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ARTICLE TYPE

# Highly regioselective *para*-methylthiolation/bridging methylenation of arylamines promoted by NH<sub>4</sub>I

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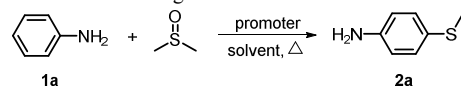
Aryl methyl thioethers and methylene-bridged arylamines were synthesized *via* highly regioselective *para*-methylthiolation/bridging methylenation of arylamines using DMSO as the methylthio or methylene source in the presence of NH<sub>4</sub>I under metal-free conditions. For the substrates with both electron-donating and electron-withdrawing substituents, the reaction proceeded smoothly and gave moderate to good yields.

Aryl methyl thioethers are versatile and important structural motifs in pharmaceutical chemistry since they often show outstanding biological activity.<sup>1</sup> They also have been found wide application in organic synthesis, for example, as electrophiles in transition-metal catalyzed C–C coupling<sup>2</sup> and C–N coupling reaction,<sup>3</sup> and the carbothiolation of terminal alkynes.<sup>4</sup> The reduction of sulfoxides,<sup>5</sup> the nucleophilic substitution to iodomethane with aryl thiols<sup>6</sup> and the electrophilic substitution to aryl lithium with dimethyl disulfide<sup>7</sup> are well-established for the synthesis of aryl methyl thioethers. Transition-metal catalyzed cross-coupling reaction of thiols or disulfides with aryl halides provided a new route for the preparation of aryl sulfides,<sup>8</sup> but the methylthiolation using this strategy was limited. In 2011, Cheng et al developed a methylthiolation of aryl halides by using a widely available and cheap reagent DMSO as the “MeS” source in the presence of CuBr/ZnF<sub>2</sub>.<sup>9</sup> Subsequently, in 2013, Kantam et al performed this methylthiolation in CuI/Zn(OAc)<sub>2</sub> system.<sup>10</sup> A CuI/DABCO-mediated methylthiolation of haloarenes with DMSO was also reported very recently by Mal et al.<sup>11</sup> Using DMSO as the source of the thiomethyl moiety, Magolan et al synthesized aryl methyl thioethers via a S<sub>N</sub>Ar reaction in the presence of diisopropylethylamine (DIPEA).<sup>12</sup> It is noticeable that the direct C–S bond formation *via* C–H bond activation brought about a new insight in last decade, which provided a straightforward and economical sequences to prepare sulfides from non-prehalogenated arenes.<sup>13</sup> Several pyridyl directed regioselective methylthiolations on aromatic C(sp<sup>2</sup>)-H bond were reported.<sup>14</sup> Employing DMSO as the methylthiolating reagent, the methylthiolations on heteroarenes without coordinating directing-groups were developed in the presence or in absence of transition-metal.<sup>15</sup> Very recently, Cai et al reported a Pd-catalyzed decarboxylation of benzoic acids with DMSO to obtain aryl methyl thioethers.<sup>16</sup> Xiao et al developed a three-component coupling reaction of arynes,  $\alpha$ -bromocarbonyl

compounds and DMSO in the presence of KF and 18-crown-6 to form aryl methyl thioethers.<sup>17</sup> Fu et al reported an arylthiolation of arylamines using (aryltio)pyrrolidine-2,5-diones as the arylthiolating reagents, but only aryl sulfides were synthesized by this protocol.<sup>18</sup> As the continuous study of our group on C–H bond functionalization, especially the coupling reactions under metal-free conditions,<sup>19</sup> herein we want to disclose a regioselective *para*-methylthiolation of arylamines promoted by NH<sub>4</sub>I. And bridging methylenation products diaryl methanes were also obtained for some reactants.

Initially, aniline (**1a**) was employed as the reactant for the reaction conditions research (Table 1). DMSO was used as both methylthiolating reagent and the solvent. Without the promoter, the reaction could not take place at all (entry 1). Thus, some iodides or bromide, such as I<sub>2</sub>, KI, TBAI (tetrabutylammonium iodide), TBAB (tetrabutylammonium bromide) and NH<sub>4</sub>I were tested as the promoter for this reaction, in which NH<sub>4</sub>I gave the best result, and the others showed very poor promotion effect for this transformation (entries 2-6). A *para*-methylthiolation product **2a** was obtained in 46% yield in the presence of 2 equiv. NH<sub>4</sub>I at 140 °C after 16 h (entry 6). Encouraged by this result, further optimization to the reaction conditions was attempted. To our delight, a higher yield of 68% was further achieved when the amount of NH<sub>4</sub>I was increased to 4 equiv. (entry 7). The solvent was then screened. It was showed that the addition of water not only did not lower the yield but also promoted the reaction in a manner (entries 8, 9). When the reaction took place in a 1:1 (v/v) DMSO/H<sub>2</sub>O mixed solvent, the highest yield of 80% was given (entry 9). But excessive water might lead to the decrease of the yield (entry 10). It should also be noted that the reaction was strongly affected by the temperature. The lower reaction temperature brought about the lower conversion (entry 11, 12). The best result was achieved at 140 °C.

**Table 1** Screening of reaction conditions<sup>a</sup>



Entry	Promoter (equiv.)	Solvent	T (°C)	Yield (%) <sup>b</sup>
1	-	DMSO	140	0
2	I <sub>2</sub> (2)	DMSO	140	trace
3	KI (2)	DMSO	140	<10
4	TBAI (2)	DMSO	140	15
5	TBAB (2)	DMSO	140	0

6	NH <sub>4</sub> I (2)	DMSO	140	46
7	NH <sub>4</sub> I (4)	DMSO	140	68
8	NH <sub>4</sub> I (4)	DMSO/H <sub>2</sub> O (2:1)	140	74
9	NH <sub>4</sub> I (4)	DMSO/H <sub>2</sub> O (1:1)	140	80
10	NH <sub>4</sub> I (4)	DMSO/H <sub>2</sub> O (1:2)	140	45
11	NH <sub>4</sub> I (4)	DMSO/H <sub>2</sub> O (1:1)	100	17
12	NH <sub>4</sub> I (4)	DMSO/H <sub>2</sub> O (1:1)	120	48

<sup>a</sup>Unless otherwise specified, the reactions were carried out in a sealed tube in the presence of **1a** (0.3 mmol), promoter and solvent (2 mL) for 16 h. <sup>b</sup>Isolated yields based on **1a**.

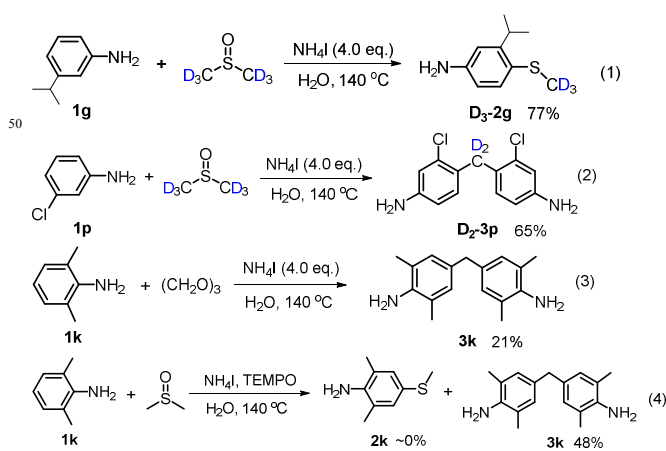
With the optimized conditions in hand, we explored the scope of this NH<sub>4</sub>I promoted reaction of arylamines with DMSO. The results are summarized in Table 2. To our surprise, when *o*-methylaniline (**1b**) was used as the reactant, in addition to the desired product **2b** in 53% yield, a methylene-bridged product 4,4'-methylene-bis(2-methylaniline) **3b** was also obtained in 36% yield. Various anilines bearing electron-withdrawing or electron-donating moieties on benzene ring were investigated. In most cases, the reactions of anilines with electron-donating group (e.g., OMe, Me, Et, *i*-Pr, *t*-Bu) (**1a-i**) on the benzene ring mainly gave methylthiolation products in moderate to good yields, and the methylthiolation regioselectively took place on *para*-position. Some disubstituted or phenyl substituted anilines (**1k-n**) gave both methylthiolation (**2k-n**) and bridging methylenation (**3k-n**) products. Specially, the reactions of anilines with some electron-withdrawing group (e.g., Cl, CN) (**1o-q**) on the benzene ring only gave methylene-bridged products (**3o-q**). However, fluorinated substrate **1j** afforded methylthiolation product **2j** simply. The relationship between the generation of the two products (**2** or **3**) and the substituent on benzene ring did not show evident regularity. Importantly, for the substrates with one or two alkyls on amino group (**1r-w**), the reaction also proceeded. Furthermore, nitrogenous heterocycle substituted arene derivatives 1-phenylpiperidine (**1x**), 4-phenylmorpholine (**1y**) and 1,2,3,4-tetrahydroquinoline (**1z**) could also react with DMSO to give the corresponding methylthiolation or/and methylene-bridged products in moderate yields.

In order to investigate the reaction mechanism, a series of control experiments were carried out (Scheme 1). The deuterium labeling experiment with DMSO-*d*<sub>6</sub> confirmed that methylthio group (MeS-) in the product **2** originated from DMSO (eq. (1)). When 3-chloroaniline was used to react with DMSO-*d*<sub>6</sub>, *d*<sub>2</sub>-4,4'-methylenebis(3-chloroaniline) (**D<sub>2</sub>-3p**) was obtained, which confirmed that the methylene in the product **3** also originated from DMSO (eq. (2)). Using triformal to replace DMSO in water solution, 4,4'-methylenebis(2,6-dimethylaniline) (**3k**) was obtained in 21% yield (eq. (3)), which indicated that the methylene in **3** might come from HCHO that was generated from the decomposition of DMSO. In addition, when the reaction was performed in the presence of 4.0 equiv. of TEMPO under the standard reaction conditions, **2k** was almost not formed, but **3k** was obtained in 48% yield (eq. (4)). These results suggested that the methylthiolation presumably proceeded through a radical pathway, but this radical pathway was not involved in the bridging methylenation process.

**Table 2** The reaction results of anilines with DMSO<sup>a</sup>

Entr	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield ( <b>2</b> ) <sup>b</sup>	Yield ( <b>3</b> ) <sup>b</sup>
1	H	H	H	80% ( <b>2a</b> )	--
2	2-Me	H	H	53% ( <b>2b</b> )	36% ( <b>3b</b> )
3	2-OMe	H	H	56% ( <b>2c</b> )	--
4	3-Me	H	H	42% ( <b>2d</b> )	--
5	3-OMe	H	H	67% ( <b>2e</b> )	--
6	3-Et	H	H	79% ( <b>2f</b> )	--
7	3- <sup>i</sup> Pr	H	H	82% ( <b>2g</b> )	--
8	3- <sup>t</sup> Bu	H	H	57% ( <b>2h</b> )	--
9	3,5-di-Me	H	H	34% ( <b>2i</b> )	--
10	3-F	H	H	67% ( <b>2j</b> )	--
11	2,6-di-Me	H	H	42% ( <b>2k</b> )	52% ( <b>3k</b> )
12	2,6-di- <sup>i</sup> Pr	H	H	31% ( <b>2l</b> )	60% ( <b>3l</b> )
13	2-F-3-Me	H	H	46% ( <b>2m</b> )	45% ( <b>3m</b> )
14	2-Ph	H	H	21% ( <b>2n</b> )	63% ( <b>3n</b> )
15	2-Cl	H	H	--	56% ( <b>3o</b> )
16	3-Cl	H	H	--	69% ( <b>3p</b> )
17	2-CN	H	H	--	44% ( <b>3q</b> )
18	H	H	Me	--	66% ( <b>3r</b> )
19	3-Me	H	Me	63% ( <b>2s</b> )	24% ( <b>3s</b> )
20	H	Me	Me	--	71% ( <b>3t</b> )
21	3-Me	Me	Me	41% ( <b>2u</b> )	43% ( <b>3u</b> )
22	H	Et	Et	34% ( <b>2v</b> )	55% ( <b>3v</b> )
23	H	<i>n</i> -Bu	<i>n</i> -Bu	--	73% ( <b>3w</b> )
24				--	71% ( <b>3x</b> )
25				38% ( <b>2y</b> )	--
26				35% ( <b>2z</b> )	39% ( <b>3z</b> )

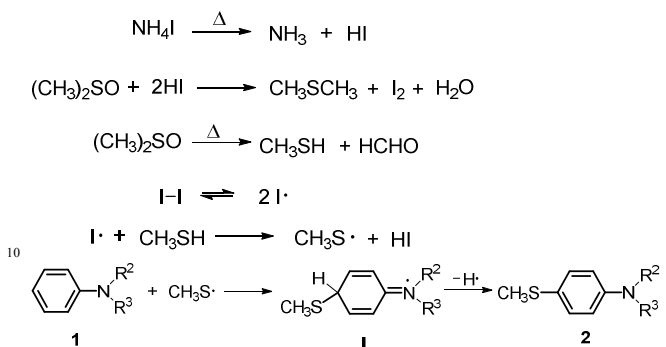
<sup>a</sup>The reactions were carried out in a sealed tube in the presence of **1** (0.3 mmol), NH<sub>4</sub>I (1.2 mmol) in DMSO/H<sub>2</sub>O (2 mL, 1:1) at 140 °C for 16 h. <sup>b</sup>Isolated yields based on **1**.



**Scheme 1** Control experiments.

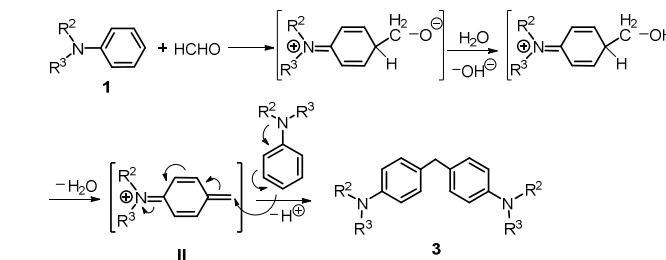
Based on the above results and the related reports,<sup>15-17</sup> a plausible reaction mechanism for the formation of **2** was proposed in Scheme 2. First, the precursor **I<sub>2</sub>** was generated

through the decomposition of  $\text{NH}_4\text{I}$  and the subsequent reaction with DMSO; meanwhile the decomposition of DMSO formed MeSH and HCHO.<sup>14c,20</sup> Then the homolysis of  $\text{I}_2$  produced iodine radical, followed to react with MeSH to give a methylthio radical  $\text{MeS}\cdot$ .<sup>20b</sup> Subsequently, the addition of radical  $\text{MeS}\cdot$  to the *para*-position of aniline generated a radical intermediate **I**. The methylthiolated product **2** finally produced *via* the elimination of hydrogen radical from **I**.



**Scheme 2** Proposed reaction mechanism for the formation of **2**.

As shown above, the thermal decomposition of DMSO generated HCHO. Several ammonium-promoted formylations by DMSO were also reported.<sup>21</sup> Based on these works, we therefore proposed that a Mannich-type reaction mechanism might be involved in the formation of the methylene-bridged product **3** (Scheme 3). The nucleophilic addition of aniline to HCHO and next elimination of  $\text{H}_2\text{O}$  formed methylenated intermediate **II**, and the nucleophilic substitution of this electron-deficient intermediate to another aniline on the *para*-position generated **3**.



**Scheme 3** Proposed reaction mechanism for the formation of **3**.

## Conclusions

In conclusion, we developed the highly regioselective *para*-methylthiolation/bridging methylenation of arylamines by using DMSO as the methylthio or methylene source in the presence of  $\text{NH}_4\text{I}$ . A series of aryl methyl thioethers and methylene-bridged arylamines were synthesized *via* this very simple procedure in moderate to good yields. The reaction was applicable to various aromatic amine derivatives. The mild reaction conditions and convenient operation provided possibility for future research to apply this methodology in the synthesis of pharmaceuticals and other useful compounds.

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