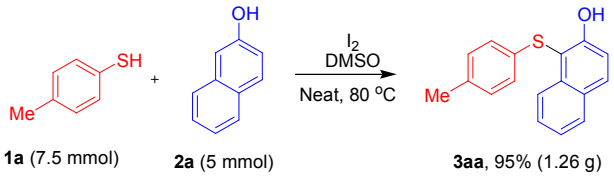
Table 3. Reaction of aryl thiols with hydroxycoumarin **2f** and dithioacetal **2g**.[a]





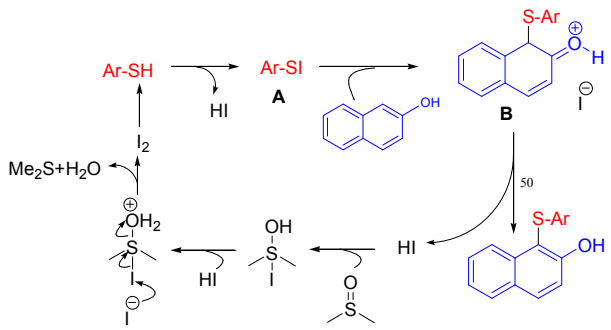
[a] Conditions: **1** (0.75 mmol), **2f,g** (0.5 mmol), iodine (0.05 mmol), DMSO (1.5 mmol).

Inspired by this green and simple protocol for the synthesis of aryl sulfides, we then conducted a scale up experiment in order to prove the potential of the present protocol. For this, we carried out the reaction of 2-naphthol (**2a**, 5 mmol) with 4-methylthiophenol (**1a**) under optimized conditions to afford the corresponding aryl sulfide **3aa** in excellent yield, demonstrating the efficiency of the present protocol for gram scale synthesis of aryl sulfides.



Scheme 1. Gram scale synthesis of aryl sulfide **3aa**.

A plausible mechanism for the direct sulfenylation of 2-naphthol is depicted in Scheme 2. Initially the nucleophilic aryl thiol attacks the electrophilic iodine centre leading to the formation of disulfide. Thus formed disulfide reacts with iodine to form the electrophilic intermediate Ar-SI (**A**). The species Ar-SI liberates the electrophile RS^+ which reacts with 2-naphthol to produce the intermediate **B**. This intermediate loses a proton to afford the desired aryl sulfide **3aa** and HI. The by-product HI reduces DMSO into DMS with concomitant regeneration of iodine to participate in the catalytic cycle. Though there is no direct evidence for the formation of ArSI species, its formation from disulfides is also suggested in the literature.[15h,k,o,16a,17]



Scheme 2. Plausible mechanism.

Conclusion

In conclusion, we have developed a metal-free, green and environmentally friendly method for the synthesis of aryl sulfides from umpolung strategy of readily available aryl thiols and electron-rich scaffolds. This protocol involves the cross-dehydrogenative coupling of aryl thiols with various carbon nucleophiles through C(sp^2)–H bond activation under solvent-free and aerobic conditions using an inexpensive, non-toxic and eco-friendly iodine/DMSO catalytic oxidation system. The iodine-mediated synthesis of various sulfur containing compounds is under investigation in our laboratory.

Experimental

Procedure for the synthesis of 1-(*p*-tolylthio)naphthalen-2-ol (3aa)

To a mixture of 4-methylthiophenol (**1a**, 0.75 mmol, 0.093 g) and 2-naphthol (**2a**, 0.5 mmol, 0.072 g) was added DMSO (1.5 mmol, 0.1 mL) followed by iodine (10 mol%, 0.05 mmol, 0.013 g). Then the reaction mixture was heated on a pre-heated oil bath at 80 ^{o}C for 3 h under solvent-free conditions. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2, and quenched with saturated sodium thiosulfate solution and extracted twice with CH_2Cl_2 (2 X 15 mL). The organic layer was washed with water and dried over anhyd. sodium sulfate. The solvent was evaporated *in vacuo*, and the residue was subjected to column chromatography using ethyl acetate in hexanes as eluent to afford pure 1-(*p*-tolylthio)naphthalen-2-ol (**3aa**) as a yellow solid (0.130 g, 99%).

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† Electronic Supplementary Information available: [Experimental procedures, spectroscopic data, copies of ^{1}H NMR and ^{13}C NMR are provided]. See DOI: 10.1039/b000000x/

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