Tetrahedron Letters 55 (2014) 7190–7193

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

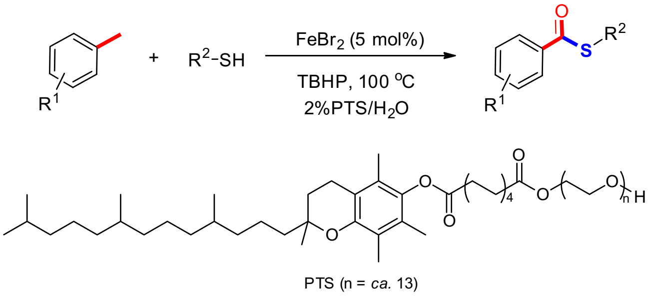
ABSTRACT

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 α-tocopheryl sebacate (PTS) as the surfactant. The reaction medium is compatible with a series of functional groups and can be reused.

Thioesters are important building blocks since they are ubiquitous in natural products.[1] Generally, thioesters are prepared via the following pathway: (i) thioesterification of carboxylic acids or their derivatives;[2–4] (ii) palladium-catalyzed thiocarbonylation of aryl halides with thiols and carbon monoxide;[5] (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 $FeBr_2$.[6–10] 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;[6] the NHC catalyst was much more expensive and could not be recycled;[7] and much more amount of Dess–Martin periodinane was required.[8] 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.[9] A modified procedure was then reported by the same group by using a cheap and nontoxic iron catalyst.[10] Just recently, Patel reported a copper-catalyzed CDC reaction between alkylbenzenes and thiols, where alkylbenzenes were utilized as aroyl surrogates.[11] 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 α-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.[12] Notably, the PTS/water system could be recovered and reused. In continuation of our interest in C—S bond formation[13] as well as micellar catalysis,[13b] herein, we report a S-aroylation of thiols using methylarenes as aroyl surrogates in the presence of $FeBr_2$/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_2O system. The results suggested that $FeBr_2$ 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 $FeBr_2$ or TBHP. Screening other surfactants



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

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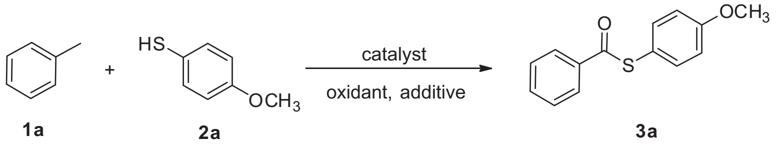
http://dx.doi.org/10.1016/j.tetlet.2014.10.155
0040-4039/

Table 1
Optimized reaction conditions[a]



Entry	Catalyst (mol %)	Oxidant (equiv)	Additive	Yield[b] (%)
1	$FeCl_2$ (5)	TBHP (4)	PTS	74
2	$Fe(OAc)_2$ (5)	TBHP (4)	PTS	29
3	$FeCl_3$ (5)	TBHP (4)	PTS	54
4	$Fe(NO_3)_3.9H_2O$ (5)	TBHP (4)	PTS	37
5	**$FeBr_2$ (5)**	**TBHP (4)**	**PTS**	**85**
6	$Cu(OAc)_2$ (5)	TBHP (4)	PTS	59
7	$CuBr_2$ (5)	TBHP (4)	PTS	18
8	Cu_2O (5)	TBHP (4)	PTS	25
9	CuCl (5)	TBHP (4)	PTS	30
10	–	TBHP (4)	PTS	0
11	$FeBr_2$ (5)	–	PTS	0
12	$FeBr_2$ (5)	TBHP (4)	–	21
13	$FeBr_2$ (5)	TBHP (4)	Trion X-100	15
14	$FeBr_2$ (5)	TBHP (4)	SDS	70
15	$FeBr_2$ (5)	TBHP (4)	TBAB	31
16	$FeBr_2$ (5)	DTBP (4)	PTS	0
17	$FeBr_2$ (5)	BPO (4)	PTS	0
18	$FeBr_2$ (5)	H_2O_2 (4)	PTS	0
19	$FeBr_2$ (5)	$K_2S_2O_8$ (4)	PTS	0
20	$FeBr_2$ (5)	O_2	PTS	0
21	$FeBr_2$ (2.5)	TBHP (4)	PTS	57
22	$FeBr_2$ (10)	TBHP (4)	PTS	76
23	$FeBr_2$ (5)	TBHP (3)	PTS	53
24	$FeBr_2$ (5)	TBHP (5)	PTS	80

The bold value specifies the best reaction condition.

[a] Reaction conditions: **1a** (2.5 mmol), **2a** (0.5 mmol), 2 wt % additive/H_2O (1.5 mL), oxidant (2 mmol, 4 equiv), 100 °C, 12 h.

[b] 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_2O_2, $K_2S_2O_8$, and O_2 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 $FeBr_2$ and 4 equiv of TBHP were the best.

With the optimized yields in hand, the scope of different methylarenes and thiols was explored.[14] 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**).

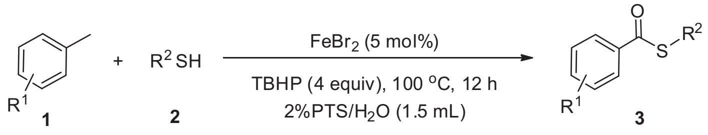
To gain insight into the reaction mechanism, a series of control experiments were performed (Scheme 2). Initially, replacement of toluene with benzoic acid under the standard conditions failed to afford the thioester product, thereby ruling out this reaction pathway [Scheme 2 (i)]. Next, oxidation of 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-methoxylbenzenethiol, product **3a** was obtained exclusively, suggesting the coupling of benzoyl radical with thiol may be involved in this reaction.

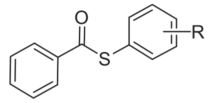
Based on the above results and the similar study that was previously reported,[10,11] a possible mechanism was proposed (Scheme 3). Initially, $FeBr_2$ reacted with TBHP to form iron complex **A** Fe(III)Br_2(OH) and *t*-BuOO**.** radical. Then complex **A** reacted with thiols to give intermediate **B**. Meanwhile, under the $FeBr_2$/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 $FeBr_2$, 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.

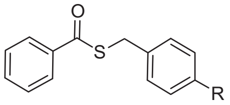
In summary, a direct synthesis of thioesters through coupling reaction of methylarenes with thiols has been realized with moderate to good yields in water. The $FeBr_2$/TBHP system shows good

Table 2
Substrate scope of methylarenes and thiols[a]

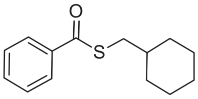




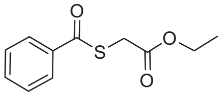
R = p-OCH$_3$, **3a**, 85%
R = p-CH$_3$, **3b**, 71%
R = p-Cl, **3c**, 83%
R = p-F, **3d**, 69%
R = o-CH$_3$, **3e**, 52%



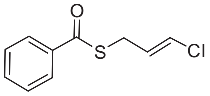
R = H, **3f**, 72%
R = p-CH$_3$, **3g**, 75%
R = p-F, **3h**, 68%



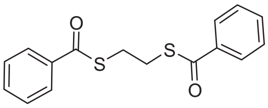
3i, 70%



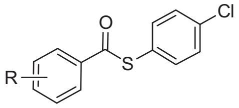
3j, 42%



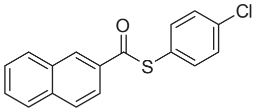
3k, 56%



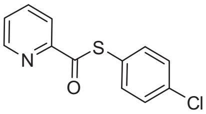
3l, 48%



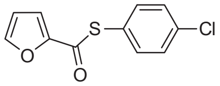
R = p-CH$_3$, **3m**, 73%
R = p-OCH$_3$, **3n**, 82%
R = p-Cl, **3o**, 80%
R = p-NO$_2$, **3p**, 55%
R = p-CF$_3$, **3q**, trace
R = m-Br, **3r**, 74%



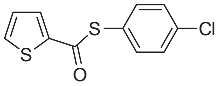
3s, 77%



3t, 36%

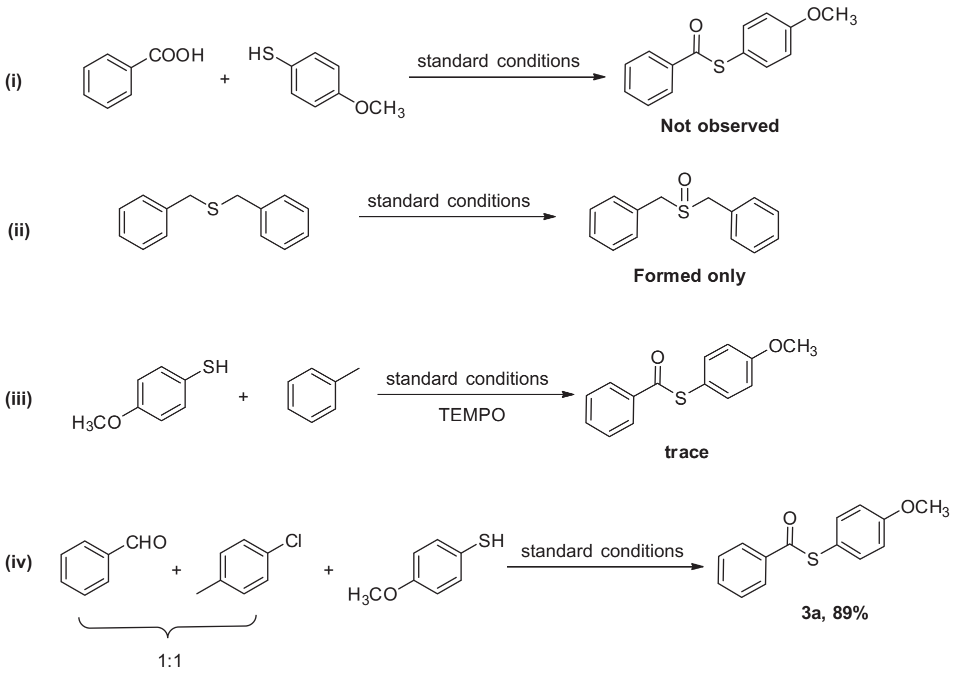


3u, 48%

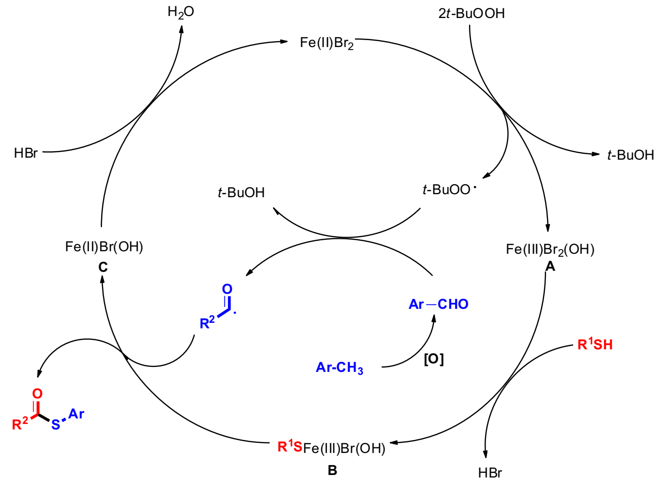


3v, 72%

[a] Reaction conditions: **1** (2.5 mmol), **2** (0.5 mmol), 2 wt % PTS/H$_2$O (1.5 mL), TBHP (2 mmol, 4 equiv), 100 °C, 12 h, isolated yields.



Scheme 2. Control experiments.



Scheme 3. Proposed mechanism.

reactivity as well as compatibility with a series of methylarenes and thiols. The methylarenes, as aroyl surrogates, are much more cheap and available compared with the corresponding aldehydes. Moreover, the micellar aqueous system can be easily recovered and reused for several runs with a slight decrease in its activity.

Acknowledgments

This project was financially supported by the National Natural Science Foundation of China (No. 21302014), the Natural Science Foundation for Colleges and Universities of Jiangsu Province (13KJB150002), and the Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology (Grant No. BM2012110).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.155.

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14. *Typical procedure for the synthesis of thioester **3a***: A sealed tube was charged with toluene (230 mg, 2.5 mmol), 4-methoxybenzenethiol (70 mg, 0.5 mmol), $FeBr_2$ (5.6 mg, 0.025 mmol), TBHP (2.0 mmol) and 2 wt % PTS/H_2O (1.5 ml). The reaction mixture was stirred at 100 °C in an oil bath for 12 h. After cooling to room temperature, the mixture was extracted with ethyl acetate. The organic layer was then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1) to give the pure product **3a** (103.7 mg, 85%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, J = 7.5 Hz, 2H), 7.57–7.50 (m, 1H), 7.45–7.35 (m, 4H), 6.94 (d, J = 8.7 Hz, 2H), 3.73 (d, J = 27.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.0, 160.9, 136.7, 133.7, 128.9, 127.5, 118.0, 115.1, 55.5. MS (ESI) m/z: 244.