



Direct thiolation of methoxybenzenes with thiols under metal-free conditions by iodine catalysis



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ARTICLE INFO

Article history:

Received 10 May 2015

Revised 16 June 2015

Accepted 20 June 2015

Available online 26 June 2015

Keywords:

Thiolation

Thiol

Iodine

Metal-free

Sulfides

ABSTRACT

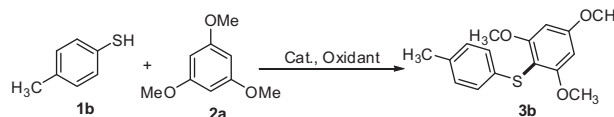
A direct thiolation of methoxybenzenes with various thiols has been developed. The protocol uses inexpensive reagents: catalytic iodine in the presence of DTBP. Importantly, no base or ligand was necessary. This method opens a new avenue to a variety of valuable thioethers that would be more difficult to access with traditional methods.

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C–S bonds widely exist in natural products and biological molecules.¹ As a consequence, a large number of methods have been developed for the selective formation of C–S bonds. Transition-metal-catalyzed cross-coupling of thiols or disulfides with aryl halides, pseudo halides, or arylboronic acids, is a versatile method for the construction of a C–S bond.² Coupling of sulfonyl chlorides with organozinc or Grignard reagents is also a useful method.³ However, these methods often suffer some drawbacks, such as harsh reaction conditions, uneasily available precursors. Recently, direct functionalization of inert C–H bonds is a straightforward transformation in synthetic chemistry.⁴ There is no doubt that direct thiolation of C–H bonds is more economical and

Table 1

I₂-catalyzed coupling reaction of 4-methylbenzenethiol (**1b**) with 1,3,5-trimethoxybenzene (**2a**) leading to *p*-tolyl(2,4,6-trimethoxyphenyl)sulfane (**3b**): optimization of conditions^a

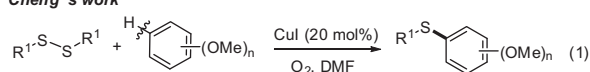


Entry	Catalyst (mol %)	Oxidant (equiv)	Temp. (°C)	Yield ^b (%)
1	I ₂ (15)	DTBP (5.0)	90	49
2	ⁿ Bu ₄ NI (15)	DTBP (5.0)	90	35
3	NIS (15)	DTBP (5.0)	90	44
4	KI (15)	DTBP (5.0)	90	41
5	I ₂ (15)	H ₂ O ₂ (5.0)	90	46
6	I ₂ (15)	TBHP (5.0)	90	22
7	I ₂ (15)	DTBP (5.0)	100	58
8	I ₂ (15)	DTBP (5.0)	110	67
9	I ₂ (15)	DTBP (5.0)	120	77
10	I ₂ (15)	DTBP (4.0)	120	73
11	I ₂ (15)	DTBP (3.0)	120	66
12	–	DTBP (5.0)	120	19
13	I ₂ (20)	DTBP (5.0)	120	85
14	I ₂ (25)	DTBP (5.0)	120	85

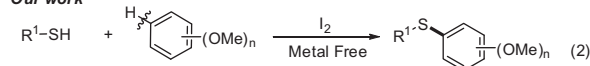
^a Reaction conditions: 4-methylbenzenethiol (**1b**) (0.5 mmol), 1,3,5-trimethoxybenzene (**2a**) (1.0 mmol), catalyst (0.075 mmol), oxidant (2.5 mmol), reaction time (24 h), under a nitrogen atmosphere.

^b Isolated yield.

Cheng's work



Our work



Scheme 1. Methods for the synthesis of diarylsulfides.

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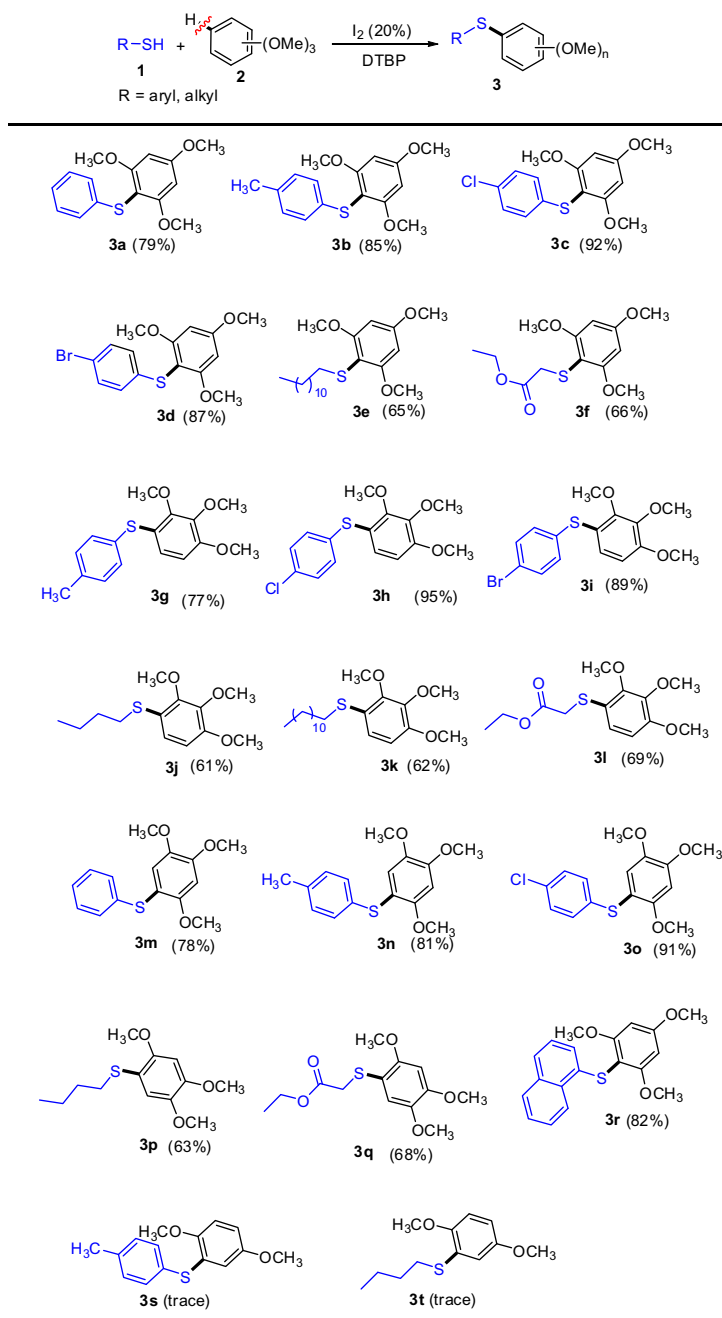
<http://dx.doi.org/10.1016/j.tetlet.2015.06.057>

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practical. However, a literature survey indicated that using this synthetic strategy for the preparation of thioether compounds is rare, and in this respect, several examples using diaryl disulfides or 1-(substituted phenylthio)pyrrolidine-2,5-dione as the thiolation reagents under Cu, Fe, and Pd catalytic conditions have been reported.⁵ For example, in 2010, Cheng and co-workers reported an elegant copper-catalyzed thiolation of electron-rich arene C–H bonds with diphenyl disulfide and diselenide (Scheme 1, Eq. 1).^{5a} However, transition-metal-catalyzed or mediated coupling reactions are still limited in some cases and confront challenges to applications, owing to the instinctive drawbacks of the catalytic systems, and trace-metal impurities in the end products. Hence, the development of a metal-free protocol for the C–S bond formation via direct inert C–H bond functionalization appears desirable and synthetically attractive. In 2013, Deng's

group developed an I₂-mediated approach for the synthesis of 2-arylsulfanylphenols under mild conditions.⁶ In 2014, Fu and co-workers demonstrated an elegant work for the synthesis of diaryl sulfides via boron-catalyzed C–H arylthiation of phenols at room temperature.⁷ Very recently, Huang's group reported the direct use of arylsulfonfyl hydrazide as the thiolation reagents for iodine-mediated thiolation of substituted naphthols and naphthylamines.⁸ However, the thiolation reagents mainly focus on aryl ones, while alkyls are rare. Herein, we wish to report a molecular iodine-catalyzed approach to diaryl sulfides from readily available aryl/alkyl thiols and substituted methoxybenzenes under metal- and solvent-free conditions (Scheme 1, Eq. 2).

Initially, 4-methylbenzenethiol (**1b**) and 1,3,5-trimethoxybenzene (**2a**) were selected as the model substrates to optimize the reaction conditions (Table 1). The oxidative coupling product



Scheme 2. Direct thiolation of different methoxybenzenes. Reaction conditions: under nitrogen atmosphere, thiols (0.5 mmol), multi-substituted methoxybenzenes (1.0 mmol), I₂ (0.1 mmol), DTBP (2.5 mmol), 120 °C, 24 h, under a nitrogen atmosphere. Isolated yield.

p-tolyl(2,4,6-trimethoxyphenyl)sulfane (**3b**) could be obtained in 49% yield at 90 °C by using I₂ as the catalyst and 5.0 equiv of DTBP (Di-*tert*-butyl peroxide) as the oxidant. Encouraged by this result, we investigated other different catalysts such as ⁿBu₄NI, NIS and KI, and I₂ showed the best activity (entry 1). Different oxidants were compared (compare entries 1, 5 and 6), and DTBP was superior to the other oxidants (entry 1). In addition, various reaction temperatures were investigated (entries 7–9), and 120 °C provided the highest yield 77% (entry 9). Furthermore, different amounts of DTBP were employed in the reactions (compare entries 9–11), and the 5 equiv of DTBP was discovered to be more suitable for this reaction (entry 9). When the amount of the catalysts was changed from 15 mol % to 25 mol %, the reaction yield increased, and the yield was reached to maximum when the amount of the catalyst was 20 mol % (entries 11–14). Notably, a low yield of product was observed in the absence of iodine (entry 12). After the optimization process for catalysts, oxidants, and temperature, various diaryl sulfide derivatives were synthesized under our standard conditions: 20 mol % I₂ as the catalyst, 5 equiv of DTBP as the oxidant under solvent-free conditions at 120 °C.

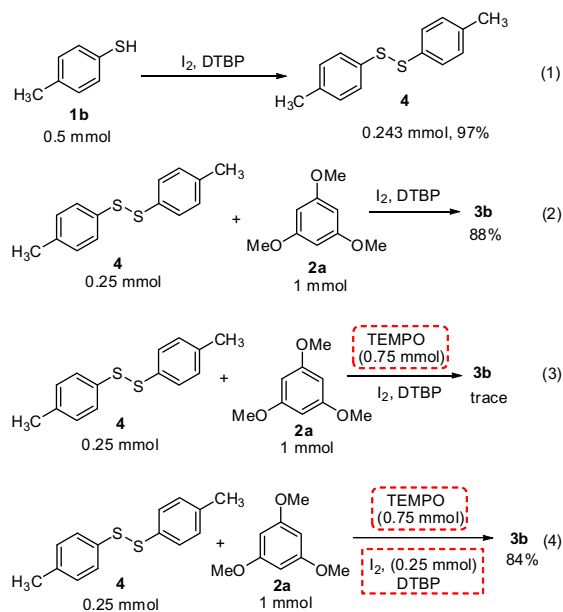
After established the optimized reaction conditions for the iodine-catalyzed direct arylation of electron-rich arenes, we surveyed the generality and scope of the protocol by varying the range of thiols and substituted methoxybenzenes. As shown in Scheme 2, the direct thiolation reactions proceeded well for all substrates examined. To our delight, aryl thiols which have electron-donating or withdrawing groups could be converted to the desired diaryl sulfides in good to excellent yields. Several aliphatic thiols including ethyl 2-mercaptoacetate, butane-1-thiol, and dodecane-1-thiol were also examined, which afforded the desired products in good yields (Scheme 2, **3e**, **3f**, **3j**, **3k**, **3l**, **3p** and **3q**). Also, naphthalene-2-thiol could be employed in the reaction to generate the desired product **3r** in high yield. Notably, we did not observe any other regioisomers in the thiolation of 1,2,3-trimethoxybenzene and 1,2,4-trimethoxybenzene. Although three substituted arenes showed high reactivity, unfortunately, the two substituted ones were poor substrates (Scheme 2, **3s** and **3t**). A variety of functional groups such as methyl, methoxyl, ester, C–Cl bond, and C–Br bond were found to be quite compatible with the present protocol.

Next, we explored our present methodology to other aromatic substrates (**4**) like 4-(methylthio)aniline, imidazo[2,1-*b*]thiazole, methyl indolizine-1-carboxylate and benzo[*d*]imidazo[2,1-*b*]thiazole to prove the general applicability of the present protocol. To

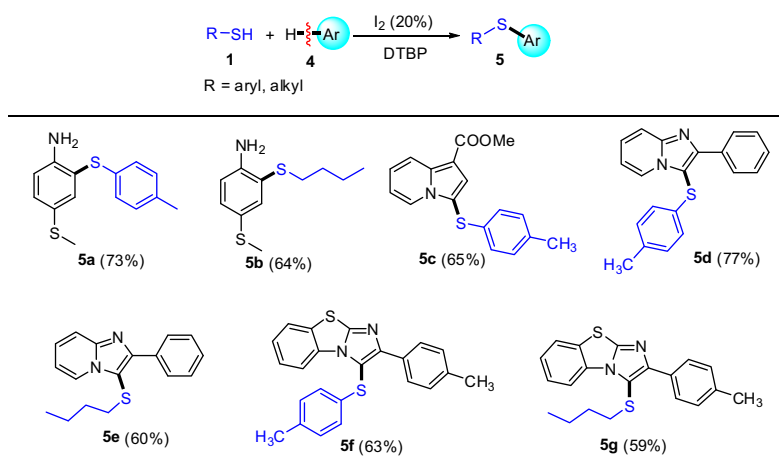
our delight, the corresponding diaryl or dialkyl sulfides products (**5**) were obtained regioselectively in good yields (Scheme 3).

To further explore the mechanism of this reaction, several control experiments were carried out as shown in Scheme 4. Treatment of 4-methylbenzenethiol (**1b**) only under the standard conditions, 1,2-dip-tolyldisulfane (**4**) was obtained in 97% yield (Eq. 1). Furthermore, the reaction of **4** with **2a** gave the desired **3b** in 88% yield (Eq. 2). Besides, the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) completely inhibited the **3b** formation (Eq. 3). This result indicated that the present transformation might involve a radical process. However, treatment of 1,2-dip-tolyldisulfane (**4**) with **2a** under 0.25 mmol of I₂ afforded the desired product **3b** in 84% yields (Eq. 4).

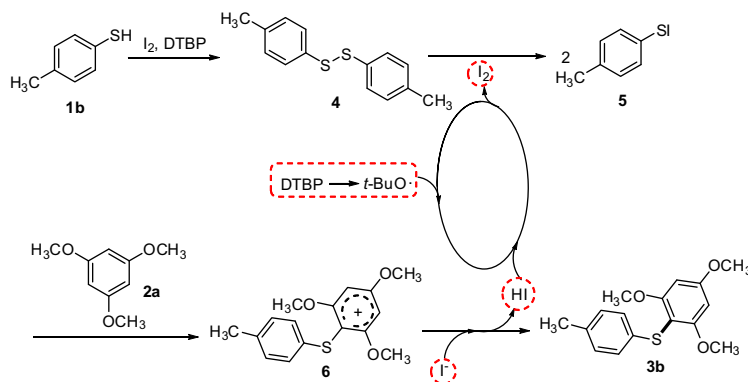
Based on the preliminary results above and the previous report, a tentative mechanism for the iodine-catalyzed arylthiolation process is illustrated in Scheme 5. Initially, 4-methylbenzenethiol (**1b**) was transformed to 1,2-dip-tolyldisulfane (**4**) under the present reaction conditions. Next, 1,2-dip-tolyldisulfane (**4**) reacted with



Scheme 4. Control experiments.



Scheme 3. Investigation of substrates scope. Reaction conditions: under nitrogen atmosphere, thiols (0.5 mmol), aromatic substrates (1.0 mmol), I₂ (0.1 mmol), DTBP (2.5 mmol), 120 °C, 24 h. Isolated yield.

Scheme 5. Plausible mechanism of **1b** with **2a**.

I₂ to provide an electrophilic species *p*-MePhSI (**5**),⁹ which attacked 1,3,5-trimethoxybenzene (**2a**) to yield **6**, which underwent aromatization to give the desired product **3b** and HI. Finally, treatment of *t*-BuO[•] radical with HI led to the catalyst I₂ which can be realized in the reaction cycle.

In conclusion, we have described an oxidative coupling of electron-rich arenes with thiols to give thioethers in good to excellent yields. The reaction was proposed to go through an electrophilic aromatic substitution path way. Most attractively, the reaction made direct use of simple and abundant starting materials without requiring transition metal catalysts, thus facilitating operation on the benchtop. Therefore, the protocol will open a new avenue for the C–S bond-forming reactions and should find broad application in synthetic chemistry.

Acknowledgments

The authors gratefully acknowledge the financial support from the National Natural Science Foundation of China (Nos. 21302110, 21302109 and 21375075), the Project of Shandong Province Higher Educational Science and Technology Program (J13LD14), the Taishan Scholar Foundation of Shandong Province, and the Natural Science Foundation of Shandong Province (ZR2013BQ017). We thank Xiao Zhu in this group for reproducing the results of **3a** and **3p**.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2015.06.057>.

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