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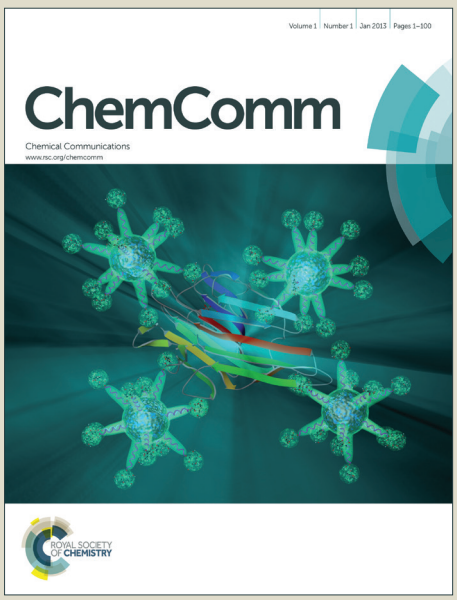

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Cite this: DOI: 10.1039/c0xx00000x

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Communication

Iron or boron-catalyzed C-H arylthiation of substituted phenols at room temperature†

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

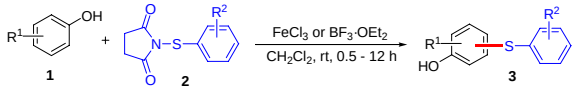
DOI: 10.1039/b000000x

A simple, efficient and environmentally friendly method for iron or boron-catalyzed C-H arylthiation of substituted phenols at room temperature has been developed, and the corresponding diaryl sulfides were prepared in good to excellent yields. The protocol uses readily available 1-(substituted phenylthio)pyrrolidine-2,5-dione as the arylthiation reagents, inexpensive and environmentally friendly $FeCl_3$ or $BF_3{\cdot}OEt_2$ as the catalyst, no ligand, additive and extrusion of air were required, and the reactions were performed very well at room temperature.

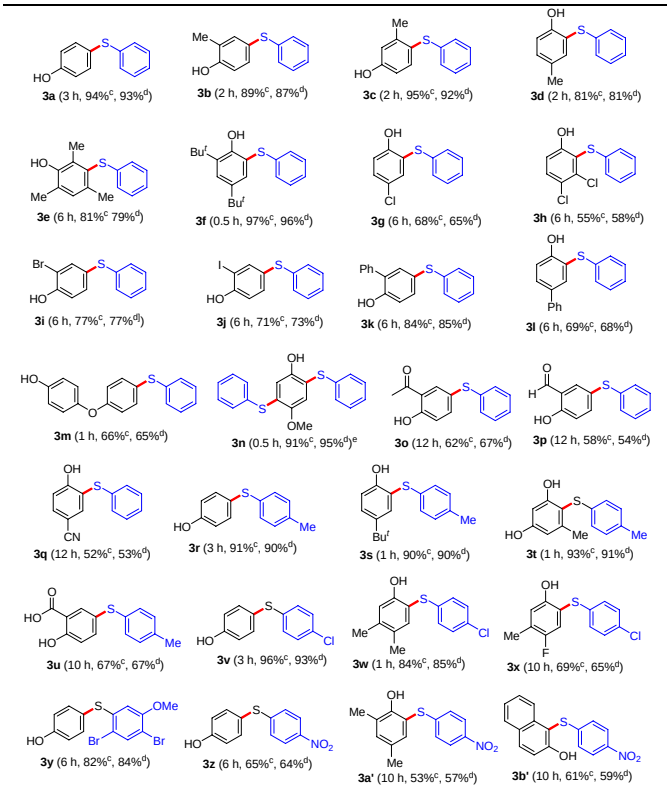
Aryl sulfides are important building blocks in organic synthesis, materials science and the pharmaceutical industry.[1] For example, they are used in treatment of inflammation,[2] Alzheimer's and Parkinson's diseases,[3] human immunodeficiency virus,[4] and cancer.[5] Transition metal-catalyzed cross-couplings of thiols or disulfides with aryl halides or pseudo halides are the most powerful approaches for the synthesis of aryl sulfides,[6] and the used transition metal catalysts mainly include palladium,[7] copper,[8] cobalt,[9] indium,[10] gold,[11] rhodium,[12] iron,[13] and Ni.[14] In addition, the diaryl sulfides were also prepared via the reactions of arylmagnesium halides[15] or arylboronic acid derivatives[16] in the presence of suitable electrophilic arylsulfur reagents and catalysts. Recently, the transition metal-catalyzed C-H functionalization has become a subject of intensive studies.[17] Obviously, a C-S bond formation via the direct C-H functionalization is more economical and practical. However, the examples by this approach are very limited thus far,[18] so it is highly desirable to develop an efficient, practical and environmentally friendly method for synthesis of diaryl sulfides through C-H functionalization strategy. Herein, we reported a novel, simple, efficient and environmentally friendly iron or boron-catalyzed arylthiation of substituted phenols at room temperature.

Reaction conditions including catalysts, solvents, temperature and time were first investigated for synthesis of 4-(phenylthio)phenol (**3a**) via reaction of phenol with 1-(phenylthio)pyrrolidine-2,5-dione, and the results showed that the optimal conditions were as follows: using 10 mol % $FeCl_3$ or $BF_3{\cdot}OEt_2$ as the catalyst, CH_2Cl_2 (DCM) as the solvent at room temperature without extrusion of air (*see Supporting Information for details*). After getting the optimum reaction conditions, we investigated the scope for iron or boron-catalyzed arylthiation of substituted phenols (**1**) with 1-(substituted phenylthio)pyrrolidine-2,5-diones (**2**). As shown in Table 1, the tested substrates provided good to excellent yields, and the reaction site for the arylthiation of substituted phenols depends on electronic and steric hindrance effects of phenols. For substituted phenols (**1**), the substrates containing electron-donating groups displayed higher reactivity than those with electron-withdrawing groups, the arylthiation mainly occurred at *para*-site of hydroxyl in phenols because of *ortho* steric hindrance effect, and the reaction was performed at *ortho*-site of hydroxyl when *para*-site of hydroxyl was occupied by a substituent. For 3,4-dichlorophenol, the arylthiation occurred at *ortho*-site of OH and 3-Cl (see **3h**). However, the electrophilic substitution of 2,4-dimethylphenol was not at OH and 3-Me because of steric hindrance of methyl (see **3w**). For 4-phenoxyphenol, the reaction was carried out at *para*-site of ether because of low steric hindrance (see **3m**). The arylthiation of 2-naphthalenol was performed on *ortho* α-carbon of OH because of its highest electron density for carbons of 2-naphthalenol (see **3b'**). When 1.1 equiv of 1-(phenylthio)pyrrolidine-2,5-dione reacted with 4-methoxyphenol, only bis-substituted product **3n** was observed because mono-substituted product displayed more higher reactive activity than 4-methoxyphenol (see **3n**), so 2.2 equiv of 4-methoxyphenol was used as the arylthiating agent to improve yield of **3n**. For 1-(substituted phenylthio)pyrrolidine-2,5-diones (**2**), the substrates containing electron-withdrawing groups afforded lower yields than those with electron-donating groups. The iron or boron-catalyzed arylthiation of substituted phenols could tolerate various functional groups including C-F bond (see **3x**), C-Cl bond (see **3g**, **3h**, **3v-x**), C-Br bond (see **3i**, **3y**), C-I bond (see **3j**), ethers (see **3m**, **3n**), acetyl (see **3o**), aldehyde (see **3p**), cyan (see **3q**), carboxyl (see **3u**), and nitro (see **3z-b'**).

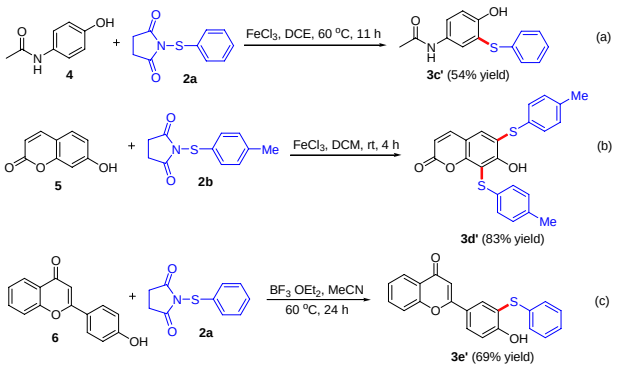
Table 1 Arylthiation of substituted phenols (**1**) at room temperature[a]



3 (Time, Yield[b])



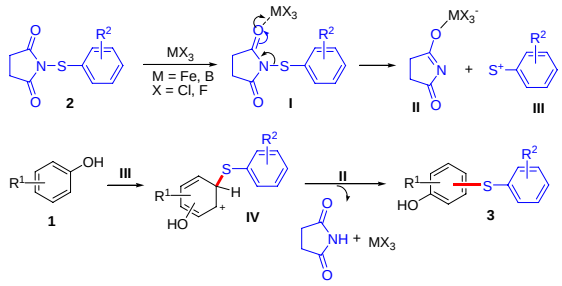
[a] Reaction conditions: substituted phenol (**1**) (0.3 mmol), 1-(substituted phenylthio)pyrrolidine-2,5-dione (**2**) (0.33 mmol), dry CH_2Cl_2 (2 mL), temperature (rt, ~25 °C), reaction time (0.5 - 12 h). [b] Isolated yield. [c] Using $FeCl_3$ (0.03 mmol) as the catalyst. [d] Using $BF_3{\cdot}OEt_2$ (0.03 mmol) as the catalyst. [e] Using 0.66 mmol of 1-(phenylthio)pyrrolidine-2,5-dione.



Scheme 1 Iron or boron-catalyzed arylthiation of aminophenol, coumarin and flavonoid derivatives.

Inspired by the excellent results above, we extended the scope of substrates. As shown in Scheme 1, iron-catalyzed reaction of *N*-(4-hydroxyphenyl)acetamide (**4**) with 1-(phenylthio)pyrrolidine-2,5-dione (**2a**) at 60 °C in dichloroethane (DCE) provided the target product (**3c'**) in 54% yield (*Unfortunately, the reaction did not work at room temperature*) (Scheme 1a). Arylthiations of biologically active molecules, coumarin and flavonoid derivatives, were also investigated. Iron-catalyzed arylthiation of 7-hydroxy-2*H*-chromen-2-one with 2.2 equiv of 1-(*p*-tolylthio)pyrrolidine-2,5-dione gave bis-substituted product **3d'** under the standard conditions (Scheme 1b), and boron-catalyzed arylthiation of 2-(4-hydroxyphenyl)-4*H*-chromen-4-one with **2a** afforded **3e'** in 69% yield in MeCN at 60 °C (Scheme 1c).

During optimization of conditions, we found that $FeCl_3$, $BF_3{\cdot}OEt_2$, $AlCl_3$ and H_2SO_4 exhibited the higher catalytic activity (*see Supporting Information for details*). Therefore, a possible mechanism on the arylthiation of substituted phenols is proposed in Scheme 2 according to the results above and the previous reference.[19] Treatment of **2** with $FeCl_3$ or $BF_3{\cdot}OEt_2$ leads to complex **I**, and cleavage of N-S bond in **I** gives anion complex **II** and cation **III**. Electrophilic reaction of **III** to substituted phenol (**1**) yields **IV**, and treatment of **IV** with **II** provides the target product (**3**) freeing succinimide and the catalyst.



Scheme 2 Possible mechanism for the iron or boron-catalyzed arylthiation of substituted phenols.

In summary, we have developed a simple, efficient and practical arylthiation of substituted phenols. The protocol uses readily available 1-(substituted phenylthio)pyrrolidine-2,5-dione as the arylthiation reagents, inexpensive and environmentally friendly $FeCl_3$ or $BF_3{\cdot}OEt_2$ as the catalyst, no ligand, additive and extrusion of air were required, and the reactions were performed very well at room temperature with wide tolerance of functional groups. We believe that the present strategy will find wide application in synthesis of diaryl sulfides.

The authors wish to thank the National Natural Science Foundation of China (Grant Nos. 21172128, 21372139 and 21221062), and the Ministry of Science and Technology of China (Grant No. 2012CB722605) for financial support.

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† Electronic Supplementary Information (ESI) available: Full experimental details, characterization and NMR spectra of the target products are provided. See DOI: 10.1039/b000000x/

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