



# Investigation of the scope and mechanism of copper catalyzed regioselective methylthiolation of aryl halides



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## ABSTRACT

Methylthiolation of structurally diverse aryl halides was accomplished under fluoride free conditions using catalytic amounts of CuI, and DMSO as the methylthiolation source. Optimization studies unveiled several varieties of promoters among which Zn(OAc)<sub>2</sub> was found ideal. The analogous reaction with DMSO-*d*<sub>6</sub> afforded corresponding deuterated aryl methyl thioether with 99% purity. Mechanistic studies revealed CuSMe as the active methylthiolation agent.

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## 1. Introduction

Aryl methyl thioethers are ubiquitous structural constituents that are present in pharmaceuticals and various biologically active compounds.<sup>1</sup> In addition, they are versatile intermediates that can be converted into sulfoxides,<sup>2</sup> thiols and arenes,<sup>3</sup> and also finds application in C–C coupling reactions.<sup>4</sup> Straightforward methods for the synthesis of aryl methyl thioethers include reduction of sulfoxides,<sup>5</sup> reaction of aryl thiols with iodomethane<sup>6</sup> and aryl halides with dimethyl disulfide.<sup>7</sup> Multistep processes, such as lithiation of aryl halide or heteroatom-assisted lithiation of aromatic C–H bonds and subsequent electrophilic substitution with dimethyl disulfide were utilized for their synthesis.<sup>8</sup> A direct *ortho*-methylthiolation of 2-phenylpyridine with dimethyl disulfide promoted by copper(II) acetate under air atmosphere has also been realized.<sup>9</sup> Notably, Jiang et al. has reported an important catalytic process involving the coupling of aryl halide with sulfur in presence of copper(I)iodide followed by subsequent reduction and reaction with iodomethane.<sup>10</sup>

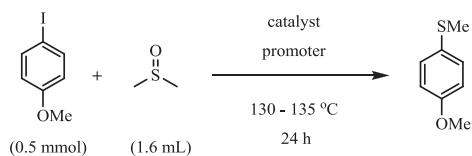
Recently, DMSO was used as a methylthiolation source for *ortho*-methylthiolation of the 2-arylpipridine and C–H thiolation of heteroarenes.<sup>11</sup> These protocols evade the direct usage of gaseous

methanethiol or toxic dimethyl disulfide; however, their utility is confined to heteroarene substrates. An important advancement in this field is the report by Cheng et al. of CuI catalyzed methylthiolation of aryl iodides and aryl bromides with DMSO using ZnF<sub>2</sub> at 150 °C.<sup>12</sup> The procedure has the merit of starting from available or easy to prepare aryl halides. Importantly, their study demonstrated that the presence of fluoride as a promoter was essential for the process. Therefore, to ascertain the mechanistic aspects of methylthiolation and to evaluate the scope of the reaction under fluoride free conditions; herein, we report a convenient process for methylthiolation of aryl halides involving CuI and Zn(OAc)<sub>2</sub> using DMSO as the methylthiolation source under comparatively mild conditions.

## 2. Results and discussion

The preliminary studies for the methylthiolation of aryl halides were aimed to find the best promoter. For this, several reactions were carried out on a 0.5 mmol scale with different promoters using 4-iodoanisole as the model substrate and 10 mol % of CuI catalyst in 1.6 mL of DMSO. Selected results of the optimization studies are tabulated in Table 1, which clearly demonstrate that fluorides are not essential for accomplishing methylthiolation. Moreover, these studies prove that acetates, amines and ammonium salts are comparatively better promoters than fluorides.<sup>13</sup> Among the promoters screened, good results were obtained with

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**Table 1**  
Optimization of reaction parameters for methylthiolation of 4-iodoanisole<sup>a</sup>

Entry	Catalyst	Promoter (equiv)	Yield <sup>e</sup> /%
1	CuI	NH <sub>4</sub> F (4)	4
2	CuI	NH <sub>5</sub> F <sub>2</sub> (4)	56
3	CuI	Et <sub>3</sub> N·3HF (4)	35
4	CuI	Pyrrrolidine (4)	80
5	CuI	Piperidine (4)	52
6	CuI	Morpholine (4)	32
7	CuI	<i>N</i> -Methylpyrrolidine (4)	10
8	CuI	2-Methylpiperidine (4)	8
9	CuI	ZnF <sub>2</sub> (2)	25
10	CuI	AgF (2)	27
11	—	Cu <sub>2</sub> O (2)	0
12	—	CuI (2)	0
13	—	Cu(OSO <sub>2</sub> CF <sub>3</sub> )(2)	0
14	—	Cu(acac) <sub>2</sub> (2)	27 <sup>b</sup>
15	—	CuOAc (2)	93
16	—	Cu(OAc) <sub>2</sub> (1.5)	95
17	CuI	Zn(OAc) <sub>2</sub> (2)	85
18	CuI	Ni(OAc) <sub>2</sub> (2)	48 <sup>b</sup>
19	CuI	Mn(OAc) <sub>2</sub> (2)	74 <sup>b</sup>
20	CuI	Zn(OAc) <sub>2</sub> (2)	95 <sup>b</sup>
21	CuI	K(OAc) (2)	5 <sup>b</sup>
22	CuI	Ni(OCOFCF <sub>3</sub> )(2)	46 <sup>b</sup>
23	CuBr	Zn(OAc) <sub>2</sub> (2)	93 <sup>b</sup>
24	Cu <sub>2</sub> O	Zn(OAc) <sub>2</sub> (2)	90 <sup>b</sup>
25	Cu powder	Zn(OAc) <sub>2</sub> (2)	93 <sup>b</sup>
26	CuBr <sub>2</sub>	Zn(OAc) <sub>2</sub> (2)	83 <sup>b</sup>
27	CuI	Zn(OAc) <sub>2</sub> (1)	80 <sup>b</sup>
28	CuI	Zn(OAc) <sub>2</sub> (1.5)	94 <sup>b</sup>
29	—	Zn(OAc) <sub>2</sub> (2)	14 <sup>b,d</sup>
30	—	Zn(OAc) <sub>2</sub> (2)	48 <sup>c,d</sup>

<sup>a</sup> Unless otherwise stated, the reactions were performed on a 0.5 mmol scale with 4-iodoanisole (0.5 mmol), catalyst (10 mol %) and promoter (1–4 equiv) in 1.6 mL of DMSO at 130 °C for 24 h.

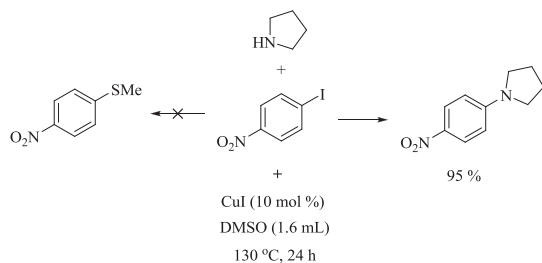
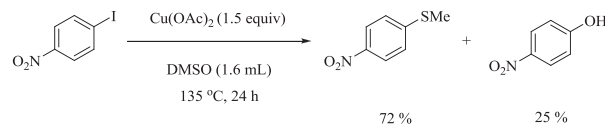
<sup>b</sup> Temperature=135 °C.

<sup>c</sup> Temperature=140 °C.

<sup>d</sup> Reaction performed in the absence of catalyst.

<sup>e</sup> Isolated yield.

pyrrolidine, Cu(OAc)<sub>2</sub>, Cu(OAc) and Zn(OAc)<sub>2</sub>. However, pyrrolidine, Cu(OAc)<sub>2</sub> and Cu(OAc) cannot be employed as promoters for methylthiolation of electron-deficient aryl halides like 4-iodonitrobenzene, since pyrrolidine exclusively undergoes *N*-arylation with 4-iodonitrobenzene instead of methylthiolation (Scheme 1), whereas significant amounts of 4-nitrophenol were formed when Cu(OAc)<sub>2</sub> and Cu(OAc) were used as promoters (Scheme 2). Thereafter, Zn(OAc)<sub>2</sub> was selected as the promoter and further screening studies were carried out to find the best catalyst. Notably, comparable results were obtained for most of the copper salts, although CuI, CuBr and copper powder showed slightly superior yields. Thus as illustrated in Table 1, the most promising

**Scheme 1.** *N*-Arylation versus methylthiolation.**Scheme 2.** Methylthiolation versus hydroxylation.

result was obtained by employing 10 mol % CuI, 1.5 equiv Zn(OAc)<sub>2</sub> and 1.6 mL DMSO at 135 °C for 24 h (Table 1, entry 28). In addition, we have also studied the effect of ligands and secondary additives in altering the reaction outcome. Contrarily, the ligand did not show any effect on the reactions using Zn(OAc)<sub>2</sub> and Cu(OAc)<sub>2</sub> as promoters. Nevertheless, some of the interesting combinations evaluated during the optimization studies are presented in Table S1 (see Supplementary data).

With the above optimized reaction conditions in hand (i.e., Table 1, entry 28), various structurally diverse aryl iodides were tested for methylthiolation. Electron-rich aryl iodides like 4-iodotoluene, 1-(*tert*-butyl)-4-iodobenzene, 1-(benzyloxy)-3-iodobenzene and 4-iodo-1,1'-biphenyl (Table 2, entries 2–4 and 6) underwent the reaction smoothly to afford the corresponding products in excellent

**Table 2**  
Copper catalyzed methylthiolation of aryl halides

Entry	ArX (0.5 mmol)	DMSO (1.6 mL)	CuI, Zn(OAc) <sub>2</sub> or Cu(OAc) <sub>2</sub>		ArSMe	Yield <sup>f</sup> /%
			130–135 °C 24–36 h			
1						94, <sup>a</sup> 95 <sup>b</sup>
2						82, <sup>a</sup> 84 <sup>b</sup>
3						94, <sup>a</sup> 93 <sup>b</sup>
4						75 <sup>a</sup>
5						78 <sup>a</sup>
6						87 <sup>a</sup>
7						78 <sup>a</sup>
8						79 <sup>a,c</sup>
9						78 <sup>a</sup>
10						80 <sup>a</sup>
11						96 <sup>a</sup>

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