Direct Thiolation of Methoxybenzenes with Thiols under Metal-Free Conditions by Iodine Catalysis

Kelu Yan, Daoshan Yang, Pengfei Sun, Wei Wei, Yao Liu, Guoqing Li,
Shenglei Lu, Hua Wang

PII: S0040-4039(15)01063-1
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.06.057
Reference: TETL 46449

To appear in: *Tetrahedron Letters*

Received Date: 10 May 2015
Revised Date: 16 June 2015
Accepted Date: 20 June 2015

Please cite this article as: Yan, K., Yang, D., Sun, P., Wei, W., Liu, Y., Li, G., Lu, S., Wang, H., Direct Thiolation of Methoxybenzenes with Thiols under Metal-Free Conditions by Iodine Catalysis, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.06.057

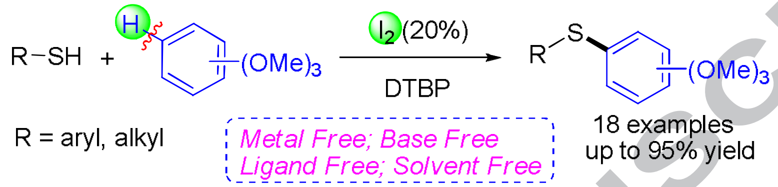
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Direct Thiolation of Methoxybenzenes with Thiols under Metal-Free Conditions by Iodine Catalysis

Leave this area blank for abstract info.

Kelu Yan, Daoshan Yang,* Pengfei Sun, Wei Wei, Yao Liu, Guoqing Li, Shenglei Lu, Hua Wang*



Tetrahedron Letters
journal homepage: www.elsevier.com

Direct Thiolation of Methoxybenzenes with Thiols under Metal-Free Conditions by Iodine Catalysis

Kelu Yan, Daoshan Yang∗, Pengfei Sun, Wei Wei, Yao Liu, Guoqing Li, Shenglei Lu, Hua Wang∗

The Key Laboratory of Life-Organic Analysis and Key Laboratory of Pharmaceutical Intermediates and Analysis of Natural Medicine, School of Chemistry and Chemical Engineering, Qufu Normal University, Qufu 273165, Shandong P. R. China.

ARTICLE INFO

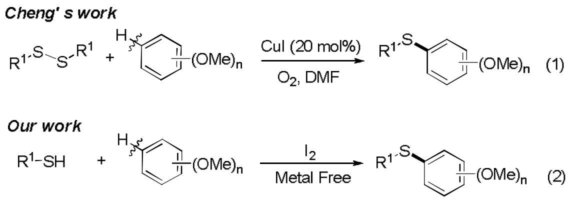
Article history:
Received
Received in revised form
Accepted
Available online

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.

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 verstile method for the construction of a C-S bond.[2] Coupling of sulfenyl 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 are straightforward transformations in synthetic chemistry.[4] There is no doubt that direct thiolation of C-H bonds is more economical and practical. However, a literature survey indicated that using this synthetic strategy for the preparation of thioether compounds are 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 I_2-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' group reported the direct use of arylsulfonyl hydrazide as the thiolation reagents for iodine-mediated thiolation of substituted naphthols and naphthylamines.[8] However, the thiolation reagents are mainly focus on aryl ones, and 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).



Scheme 1. Methods for the synthesis of diarylsulfides

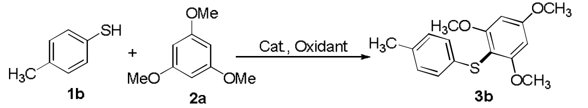
Initially, 4-methylbenzenethiol (**1b**) and 1,3,5-trimethoxybenzene (**2a**) were selected as the model substrates to optimize the reaction conditions (Table 1). The oxidative

---

∗ Corresponding author. E-mail address: yangdaoshan@tsinghua.org.cn (D. Yang); huawang_qfnu@126.com (H. Wang)

coupling product *p*-tolyl(2,4,6-trimethoxyphenyl)sulfane (**3b**) could be obtained in 49% yield at 90 °C by using I_2 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 $^nBu_4NI$, NIS and KI, and I_2 showed the best activity (entry 1). Different oxidants was 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, the various diaryl sulfide derivatives were synthesized under our standard conditions: 20 mol % I_2 as the catalyst, 5 equiv. of DTBP as the oxidant under solvent-free conditions at 120 °C.

Table 1. I_2-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]



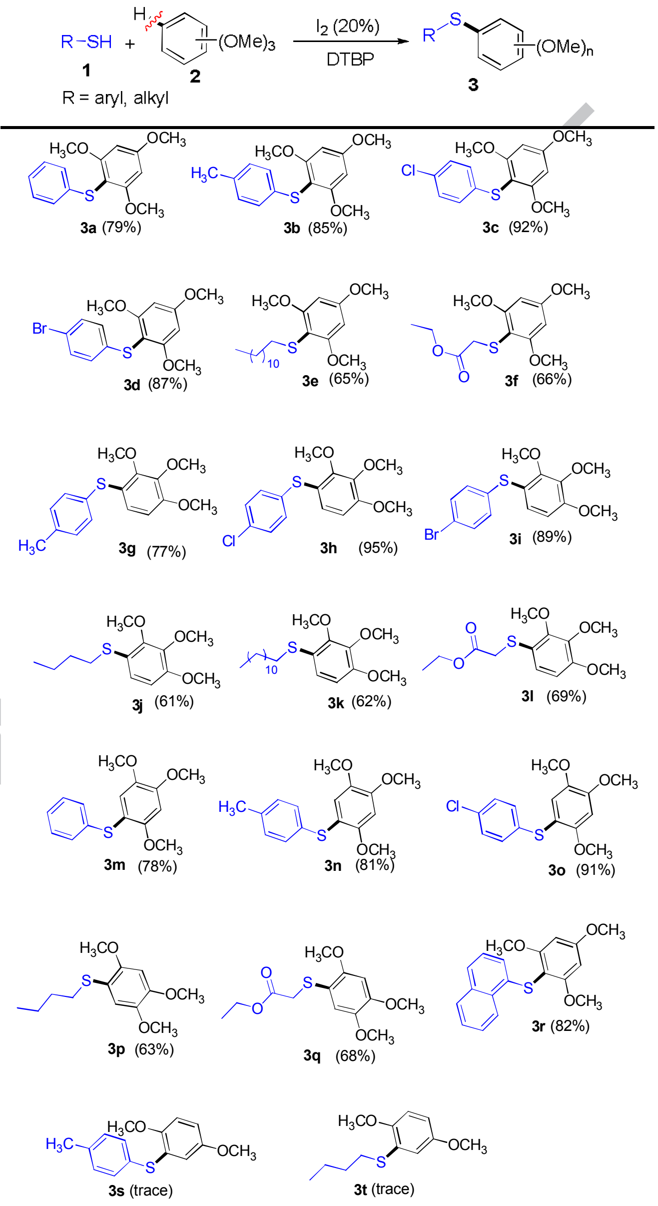
Entry	Catalyst (mol %)	Oxidant (equiv)	Temp. [°C]	Yield [%][b]
1	I_2 (15)	DTBP (5.0)	90	49
2	$^nBu_4NI$ (15)	DTBP (5.0)	90	35
3	NIS (15)	DTBP (5.0)	90	44
4	KI (15)	DTBP (5.0)	90	41
5	I_2 (15)	H_2O_2 (5.0)	90	46
6	I_2 (15)	TBHP (5.0)	90	22
7	I_2 (15)	DTBP (5.0)	100	58
8	I_2 (15)	DTBP (5.0)	110	67
9	I_2 (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.

After established the optimized reaction conditions for the iodine-catalyzed direct arylthiolation 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.

Scheme 2. Direct thiolation of different methoxybenzenes [a], [b]

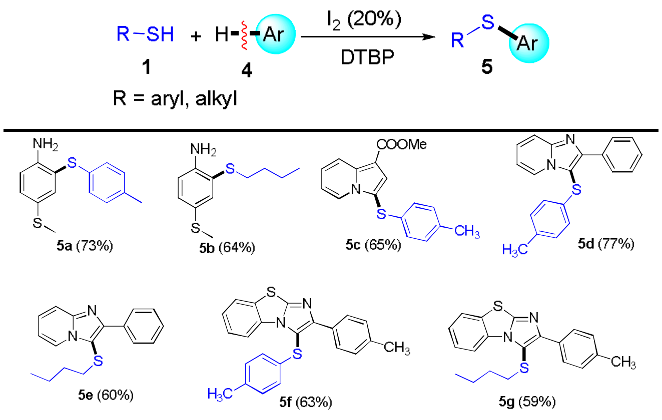


[a] *Reaction conditions:* under nitrogen atmosphere, thiols (0.5 mmol), muti-substituted methoxybenzenes (1.0 mmol), I_2 (0.1 mmol), DTBP (2.5 mmol), 120 °C, 24h, under a nitrogen atmosphere..

[b] Isolated yield.

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).

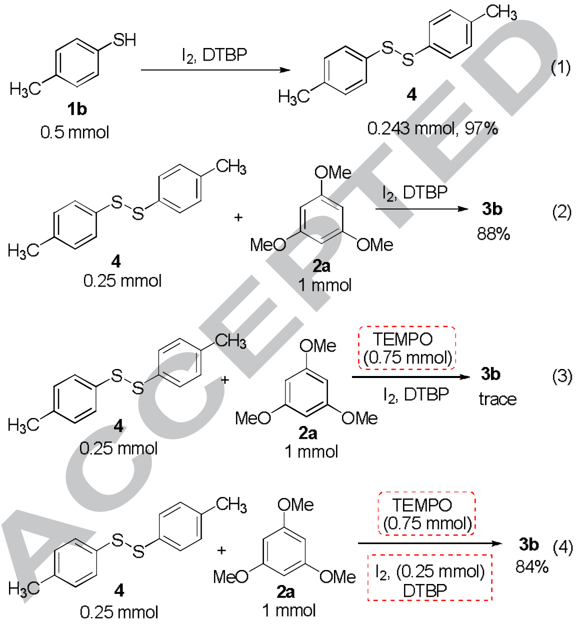
Scheme 3. Investigation of substrates scope [a], [b]



[a] *Reaction conditions:* under nitrogen atmosphere, thiols (0.5 mmol), aromatic substrates (1.0 mmol), I_2 (0.1 mmol), DTBP (2.5 mmol), 120 °C, 24h.

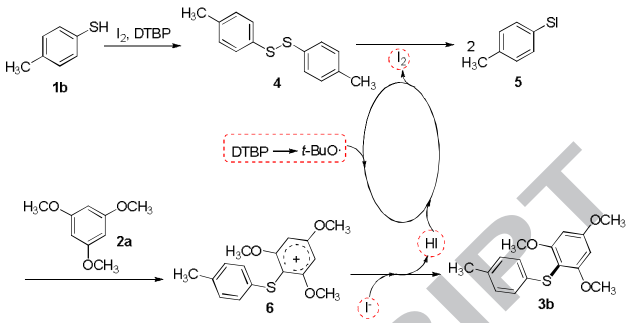
[b] Isolated yield.

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-di*p*-tolyldisulfane (**4**) was obtained in 97% yield (eq 1). Furthermore, the reaction of **4** with **2a** gave te desired **3b** in 88% yield (eq 2). Besides that, 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-di*p*-tolyldisulfane (**4**) with **2a** under 0.25 mmol of I_2 afforded the desired product **3b** in 84% yields (eq 4).



Scheme 4. Control experiments

Based on the preliminary results above and the previous report, a tentative mechanism for the iodine-catalyzed arylthiolation process was illustrated in Scheme 5. Initially, 4-methylbenzenethiol (**1b**) was transformed to 1,2-di*p*-tolyldisulfane (**4**) under the present reaction conditions. Next, 1,2-di*p*-tolyldisulfane (**4**) reacted with I_2 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 I_2 which can realized the reaction cycle.



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

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**.

References and notes

(1) (a) Nakazawa, T.; Xu, J.; Nishikawa, T.; Oda, T.; Fujita, A.; Ukai, K.; Mangindaan, R. E. P.; Rotinsulu, H.; Kobayashi, H.; Namikoshi, M. *J. Nat. Prod.* **2007**, *70*, 439−442; (b) Gangjee, A.; Zeng, Y. B.; Talreja, T.; McGuire, J. J.; Kisliuk, R. L.; Queener, S. F. *J. Med. Chem.* **2007**, *50*, 3046−3053; (c) Osaka, I.; Takimiya, K. *J. Am. Chem. Soc.* **2013**, *135*, 13900−13913. (d) Yadav, J. S.; Reddy, B. V. S.; Reddy, Y. J.; Praneeth, K. *Synthesis.* **2009**, 1520−1524; (e) Takimiya, K.; Shinamura, S.; Osaka, I.; Miyazaki, E. *Adv. Mater.* **2011**, *23*, 4347−4370.

(2) For selected examples, see: (a) Kondo, T.; Mitsudo, T.-a. *Chem. Rev.* **2000**, *100*, 3205−3220; (b) Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 9205−9219; (c) Jiang, Z.; She, J.; Lin, X. *Adv. Synth. Catal.* **2009**, *351*, 2558−2562; (d) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450−1460; (e) Bhadra, S.; Sreedhar, B.; Ranu. B. C. *Adv. Synth. Catal.* **2009**, *351*, 2369−2378. (f) Rout, L.; Sen, T. K.; Punniyamurthy, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5583−5586; (g) Arisawa, M.; Suzuki, T.; Ishikawa, T.; Yamaguchi, M. *J. Am. Chem. Soc.* **2008**, *130*, 12214−12215.

(3) (a) Cheng, J.-H.; Ramesh, C.; Kao, H.-L.; Wang, Y.-J.; Chan, C.-C.; Lee, C.-F. *J. Org. Chem.* **2012**, *77*, 10369−10374; (b) Yonova, I. M.; Osborne, C. A.; Morrissette, N. S.; Jarvo, E. R. *J. Org. Chem.* **2014**, *79*, 1947−1953.

(4) For recent reviews, see: (a) Lewis, J. C.; Bergman, R. G. Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013−1025; (b) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890−931; (c) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814−825; (d) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788−802.

(5) (a) Zhang, S.; Qian, P.; Zhang, M.; Hu, M.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 6732−6735; (b) Tudge, M.; Tamiya, M.; Savarin, C.; Humphrey, G. R. *Org. Lett.* **2006**, *8*, 565−568; (c) Anbarasan, P.; Neumann, H.; Beller, M. *Chem. Commun.* **2011**, *47*, 3233−3235; (d) Zhang, S.; Qian, P.; Zhang, M.; Hu, M.; Cheng,J. *J. Org. Chem.* **2010**, *75*, 6732−6735; (e) Ranjit, S.; Lee,

R.; Heryadi, D.; Shen, C.; Wu, J. E.; Zhang, P.; Huang, K.-W.; Liu, X. *J. Org. Chem.* **2011**, 76, 8999–9007; (f) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790–6791; (g) Fang, X.-L.; Tang, R.-Y.; Zhang, X.-G.; Li, J.-H. *Synthesis.* **2011**, 1099–1105; (h) Zhang, M.; Zhang, S.; Pan, C.; Chen, F. *Synth. Commun.* **2012**, *42*, 2844–2853.

(6) Liao, Y.; Jiang, P.; Chen, S.; Qia, H.; Deng, G.-J. *Green Chem.* **2013**, *15*, 3302–3306.

(7) Tian, H.; Zhu, C.; Yang, H.; Fu, H. *Chem. Commun.* **2014**, *50*, 8875–8877.

(8) Kang, X.; Yan, R.; Yu, G.; Pang, X.; Liu, X.; Li, X.; Xiang, L.; Huang, G. *J. Org. Chem.* **2014**, *79*, 10605–10610.

(9) Du, H. A.; Tang, R. Y.; Deng, C. L.; Liu, Y.; Li, J. H.; Zhang, X. G. *Adv. Synth. Catal.* **2011**, *353*, 2739–2748.

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the