



# Iron-catalyzed thioesterification of methylarenes with thiols in water



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## ARTICLE INFO

### Article history:

Received 18 September 2014

Revised 21 October 2014

Accepted 31 October 2014

Available online 6 November 2014

### Keywords:

Thioester

Cross-dehydrogenative coupling

Iron catalysis

Micellar catalysis

## ABSTRACT

An iron-catalyzed coupling reaction of methylarenes with thiols leading to thioesters has been developed. The reactions were carried out in water with *tert*-butyl hydroperoxide (TBHP) as the oxidant and polyoxyethanyl  $\alpha$ -tocopheryl sebacate (PTS) as the surfactant. The reaction medium is compatible with a series of functional groups and can be reused.

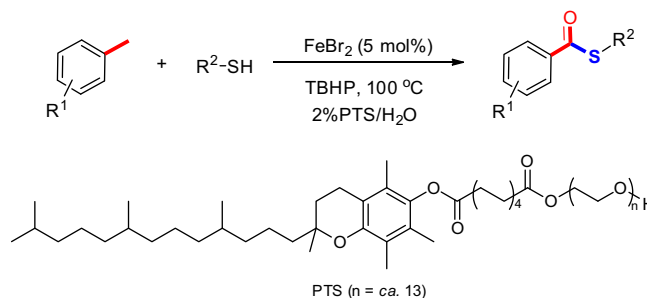
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Thioesters are important building blocks since they are ubiquitous in natural products.<sup>1</sup> Generally, thioesters are prepared via the following pathway: (i) thioesterification of carboxylic acids or their derivatives;<sup>2–4</sup> (ii) palladium-catalyzed thiocarbonylation of aryl halides with thiols and carbon monoxide;<sup>5</sup> (iii) cross-dehydrogenative coupling (CDC) of aldehydes with thiols or disulfides in the presence of radical initiator, with the combination of *N*-Heterocyclic carbene (NHC) catalyst, Dess–Martin periodinane, and metal catalyst such as CuCl and FeBr<sub>2</sub>.<sup>6–10</sup> Among the reported methodologies, the CDC strategy is the most powerful since no prefunctionalization step is required, thereby making the reactions more atom economic. However, some problems still existed in these reported procedures. For example, diaryl and dialkyl sulfides were not compatible with Kita's procedure;<sup>6</sup> the NHC catalyst was much more expensive and could not be recycled;<sup>7</sup> and much more amount of Dess–Martin periodinane was required.<sup>8</sup> Alternatively, Lee developed a copper-catalyzed direct coupling of aldehydes with thiols in water assisted by TBHP. However, heterocyclo-containing aldehydes were not suitable for the system.<sup>9</sup> A modified procedure was then reported by the same group by using a cheap and nontoxic iron catalyst.<sup>10</sup> Just recently, Patel reported a copper-catalyzed CDC reaction between alkylbenzenes and thiols, where alkylbenzenes were utilized as aroyl surrogates.<sup>11</sup> However, the activities of heterocyclo-containing arenes were not reported.

Water has received wide interest as a solvent since it is inexpensive, nontoxic, and safe. The problem in this field is the solubility of organic substrates. In this context, micellar catalysis provides

an efficient way to solve the 'bottle-neck'. Recently, much effort has been made by Lipshutz in the micellar catalysis by using a non-ionic amphiphile, polyoxyethanyl  $\alpha$ -tocopheryl sebacate (PTS), as the surfactant. Micelles with diameter at ca. 25 nm were formed in PTS/water system, in which, a series of C–C coupling reactions were realized under mild conditions.<sup>12</sup> Notably, the PTS/water system could be recovered and reused. In continuation of our interest in C–S bond formation<sup>13</sup> as well as micellar catalysis,<sup>13b</sup> herein, we report a *S*-arylation of thiols using methylarenes as aroyl surrogates in the presence of FeBr<sub>2</sub>/TBHP in water (Scheme 1).

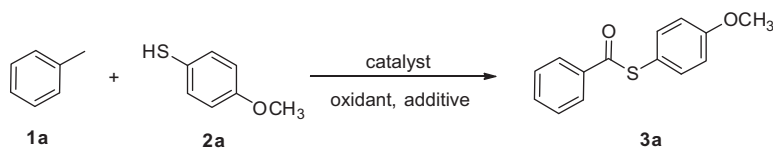
Initially, toluene **1a** and 4-methoxybenzenethiol **2a** were selected as the substrates to optimize the reaction conditions (Table 1). A series of iron salts and copper salts were investigated by using TBHP as the oxidant in PTS/H<sub>2</sub>O system. The results suggested that FeBr<sub>2</sub> was the best choice, giving the desired product **3a** in 85% yield (Table 1, entry 5). No product was observed in the absence of either FeBr<sub>2</sub> or TBHP. Screening other surfactants



Scheme 1. Iron-catalyzed thioesterification of alkylbenzenes with thiols.

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**Table 1**  
Optimized reaction conditions<sup>a</sup>

Entry	Catalyst (mol %)	Oxidant (equiv)	Additive	Yield <sup>b</sup> (%)
1	FeCl <sub>2</sub> (5)	TBHP (4)	PTS	74
2	Fe(OAc) <sub>2</sub> (5)	TBHP (4)	PTS	29
3	FeCl <sub>3</sub> (5)	TBHP (4)	PTS	54
4	Fe(NO <sub>3</sub> ) <sub>3</sub> ·9H <sub>2</sub> O (5)	TBHP (4)	PTS	37
5	<b>FeBr<sub>2</sub> (5)</b>	<b>TBHP (4)</b>	<b>PTS</b>	<b>85</b>
6	Cu(OAc) <sub>2</sub> (5)	TBHP (4)	PTS	59
7	CuBr <sub>2</sub> (5)	TBHP (4)	PTS	18
8	Cu <sub>2</sub> O (5)	TBHP (4)	PTS	25
9	CuCl (5)	TBHP (4)	PTS	30
10	—	TBHP (4)	PTS	0
11	FeBr <sub>2</sub> (5)	—	PTS	0
12	FeBr <sub>2</sub> (5)	TBHP (4)	—	21
13	FeBr <sub>2</sub> (5)	TBHP (4)	Trion X-100	15
14	FeBr <sub>2</sub> (5)	TBHP (4)	SDS	70
15	FeBr <sub>2</sub> (5)	TBHP (4)	TBAB	31
16	FeBr <sub>2</sub> (5)	DTBP (4)	PTS	0
17	FeBr <sub>2</sub> (5)	BPO (4)	PTS	0
18	FeBr <sub>2</sub> (5)	H <sub>2</sub> O <sub>2</sub> (4)	PTS	0
19	FeBr <sub>2</sub> (5)	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub> (4)	PTS	0
20	FeBr <sub>2</sub> (5)	O <sub>2</sub>	PTS	0
21	FeBr <sub>2</sub> (2.5)	TBHP (4)	PTS	57
22	FeBr <sub>2</sub> (10)	TBHP (4)	PTS	76
23	FeBr <sub>2</sub> (5)	TBHP (3)	PTS	53
24	FeBr <sub>2</sub> (5)	TBHP (5)	PTS	80

The bold value specifies the best reaction condition.

<sup>a</sup> Reaction conditions: **1a** (2.5 mmol), **2a** (0.5 mmol), 2 wt % additive/H<sub>2</sub>O (1.5 mL), oxidant (2 mmol, 4 equiv), 100 °C, 12 h.

<sup>b</sup> Isolated yields.

including Trion X-100, sodium dodecyl sulfate (SDS), and tetrabutylammonium bromide (TBAB) revealed that they were less effective than PTS (Table 1, entries 12–15). Reaction in pure water or solvent-free conditions dramatically decreased the yield. Other oxidants such as di-*tert*-butyl peroxide (DTBP), benzoyl peroxide (BPO), H<sub>2</sub>O<sub>2</sub>, K<sub>2</sub>S<sub>2</sub>O<sub>8</sub>, and O<sub>2</sub> were also evaluated. However, no products were obtained in these conditions (Table 1, entries 17–20). Finally, study on the amount of catalyst and oxidant clearly showed that 5 mol % of FeBr<sub>2</sub> and 4 equiv of TBHP were the best.

With the optimized yields in hand, the scope of different methylarenes and thiols was explored.<sup>14</sup> The results are summarized in Table 2. Aryl thiols with different functional groups including methyl, methoxyl, chloro, and fluoro reacted smoothly to give the thioesters in good yields (**3a–3d**, 69–85%), albeit a moderate yield was obtained for *o*-xylene (**3e**, 52%). Alkyl thiols such as benzylic thiols and cyclohexylmethanethiol also showed good reactivities, affording the corresponding products in good yields (**3f–3i**). Other thiols containing ester and alkenyl groups survived the reaction conditions (**3j**, 42%; **3k**, 56%). Di-thioester could be obtained by using ethylene mercaptan as the substrate (**3l**, 48%).

Next, various methylarenes were evaluated. As shown in Table 2, this reaction system showed good compatibility. Once again, methylarenes with functional groups such as methyl, methoxyl, chloro, bromo, and nitro were all tolerated under the reaction conditions (**3m–3r**, 55–82%). The electron-withdrawing groups dramatically decreased the yields (**3p**, 55%; **3q**, trace). 2-Methylnaphthalene also proceeded smoothly to give **3s** in 77% yield. Notably, pyridine-, furan-, and thiophene-containing methylarenes also coupled with thiols to deliver thiol esters in acceptable to good yields (**3t–3v**).

To gain insight into the reaction mechanism, a series of control experiments were performed (Scheme 2). Initially, replacement of

toluene with benzoic acid under the standard conditions failed to afford the thioester product, thereby ruling out this reaction pathway [Scheme 2 (i)]. Next, oxidation of dibenzylsulfane under this system gave only the corresponding sulfide as the product [Scheme 2 (ii)]. A radical scavenger (TEMPO) was also introduced to the reaction system, and only trace amount of product was observed, indicating a radical pathway may be involved. Moreover, when a mixture of benzaldehyde and 4-chlorotoluene (1:1) was coupled with 4-methoxybenzenethiol, product **3a** was obtained exclusively, suggesting the coupling of benzoyl radical with thiol may be involved in this reaction.

Based on the above results and the similar study that was previously reported,<sup>10,11</sup> a possible mechanism was proposed (Scheme 3). Initially, FeBr<sub>2</sub> reacted with TBHP to form iron complex **A** Fe(III)Br<sub>2</sub>(OH) and *t*-BuOO· radical. Then complex **A** reacted with thiols to give intermediate **B**. Meanwhile, under the FeBr<sub>2</sub>/TBHP system methylarene was oxidized to benzaldehyde. Subsequently, the *t*-BuOO· radical abstracted a hydrogen atom from the aromatic aldehyde to give a benzoyl radical. The complex **B** trapped the benzoyl radical to provide the thioester and a complex **C**. The complex **C** was further reacted with HBr to release the FeBr<sub>2</sub>, thereby finishing the catalytic cycle.

Another advantage of this protocol is the recyclability of the micellar aqueous medium due to the preferred solubility of PTS in water. When the reaction is finished, the reaction mixture was extracted with minimal amount of ethyl acetate. After that, the starting materials, iron catalyst as well as the oxidant were added to the aqueous medium. Using the synthesis of **3a** as example, almost the same isolated yields were obtained after 6 runs.

In summary, a direct synthesis of thioesters through coupling reaction of methylarenes with thiols has been realized with moderate to good yields in water. The FeBr<sub>2</sub>/TBHP system shows good

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